A First-in-Human Phase 1/2 Study of XTX501, a PD-1 / Masked IL-2 Bispecific, in Metastatic Non-Small Cell Lung Cancer (NSCLC)

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SCAN ME

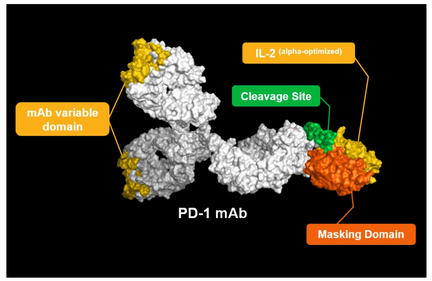
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XTX501: PD-1 / MASKED IL-2(alpha-optimized) BISPECIFIC ANTIBODY FUSION PROTEIN

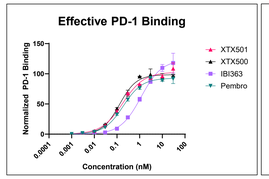
Non-Masked PD-1 Antibody, Fc-Silenced IgG1 Backbone, Fused to Masked IL-2

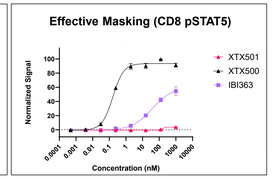
- **Dual mechanism:** combines two complementary mechanisms in a single molecule: selective inhibition of the PD-1/PD-L1 pathway and potent IL-2-driven expansion of T cells
- **Targeted delivery:** designed to direct IL-2 to PD-1+ T cells, selectively expanding tumor-specific CD8+ T cells without activating peripheral T cells that drive toxicity
- **High potency, alpha-optimized IL-2:** affinity-tuned with optimal receptor binding profile for IL-2
- **IL-2 masking:** designed to overcome IL-2 receptor-mediated clearance, peripheral activity and tolerability challenges associated with non-masked IL-2 therapies



XTX501: DIFFERENTIATED PRECLINICAL PROFILE

Meaningful Preclinical Activity Profile Compared to Non-Masked Bispecifics

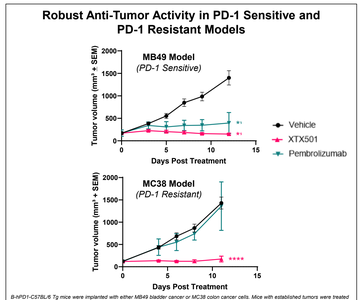




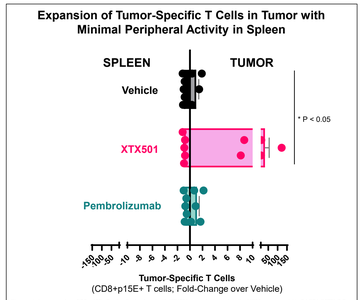
	PD-1 Binding mean K_D (nM)	Potency CD8 T Cell pSTAT5 EC50 (nM)
XTX501 (masked)	0.165	>1000
XTX500 (non-masked)	0.111	0.168
IBI363 (non-masked PD-1/IL-2)	1.025	31

XTX500 is XTX501 without a mask
Analogue of IBI363 generated by Xilio for research use only

XTX501 Demonstrated Potent Anti-Tumor Activity and Tumor-Specific Pharmacology In Vivo

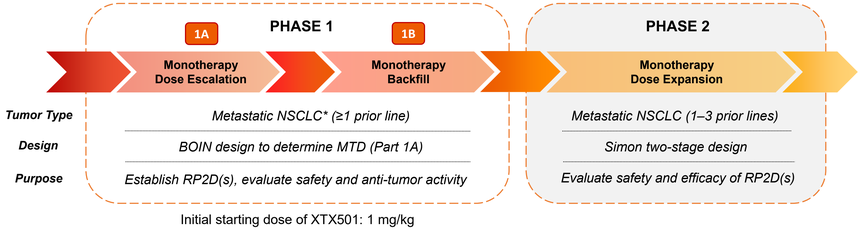


*B-hPD1-C57BL/6 Tg mice were implanted with either MB49 bladder cancer or MC38 colon cancer cells. Mice with established tumors were treated with the indicated test articles Q2Dx2 (pembrolizumab was matched dumbbell to 10 mg/kg XTX501). Tumor volume was plotted as an average ± SEM. n=10 per group. To determine statistical significance of treatment versus vehicle control, two-way ANOVA was performed with Tukey's multiple comparisons test (MB49: **P < 0.005, ***P ≤ 0.0005 on Day 12; MC38: ***P < 0.0001 on Day 11, compared with the vehicle group).*



*Changes in tumor or spleen CD8+p15E+ T cells after treatment with XTX501 or pembrolizumab in the MC38 mouse model in B-hPD1-C57BL/6 Tg mice. Average ± SEM is shown as the fold-change over vehicle control. To determine statistical significance of treatment versus vehicle (PBS) control, a one-way ANOVA was performed (*P < 0.05) with nonparametric Dunn's multiple comparison test.*

XTX501 PHASE 1/2 CLINICAL TRIAL DESIGN[1]



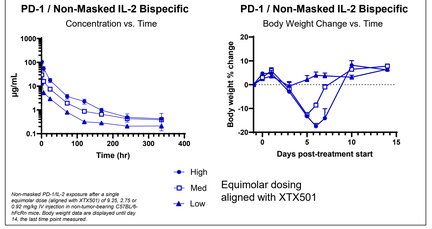
Initial starting dose of XTX501: 1 mg/kg

KEY STUDY DETAILS

- Enrollment planned at multiple US sites: Part 1A up to n≈60; Part 1B up to n≈40; Phase 2 up to n≈80
- *In Phase 1, participants with select advanced solid tumors may be enrolled to enable dose escalation

XTX501: ANTIBODY-LIKE PK AND FAVORABLE TOLERABILITY

Non-Masked Molecule was Rapidly Cleared and Poorly Tolerated

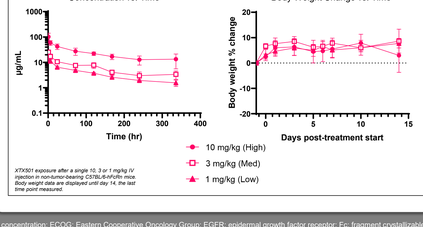


Non-masked PD-1/IL-2 exposure after a single equimolar dose (aligned with XTX501) of 9.25, 2.75 or 0.92 mg/kg IV injection in non-tumor-bearing C57BL/6-hPD/hn mice. Body weight data are displayed until day 14, the last time point measured.

High
Med
Low

Equimolar dosing aligned with XTX501

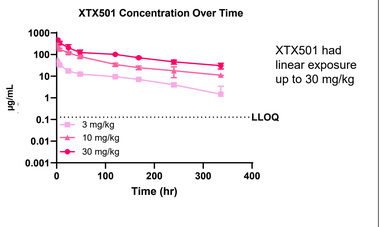
Antibody-Like Exposures and Well-Tolerated at High Doses



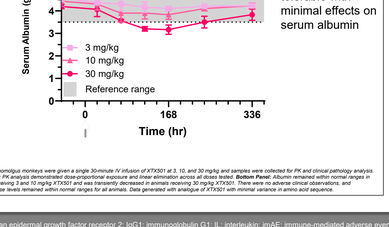
XTX501 exposure after a single 10, 3 or 1 mg/kg IV injection in non-tumor-bearing C57BL/6-hPD/hn mice. Body weight data are displayed until day 14, the last time point measured.

10 mg/kg (High)
3 mg/kg (Med)
1 mg/kg (Low)

Favorable Exposure and Tolerability in Non-Human Primates



XTX501 had linear exposure up to 30 mg/kg



XTX501 was tolerable with minimal effects on serum albumin

*Female cynomolgus monkeys were given a single 30-minute IV infusion of XTX501 at 3, 10, and 30 mg/kg and samples were collected for PK and clinical pathology analysis. **Top Panel:** PK analysis demonstrated dose-proportional exposure and linear elimination across all doses tested. **Bottom Panel:** Albumin remained within normal ranges in animals receiving 3 and 10 mg/kg XTX501 and was transiently decreased in animals receiving 30 mg/kg XTX501. There were no adverse clinical observations, and transaminase levels remained within normal ranges for all animals. Data generated with analogue of XTX501 with minimal variance in amino acid sequence.*

NSCLC PATIENT POPULATION

KEY INCLUSION CRITERIA

- Histologically confirmed metastatic NSCLC (no small cell elements)
- Prior benefit from a PD-1/PD-L1 inhibitor or PD-1/PD-L1 bispecific without progression for ≥6 months
- Progression on or after platinum-based chemotherapy, given sequentially or concurrently with PD-(L)1 therapy
- Prior approved targeted therapy required for allowable genomic alterations (e.g., BRAF V600E, KRAS G12C)
- Measurable disease (RECIST v1.1); ECOG performance status 0–1

KEY EXCLUSION CRITERIA

- EGFR or ALK driver mutations; known alterations of ROS1, RET, MET, HER2, or NTRK 1/2/3
- Prior IL-2 or IL-15 therapy (any form)
- History of Grade ≥3 imAEs with prior immunotherapy, unless adequately resolved or successfully rechallenged
- Active CNS metastases (treated, stable brain metastases allowed)
- Significant pulmonary or cardiovascular disease; active autoimmune disease; immunodeficiency or chronic immunosuppressive therapy

OBJECTIVES AND ENDPOINTS

		Objectives	Endpoints
Phase 1	Primary	• Evaluate safety and tolerability of XTX501 • Determine RP2D(s)	• Treatment-emergent and serious adverse events, laboratory changes, dose-limiting toxicities (Part 1A)
	Secondary	• Characterize plasma PK • Evaluate immunogenicity • Evaluate preliminary anti-tumor activity	• PK parameters • ADAs • Objective response rate, duration of response (RECIST v1.1)
	Exploratory	• Evaluate pharmacodynamic profile • Further evaluate anti-tumor activity	• Pharmacodynamic markers in blood and tumor • Disease control rate, progression-free survival (RECIST v1.1)
Phase 2	Primary	• Evaluate efficacy of XTX501 • Evaluate safety and tolerability of XTX501	• Objective response rate (RECIST v1.1) • Treatment-emergent and serious adverse events, laboratory changes
	Secondary	• Characterize plasma PK • Evaluate immunogenicity • Further evaluate efficacy parameters	• PK parameters • ADAs • Duration of response, disease control rate, progression-free survival rate (RECIST v1.1)
	Exploratory	• Evaluate pharmacodynamic profile	• Pharmacodynamic markers in blood and tumor

CONCLUSIONS

- XTX501 is a PD-1 / masked IL-2(alpha-optimized) bispecific antibody fusion protein that combines two complementary mechanisms in a single molecule: selective inhibition of the PD-1/PD-L1 pathway and potent IL-2-driven expansion of T cells
- Masking aims to overcome IL-2 receptor-mediated clearance, peripheral activity and tolerability challenges associated with non-masked IL-2 therapies
- XTX501 demonstrated preclinical anti-tumor activity in PD-1 sensitive and resistant tumor models, with antibody-like PK and favorable tolerability compared to a non-masked bispecific
- The Phase 1/2 trial will evaluate the safety and preliminary efficacy of XTX501 in metastatic NSCLC
- Potential for XTX501 to become a foundational backbone immunotherapy regimen in both monotherapy and combination settings

ABBREVIATIONS: ADA: antidrug antibody; ALK: anaplastic lymphoma kinase; ANOVA: analysis of variance; BOIN: Bayesian Optimal Interval; BRAF: B-Raf proto-oncogene; CNS: central nervous system; EC50: half-maximal effective concentration; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Fc: fragment crystallizable; HER2: human epidermal growth factor receptor 2; IgG1: immunoglobulin G1; IL: interleukin; imAE: immune-mediated adverse event; IV: intravenous; Kd: equilibrium dissociation constant; KRAS: Kirsten rat sarcoma viral oncogene homolog; LLOQ: lower limit of quantification; mAb: monoclonal antibody; MET: mesenchymal-epithelial transition factor; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; NTRK: neurotrophic tyrosine receptor kinase; PBS: phosphate-buffered saline; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1; PK: pharmacokinetics; pSTAT5: phosphorylated signal transducer and activator of transcription 5; Q5Dx2: every 5 days for 2 doses; RECIST: Response Evaluation Criteria in Solid Tumors; RET: rearranged during transfection; ROS1: ROS proto-oncogene 1; RP2D: recommended phase 2 dose; SEM: standard error of the mean; TME: tumor microenvironment.

REFERENCES: 1. NCT07688577 on www.clinicaltrials.gov ;

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