Phase 1/2 Study of XTX101, a Masked, Tumor-Activated Fc-enhanced Anti-CTLA-4, in Patients with Advanced Solid Tumors

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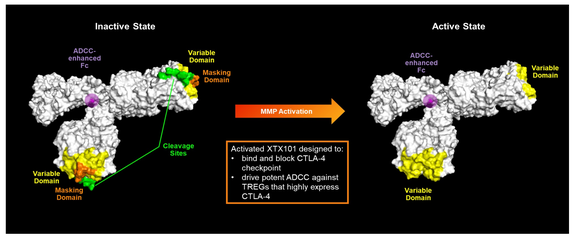
BACKGROUND

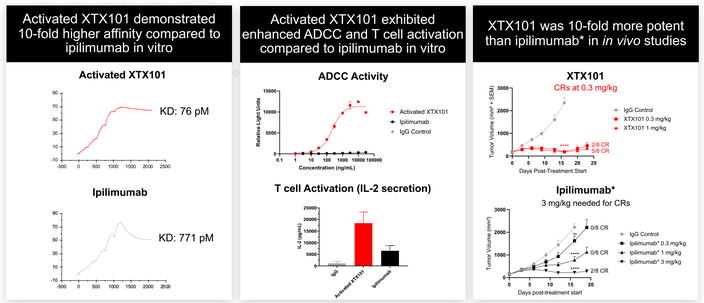
- Anti-CTLA-4 monoclonal antibodies (mAb) such as ipilimumab, have demonstrated clinical benefit, especially in combination therapy with anti-PD-(L)1 in a variety of tumors, while monotherapy benefit has been modest. However, the clinical efficacy has been limited by dose-dependent immune-related adverse events.
- Studies have shown that antibodies with increased potency and incorporating mutations that enhance binding to Fc receptors can improve clinical outcomes in microsatellite stable colorectal cancer (MSS CRC) and other cold tumors when combined with an anti-PD-1 mAb.[1,2]

XTX101: Tumor-Activated, High Affinity Binding, Fc-Enhanced Anti-CTLA-4

- XTX101 is an investigational tumor-activated, high affinity, Fc-Enhanced anti-CTLA-4 mAb designed to be inactive in the periphery via a masking peptide that blocks the CTLA-4 binding regions to minimize systemic immune-related adverse events (irAEs) and activated by proteases in the tumor microenvironment
- XTX101 is designed to block CTLA-4 checkpoint and drive ADCC against regulatory T-cells (TREGs) that highly express CTLA-4

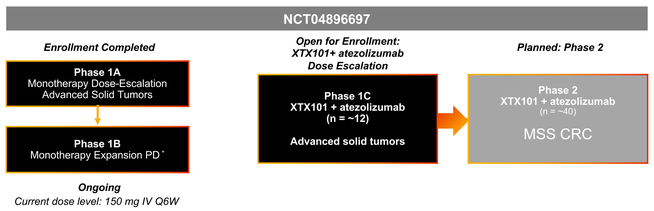


XTX101 Demonstrated 10-fold Enhanced Potency Relative to Ipilimumab in Preclinical Studies



Left panel: Activated, (i.e. non-masked) XTX101 or ipilimumab affinity for human CTLA-4 was determined by surface plasmon resonance on a Biacore instrument.
Middle panel: Top: ADCC activity of activated XTX101 or ipilimumab was assessed using a reporter gene assay comprised of human CTLA-4 expressing Raji cells and NFAT-luciferase expressing human FcγRIIIa F158 (low affinity) variant positive reporter cells. Bottom: T cell activation measured in SEB (Staphylococcal enterotoxin b superantigen) assay with test articles at 100 nM concentration.
Right panel: MB49 cells were inoculated subcutaneously into C57BL/6-huCTLA-4 mice. When tumors reached approximately 150 mm3, mice received a single IV dose with the indicated test articles at the dose level indicated in the figure. 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).
*Ipilimumab analog comprising a monoclonal antibody of identical amino acid sequence to ipilimumab that was produced at Xilio for research purposes. CR: complete regression.

Study Design for First-In-Human Clinical Trial of XTX101 in Advanced Solid Tumors



*Eligible histology includes, but is not limited to, the following: melanoma, squamous cell skin cancer, NSCLC, head and neck squamous cell carcinoma, esophageal squamous cell carcinoma, RCC, urothelial carcinoma, MSS instability-high/mismatch repair deficient colorectal or endometrial cancer, cervical cancer, TNBC and mesothelioma.

RESULTS

Baseline Patient Demographics and Disease Characteristics

Patient Characteristics	Total (N=36)
Demographics	
Age, median (range)	63 (43, 80)
Female	19 (53%)
ECOG PS 0	10 (28%)
ECOG PS 1	26 (72%)
Prior Lines of Anti-Cancer Treatment	**Median 4 (1-12)**
1	2 (6%)
2	4 (11%)
3	8 (22%)
4	9 (25%)
5	5 (14%)
6 and more	8 (22%)
Progressed on Prior Treatment with IO	
≥1	18 (50%)

- 83% of patients had 3 or more prior lines of treatment
- 50% of patients progressed on prior IO treatment

Treatment Status	Total (N=36)
Continuing on Treatment	**3**
Discontinued Treatment	**33**
Progressive Disease	18
Adverse Events	4
Consent Withdrawal (Hospice)	5
Death	3
Other	3

Tumor Types	Total (N=36)
Colorectal cancer	11
NSCLC	5
Pancreatic cancer	3
Squamous cell skin cancer	2
Breast cancer	3
Uterine cancer	2
Merkel cell carcinoma	2
Melanoma	2
Cervical cancer	1
Esophageal cancer	1
Prostate cancer	1
Gastric cancer	1
Fallopian tube cancer	1
Leiomyosarcoma	1

20 patients dosed in Phase 1A and 16 patients dosed in Phase 1B.

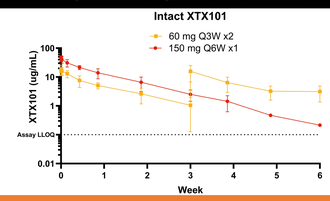
XTX101 Administered at 150 mg Q6W Identified as the RP2D in Part 1A

Target dose designed to be comparable to 10 mg/kg ipilimumab based on 10-fold higher XTX101 potency demonstrated in preclinical models

DL1: 7 mg Q3W N=2 — No DLT
DL2: 20 mg Q3W N=1 — No DLT
Target Dose
DL3: 60 mg Q3W N=6 — N=1 DLT Grade 3 Colitis
3X Target Dose
DL4: 180 mg Q3W N=6 — N=2 DLTs Grade 3 Colitis
RP2D
DL5: 150 mg Q6W N=5

DL5 designed to optimize Cmax from DL4 while maintaining or surpassing the AUC of DL3

Patients Dosed with 60 mg Q3W x 2 or 150 mg Q6W x 1 Demonstrate Comparable XTX101 Exposure Over a 6-week Period



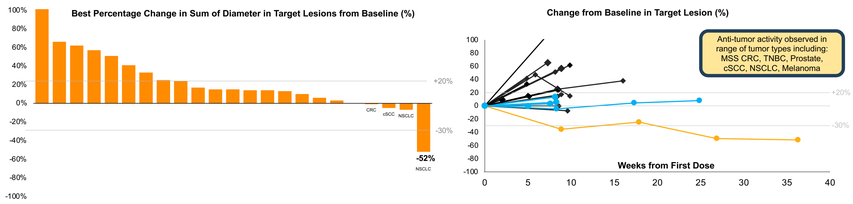
Patients on XTX101 150mg Q6W Experienced Minimal TRAEs

- No treatment discontinuations due to TRAEs at RP2D
- Among 18 patients treated at RP2D, only 2 Grade 3 TRAEs
- No Grade 4 or 5 TRAEs at any dose level
- No endocrine and limited skin irAE

AE Category / Term *All TRAEs with ≥10% incidence in any category or any Grade 3 TRAEs*	All Patients at Q3W (7-180 mg) (n=18)		RP2D 150 mg Q6W (n=18)	
	Any	Grade 3	Any	Grade 3
Diarrhea [1]	5 (28%)	1 (6%)	1 (6%)	1 (6%) [2]
Colitis [1]	5 (28%)	4 (22%)	0	0
Nausea	3 (17%)	0	0	0
Vomiting	3 (17%)	0	0	0
Abdominal pain	2 (11%)	0	0	0
Infusion related reaction [3]	5 (28%)	3 (17%)	0	0
Fatigue	1 (6%)	0	2 (11%)	0
Dermatitis	0	0	1 (6%)	1 (6%)
Dose reduction due to AE	3		1	
Treatment discontinuation due to TRAE [4]	4		0	

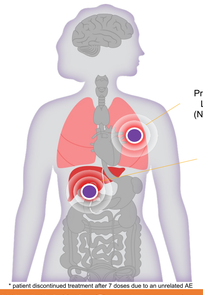
1. The PT of diarrhea or colitis was reported among 7 unique patients, with 3 patients recording both diarrhea and colitis as TRAE
2. Grade 3 diarrhea with onset 10 weeks after the start of treatment (after 2 doses), resolved within 5 days without steroid use, patient tolerated 2 additional XTX101 doses after dose reduction (to 75 mg Q6W) without any symptom recurrence.
3. Infusion related reactions associated with antidrug antibodies.
4. All treatment discontinuations due to TRAE were for an infusion reaction.

XTX101 Monotherapy Demonstrated Evidence of Anti-Tumor Activity

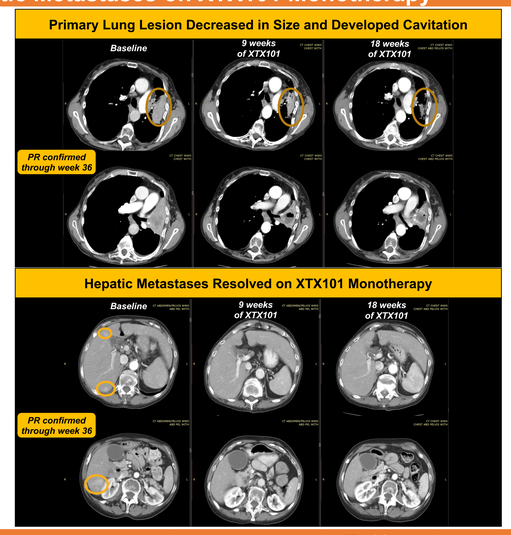


Deep and Durable Partial Response in a Patient with PD-L1 Negative NSCLC and Hepatic Metastases on XTX101 Monotherapy

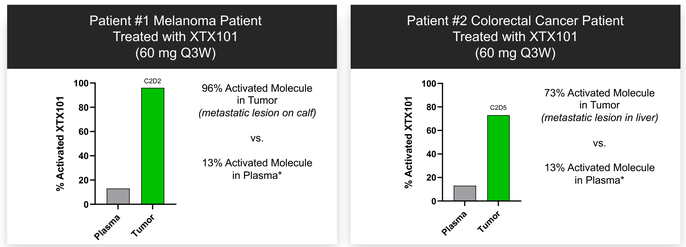
- **Patient**: 66-year-old, female
- **Diagnosis**: Stage 4 NSCLC, PD-L1 negative
- **Previous anti-cancer therapy:** 4 cycles of paclitaxel and carboplatin (non-durable response)
- **XTX101 treatment:** 150mg Q6W, 7 doses administered*
- **TRAE**: Grade 1 fatigue
- **Anti-tumor activity:** Reduction in the sum of diameters by 52% with complete resolution of liver metastases



* patient discontinued treatment after 7 doses due to an unrelated AE

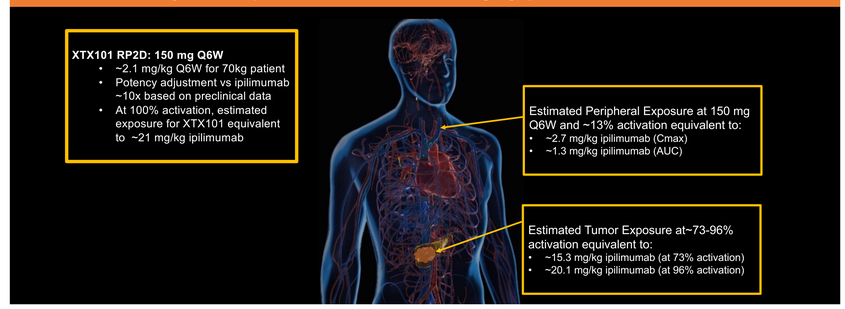


XTX101 On-Treatment Patient Biopsies Demonstrated >70% Activated Molecule in Tumor vs 13% Activated Molecule in Plasma



Patients were the only two patients treated with XTX101 in Part 1B for whom a tumor biopsy pharmacokinetic (PK) analysis was available. Percent activated molecule in tumor was calculated using raw liquid chromatography / mass spectrometry data. Percent activated molecule in plasma represents the area under the curve (AUC) for Cycle 1.
* XTX101 designed to deliver 10-15% activated molecule in periphery.

Activated XTX101 at RP2D Similar to $1.3_{(AUC)}$ / $2.7_{(Cmax)}$ mg/kg Ipilimumab in Periphery and Projected Exposure Similar to ~15-20 mg/kg Ipilimumab in Tumors



Estimates based on preclinical data and tumor biopsy BA analysis for two patients treated with XTX101 in Part 1B.

CONCLUSIONS

XTX101 is a novel tumor-activated, high affinity binding, Fc-enhanced anti-CTLA-4 mAb with 10-fold enhanced potency relative to ipilimumab in preclinical studies

- **Initial Phase 1 data suggest XTX101 has a differentiated safety profile from systemically active anti-CTLA4, consistent with tumor selective activation and effective peripheral masking:**
  - **XTX101 is generally well-tolerated at the RP2D of 150 mg Q6W; among 18 patients dosed at the RP2D:**
    - **only 2 grade 3 TRAEs, no grade 4-5 TRAEs, no endocrine and a single skin-related irAE**
    - **no treatment discontinuations due to TRAEs,**
    - **well-tolerated after repeat administration (over 8 months on therapy)**
- **Evidence of tumor-selective activation:**
  - **confirmed PR in a PD-L1 negative NSCLC patient, with resolution of hepatic metastases, in the absence of immune-related TRAEs**
  - **BA from the tumor biopsy demonstrated > 70% activated molecule in tumor (including a liver metastasis of CRC) vs 13% activation in plasma**
  - **adjusted for 10-fold higher potency based on preclinical data, XTX101 dosing at 150 mg Q6W demonstrated peripheral exposures of activated molecule in concentrations estimated to be similar to 1.3 (AUC) or 2.7 mg/kg of ipilimumab (Cmax), and 73-96% activated molecule in the tumor estimated to lead to exposure comparable to approximately 15-20 mg/kg ipilimumab.**
- **Plan for further evaluation in combination with atezolizumab, including a planned proof-of-concept trial in MSS CRC**

Data cutoff date: November 13, 2023

Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; AE: adverse event; AUC: area under curve; BOR: best overall response; BA: bio-analytical; CTLA-4: cytotoxic T-Lymphocyte Associated Protein 4; DL: dose level; DLT: dose limiting toxicity; ECOG PS: ECOG Performance Status; IL-2: interleukin 2; IO: immuno-oncology; irAE: immune-related adverse event; IV: intra-venous(ly); KD: dissociation constant; MMP: matrix metalloprotease; MSS CRC: microsatellite stable colorectal cancer; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; PK: pharmacokinetic; PR: partial response; PT: preferred term; Q3W: every 3 weeks; Q6W: every 6 weeks; RP2D: recommended phase 2 dose; TNBC: triple-negative breast cancer; TRAE: treatment related adverse event; TREG: regulatory T-cell.

References:
1. Bullock et al. ESMO GI 2023
2. Wilky et al. SITC 2022

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