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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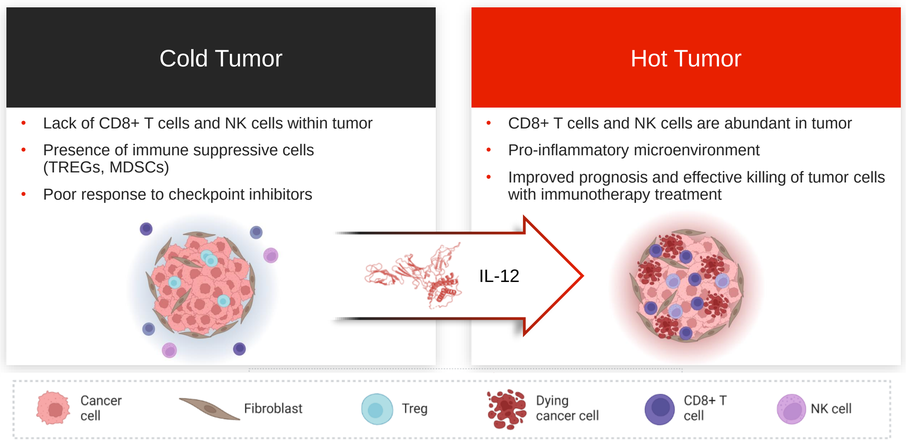
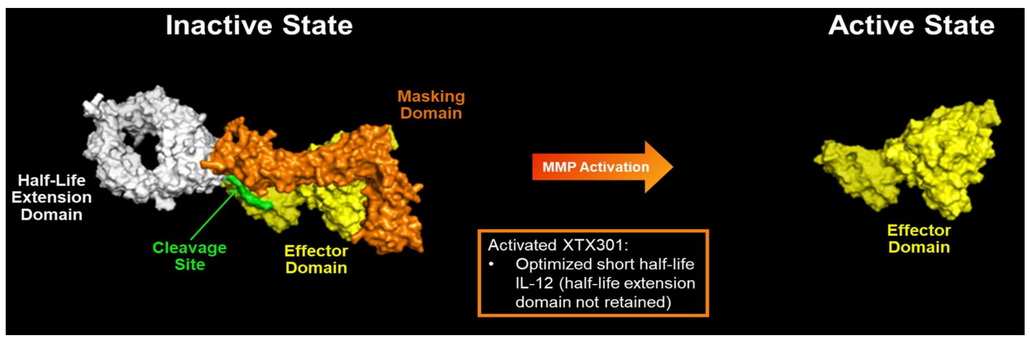
Background

Interleukin-12 (IL-12) is a proinflammatory cytokine that has shown promise as an immunotherapy for cancer.



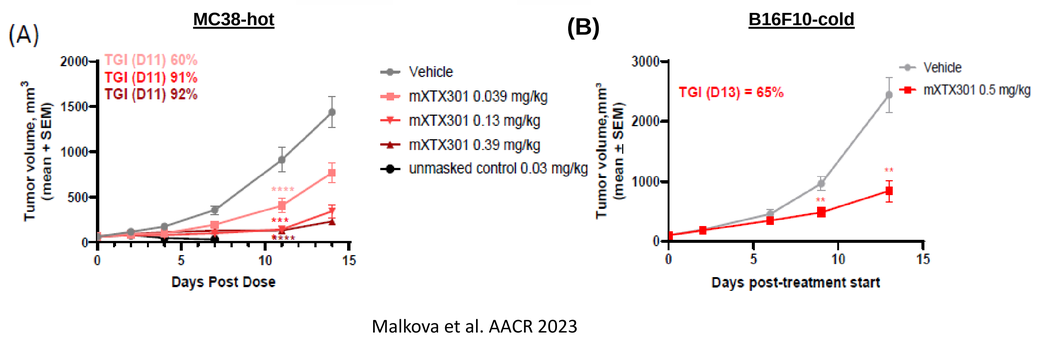
Although IL-12 has demonstrated potent antitumor activity in mouse models of cancer, its development in the clinical setting has been limited by severe systemic toxicities.

XTX301 is a half-life extended, masked and tumor-activated IL-12. XTX301 is designed to be pharmacologically inactive in non-tumor tissue when circulating systemically and unmasked by matrix metalloproteases (MMPs) preferentially active in the tumor microenvironment. The masking domain is engineered to be removed via cleavage at a protease cleavage site in the XTX301 linker by MMPs.



Preclinical data support potential for broad therapeutic index

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

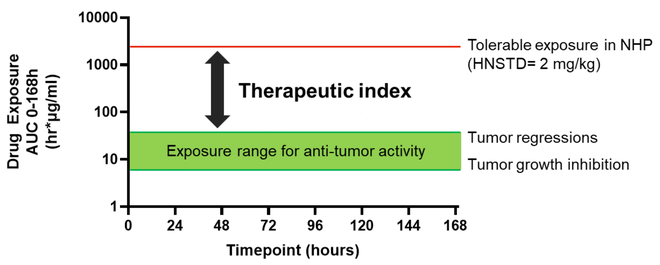


Malkova et al. AACR 2023

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 (B) 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. AACR 2023].

- XTX301 was tolerated at doses up to 2.0 mg/kg Q1W x4 in NHP (HNSTD)
- mXTX301 induced tumor regressions in murine model following a **single dose** of 0.13 mg/kg



Compound	*In Vivo* Model	Dose (mg/kg)	$AUC_{0\text{-}168}$ (hr*µg/mL)	Estimated Therapeutic Index (AUC_{Safety} / $AUC_{Activity}$)
mXTX301	**Anti-tumor activity** (murine)	0.13	37.8	**67**
XTX301	**Safety** (NHP)	2.0	2540	

Figure 2: A large exposure difference in the group mean $AUC_{0\text{-}168hr}$ between HNSTD in non-human primates and dose with anti-tumor activity in mice supports the potential for a broad therapeutic index for XTX301.

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

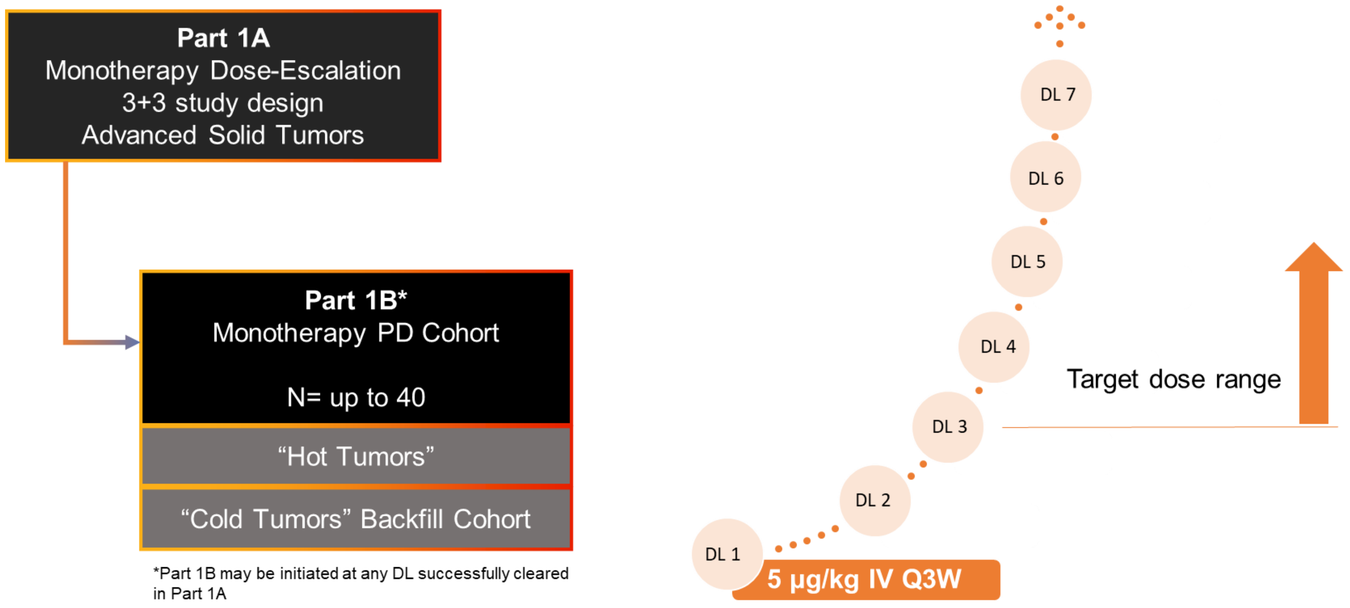
Secondary objectives

- 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



Key eligibility criteria

Inclusion criteria	Exclusion criteria
• **Disease Criteria:** locally advanced or metastatic disease that has failed standard therapy Part 1A: - any solid tumor malignancy (including lymphoma) Part 1B: - melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, triple-negative breast cancer, MSI-H/dMMR colorectal cancer and MSI-H/dMMR endometrial cancer (if they have previously derived benefit from PD-1/PD-L1 inhibitor therapy). Sponsor may open a "backfill cohort" in Part 1B for: - prostate cancer, ovarian cancer, pancreatic cancer, microsatellite stable colorectal cancer.	Prior treatment with IL-12 therapy (any form, e.g. recombinant human, prodrug, intratumoral, etc).
	Known liver metastasis based on imaging
	Possible area of ongoing necrosis (non-disease-related), such as active ulcer, nonhealing wound, or intercurrent bone fracture.
	Active primary central nervous system (CNS) malignancy, CNS metastases, and/or carcinomatous meningitis.
	Active autoimmune disease
	History of Grade ≥ 3 immune-related adverse events associated with prior immunotherapy unless these were adequately resolved with therapy within 14 days.
ECOG performance status of 0-2	
Adequate organ function	Immunodeficiency; or chronic systemic therapy exceeding prednisone equivalent of 10 mg daily
Tumor tissue samples: Part 1A: archival tumor tissue available or provide a fresh tumor biopsy. Part 1B: fresh tumor biopsies before and after initiation of treatment	Active hepatitis B or active hepatitis C infection.
Recovered from major surgery.	Prior treatment with gene therapy, organ transplant, or hematopoietic stem-cell transplant.

ClinicalTrials.gov Identifier: NCT05684965

References

Figure in top left adapted from "Cold vs Hot Tumors", by BioRender.com, 2022. Retrieved from https://app.biorender.com/biorender-templates Barraondo et al., Clin. Cancer Res., 2018. Nguyen et al., Front. Immunol., 2020.
Malkova et al. AACR (2023)

Abbreviations: MC38: murine colon carcinoma; B16F10: murine melanoma; NHP: non-human primates; HNSTD: highest non-severely toxic dose: AUC: area under the curve; MSI-H/dMMR: microsatellite instability-high/mismatch repair-deficient; PD-1: programmed death receptor-1; PD-L1: programmed death ligand 1; IV: intravenous; Q1W: once a week; Q3W: every 3 weeks; DL: dose level

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