Xilio Therapeutics: Pipeline Progress and SITC Update

November 6, 2023

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- Introduction
- XTX101 (tumor-activated anti-CTLA-4)
- XTX202 (tumor-activated IL-2)
- Closing Remarks
- Q&A

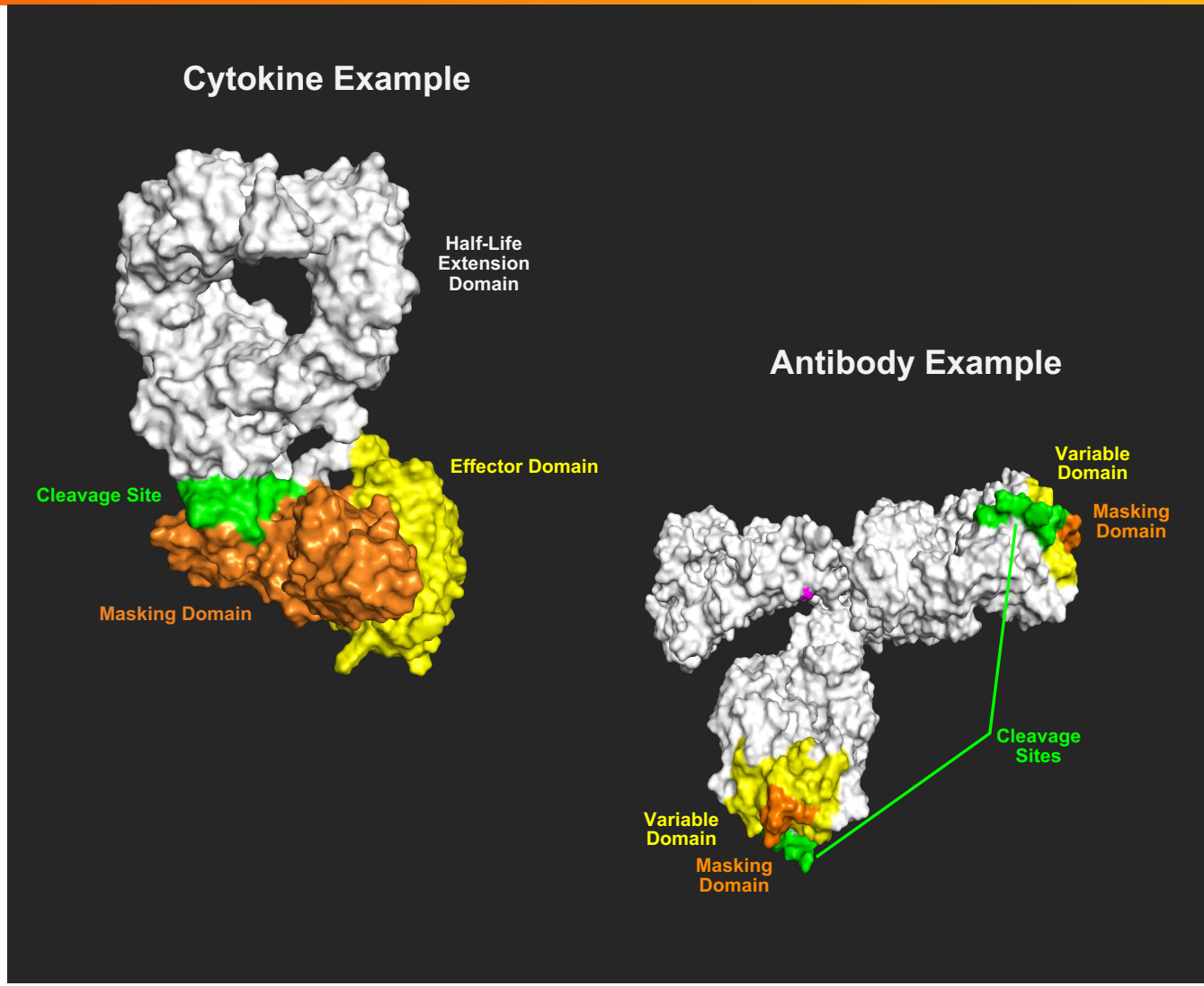
Immuno-Oncology Therapy has Curative Potential

Treatment potential for some of the most exciting immuno-oncology (IO) targets has been impeded by **dose-limiting systemic toxicity**

Xilio (*ex*-il-ee-oh) believes the next revolution in IO cancer therapies will **trick tumors into activating their own treatments**, while simultaneously **sparing healthy tissues and cells**, by **leveraging dysregulated matrix metalloproteases (MMPs)**

Xilio's Molecules are Activated by Dysregulated MMPs in Tumors

- Novel design to **outsmart tumors** – using tumor growth activity against itself
- Dysregulated MMPs in the tumor **activate a switch** in molecules to unleash active agent inside tumor microenvironment (TME)
- Molecules designed for **tumor-selectivity** with a masking domain that seeks to minimize interaction with healthy tissue and cells
- **Initial clinical validation** in Phase 1 clinical trials with over 100 patients treated to date across programs



3 Tumor-Activated Programs in Clinical Development

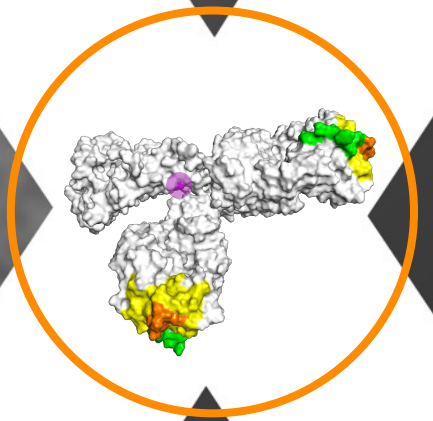
Program	Tumor Types	Mechanism of Action	Discovery	IND-Enabling	Phase 1	Phase 2	Phase 3
XTX101 in combination with atezolizumab (1)	Advanced MSS CRC	Anti-CTLA-4 + PD-L1				Advancing under co-funded clinical collaboration with Roche	
XTX202 (2)	Advanced RCC and Melanoma	IL-2βγ					
XTX301 (3)	Advanced Solid Tumors	IL-12					
Bispecific	Advanced Solid Tumors	PD-1/IL-2 fusion					

1. Xilio plans to evaluate XTX101 in combination with atezolizumab (Tecentriq®) in a Phase 1/2 clinical trial under a clinical trial collaboration with Roche. The Phase 1 portion is designed to assess the safety and tolerability of the combination in dose escalation in patients with advanced solid tumors, and the planned Phase 2 portion is designed to assess the safety and efficacy of the combination in patients with MSS CRC.
2. Initially evaluating XTX202 as a monotherapy in patients with unresectable or metastatic melanoma and metastatic RCC.
3. Initially plan to evaluate XTX301 as a monotherapy for the treatment of advanced solid tumors.

MSS CRC: microsatellite stable colorectal cancer; RCC: renal cell carcinoma.

Opportunity for XTX101 in MSS CRC

Pursuing XTX101 in Combination with Atezolizumab in MSS CRC



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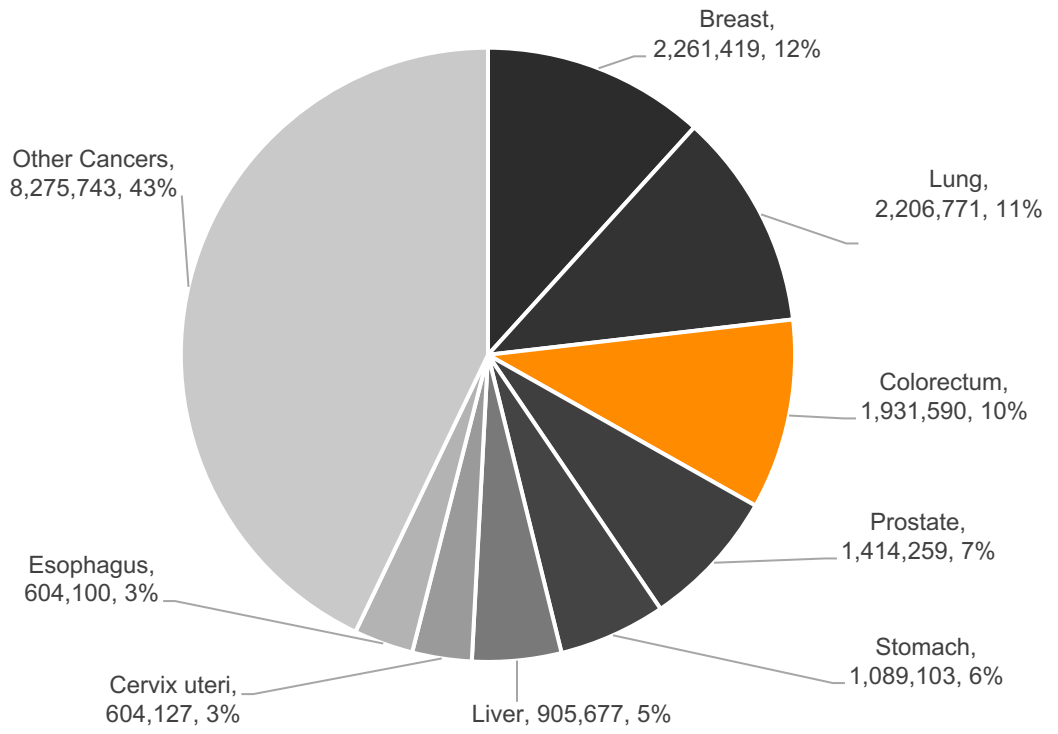
Colorectal Cancer is 3rd in Total Annual New Cases Globally

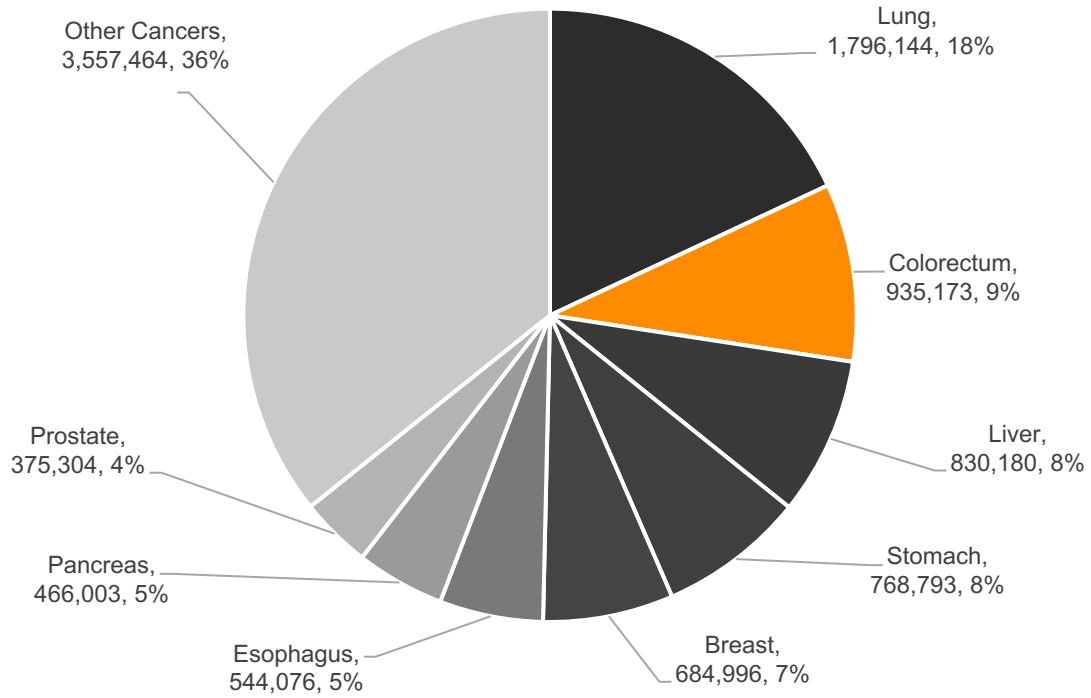
Number of new cases in 2020

(Global, both sexes, all ages)



Number of deaths in 2020

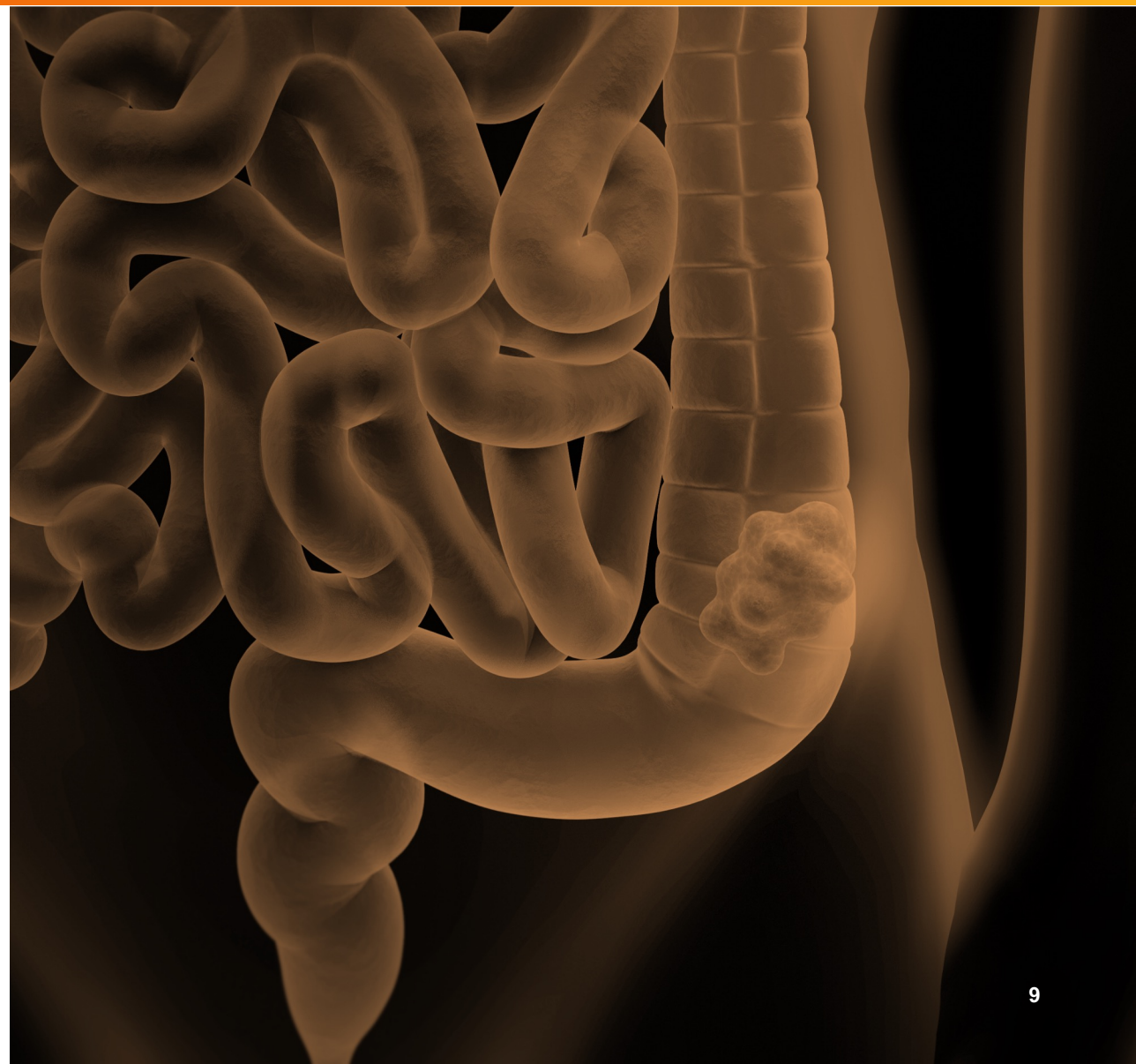
(Global, both sexes, all ages)



World Health Organization, Global Cancer Observatory, December 2020

In US, CRC is Leading Cause of Cancer Related Deaths in Men Younger Than 50, With Majority of All Patients Diagnosed at Stage 4

- Over 150,000 patients diagnosed annually, with ~60% anticipated to have Stage 4 disease at diagnosis (1)
- CRC ranks second in cancer-related deaths (52,550 deaths projected in 2023) and is leading cause of cancer-related death in men younger than 50 (1)
- Majority of patients diagnosed with metastatic disease (~60%) are not eligible for surgery and primary treatment includes chemotherapy and/or radiation (2)
- Only 2-4% of Stage 4 patients classified as MSI-H are eligible for treatment with immunotherapy, and a subset of these quickly develop immune resistance (3)



1. Siegel et al, Colorectal Cancer Statistics, (2023).
2. Cerner Enviza, CancerMPact® Treatment Architecture (2022).
3. Weng et al, Journal of Hematology & Oncology, (2022).
MSI-H: microsatellite instability-high.

Vast Majority of Metastatic Colorectal Cancer is MSS CRC with No Approved IO Treatment Options

~85,000 patients with Stage 4 MSS CRC in the US alone have no IO options available to treat their disease

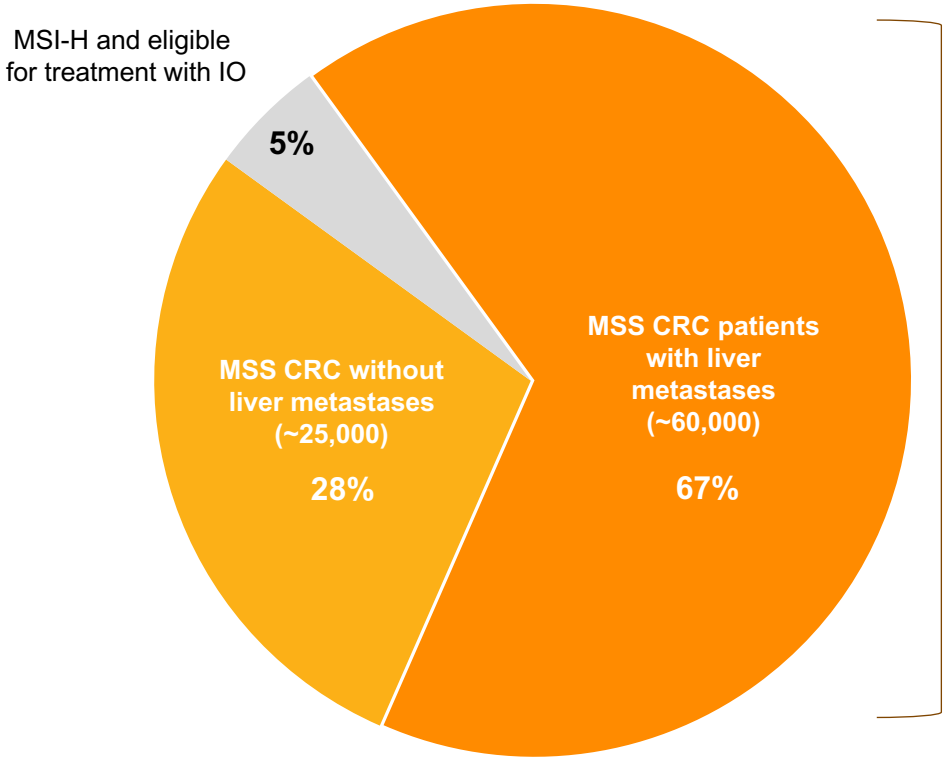
US patients projected to be diagnosed with CRC in 2023 (1) **~150,000**

~60% of patients will be diagnosed with Stage 4 disease (1) **~90,000**

~95% of Stage 4 disease is MSS CRC (2) **~85,000**

~70% of patients with Stage 4 disease develop liver metastases (3) **~60,000**

US Stage 4 Patients



1. Siegel et al, Colorectal Cancer Statistics, (2023).
2. Ooki et al, Journal of Anus Rectum Colon, (2021).
3. Cerner Enviza, (2023).

Historically, IO Therapies Have Shown Little to No Efficacy in MSS CRC

- **Checkpoint inhibitors showed 0-3% ORR in MSS CRC (alone or in combination with "first gen" anti-CTLA-4 molecules)**
- **1L and 2L treatment today continues to rely primarily on bevacizumab + FOLFOX / FOLFIRI [1]**

	Microsatellite Instability Status	Dose / Regimen	ORR, % (Number of Patients/ Total Cohort)	DCR, % (Number of Patients/Total Cohort)	Median PFS, Mo	Median OS, Mo
KEYNOTE-016; phase II, parallel cohorts; pembrolizumab *NCT01876511*	Cohort B: 18 patients with MSS CRC	Pembrolizumab, 10 mg/kg every 2 weeks	**0 (0/18)**	11 (2/18)	2.2	5
CheckMate-142; phase II, multi-cohorts; nivolumab with or without ipilimumab *NCT02060188*	23 patients with non–MSI-H CRC included	Nivolumab, 1 or 3 mg/ kg every 3 weeks + ipilimumab, 1 or 3 mg/kg every 3 weeks*	**N/A**	N/A	1.4	N/A
CCTG CO.26; phase II RCT of D+T+BSC vs. BSC *NCT02870920*	119 patients in D+T arm: 98% MSS; 1% MSI-H; 1% unknown	Durvalumab, 1,500 mg every 4 weeks + tremelimumab, 75 mg every 4 weeks (only 4 cycles)	**1 (1/119)**	22.7 (27/119)	1.8	6.6
	61 patients in BSC arm: 80% MSS; 2% MSI-H; 18% unknown		**0 (0/61)**	6.6 (4/61)	1.9	4.1**
IMblaze-370; phase III open-label RCT of atezolizumab vs. regorafenib vs. atezolizumab + cobimetinib *NCT02788279*	90 patients in atezolizumab arm: 92% MSS; 3% MSI-H; 4% unknown	Atezolizumab, 1,200 mg every 3 weeks	**2 (2/90)**	21 (19/90)	1.9***	7.1****
		Regorafenib, 160 mg daily, 21 days on/ 7 days off	**2 (2/90)**	34 (31/90)	2.0	8.5
		Atezolizumab, 840 mg every 2 weeks + cobimetinib, 60 mg daily, 21 days on 7 days off	**3 (5/183)**	26 (48/183)	1.9	8.9

Adapted from Sahin et al, 2022 ASCO Educational Book.

* Three patients were given nivolumab, 1 mg/kg 1 ipilimumab, 1 mg/kg; 10 patients each were given nivolumab, 1 mg/kg 1 ipilimumab, 3 mg/kg or nivolumab, 3 mg/kg 1 ipilimumab, 1 mg/kg.

** In a subgroup analysis of patients with MSS: HR, 0.66; 95% CI, 0.48–0.89; p5.02.

*** Atezolizumab + cobimetinib vs. regorafenib: HR, 1.25; 95% CI, 0.94–1.65; atezolizumab vs. regorafenib: HR, 1.39; 95% CI, 1.00–1.94.

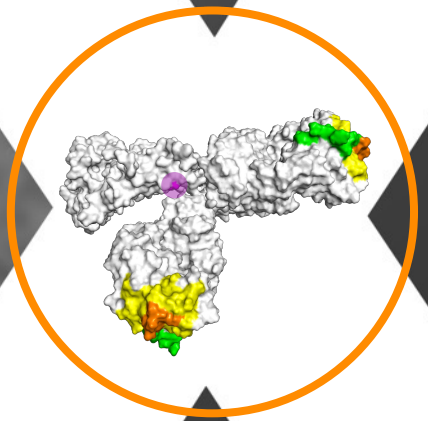
**** Atezolizumab + cobimetinib vs. regorafenib: HR, 1.00; 95% CI, 0.73–1.38; p 5 .99; atezolizumab vs. regorafenib: HR, 1.19; 95% CI, 0.83–1.71; p 5 .34.

(1) Cerner Enviza, CancerMPact® Treatment Architecture (2022)

BSC: best supportive care; CCTG: Canadian Cancer Trials Group; DCR, disease control rate; D: durvalumab; D1T: durvalumab and tremelimumab; mo: month; ORR: overall response rate; OS: overall survival; PFS: progression free survival; RCT: randomized controlled trial; T: tremelimumab.

XTX101

Tumor-Activated, Fc-enhanced Anti-CTLA-4



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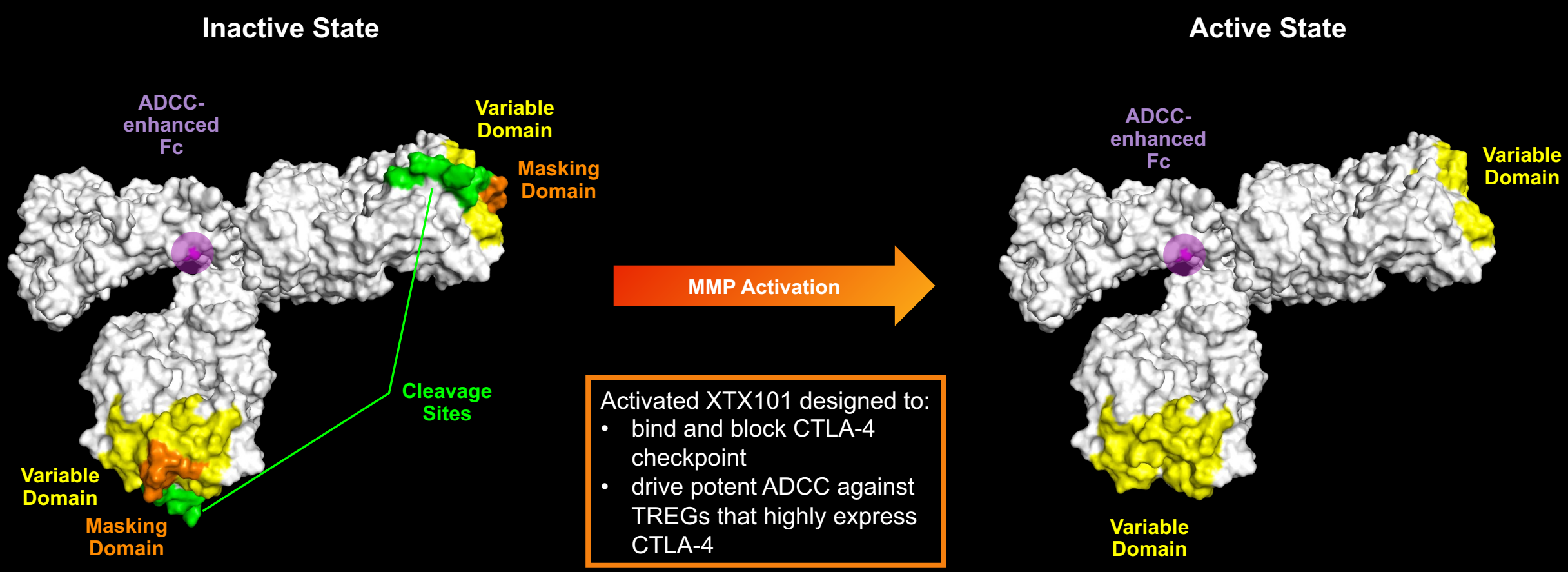
XTX101: Tumor-Activated, High Affinity Binding, Fc-Enhanced Anti-CTLA-4



Activated XTX101 designed to:

- bind and block CTLA-4 checkpoint
- drive potent ADCC against TREGs that highly express CTLA-4

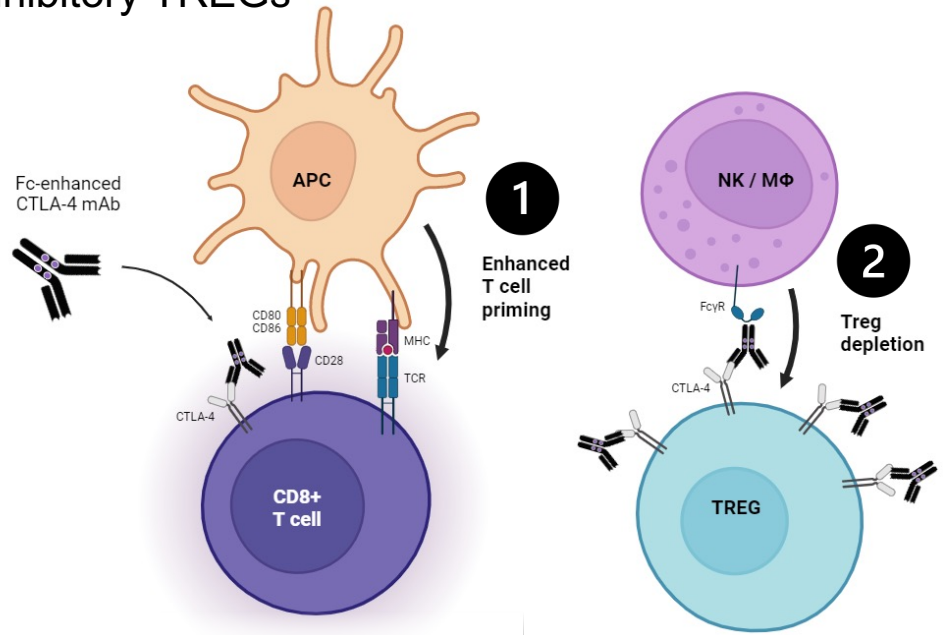
ADCC: antibody-dependent cell-mediated cytotoxicity.

Next Generation Anti-CTLA-4 with Fc-Enhancement Demonstrated Potential to Treat MSS CRC and Other Hard to Treat Tumors

Fc-Enhancement to Achieve TREG Depletion

Dual mechanism designed to boost de-novo immunity and combat immune suppression

- CTLA-4 blockade to stimulate immune priming and enhance co-stimulation
- Fc-enhancement to induce efficient depletion of inhibitory TREGs



Clinical Evidence

- Phase 1 data for third party Fc-enhanced anti-CTLA-4 in combination with a PD-1 in patients with MSS CRC demonstrated ORR >20% in MSS CRC patients (1)

Other responses include:

- Endometrial
- Pancreatic
- Cervical
- Melanoma
- Ovarian
- NSCLC
- Visceral angiosarcoma
- Leiomyosarcoma (2)

1. Phase 1 data reported by Agenus Inc. on January 21, 2023, at ASCO GI Symposium for botensilimab (AGEN1181) in combination with a balstilimab in MSS CRC patients previously treated with chemotherapy and/or with immunotherapy-resistant tumors.
2. Phase 1 data reported by Agenus Inc on November 11, 2021 at SITC (poster), "AGEN 1181, an Fc-enhanced anti-CTLA-4 antibody, alone and in combination with balstilimab (anti-PD-1) in patients with advanced solid tumors: Phase 1 results"
3. Safety data presented as all TRAEs in > 15% of the ITT population (n=101)

Illustration created with BioRender.com

NSCLC: non-small cell lung cancer; ORR: objective response rate; TRAE: treatment-related adverse event; TREG: regulatory T cells; Q4W: once every four weeks.

XTX101 Clinical Data

Phase 1: Advanced Solid Tumors

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Patient Demographics: XTX101 Phase 1 Trial With a Wide Range of Advanced/Refractory Solid Tumors

XTX101 Phase 1 Trial Design

Enrollment Completed

Phase 1A
Monotherapy Dose-Escalation
Advanced Solid Tumors
(n=20 dosed)

Phase 1B
Monotherapy Expansion PD [2]
(n=9 dosed)

Ongoing

Current dose level: 150 mg Q6W

Patient Characteristics	Total (N=27)[1]
Demographics	
Age, median (range)	67 (49, 80)
Female	15 (56%)
ECOG PS 0	7 (26%)
ECOG PS 1	20 (74%)
Prior Lines of Anti-Cancer Treatment	**Median 4 (1-12)**
1	2 (7%)
2	4 (15%)
3	6 (22%)
4	7 (26%)
5	3 (11%)
6 and more	5 (19%)
Progressed on Prior Treatment with IO	
≥1	12 (44%)

Tumor Types	Total (N=27)[1]
Colorectal	6
NSCLC	4
Pancreatic	3
Squamous cell skin	2
Breast	2
Uterine	2
Merkel cell carcinoma	2
Melanoma	1
Cervical	1
Prostate	1
Gastric	1
Fallopian tube cancer	1
Leiomyosarcoma	1

Treatment Status	Total (N=27)[1]
Continuing on Treatment	**3**
Discontinued Treatment	**24**
Progressive Disease	14
Adverse Events	4
Consent Withdrawal (Hospice)	3
Death Due to Progressive Disease	1
Other	2

- 78% of patients had 3 or more prior lines of treatment
- 44% of patients progressed on prior IO treatment

Data cutoff date: August 3, 2023. 29 patients have been dosed across all dose levels, including 20 patients dosed in Phase 1A and 9 patients dosed in Phase 1B.
1. Among the 29 patients dosed, data was not available for two patients as of the data cutoff date.
2. 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.

ECOG PS: ECOG performance status; PD: pharmacodynamic; Q6W: once every six weeks; TNBC: triple-negative breast cancer.

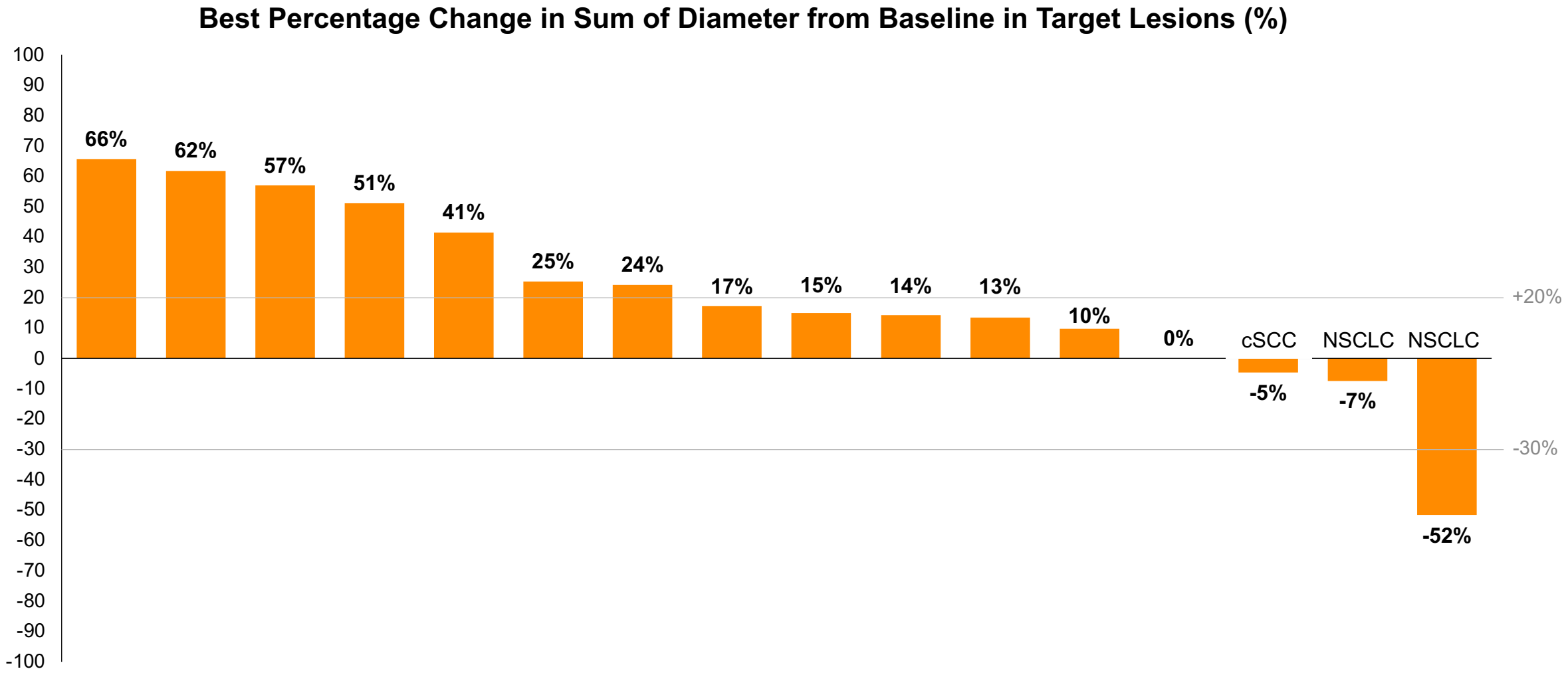
Patients on XTX101 150mg Q6W Experienced Minimal TRAEs

- No treatment discontinuations due to TRAEs at RP2D
- No Grade 4 or 5 TRAEs at any dose level
- Repeat dosing at RP2D up to 7 cycles (Q6W, 42 weeks)

AE Category / Term ***All TRAEs with ≥10% incidence in any category***	**All Patients at Q3W (7-180 mg) (n=18)**		**RP2D 150 mg Q6W (n=9)**	
	Any	**Grade 3**	**Any**	**Grade 3**
Diarrhea or Colitis	7 (39%)	4 (22%)	1 (11%)	1 (11%)
Diarrhea	5 (28%)	1 (6.0)	1 (11%)	1 (11%) (1)
Colitis	5 (28%)	4 (22.0)	0	0
Nausea	3 (17%)	0	0	0
Vomiting	3 (17%)	0	0	0
Abdominal pain	2 (11%)	0	0	0
Infusion related reaction (2)	5 (28%)	3 (17%)	0	0
Fatigue	1 (6%)	0	1 (11%)	0
Decreased appetite	1 (6%)	0	1 (11%)	0
Dermatitis	0	0	1 (11%)	1 (11%)
Dose reduction due to AE	3		1	
Treatment discontinuation due to TRAE (3)	4		0	

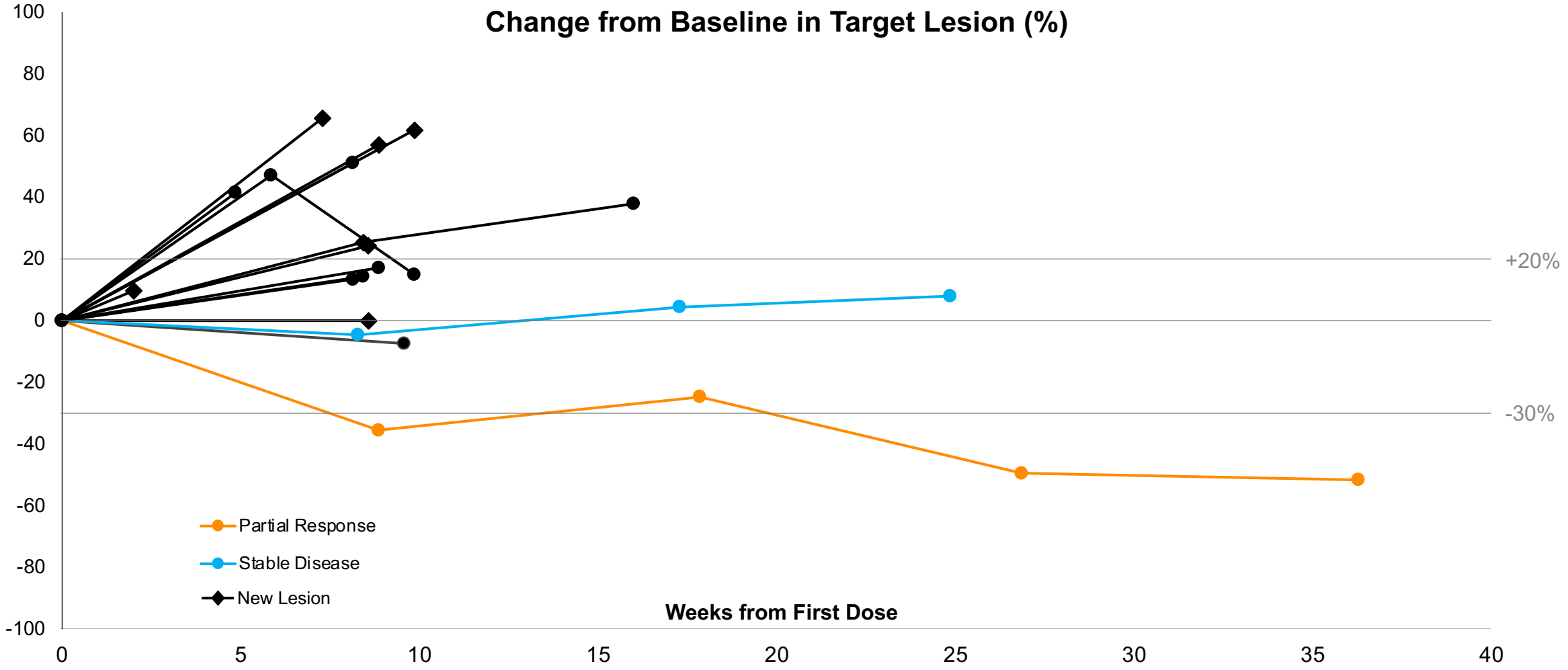
Data cutoff date: August 3, 2023. As of the data cutoff date, safety data were available for 27 patients across all dose levels, including 20 patients dosed in Phase 1A and 7 patients dosed in Phase 1B.
1. Grade 3 diarrhea with onset 10 weeks after the start of treatment (after 2 doses), resolved within 5 days without steroid use, patient tolerated 2 additional XTX101 doses after dose reduction (to 75 mg Q6W) without any symptom recurrence.
2. Infusion related reactions associated with antidrug antibodies (ADA).
3. All treatment discontinuations were due to TRAE for an infusion reaction.
TRAE: treatment-related adverse event; RP2D: recommended Phase 2 dose; Q3W: once every three weeks.

XTX101 Monotherapy Demonstrated Evidence of Anti-Tumor Activity in Phase 1 Trial



Data cutoff date: August 3, 2023.
cSCC: cutaneous squamous cell carcinoma.

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

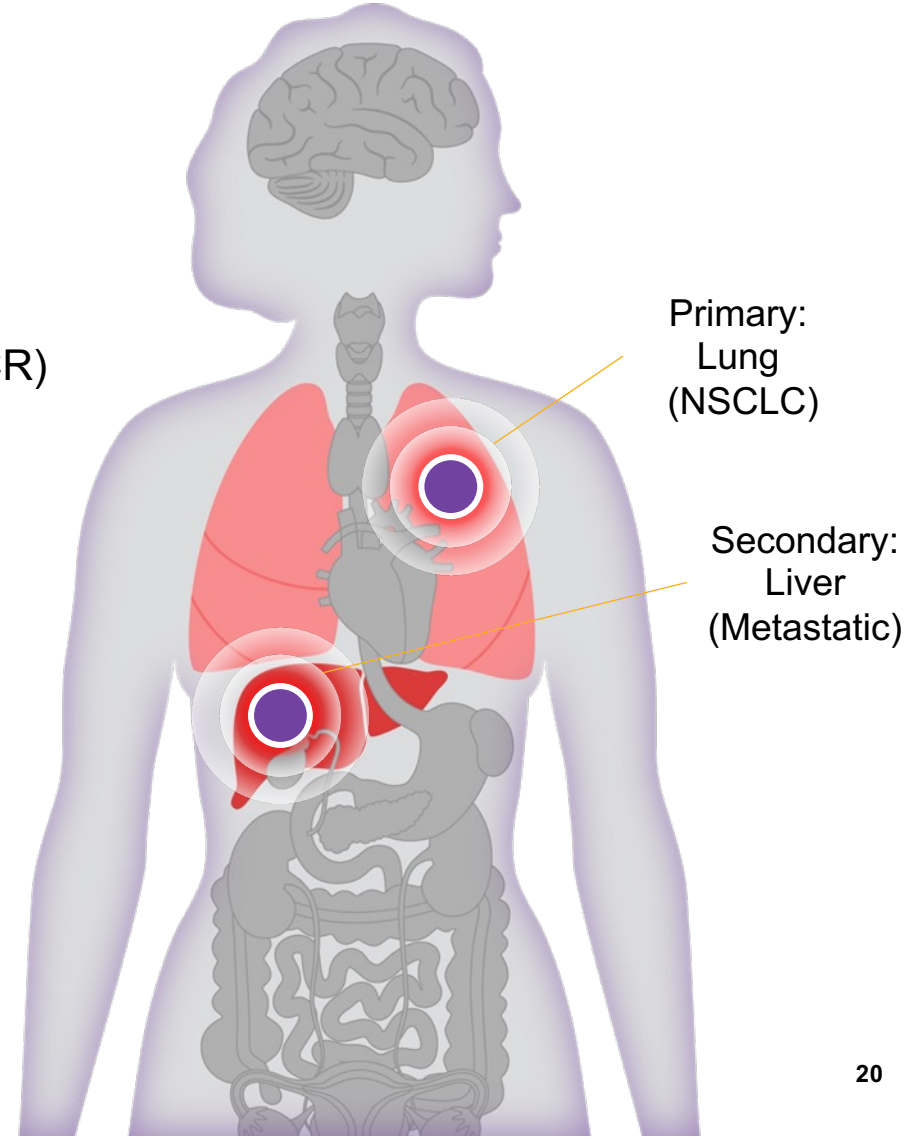


Data cutoff date: August 3, 2023. As of the data cutoff date, treatment was ongoing for one NSCLC patient with confirmed partial response and all other patients shown in figure have discontinued treatment.

Confirmed Partial Response (PR) in a Patient with PD-L1 Negative NSCLC and Innumerable Hepatic Metastases on XTX101 Monotherapy

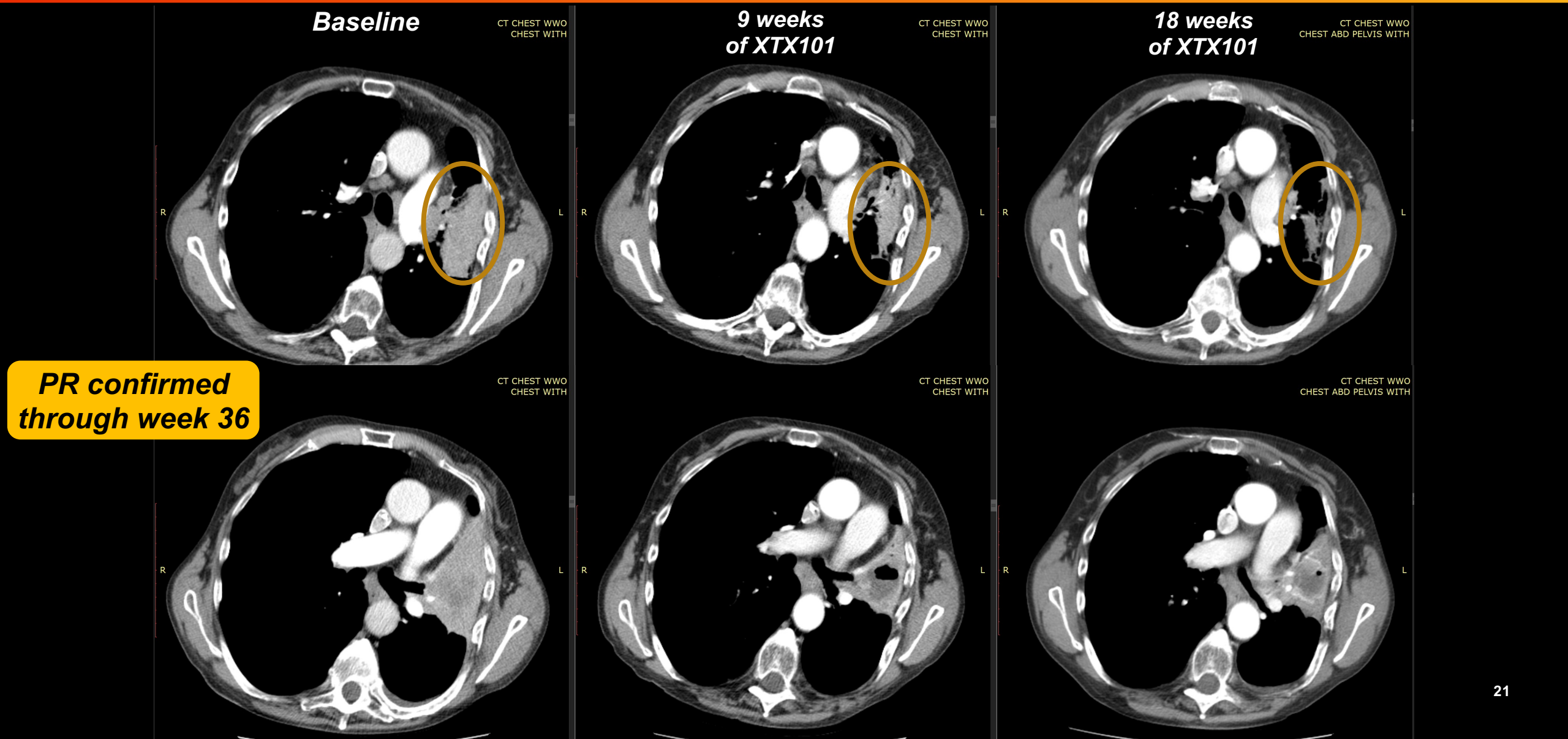
- **Patient**: 66-year-old, female
- **Diagnosis**: Stage 4 NSCLC, PD-L1 negative
- **Previous Treatment:** 4 cycles of paclitaxel and carboplatin (non-durable CR)
- **XTX101 Treatment:** 150mg Q6W, 7 doses administered
- **Related AE**: Grade 1 fatigue (only)

Confirmed PR through week 36



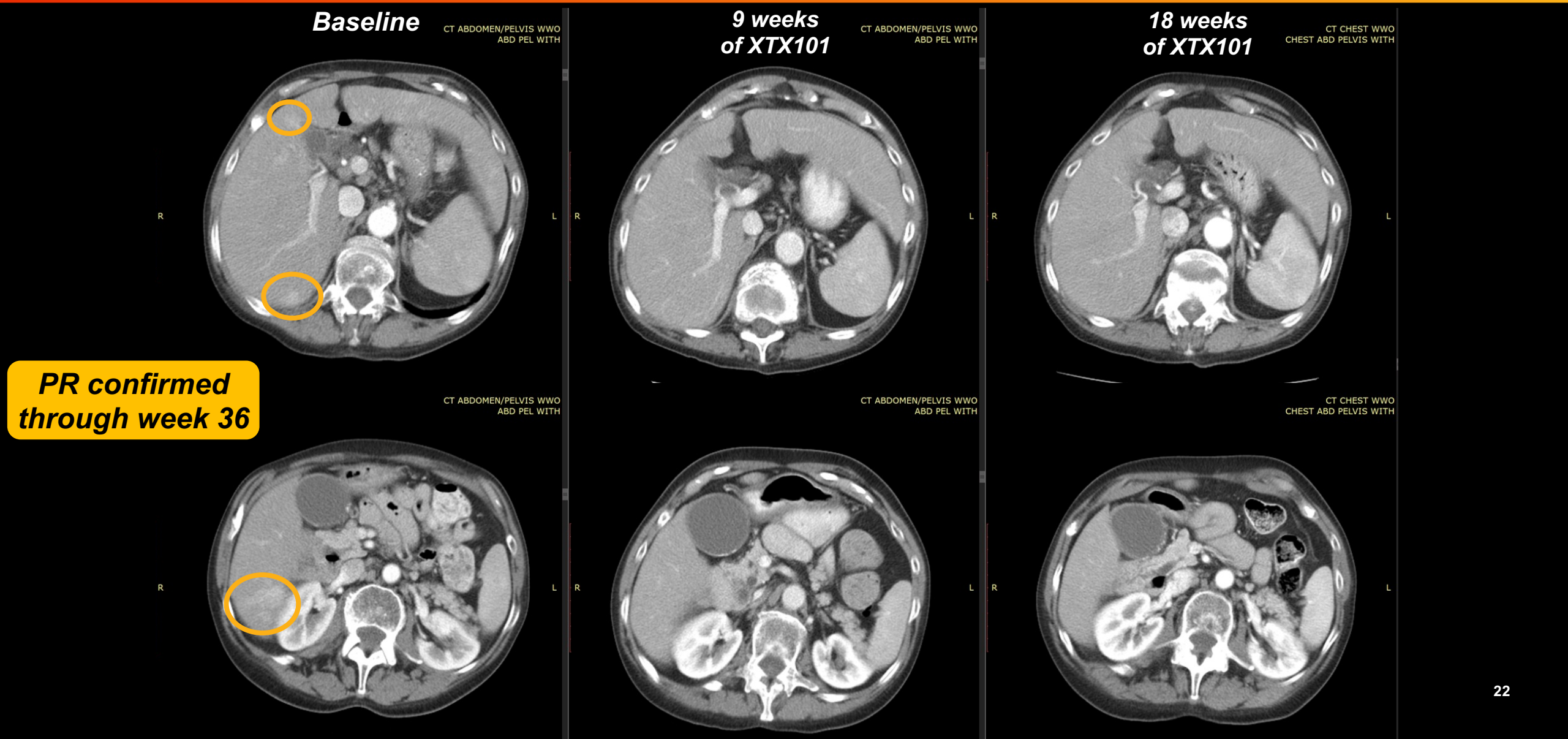
Data cutoff date: August 3, 2023.

Primary Lung Lesion Decreased in Size and Developed Cavitation



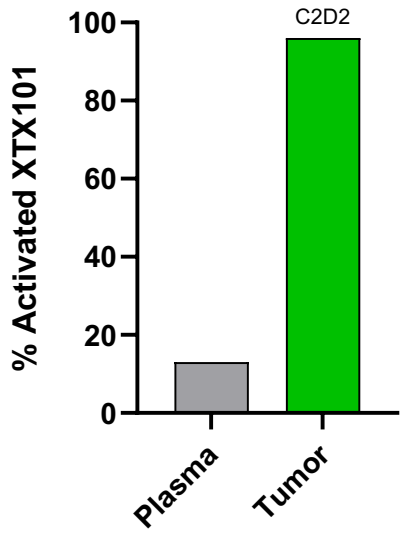
PR confirmed through week 36

Hepatic Metastases Resolved At Initial Imaging on XTX101 Monotherapy



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

Patient #1 Melanoma Patient Treated with XTX101 (60 mg Q3W)

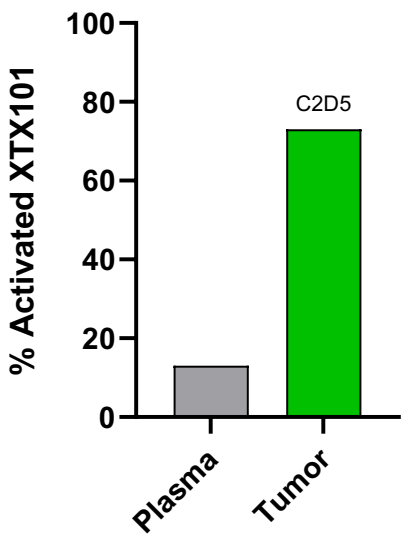


96% Activated Molecule in Tumor *(metastatic lesion on calf)*

vs.

13% Activated Molecule in Plasma*

Patient #2 Colorectal Cancer Patient Treated with XTX101 (60 mg Q3W)



73% Activated Molecule in Tumor *(metastatic lesion in liver)*

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 as of September 11, 2023. 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.
PK: pharmacokinetic;

XTX101 Advancing under Co-Funded Clinical Collaboration: Anticipate Initiating Combination with Atezolizumab in Q1 2024

Stage 4 MSS CRC 2L+

Phase 1 Dose Escalation

XTX101 + Atezolizumab
(n = ~12)

- All comers, advanced solid tumors
- Plan to evaluate two dose levels
- Starting XTX101 dose: 75 mg Q6W

Anticipated Milestones

- Sites active in Q4 2023
- FPI in Q1 2024
- Select RP2D in Q2 2024*

Phase 2 Proof-of-Concept

XTX101 + Atezolizumab
(n= ~40)

MSS CRC With and Without Liver Metastases

Anticipated Milestones

- FPI in Q3 2024*
- Initial data (n = ~20) in Q4 2024*
- Additional data (n = ~40) in Q1 2025*

Potential Pivotal Phase 2 Trial

XTX101 + Atezolizumab
(n=~200 patients:
~160 Phase 2 randomized patients +
~40 initial Phase 2 patients)

With and Without Liver Metastases

- Potential for accelerated approval pathway
- Monotherapy cohorts (to demonstrate contribution of components) and/or standard-of-care comparator arm (if required) can have early stopping rules

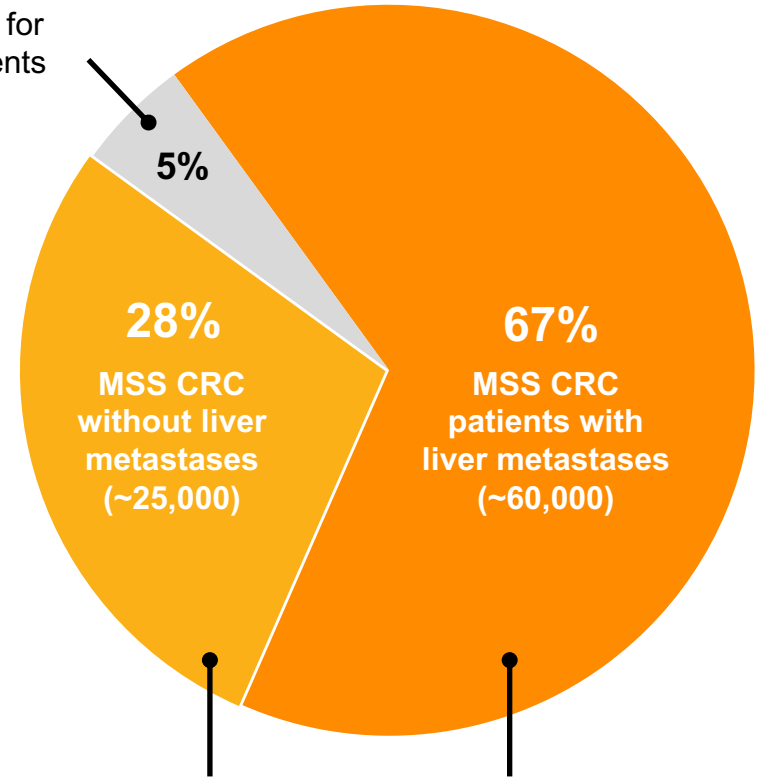
**** Milestones subject to obtaining sufficient additional capital.***

FPI: first patient dosed; 2L: second line.

XTX101 Clinical Development Pursuing Significant Unmet Need in MSS CRC Patients With and Without Liver Metastases

US Stage 4 Patients

The 5% of CRC that is MSI-H are eligible for current IO treatments



Xilio planned Phase 2 POC will enroll MSS CRC patients with and without liver metastases

Liver metastases are highly proteolytic environment (1)

→ Demonstrated molecule activation > 70% in liver lesion of CRC patient

Fc-enhancement of anti-CTLA-4 may increase potential for efficacy against liver metastases (2,3)

→ NSCLC patient treated with XTX101 monotherapy demonstrated durable resolution of liver metastases at initial on-treatment imaging

1. Adachi et al, Contribution of matrilysin (MMP-7) to the metastatic pathway of human colorectal cancers, Gut, 1999 Aug.
2. Katz et al, Regulatory T Cell Infiltration Predicts Outcome Following Resection of Colorectal Cancer Liver Metastases, Annals Surg Oncol, 2013 Mar.
3. Sharma et al, Anti-CTLA-4 immunotherapy does not deplete FOXP3+ regulatory T cells (Tregs) in human cancers, Clin Cancer Res. 2019 February.
POC: proof-of-concept

XTX101 Initial MSS CRC Proof-of-Concept Data Anticipated in 2024*

- Platform validation including monotherapy confirmed PR observed in Phase 1 trial (1)
- Advancing in MSS CRC in combination with atezolizumab under clinical collaboration with Roche
- Combination Phase 2 POC read-outs anticipated (~n=20) in Q4 2024 and (~n=40) Q1 2025*
- Potential to initiate pivotal trial in 2025*

Next Milestone

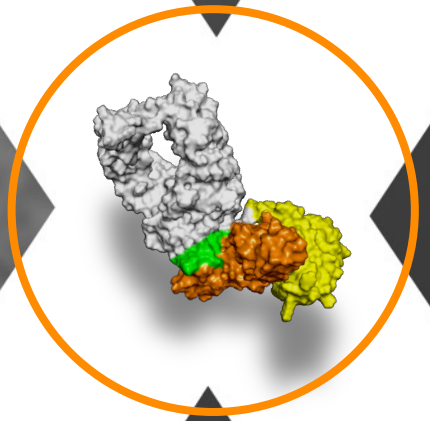
- Anticipate activating clinical trial sites for Phase 1 dose escalation evaluating XTX101 in combination with atezolizumab in Q4 2023

**** Milestones subject to obtaining sufficient additional capital.***

1. Data cutoff date: August 3, 2023. Tumor response was assessed by RECIST version 1.1.

XTX202

Tumor-Activated, Beta-Gamma IL-2



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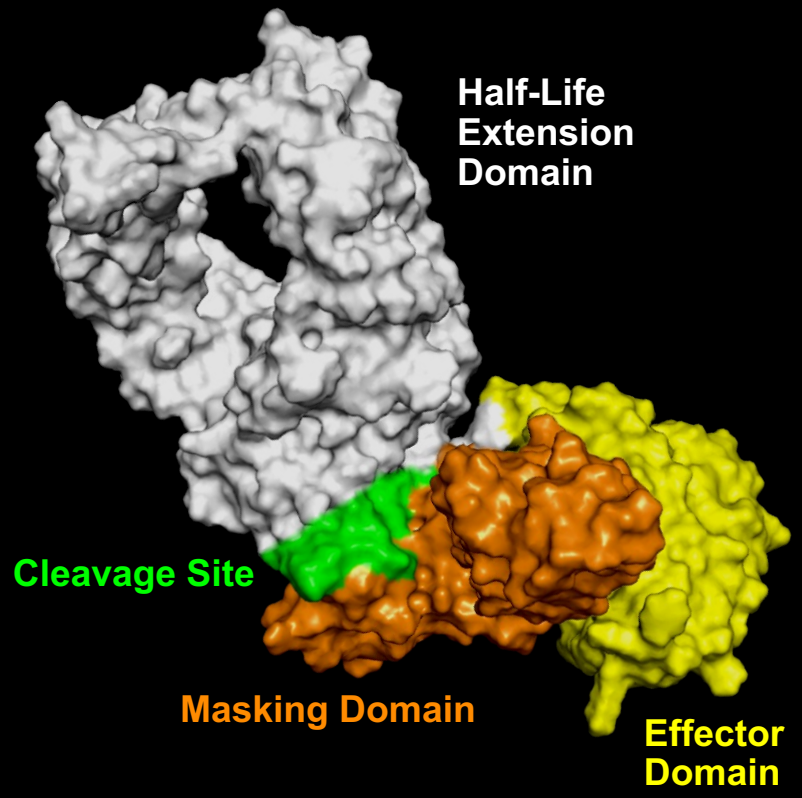
XTX202: Tumor-Activated, Beta-Gamma IL-2 Designed to Overcome the Limitations of Systemically Active Molecules

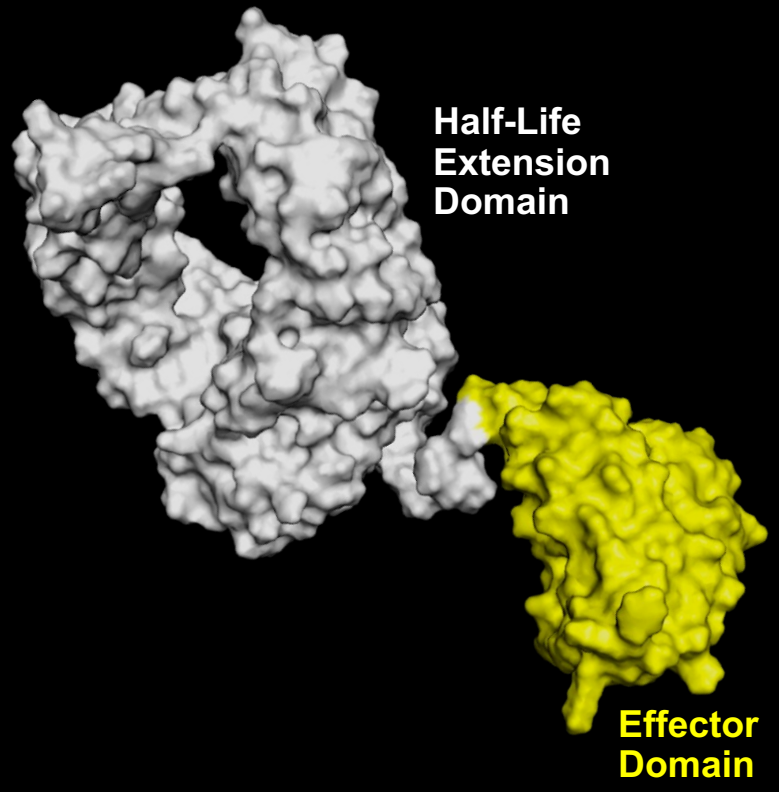
Inactive State



MMP Activation

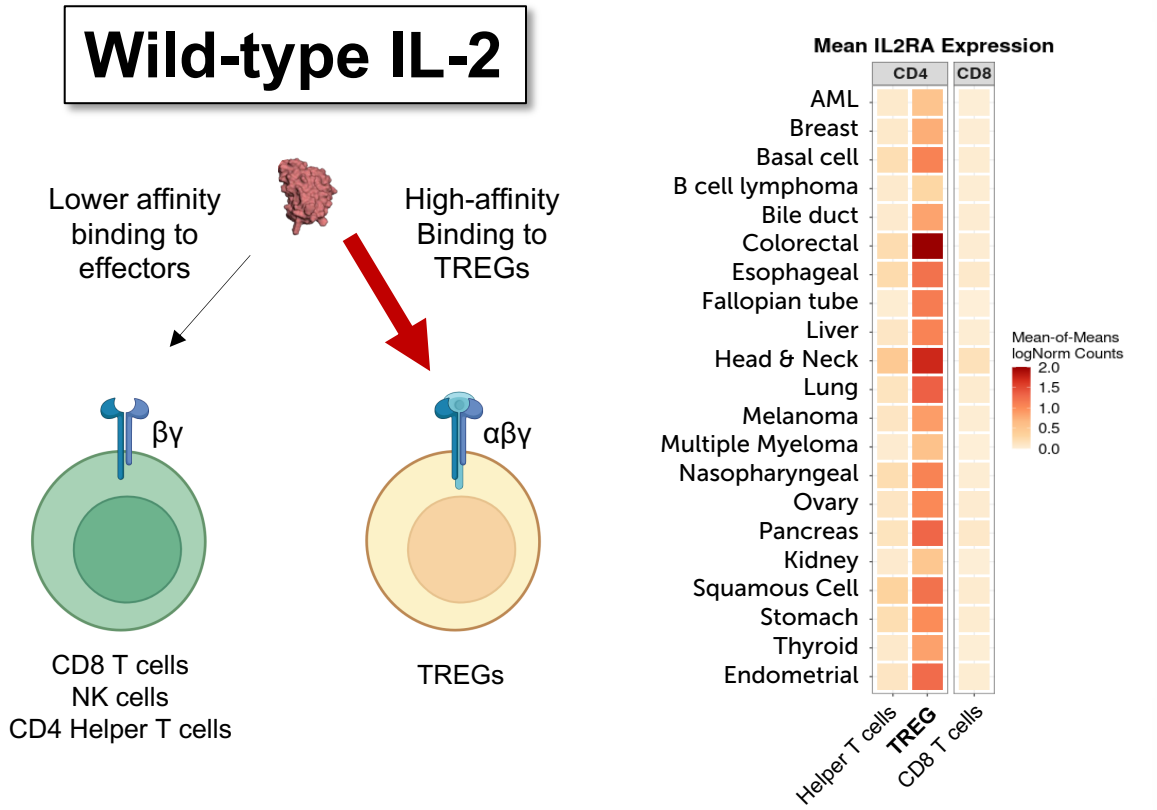
Activated XTX202:
- Beta-gamma IL-2 effector domain designed to minimize TREG activation
- Retains Fc-domain to enable prolonged tumor exposure

Active State

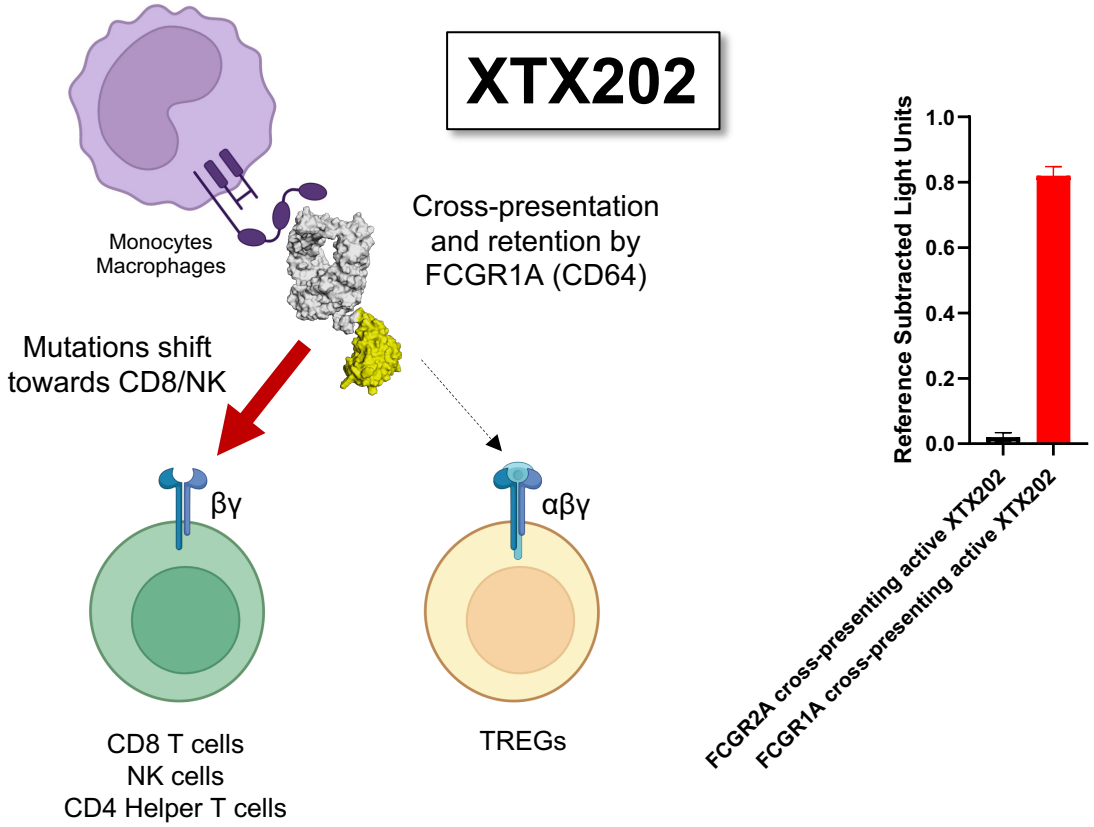


XTX202 Designed to Enable High Tumor Exposure and Cross-Presentation Enhancing IL-2 Receptor Binding Without TREG Stimulation

Wild-type IL-2 has high affinity for alpha-containing IL-2 receptor found primarily on TREGs



XTX202 designed to overcome this limitation with beta gamma bias and retention of Fc domain post-activation



Left panel: Pre-processed single cell RNA sequencing data obtained from Zheng et al., Science 2021. Heatmap showing the expression levels of a gene of interest across different cancer indications (y-axis) and different T cell subtypes (x-axis). CD4+ T cells (left) and CD8+ T cells (right) were shown in separate panels. Color intensity tracks with gene expression signal, which is mean-of-mean normalized gene expression (mean expression of the gene of interest was first computed for each T cell subtype and for each individual patient; next, a cancer indication-specific mean of means was computed and is displayed).
Right panel: Active XTX202 (12.5 nM) bound to FCGR1A or FCGR2A beads was used in a cell-based IL-2 reporter gene assay to determine the ability of Fc receptors to cross-present XTX202.
Illustrations created with BioRender.com

XTX202 Clinical Data

Initial Phase 1 / 2 Data

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XTX202 Phase 1/2 Patient Demographics: Heavily Pre-Treated and IO Refractory Patients Across a Range of Solid Tumors, Including Cold Tumors

XTX202 Phase 1 Trial Design

Current dose level: 4.0 mg/kg Q3W

- Phase 1A Monotherapy Dose Escalation Advanced Solid Tumors
- Phase 1B Monotherapy PD Cohort "Hot Tumors"

XTX202 Phase 2 Trial Design

Dose level 1: 1.4 mg/kg Q3W

Dose level 2: 4.0 mg/kg Q3W

- Phase 2A Monotherapy Expansion RCC Cohort
- Phase 2B Monotherapy Expansion Melanoma Cohort

Patient Characteristics	Phase 1 Total (N=54)	Phase 2 Total (N=8)
Demographics		
Age, median (range)	67 (25, 82)	62 (33, 74)
Female	20 (37%)	2 (25%)
ECOG PS 0	20 (37%)	4 (50%)
ECOG PS 1	34 (63%)	4 (50%)
Prior Lines of Anti-Cancer Treatment	**Median 4 (1-14)**	**Median 3.5 (1-12)**
1	5 (9%)	3 (38%)
2	9 (17%)	0
3	7 (13%)	1 (13%)
4	13 (24%)	1 (13%)
5	9 (17%)	0
≥6	11 (20%)	3 (38%)
Prior Treatment with IO		
≥1	37 (69%)	8 (100%)
Time since initial diagnosis (months)	**Median 29 (4-147)**	**Median 50 (12-198)**

Tumor Types	Phase 1 Total (N=54)*	Phase 2 Total (N=8)
Colorectal	8	
NSCLC	7	
Melanoma	6	6
Sarcoma	5	
Pancreatic	4	
RCC	4	2
Prostate	3	
Endometrial	2	
Cervical	1	
Esophageal	1	
Ovarian	1	
Other	13	

Treatment Status	Phase 1 Total (N=54)	Phase 2 Total (N=8)
Continuing on Treatment	**15**	**5**
Discontinued Treatment	**39**	**3**
Progressive Disease	30	3
Adverse Events (Not treatment related)	1	—
Consent Withdrawal (Hospice)	1	—
Death Due to Progressive Disease	4	—
Other	3	—

Phase 1

- 54 patients enrolled with a wide range of advanced and IO-treatment refractory solid tumors
- 74% of patients had ≥3 prior lines of anti-cancer treatment
- 69% of patient progressed on prior IO treatment

Phase 2

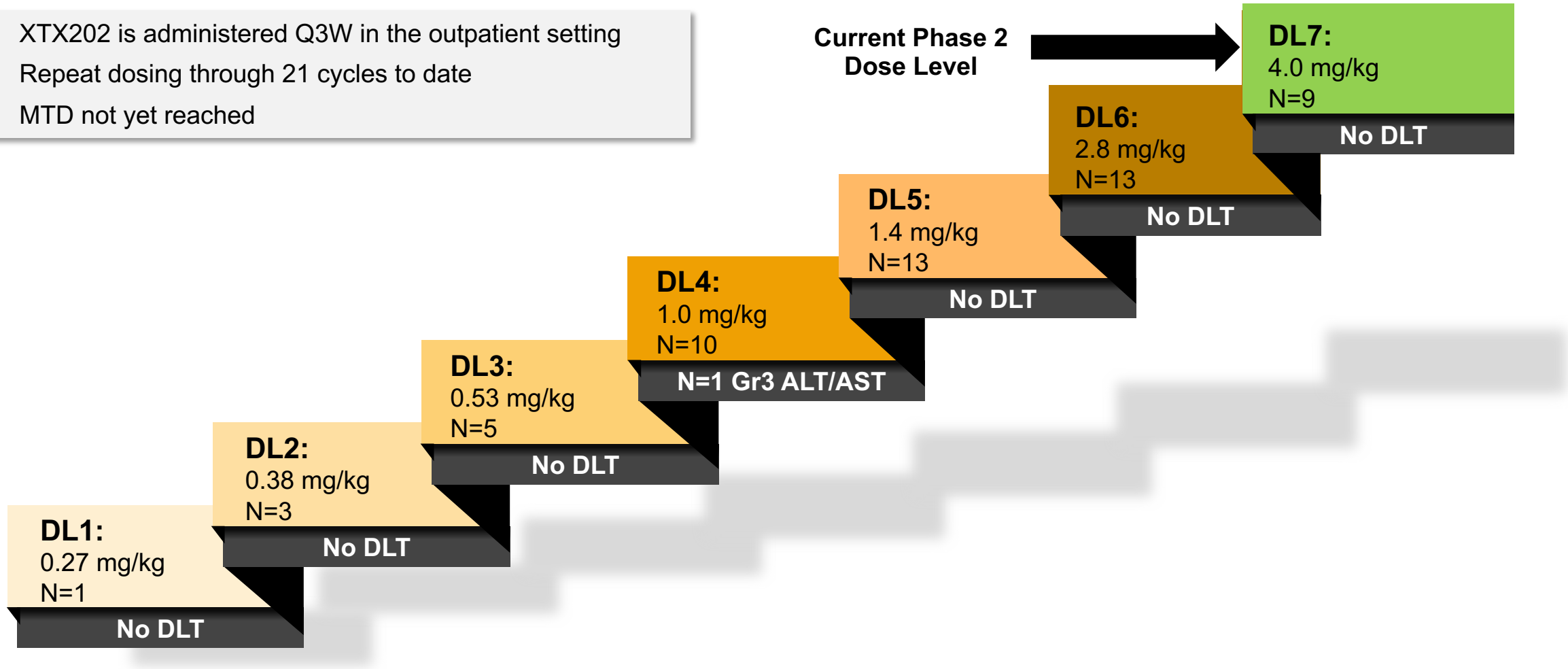
- 8 patients enrolled (2 RCC and 6 melanoma)
- All progressed on prior IO therapy

Data cutoff date: October 26, 2023.

* One patient at 2.8 mg/kg dose in Part 1A had 2 primary cancer diagnoses of pancreatic cancer and prostate cancer and is therefore included in both tumor types in the table.

No Signs or Symptoms of VLS Observed for XTX202 Through 4.0 mg/kg

- XTX202 is administered Q3W in the outpatient setting
- Repeat dosing through 21 cycles to date
- MTD not yet reached



Data cutoff date: October 26, 2023

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DL: dose level; DLT: dose limiting toxicity; MTD: maximum tolerated dose; RP2D: recommended phase 2 dose; VLS: vascular leak syndrome.

XTX202 Generally Well-Tolerated Across Dose Levels
TRAEs Primarily Grade 1-2

- No treatment discontinuations due to TRAEs
- Grade 4 TRAEs (n=2) were limited to asymptomatic laboratory abnormalities and transient (<3 days)
- No Grade 5 TRAEs

AE Category / Term *TRAEs with ≥10% incidence (any grade)*	**All Patients Phase 1 and Phase 2 All dose levels *(n=62)***		**All patients Phase 1 and Phase 2 1.4 mg/kg or higher dose level *(n=43)***	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	19% (n=12)	0	16% (n=7)	0
Pyrexia	18% (n=11)	0	23% (n=10)	0
Chills	16% (n=10)	2% (n=1)	23% (n=10)	2% (n=1)
Lymphocyte count decreased	15% (n=9)	8% (n=5)	14% (n=6)	9% (n=4)
Dose reduction due to TRAE	3% (n=2)		2% (n=1)	
Treatment discontinuation due to TRAE	0		0	

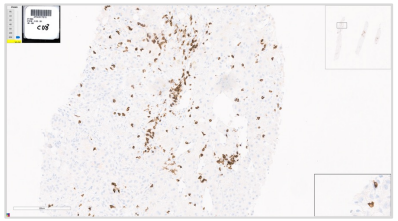
Data cutoff date: October 26, 2023
Grade 3 TRAEs not included above (n=1 each): diarrhea; colitis; myalgia; hypoxia; lymphopenia; AST/ALT increased. The events of Grade 3 diarrhea and Grade 3 colitis were reported in the same patient treated at 1.4 mg/kg. The patient was treated with steroids and the AEs resolved.
Grade 4 TRAEs (n=2) were lymphocyte count decreased/lymphopenia
AE: adverse event; TRAE: treatment related adverse event.

Tumor-Selective Increases in CD8+ Effector T Cells Observed with XTX202 in Heavily Pre-Treated Patients Across Dose Levels

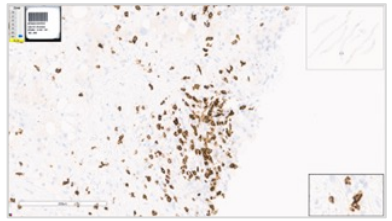
On-Treatment Tumor Biopsies vs Pre-Treatment Baseline Biopsies Collected at Enrollment

20% Increase in CD8+

Pre-Treatment



On-Treatment

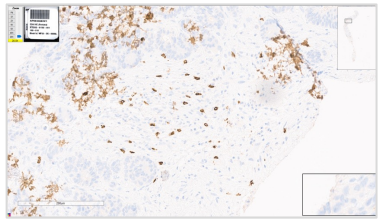


RCC patient treated with XTX202 at 1 mg/kg Q3W

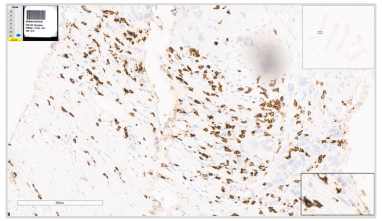
- 64M, Stage 4 RCC
- Initial diagnosis June 2016
- 5 prior lines of treatment
- Progressed on IO, multiple prior lines

120% Increase in CD8+

Pre-Treatment



On-Treatment

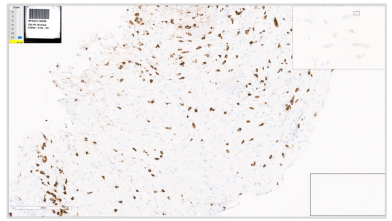


Rectal cancer patient treated with XTX202 at 2.8 mg/kg Q3W

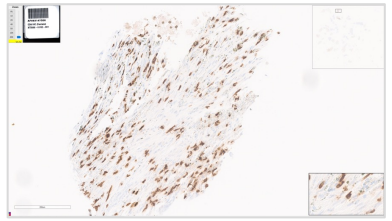
- 58F, Stage 4 rectal cancer
- Initial diagnosis August 2021
- 4 prior lines of treatment
- Progressed on IO in 3L

230% Increase in CD8+

Pre-Treatment



On-Treatment

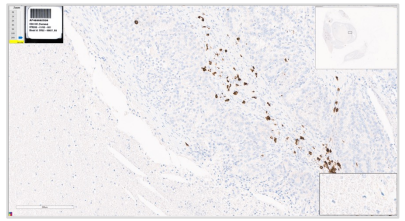


Melanoma patient treated with XTX202 at 0.38 mg/kg Q3W

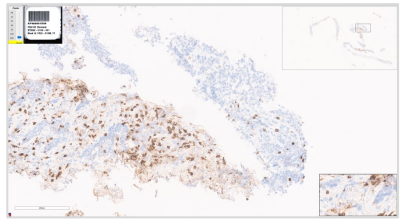
- 51M, Stage 4 melanoma
- Initial diagnosis November 2019
- 4 prior lines of treatment
- Progressed on IO in 2 prior lines

600% Increase in CD8+

Pre-Treatment



On Treatment



RCC patient treated with XTX202 at 0.53 mg/kg Q3W

- 75M, Stage 4 RCC
- Initial diagnosis May 2021
- 5 prior lines of treatment
- Progressed on IO in 1L

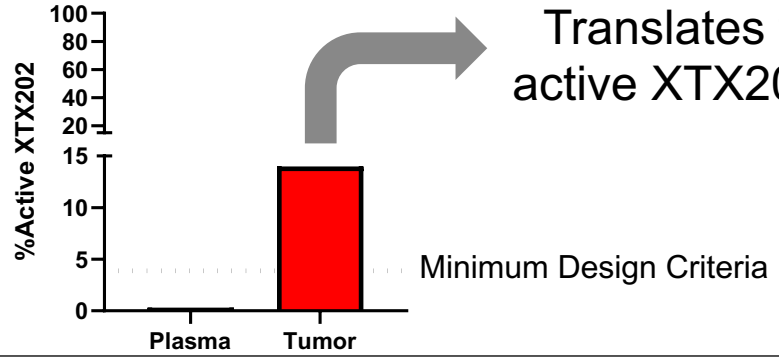
Patients had an optional on-treatment tumor biopsy and were the only four patients treated with XTX202 for whom a tumor biopsy analysis was available as of August 1, 2023. CD8+ T cells assessed by FACS for peripheral blood and IHC for tumor. Change in CD8+ cells in tumor takes into account increase in stromal TILs and CD8+ IHC.
1L: first line; 3L: third line.

XTX202 On-Treatment Biopsy Demonstrated Tumor-Selective Activation

Data suggest minimum of ≥2.8 mg/kg monotherapy doses approaching optimal range to activate CD8+ effector T cells and NK cells in the tumor

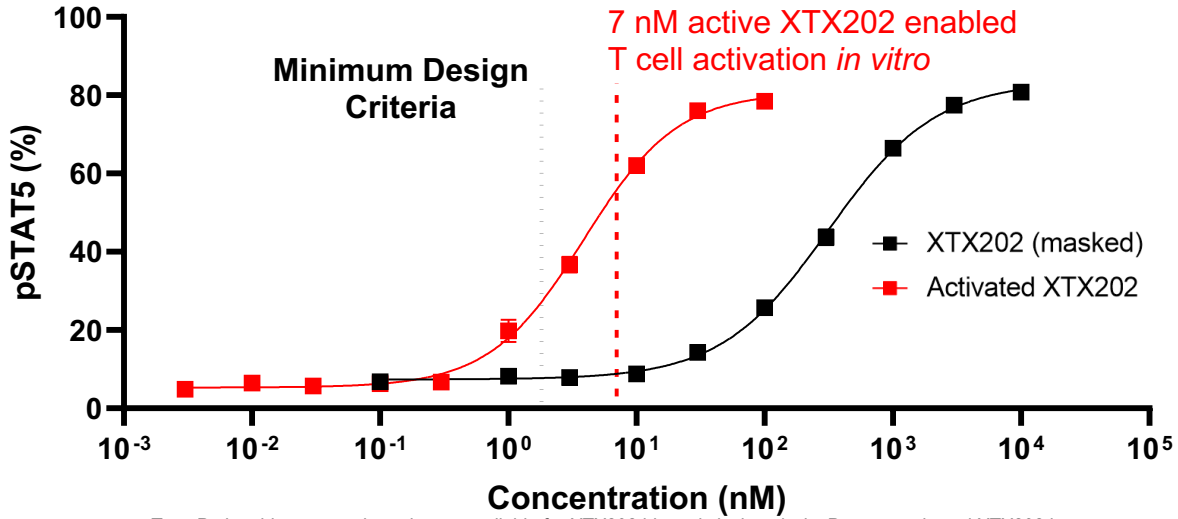
CLINICAL DATA

- Patient with leiomyosarcoma treated with XTX202 at 2.8 mg/kg Q3W, tumor specimen collected cycle 2, day 2 (C2D2)
- >40-fold increase of active XTX202 in tumor relative to plasma for patients at 2.8 mg/kg dose level
- Well above minimum design criteria and consistent with range that enabled T cell and NK cell stimulation in preclinical models

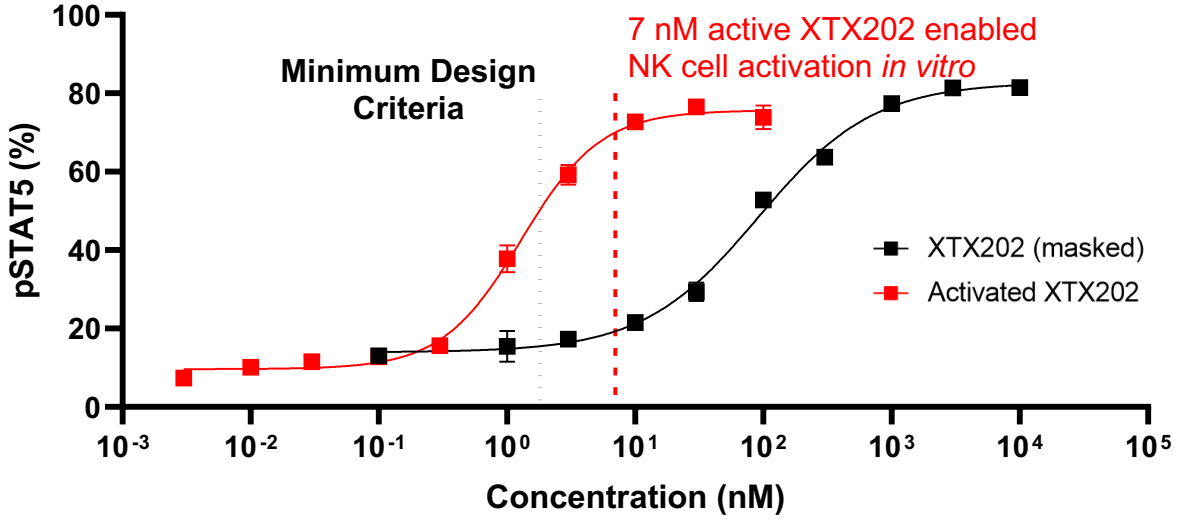


PRECLINICAL DATA

CD8+ T cells



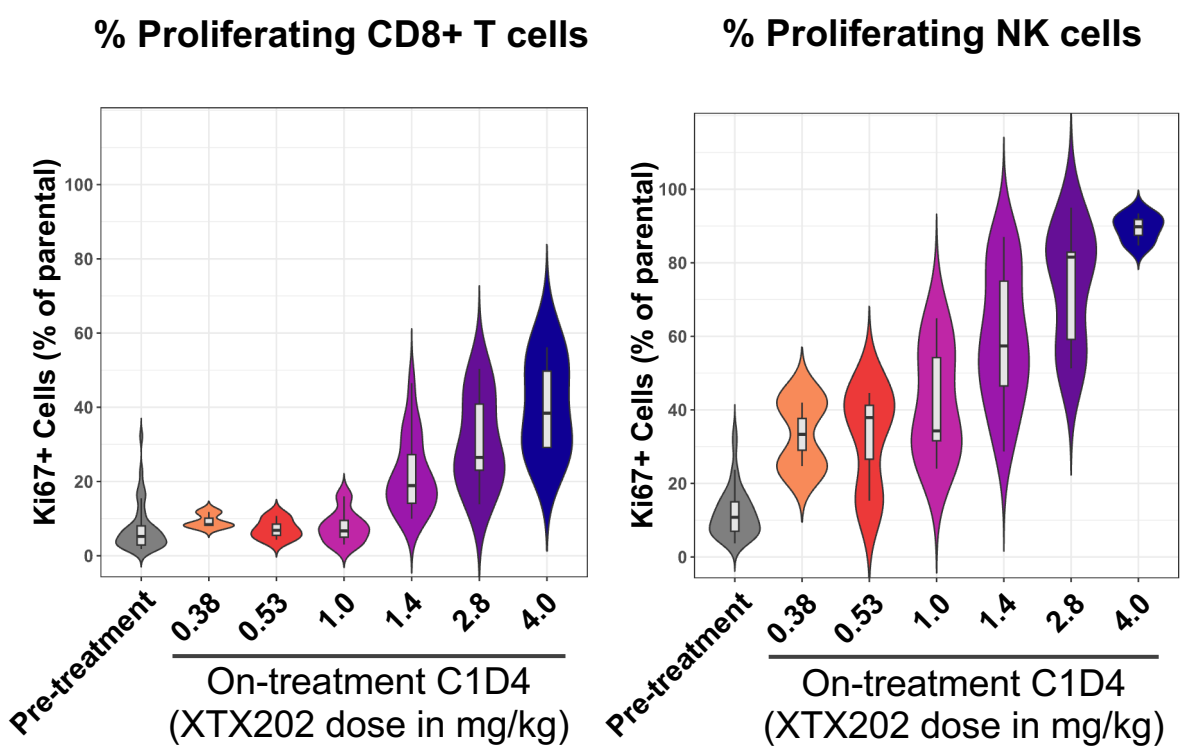
NK cells



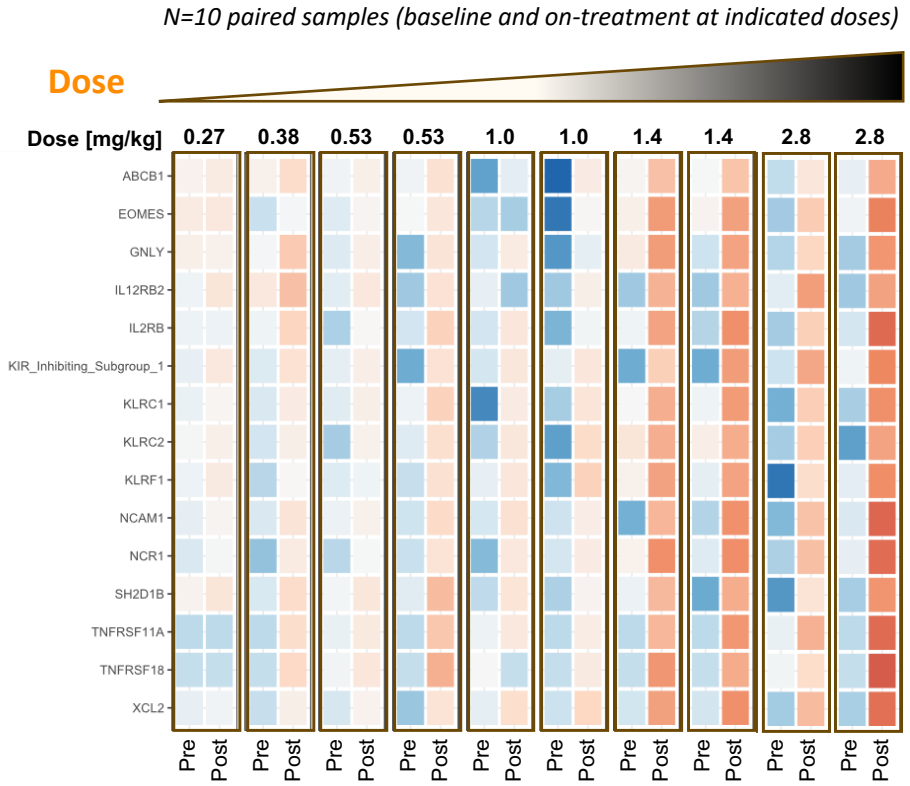
Top: Patient biopsy was the only one available for XTX202 bioanalytical analysis. Percent activated XTX202 in tumor was calculated using raw liquid chromatography / mass spectrometry data. Tumor biopsy specimen was collected C2D2. Percent activated molecule in plasma represents the average for area under the curve (AUC) for Cycle 1 for patients treated at 2.8 mg/kg dose level.
Bottom: Primary human PBMC were treated with a dose-titration of activated XTX202 (unmasked, red) or XTX202 (masked, black) and pSTAT5 positivity was assessed by FACS. The concentration of active XTX202 detected in the human biopsy (7 nM) is overlayed as a red vertical dotted line.
nM: nanomolar.

XTX202 Demonstrated Dose-Dependent Pharmacology in CD8+ T and NK Cells Consistent with IL-2 Biology

XTX202 Induced CD8+ T and NK Cell Proliferation in a Dose-Dependent Manner



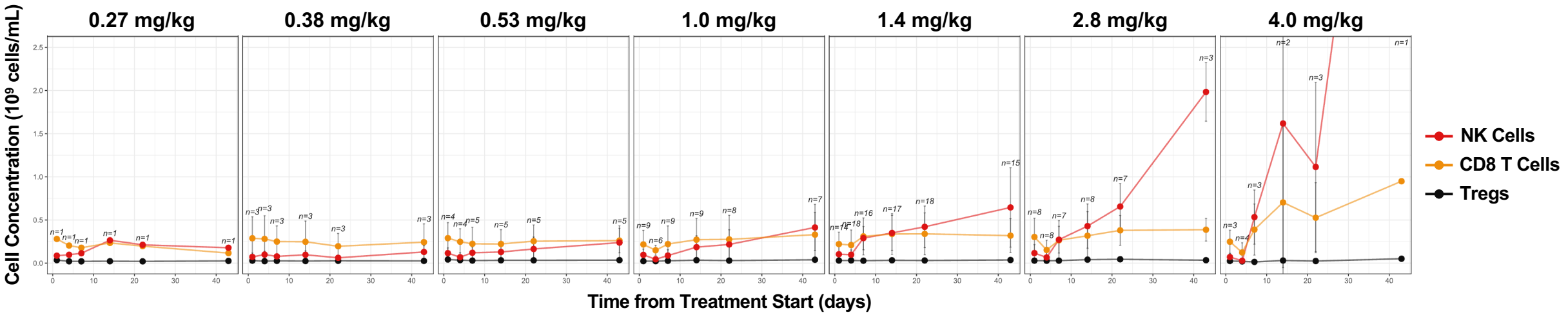
XTX202 Treatment Resulted in Dose-Dependent Upregulation of Key T and NK Cell Markers



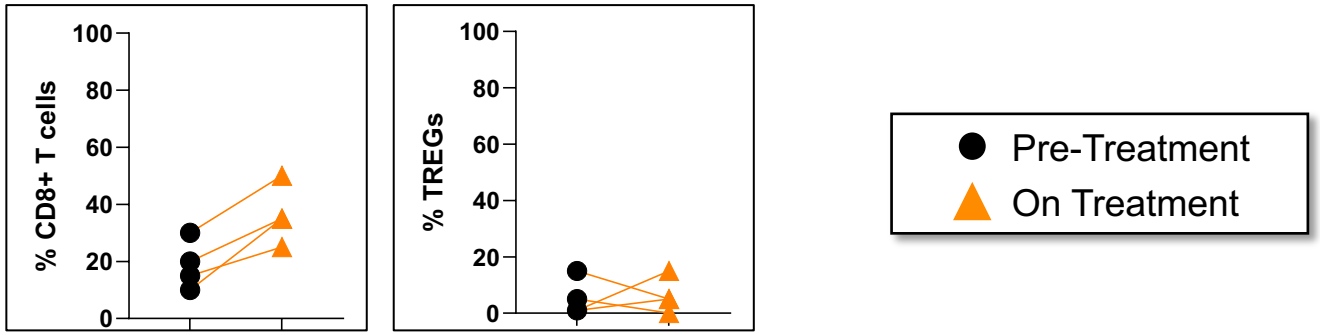
Left panel: %Ki67+ cell populations determined by flow cytometry of peripheral blood mononuclear cells at pre-dose and at cycle 1, day 4 (C1D4).
Right panel: Heatmap showing standardized expression (z-score-transformed log2-nanoString signal) of top differentially expressed genes (y-axis), separated pre vs. post treatment across all paired XTX202 samples.

XTX202 Demonstrated Stimulation of CD8+ T and NK Cells Without Expansion of TREGs

No Peripheral TREG Stimulation Observed at Any Dose Level Consistent with Beta Gamma Biased Design Intent



Intratumoral CD8+ T Cell Increase Observed Without Concomitant TREG Expansion

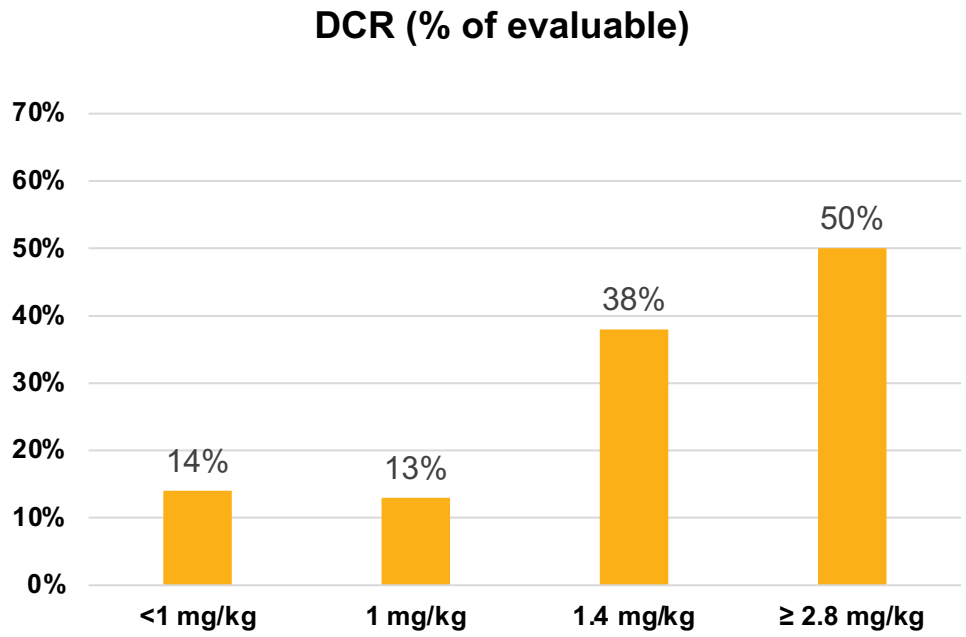


Top: Absolute Lymphocytes Count. Spaghetti graph showing the average concentration of different cell types in the periphery (y-axis, concentration expressed in 10^9 cells / L) at different timepoints (x-axis) for each treatment dose group (columns). Colors indicate cell types. Points and error bars indicate average +/- sd. The sample size is annotated for each group and timepoint.
Bottom: Patients had an optional on-treatment tumor biopsy and were the only four patients treated with XTX202 for whom a tumor biopsy analysis was available as of August 1, 2023. CD8+ T cells and TREGs assessed by IHC.

50% DCR Observed at Doses ≥2.8 mg/kg; 31% DCR Observed Across All Dose Levels in a Range of Solid Tumors, Including Cold Tumors

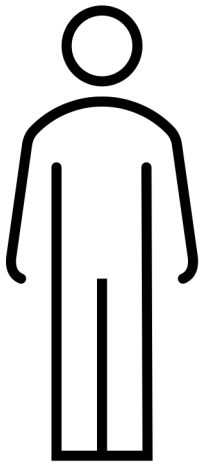
Dose dependent increase in DCR observed through dose level 7
13 patients with SD across all dose levels, with TRAEs primarily Grade 1-2
Two patients ongoing on treatment long-term (> 1 year)

Dose Level (mg/kg)*	# Patients Treated	# EOT Without Response Assessment**	# Ongoing Before 1st Response Assessment	# Response Evaluable (Phase 1 and 2)	# SD for 9+ Weeks as BOR	DCR (% of evaluable)
<1	7	0	0	7	1	14%
1	9	1	0	8	1	13%
1.4	24	1	2	21	8	38%
≥2.8	22	6	10	6	3	50%
All	62	8	12	42	13	31%



Data cutoff date: October 26, 2023. All dose levels are Q3W outpatient administration. DCR defined as SD or partial response at 9+ weeks.
SD (n=13) observed across a range of solid tumors, including cold tumors: melanoma (n=3); renal cell carcinoma (RCC) (n=2); non-small cell lung cancer (n=2); colorectal cancer (n=2); and myoepithelial carcinoma, vaginal cancer, testicular cancer and squamous penile cancer (n=1 each).
*Patients who had a dose increase (n=3) are categorized under the highest received dose level
**4 due to death, 1 consent withdrawal, 1 unrelated AE, 1 poor tolerance and 1 hospice
BOR: best overall response; DCR: disease control rate; EOT: end of treatment; SD: stable disease.

Patient With MSS CRC Treated with XTX202 > 1 Year, SD at 57 Weeks



68-year-old male with stage IV MSS CRC

Extensive disease with 4 target lesions and 4 areas of non-target lesions in lung and lymph nodes

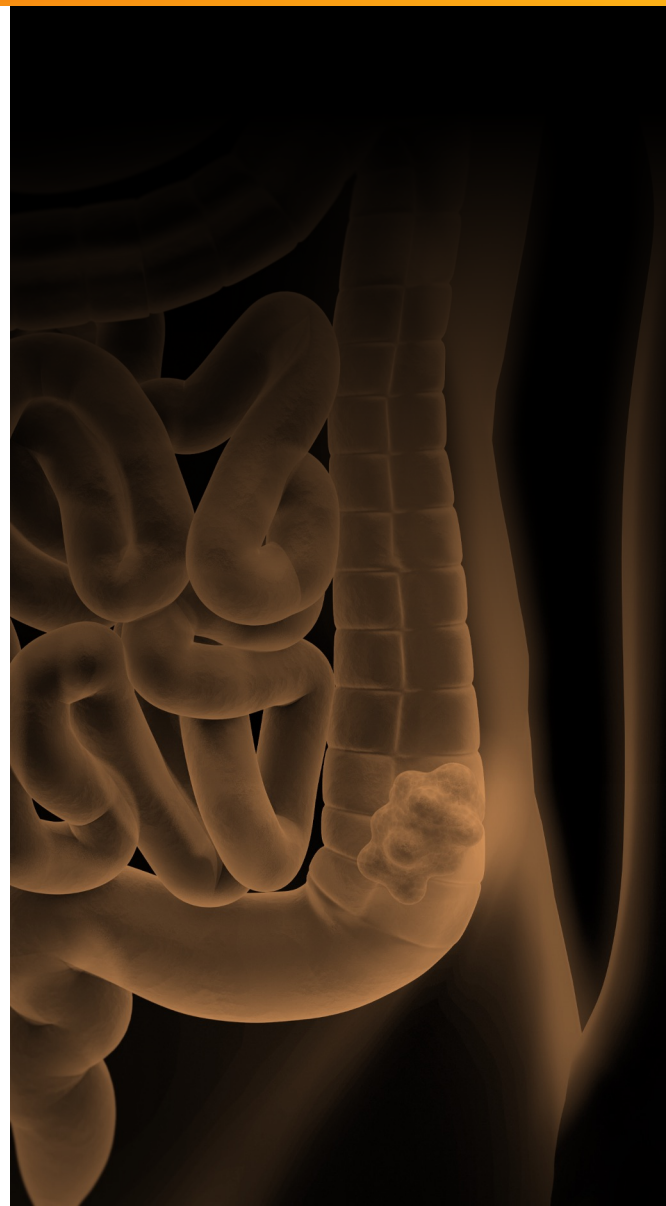
- Started XTX202 at DL2 (0.53 mg/kg, 12 cycles), DL5 (1.4 mg/kg, 9 cycles)
- No TRAEs reported with 21 cycles of treatment with XTX202

Prior treatment:

- 1L: 10 cycles of FOLFOX
- 2L: SBRT
- 3L: Irinotecan, capecitabine and bevacizumab

On XTX202:

- Long-term Stable Disease (>1 yr)
- Resolution of 75% of non-target lesions (to date)



	Screening	Week 9	Week 18	Week 27	Week 36	Week 45	Week 57
Target lesion 1 – liver lobe (R)	38 mm	46 mm	42 mm	43 mm	48 mm	57 mm	54 mm
Target lesion 2 – liver lobe (L)	27 mm	27 mm	26 mm	26 mm	23 mm	24 mm	24 mm
Target lesion 3 – adrenal gland	14 mm	13 mm	12 mm	12 mm	12 mm	14 mm	13 mm
Sum of diameters	**79 mm**	**86 mm**	**80 mm**	**81 mm**	**83 mm**	**95 mm**	**91 mm**
Non-target lesions 1,2,3,4	p/p/p/p	p/p/a/a	p/p/a/a	p/p/a/a	p/p/a/a/	p/p/a/a	p/a/a/a
Overall response		SD	SD	SD	SD	PD	SD

Non-target lesions (lung and thoracic lymph nodes): p: present; a: absent
PD: progressive disease.

Patient continuing on treatment as of October 26, 2023

XTX202 Investigator Insights

Howard Kaufman, MD, FACS
Clinical Associate, Surgical Oncology
Massachusetts General Hospital

XTX202 Melanoma and RCC Proof-of-Concept Data Anticipated in 2024*

- Over 60 patients dosed up to 4.0 mg/kg, administered Q3W as an outpatient regimen
- No signs or symptoms of VLS reported, primarily Grade 1-2 TRAEs
- Dose-dependent increase in DCR observed (n=13 SD, n=2 on treatment over 1 year)
- Tumor-selective increases in CD8+ effector T cells observed in on-treatment biopsies (n=4) (1)
- Evidence of tumor-activated concentration suggests ≥2.8 mg/kg monotherapy doses are approaching optimal range to activate CD8+ effector T cells and NK cells in the tumor (2)

Next Milestone*

- Plan to evaluate high dose monotherapy (4.0 mg/kg) Phase 2 proof-of-concept in melanoma and RCC, data anticipated (~n=20) in Q2 2024*

**** Milestones subject to obtaining sufficient additional capital.***

Data cutoff date: October 26, 2023.
1. Patients had an optional on-treatment tumor biopsy and were the only four patients treated with XTX202 for whom a tumor biopsy analysis was available as of August 1, 2023.
2. Patient with leiomyosarcoma treated with XTX202 at 2.8 mg/kg Q3W, tumor specimen collected cycle 2, day 2 (C2D2).

Clinical Data Anticipated Across 3 Programs in 2024*

XTX101 (CTLA-4) Q4'24	XTX101 + Atezolizumab Initial **Phase 2 POC** Data in MSS CRC	
XTX202 (IL-2βγ) Q2'24	XTX202 Monotherapy **Phase 2 POC** Data (4.0 mg/kg) in Melanoma and RCC	
XTX301 (IL-12) 2H'24	XTX301 Monotherapy **Phase 1** Safety and PK/PD Data in Advanced Solid Tumors	

** Milestones subject to obtaining sufficient additional capital.*

Xilio is working to deliver highly potent, localized immunotherapies in cancer and beyond

Xilio Therapeutics is a Differentiated IO Company with a Proprietary Tumor-Activated Platform and the Team to Deliver

Patient Portrayal