Unleashing the Potential of Immuno-Oncology Therapies

May 14, 2024

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Immuno-Oncology Therapy Has Curative Potential But Has Been Limited by Systemic Toxicity

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

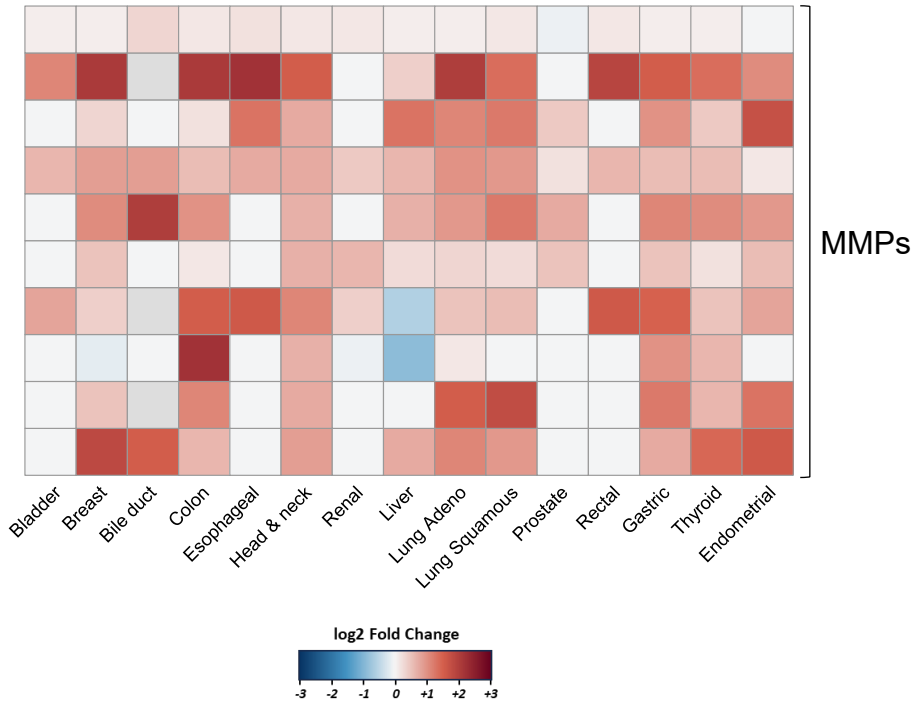
Patient Portrayal

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 Exploits Dysregulated MMP Activity, a Hallmark of Invasive Cancer, to Activate Molecules in the Tumor Microenvironment

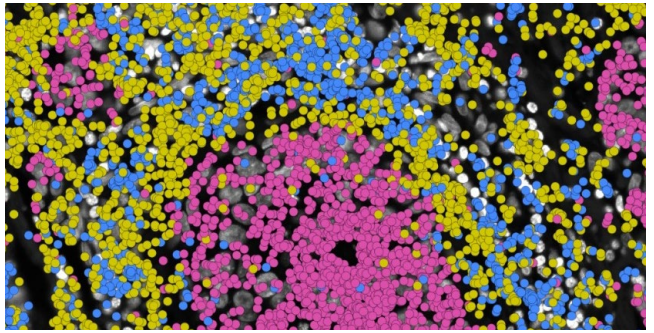
MMPs are dysregulated broadly across solid tumors

MMP mRNA expression in tumor vs. normal tissue

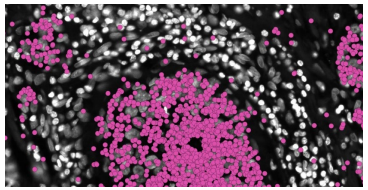


MMPs and immune cells co-localize at the invasive edge of tumors

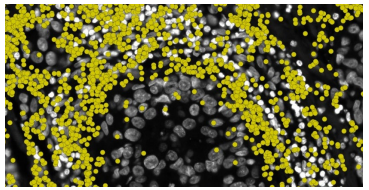
In situ mRNA expression in human breast cancer



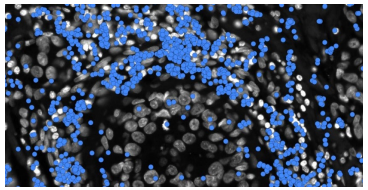
Tumor cells (TROP2)



MMP (MMP2)



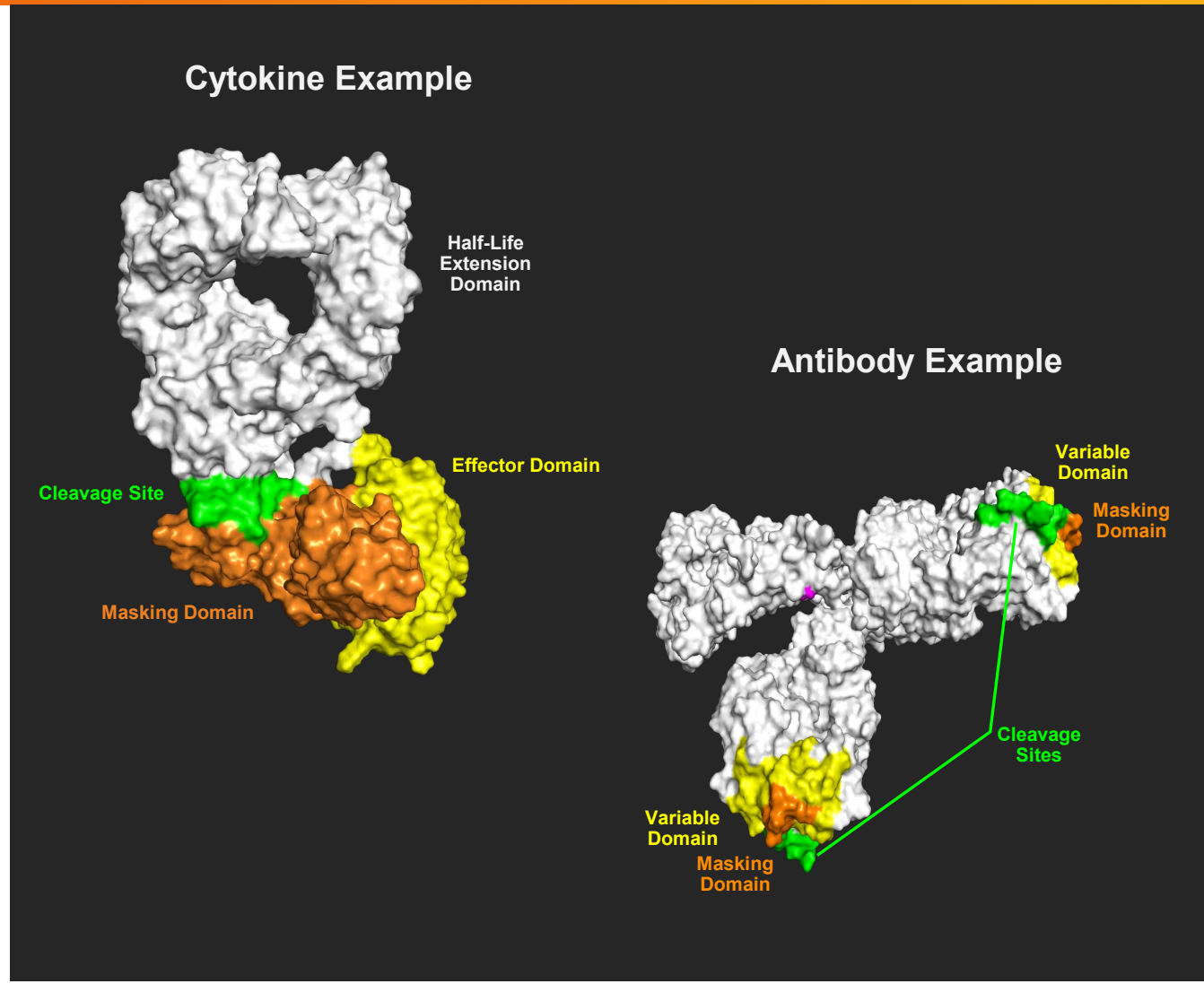
T cells (CD4, CD8A)



Left panel: Heatmap summarizing RNA expression changes of genes encoding for selected MMPs (bottom) in tumor vs. adjacent normal samples from multiple TCGA studies (x-axis). Color intensity tracks with log2-transformed fold changes (log2FC). Pre-processed TCGA data were obtained from UCSC Xena. **Right panel:** Spatial gene expression analysis using Xenium platform (10X Genomics) showing expression of TROP2 (TACSTD2, pink), MMP2 (yellow), CD4 and CD8A (blue) in a human breast cancer sample. https://www.10xgenomics.com/products/xenium-in-situ/human-breast-dataset-explorer; Xenium Explorer Version 1.2.0; Instrument Analysis Version: Xenium- 1.0.1

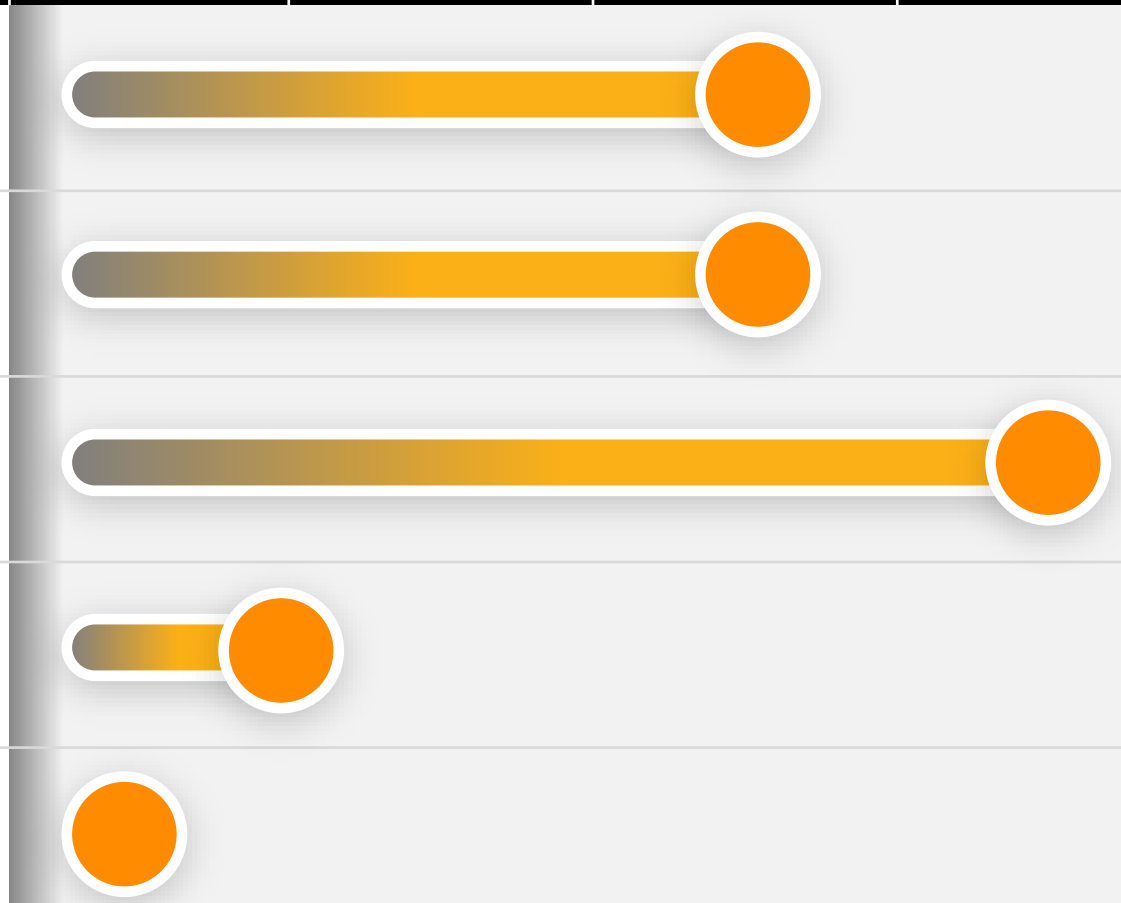
Xilio's Molecules are Designed to be Activated by Dysregulated MMPs in Tumors

- 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



Advancing Pipeline of Clinical and Preclinical Tumor-Activated Molecules

Program	Tumor Types	Mechanism of Action	Discovery	IND-Enabling	Phase 1	Phase 2	Phase 3	Partnerships
XTX101 in combination with atezolizumab [1]	Advanced MSS CRC	anti-CTLA-4 + PD-L1						**Clinical collaboration with Roche (with co-funding)**
XTX301 [2]	Advanced Solid Tumors	IL-12						**Exclusive global license with Gilead**
XTX202 [3]	Advanced RCC and Melanoma	IL-2βγ						**Plan to explore strategic opportunities to develop in combinations** [3]
XTX501	Advanced Solid Tumors	PD-1/IL2 bispecific						
Additional research-stage programs	Undisclosed	Tumor-activated cell engagers						

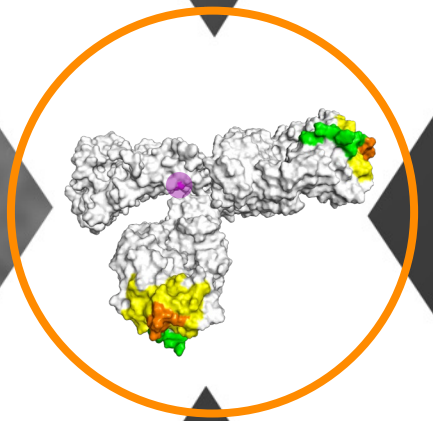


1. Evaluating XTX101 in combination with atezolizumab (Tecentriq®) in Phase 1 combination dose escalation trial and planned Phase 2 combination trial in MSS CRC.
2. Evaluating XTX301 in Phase 1 monotherapy dose escalation for the treatment of advanced solid tumors.
3. Plan to discontinue further investment in XTX202 as a monotherapy

MSS CRC: metastatic colorectal cancer; RCC: renal cell cancer

Opportunity for XTX101 in MSS CRC

Pursuing XTX101 in Combination with Atezolizumab in MSS CRC



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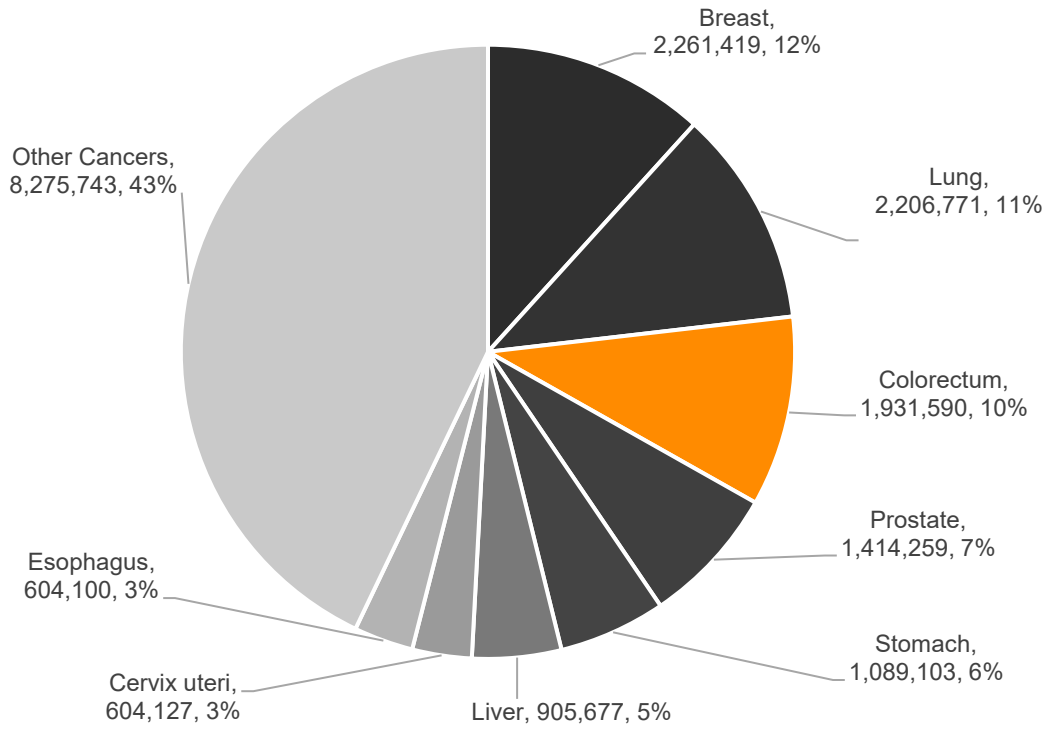
Colorectal Cancer is 3rd in Total Annual New Cases Globally

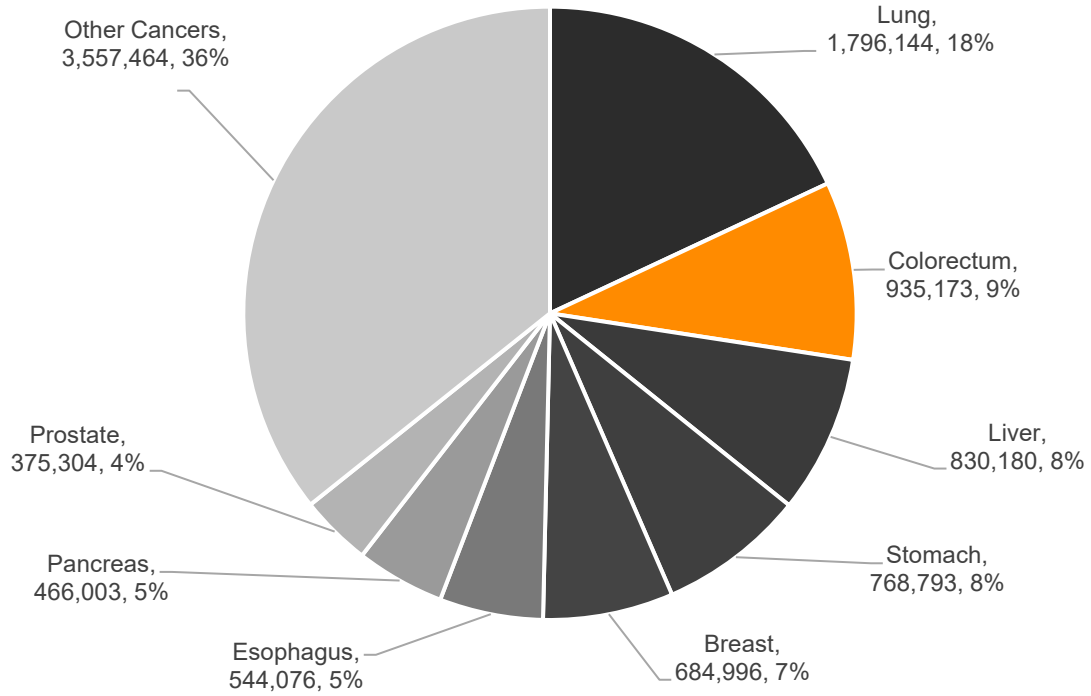
Number of new cases in 2020

(Global, both sexes, all ages)



Number of deaths in 2020

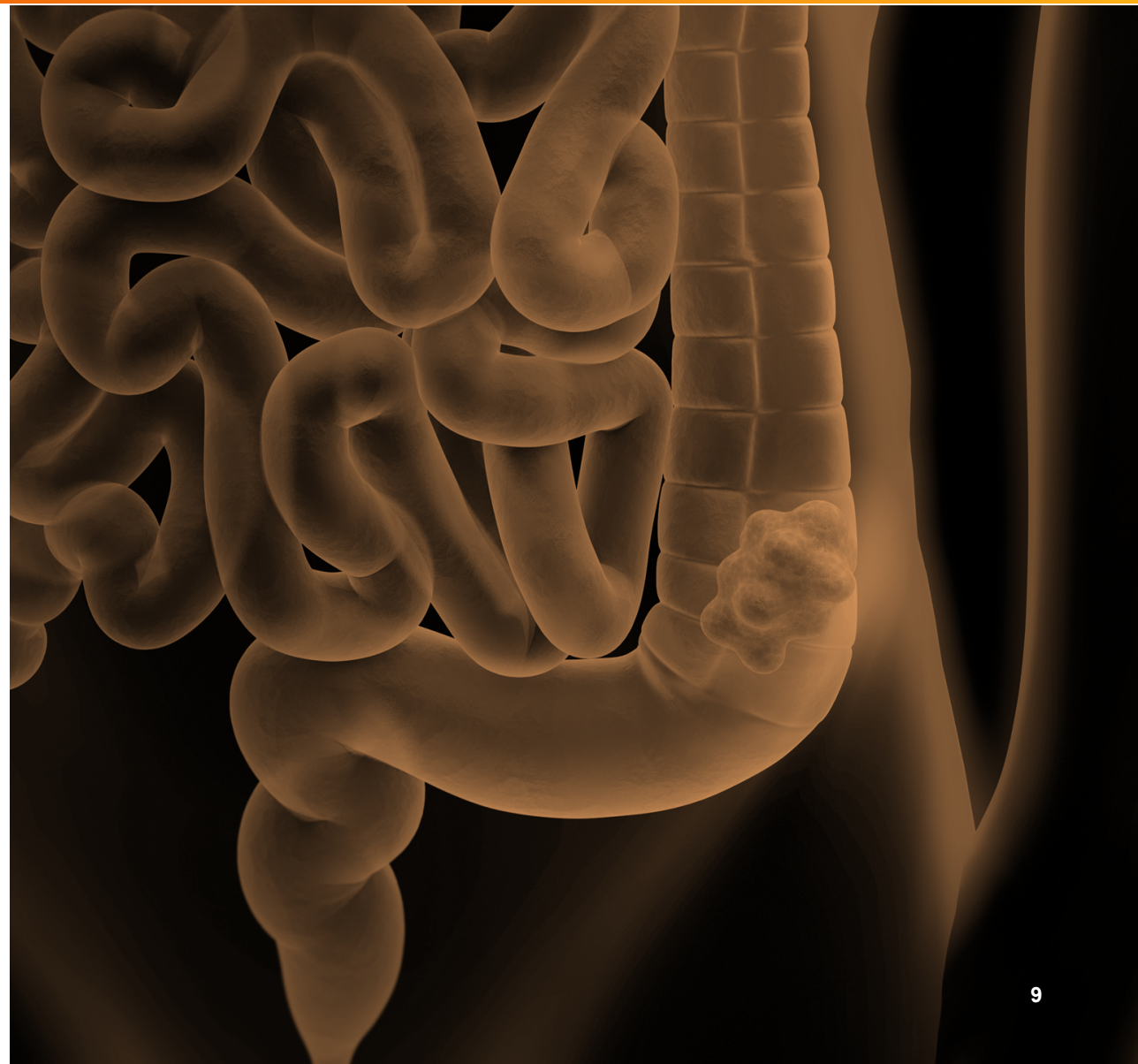
(Global, both sexes, all ages)



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**

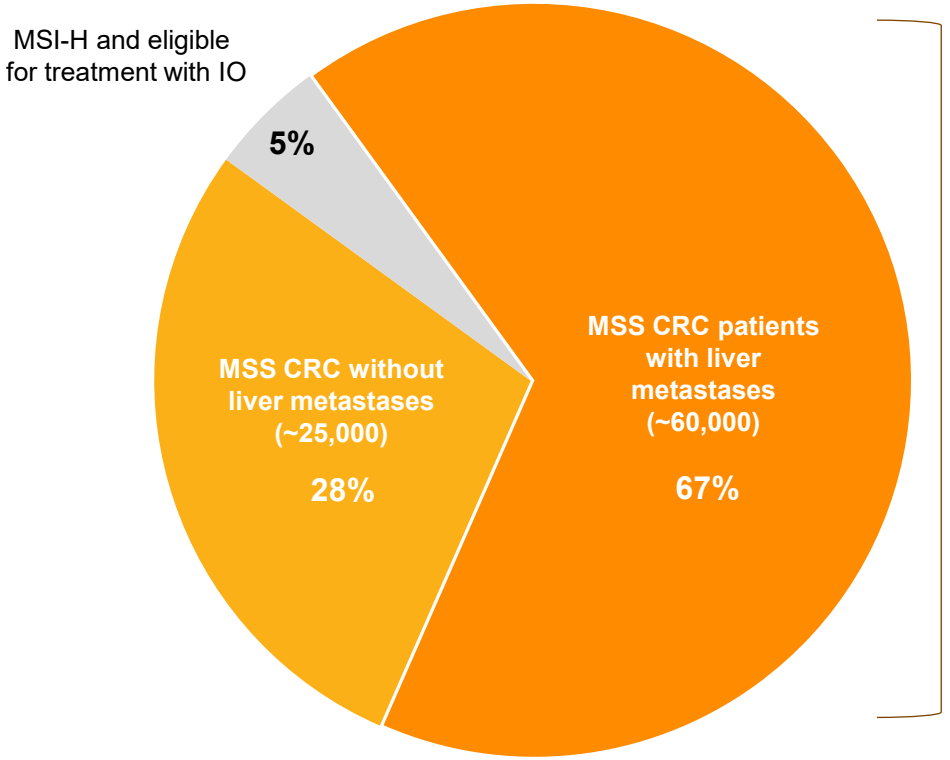
↓

~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).

MSI-H: microsatellite instability-high

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

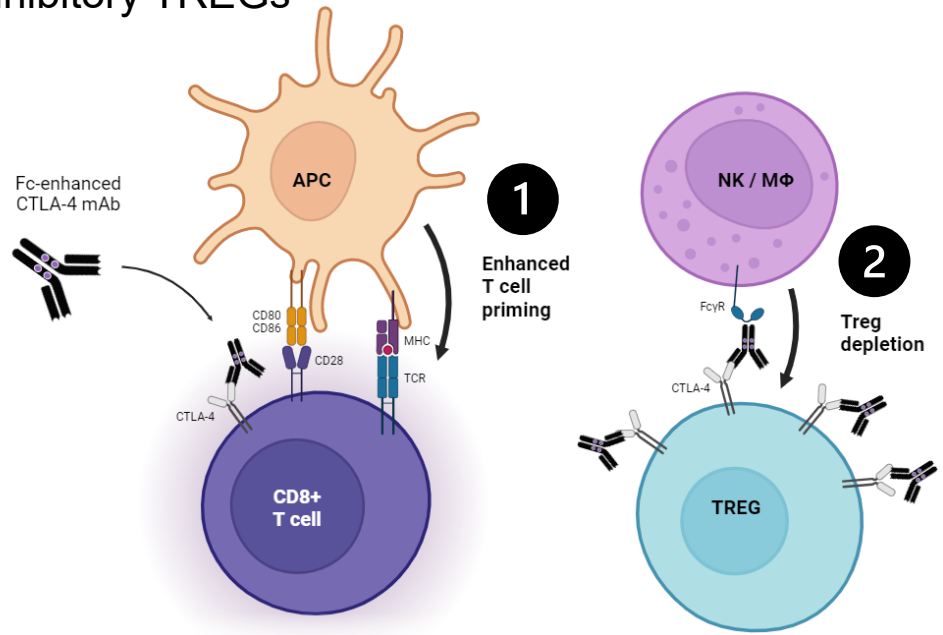
Adapted from Sahin et al, 2022 ASCO Educational Book.
* Three patients were given nivolumab, 1 mg/kg 1 ipilimumab, 1 mg/kg; 10 patients each were given nivolumab, 1 mg/kg 1 ipilimumab, 3 mg/kg or nivolumab, 3 mg/kg 1 ipilimumab, 1 mg/kg.
** In a subgroup analysis of patients with MSS: HR, 0.66; 95% CI, 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.

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)

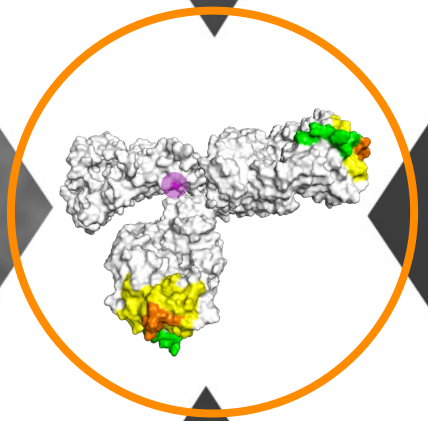
1. Phase 1 data reported by Agenus Inc. on January 21, 2023, at ASCO GI Symposium for botensilimab (AGEN1181) in combination with a balstilimab in MSS CRC patients previously treated with chemotherapy and/or with immunotherapy-resistant tumors.
2. Phase 1 data reported by Agenus Inc on November 11, 2021 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

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



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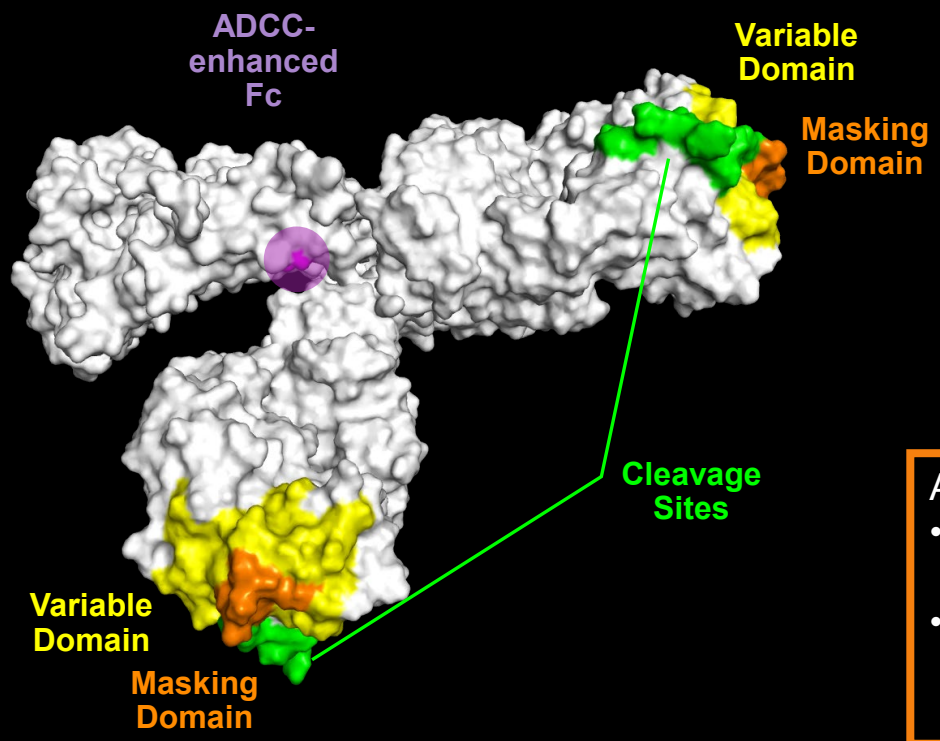
XTX101: Tumor-Activated, High Affinity Binding, Fc-Enhanced Anti-CTLA-4

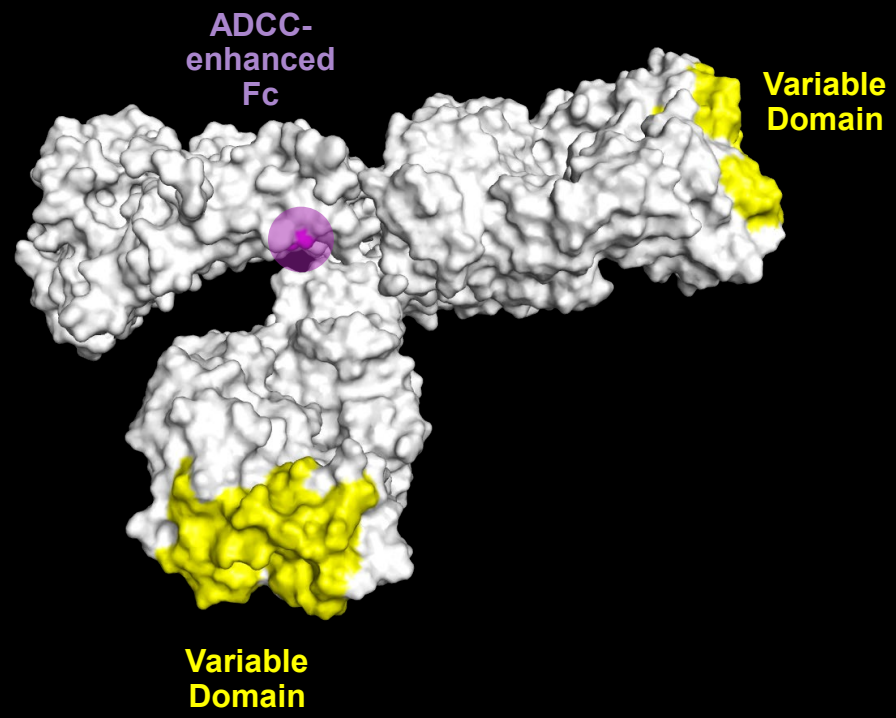
Inactive State



MMP Activation

Activated XTX101 designed to:
- bind and block CTLA-4 checkpoint
- drive potent ADCC against TREGs that highly express CTLA-4

Active State



ADCC: antibody-dependent cell-mediated cytotoxicity.

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 [1]
(n=16 dosed)

Ongoing

Current dose level: 150 mg Q6W

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%)

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

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

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

Data cutoff date: November 13, 2023.
1. 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; Q6W: once every six weeks.

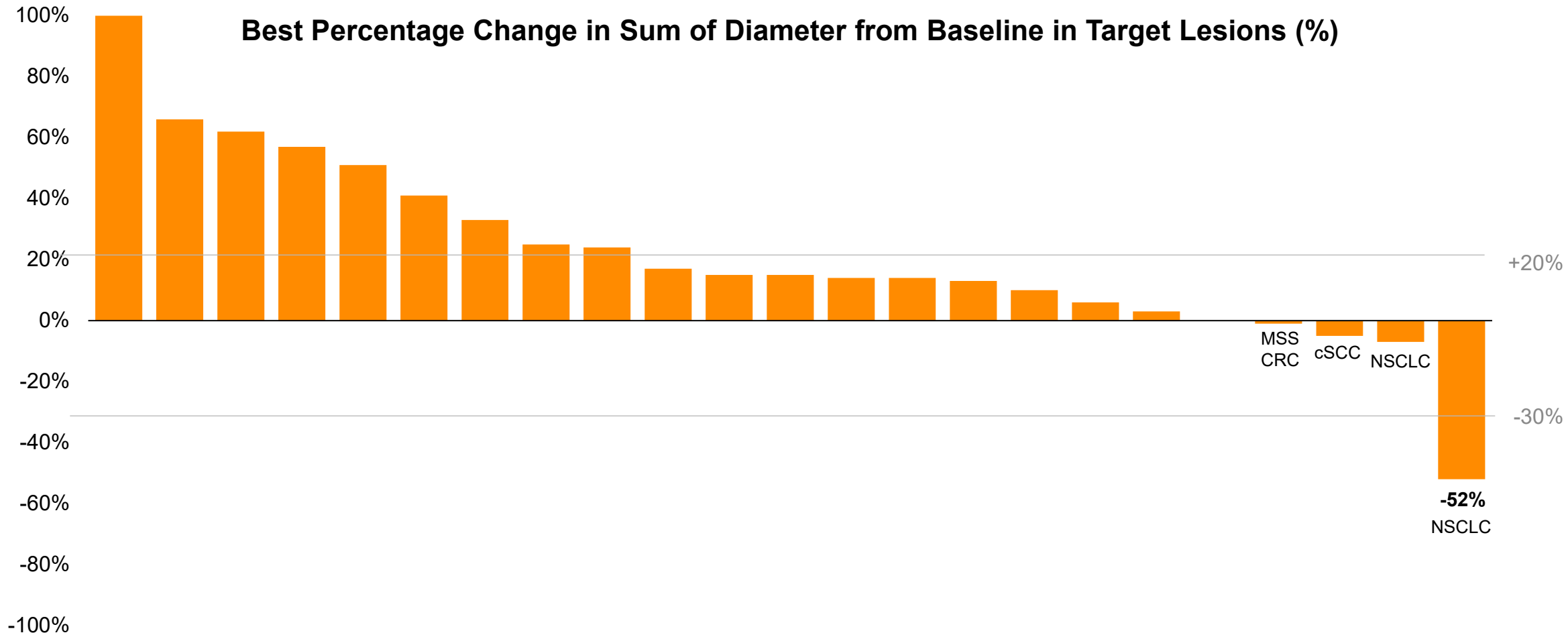
Patients on XTX101 150mg Q6W Experienced Minimal TRAEs

- No treatment discontinuations due to TRAEs at RP2D
- In N=18 patients treated at RP2D only 2 Grade 3 TRAEs observed
- 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 TRAE***	**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	

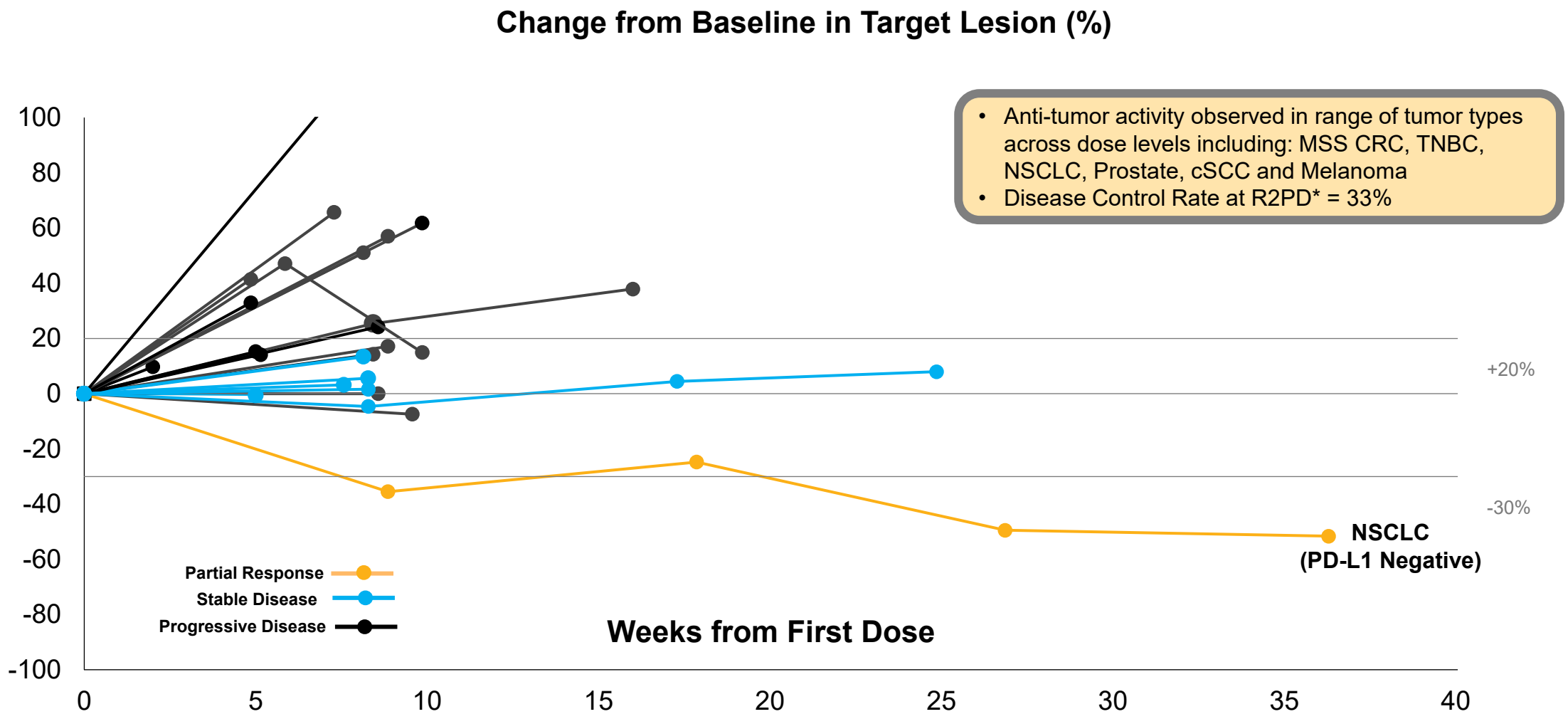
Data cutoff date: November 13, 2023.
1. The PT of diarrhea or colitis was reported among 7 unique patients, with 3 patients recording both diarrhea and colitis as TRAE
2. Grade 3 diarrhea with onset 10 weeks after the start of treatment (after 2 doses), resolved within 5 days without steroid use, patient 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.
AE: adverse event; irAE: immune-related adverse event; Q3W: once every three weeks; RP2D: recommended Phase 2 dose.

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



Data cutoff date: November 13, 2023.
cSCC: cutaneous squamous cell carcinoma.

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



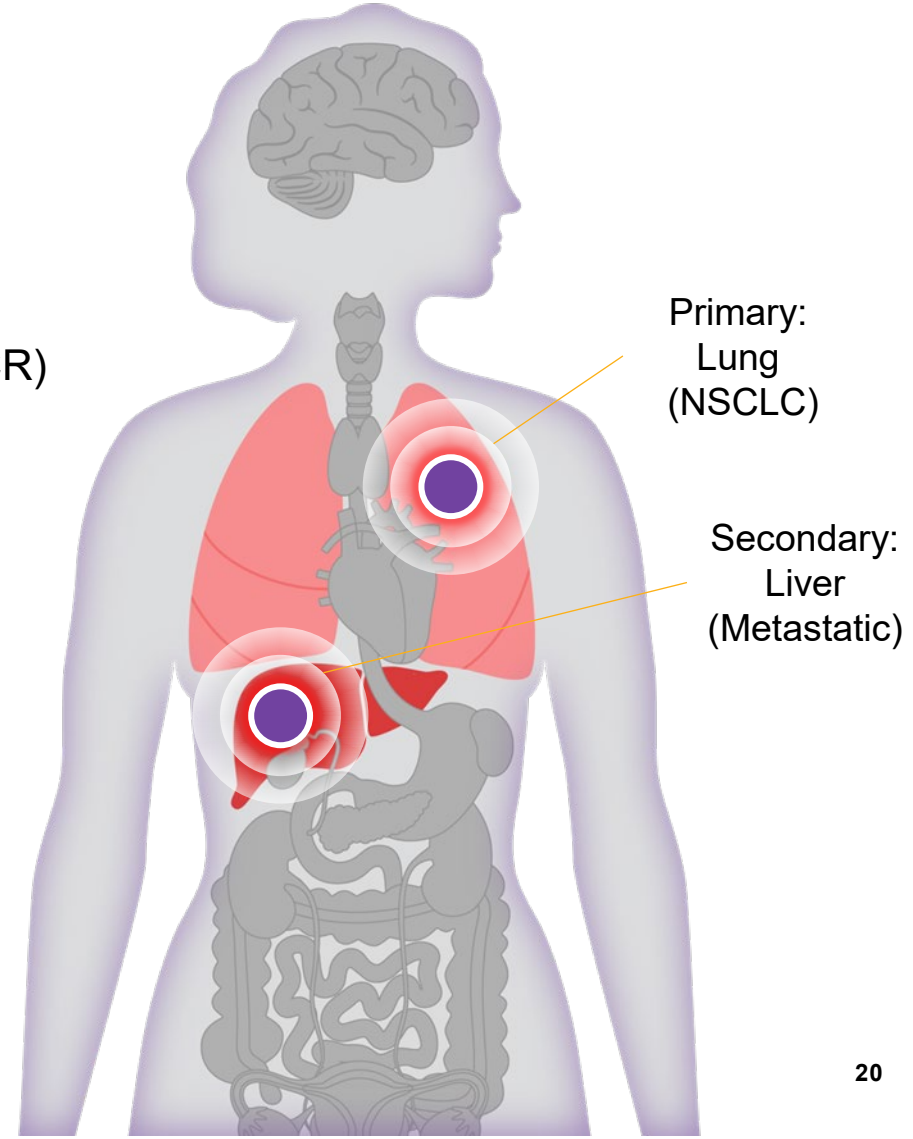
- Anti-tumor activity observed in range of tumor types across dose levels including: MSS CRC, TNBC, NSCLC, Prostate, cSCC and Melanoma
- Disease Control Rate at R2PD* = 33%

Data cutoff date: November 13, 2023.
*N=12 response-evaluable patients included in disease control rate assessment at RP2D.

Deep and Durable Confirmed Partial Response (PR) Through Week 36 in a Patient with PD-L1 Negative NSCLC and Innumerable Hepatic Metastases on XTX101 Monotherapy

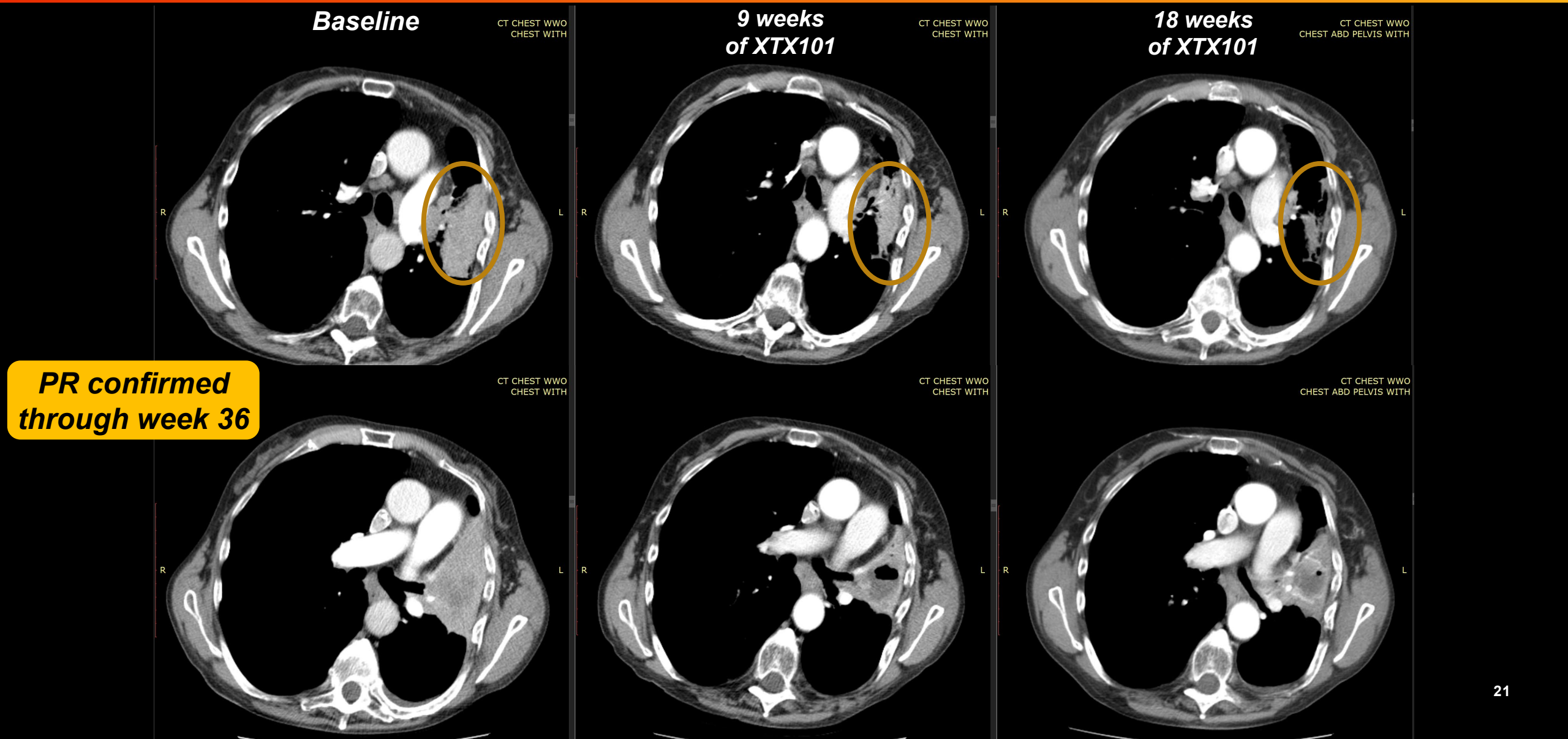
- **Patient**: 66-year-old, female
- **Diagnosis**: Stage 4 NSCLC, PD-L1 negative
- **Previous Treatment:** 4 cycles of paclitaxel and carboplatin (non-durable CR)
- **XTX101 Treatment:** 150mg Q6W, 7 doses administered (36 weeks)
- **Related AE**: Grade 1 fatigue (only)
- **Anti-Tumor Activity**: Reduction in the sum of diameters by 52% with resolution of liver metastases

Confirmed PR through week 36*



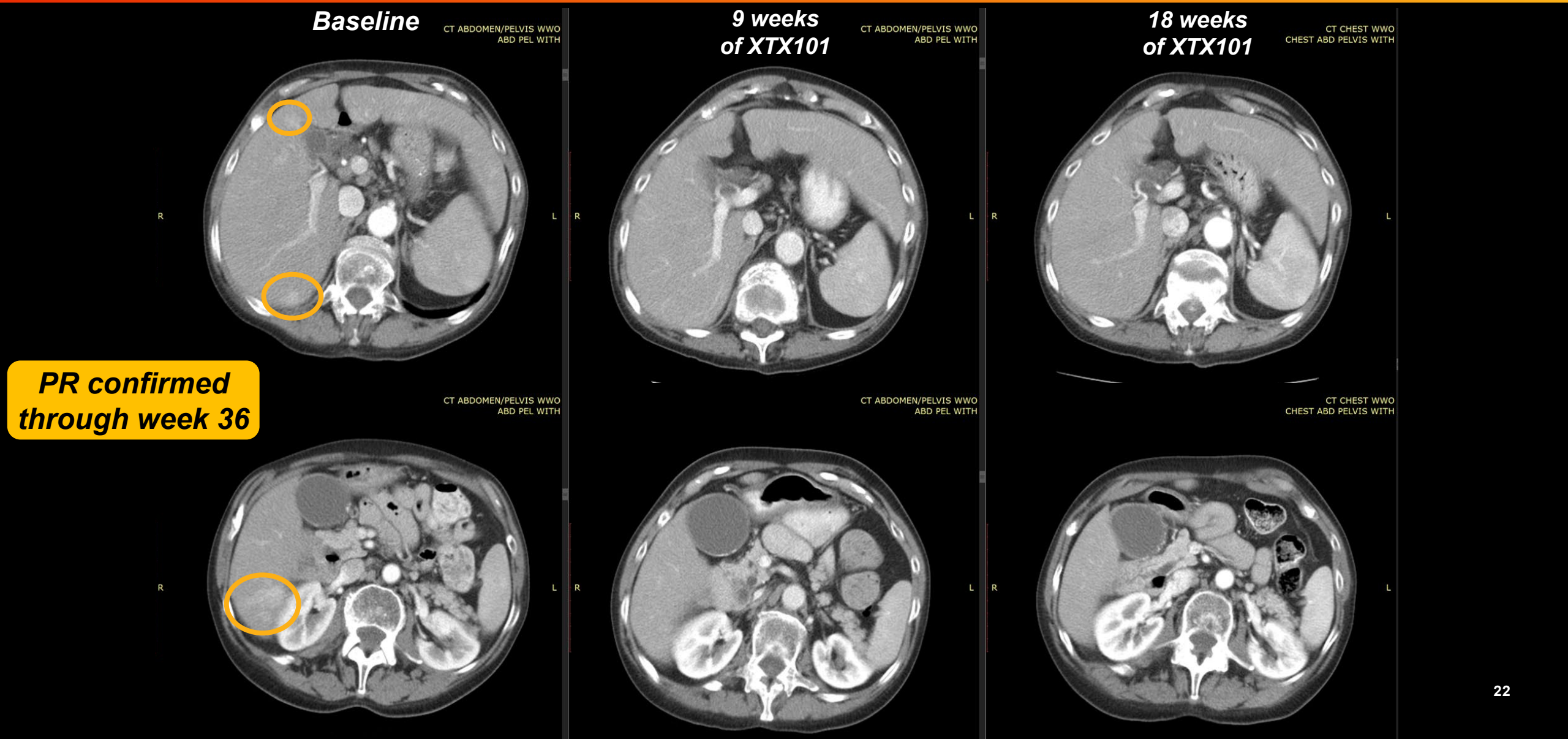
Data cutoff date: November 13, 2023. Tumor response was assessed by RECIST version 1.1.
*NSCLC patient discontinued treatment after week 36 due to an adverse event unrelated to treatment.

Primary Lung Lesion Decreased in Size and Developed Cavitation



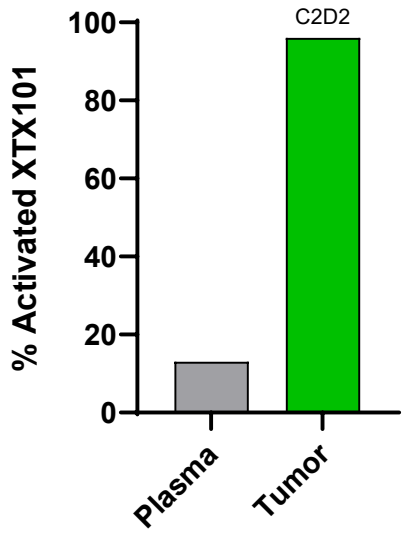
PR confirmed through week 36

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)

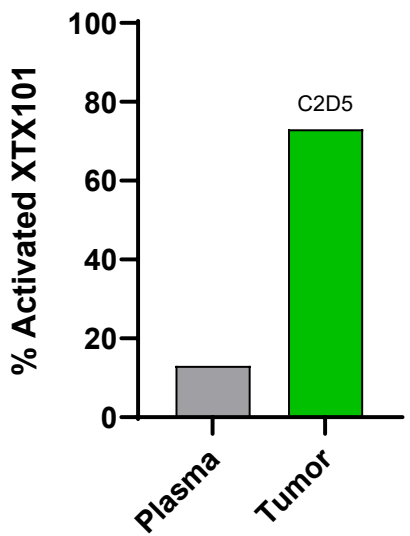


96% Activated Molecule in Tumor *(metastatic lesion on calf)*

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.

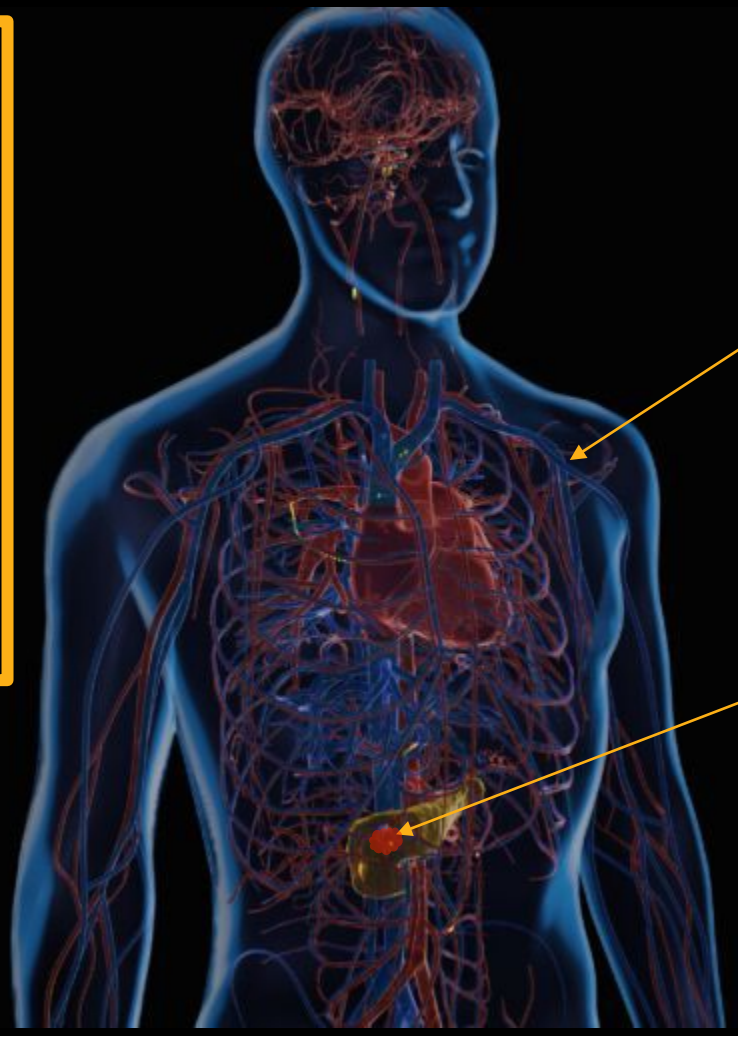
13% Activated Molecule in Plasma*

Tumor biopsy pharmacokinetic (PK) analysis for two patients treated with XTX101 in Part 1B. 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

XTX101 RP2D: 150 mg Q6W

- ~2.1 mg/kg for 70kg patient
- Potency adjustment vs ipilimumab ~10x based on preclinical data
- At 100% activation, estimated exposure for XTX101 equivalent to ~21 mg/kg ipilimumab



Estimated peripheral exposure for XTX101 at RP2D and ~13% activation equivalent to:

- ~1.3 mg/kg ipilimumab (AUC)
- ~2.7 mg/kg ipilimumab (C_{max})

Estimated tumor exposure for XTX101 at RP2D and ~73-96% activation equivalent to:

- ~15.3 mg/kg ipilimumab (@ 73% activation)
- ~20.1 mg/kg ipilimumab (@ 96% activation)

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

XTX101 Advancing Under Co-Funded Clinical Collaboration

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

- ✓ Initiated enrollment in Q4 2023
- ✓ FPI in Q4 2023
- ❑ Select RP2D in Q3 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

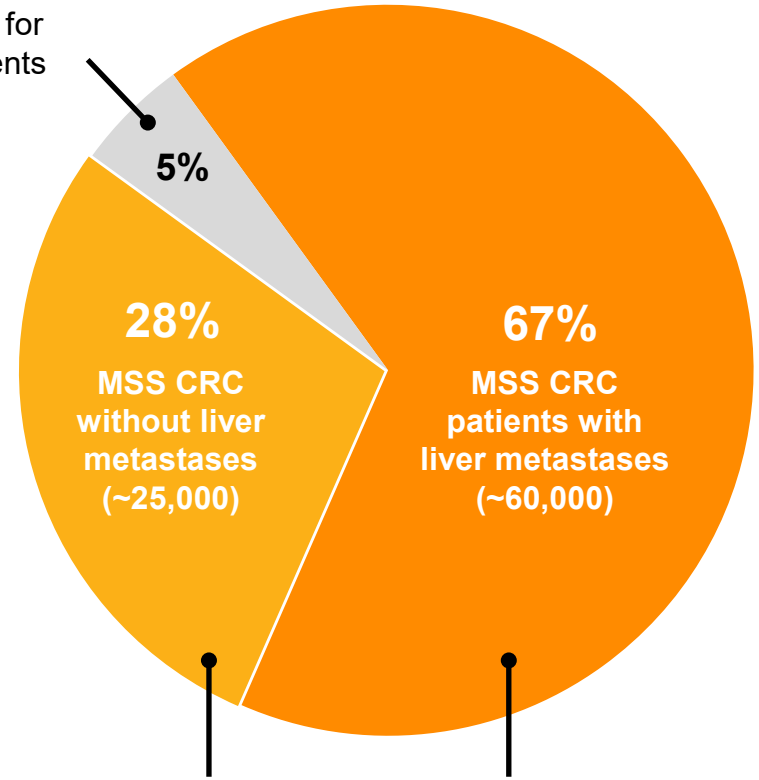
- Potential for accelerated approval pathway
- Monotherapy cohorts (to demonstrate contribution of components) and/or standard-of-care comparator arm (if required) can have early stopping rules

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 trial 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.

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

- Platform validation including monotherapy confirmed PR observed in Phase 1 trial [1]
- 33% monotherapy DCR at RP2D across range of late-line and IO refractory tumors [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

2H 2024

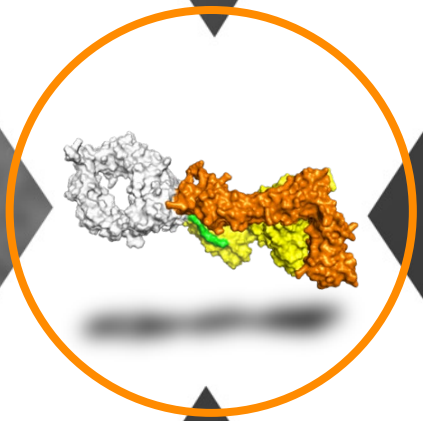
Next Anticipated Milestones

- Select RP2D for XTX101 in combination with atezolizumab and initiate Phase 2 in patients with MSS CRC in Q3 2024
- Report initial Phase 2 data for XTX101 + atezolizumab in ~20 patients with MSS CRC in Q4 2024

1. Data cutoff date: November 13, 2023. Tumor response was assessed by iRECIST version 1.1.
POC: proof-of-concept

XTX301

Tumor-Activated IL-12



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The Compelling Potential of IL-12 as a Therapeutic Agent

- IL-12 has significant potential as a potent IO therapeutic agent in cold tumors
- Poor tolerability has limited its clinical progress for decades
- No currently approved IL-12 agents

IL-12 Has Highly Compelling Biology for IO Applications

Exquisitely potent stimulator of NK and T cell cytotoxicity and INFγ production

Capable of polarizing CD4 T-cells towards Th1 phenotype, thus driving cellular immunity against infection and cancer

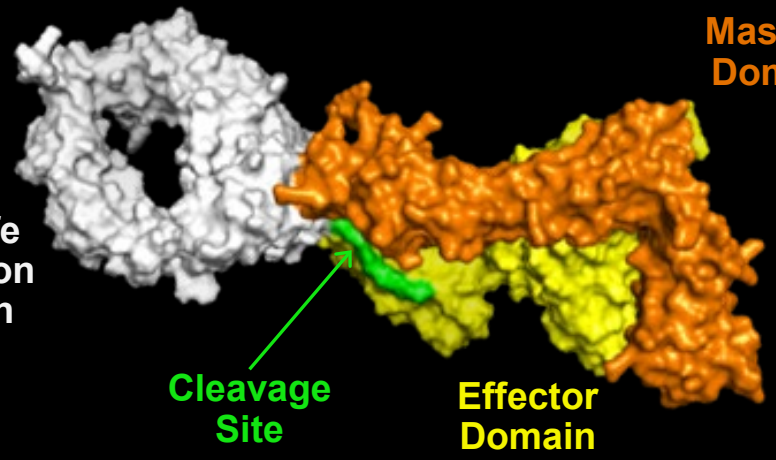
Robust INFγ induction results in broad remodeling of the TME towards a more immune-permissive environment

Demonstrated single agent objective responses in patients, but poorly tolerated (MTD <500 ng/kg on repeat dosing)

INFγ is a pleiotropic molecule with associated antiproliferative, pro-apoptotic and antitumor mechanisms. Th1-type cytokines tend to produce the proinflammatory responses responsible for killing intracellular parasites and for perpetuating autoimmune responses.
INFγ: interferon gamma; g/kg: nanograms/kilogram.

XTX301: Tumor-Activated IL-12 Designed to Overcome the Limitations of Systemic Recombinant Human IL-12

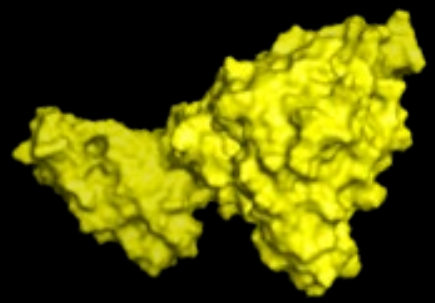
Inactive State



MMP Activation

Activated XTX301:
- Optimized short half-life IL-12 (half-life extension domain not retained)

Active State



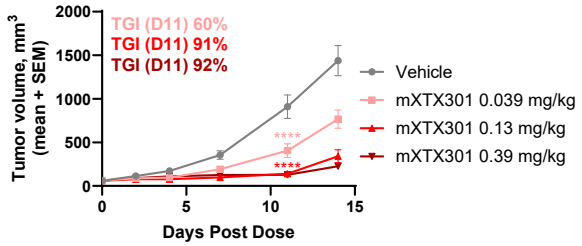
XTX301: Designed to Overcome Limitations of Systemically Active IL-12

Efficient activation by human tumors demonstrated *ex vivo*

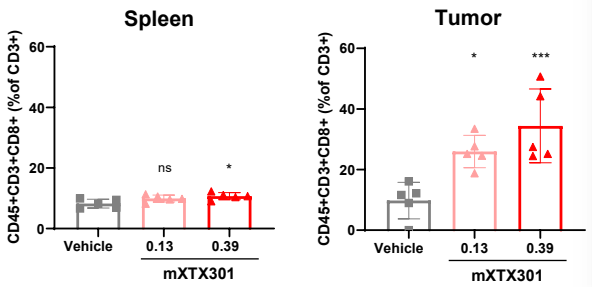
Tumor Type	Confirmed High Activation Efficiency XTX301 (IL-12)
Colon	
Head & Neck	
Prostate	
RCC	
Lung	
Melanoma	
Plasma	

Robust anti-tumor activity and tumor-selective PD *in vivo* in preclinical model

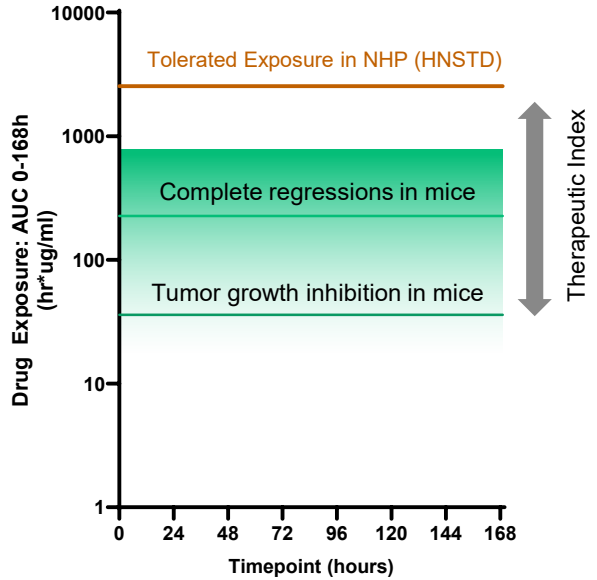
Dose-dependent anti-tumor activity



Tumor-selective increase in CD8 T cells



Potential for broad therapeutic index supported by robust preclinical data



- Exposure in mice adjusted for 6x potency relative to human XTX301

First panel: Activation of XTX301 assessed in human tumor samples ex vivo. **Third panel from left – Top:** MC38 model; single IV dose of mXTX301 or vehicle on Day 0. Tumor growth data shown as mean±SEM. Tumor volume data was assessed by a two-way Analysis of Variance (ANOVA) followed by Bonferroni post hoc test on Day 11 compared to vehicle treated animals. ****p<0.0001 for all mXTX301 treatment groups. **Second panel:** MC38 model; single IV dose of mXTX301 or vehicle on Day 0. On day 4 post treatment percent CD8 positive T cells (out of CD45+/CD3+ gate) from spleens or tumors was assessed by flow cytometry. The results were analyzed by One-way ANOVA followed by Dunnett's multiple comparisons test (*P<0.05; **P<0.005) compared to vehicle (PBS) treated animals. **Third panel:** XTX301 exposures in NHP at the 2 mg/kg dose (HNSTD) over one week plotted over exposures of mXTX301 in mice at doses enabling tumor regression and tumor growth inhibition with 6x adjustment to account for potency difference between human XTX301 and mouse surrogate mXTX301. HNSTD: highest non-severely toxic dose; NHP: non-human primate; PD: pharmacodynamic; Q1W: once every week; TI: therapeutic index; TGI: tumor growth inhibition.

Entered Into Transformational Partnership with Gilead, Designed to Explore Broad Potential of IL-12 Across Solid Tumors

$43.5M

total upfront payments

($30M cash payment +
$13.5M initial equity investment at a premium ($1.97/share)

Up to $604M

additional contingent payments:

- **Includes up to $29M prior to transition fee for up to $11.5M in additional equity investments (1) and a development milestone**
- **$75M transition fee**
- **Up to $500M for additional development, regulatory and sales-based milestones after transition fee**

Tiered royalties:

high single-digits to mid-teens

Gilead received an exclusive global license to develop and commercialize Xilio's tumor-activated IL-12 program, including XTX301

- Xilio responsible for clinical development of XTX301 in ongoing Phase 1 trial through initial planned Phase 2 trial
- Following delivery by Xilio of specified clinical data package for XTX301, Gilead can elect to pay transition fee and transition development and commercialization to Gilead (2)

GILEAD
Creating Possible

xilio THERAPEUTICS

1. Subject to 19.9% ownership cap. In April 2024, Xilio received aggregate gross proceeds of approximately $3.3 million from an additional private placement with Gilead under the stock purchase agreement and is eligible to receive up to approximately $8.2 million in additional gross proceeds from up to two additional equity investments by Gilead.
2. If Gilead elects not to transition responsibilities for development and commercialization, the agreement will automatically terminate.

XTX301 Phase 1

Monotherapy Dose Escalation Initial Data

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XTX301 Monotherapy Phase 1 Dose Escalation: No DLTs Observed Into DL3 (45 µg/kg, ~100x MTD for rhIL-12)

XTX301 Phase 1 Trial Design

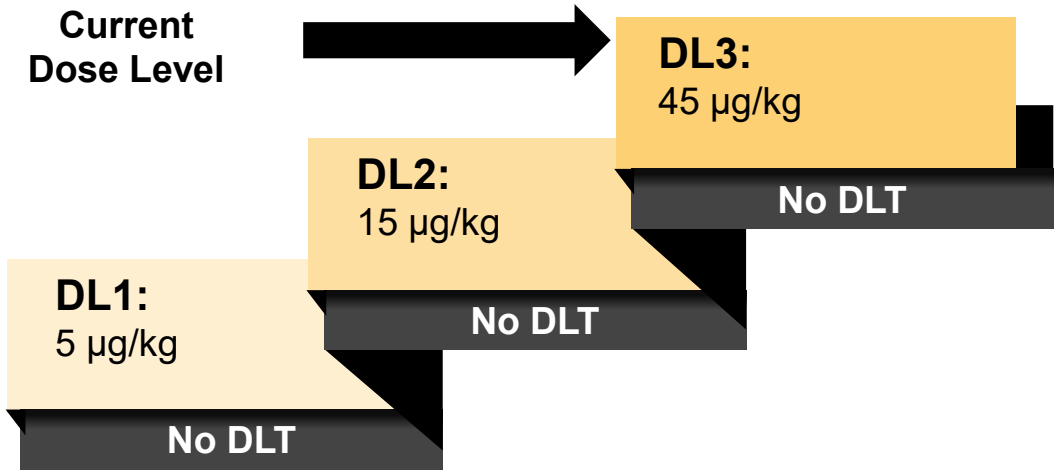
Phase 1A
Monotherapy Dose Escalation

- Advanced solid tumors
- 3+3 design with optional dose expansion (up to 10 patients per cohort)

Phase 1B
Monotherapy PD Cohort

- n = up to 40
- Selected solid tumors

XTX301 Phase 1 Dose Escalation Plan



- XTX301 is administered in the outpatient setting
- DL3 (45 ug/kg) equivalent to ~100x MTD for rhIL-12
- Generally well-tolerated into DL3
- No DLTs reported through data cutoff date

Data cutoff date: January 5, 2024, 9 patients
DL1: dose level 1; DL2: dose level 2; DL3: dose level 3; DLT: dose limiting toxicity; MTD: maximum tolerated dose; PK: pharmacokinetic; rHIL: recombinant human Interleukin 12

XTX301 Phase 1 Data (Safety and PK/PD) Anticipated in Q4 2024

- Demonstrated dose-dependent anti-tumor activity without significant body weight loss *in vivo*
- Preferentially activated in tumors vs. plasma *in vivo* and patient tumors vs. plasma *ex vivo*
- Phase 1 dose escalation enrollment ongoing, n=9 patients treated to date
  - Starting dose (dose level 1) of 5µg/kg Q3W
  - Current dose (dose level 3) of 45 µg/kg, nearly 100x MTD of rhIL-12
  - Generally well-tolerated, no dose limiting toxicities observed through data cutoff date

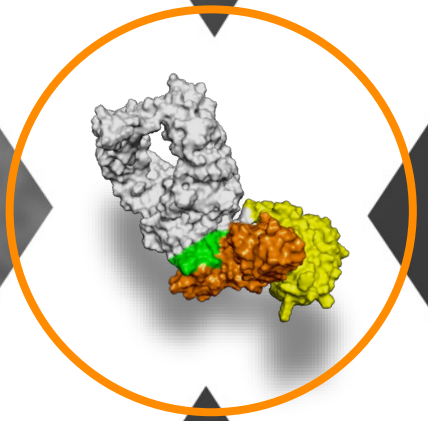
Next Anticipated Milestone

- Phase 1 safety and PK/PD data in Q4 2024

Data cutoff date: January 5, 2024

XTX202

Tumor-Activated, Beta-Gamma IL-2



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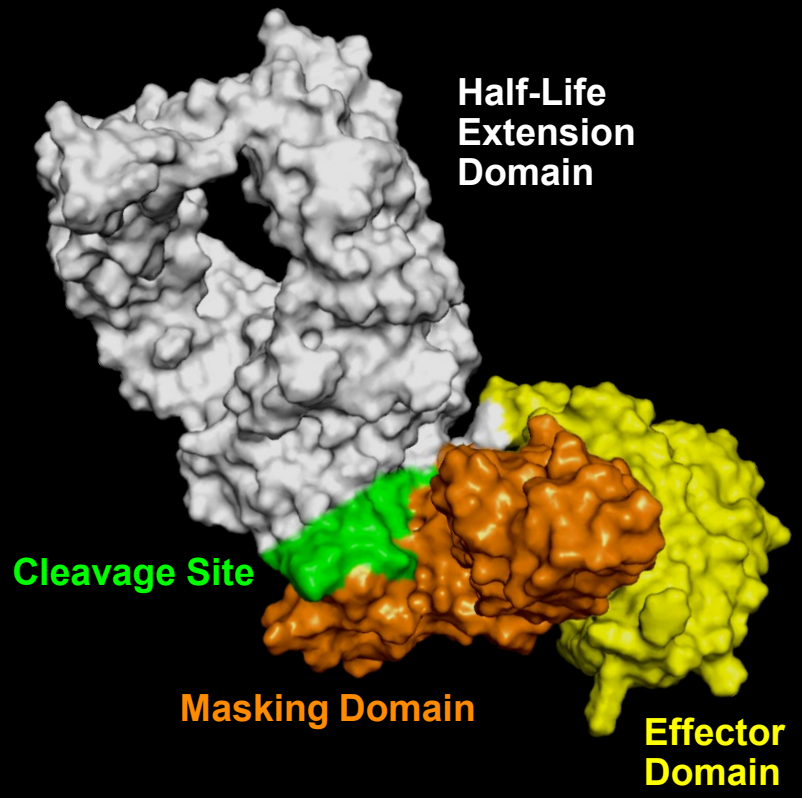
XTX202: Tumor-Activated, Beta-Gamma IL-2 Designed to Overcome the Limitations of Systemically Active Molecules

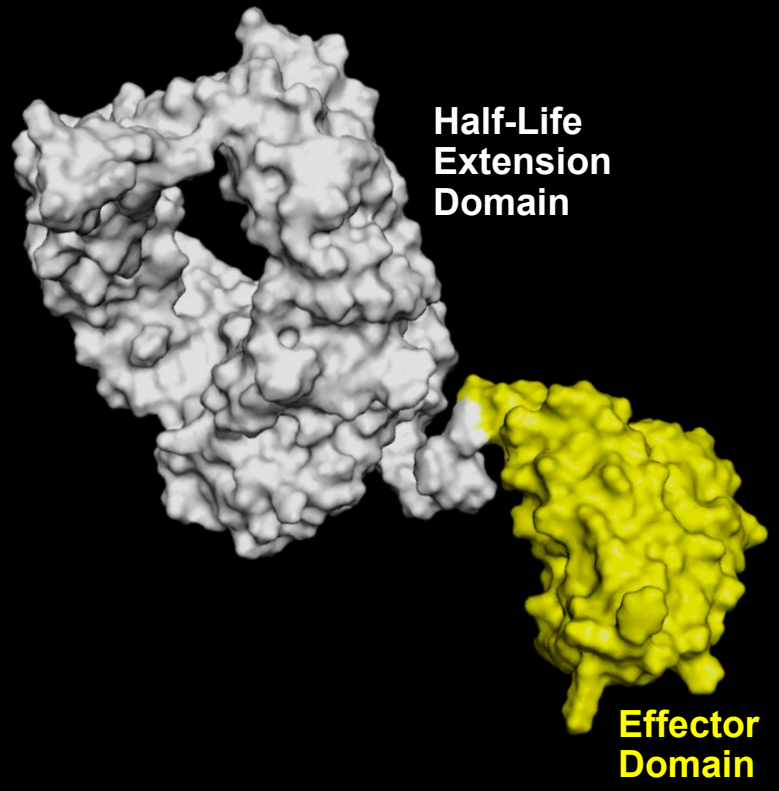
Inactive State



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

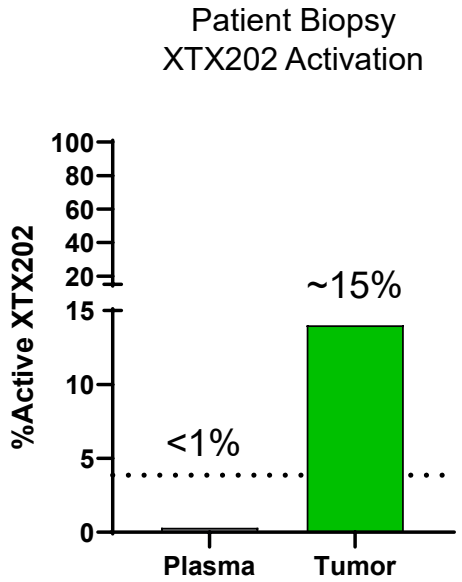


XTX202: Evidence of Tumor-Selective Activation Validating Xilio Platform

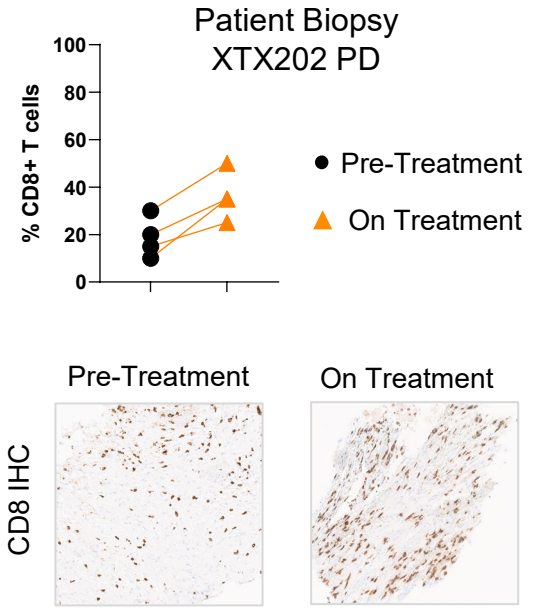
Efficient activation by human tumors demonstrated *ex vivo*

Tumor Type	Confirmed High Activation Efficiency XTX202 (IL-2)
Colon	
Head and Neck	
Prostate	
RCC	
Lung	
Melanoma	
Plasma	

Tumor-selective activation observed in clinic



Tumor-selective pharmacology consistent with βγIL-2 design

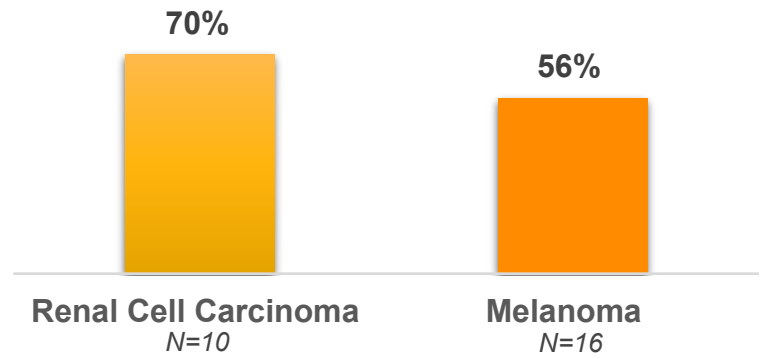


First panel: Activation of XTX202 assessed in human tumor samples ex vivo.
Second panel: Biopsy of 1 patient treated with XTX202 at 2.8 mg/kg dose level, which was the only biopsy available for XTX202 bioanalytical analysis. Percent activated XTX202 in tumor was calculated using raw liquid chromatography / mass spectrometry data. Tumor biopsy specimen was collected cycle 2, day 2. 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. **Third panel**: Intratumoral CD8+ T cell increases observed in four patient biopsies. 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. Top: CD8+ T cells assessed by IHC. Bottom: Example of biopsy from melanoma patient treated with XTX202 at 0.38 mg/kg. CD8+ T cells assessed by Fluorescence-Activated Cell Sorting (FACS) for peripheral blood and Immunohistochemistry (IHC) for tumor. Change in CD8+ cells in tumor takes into account increase in stromal TILs and CD8+ IHC.
NK: natural killer

XTX202 is Combination Ready with Dose Dependent Anti-Tumor Activity Across a Broad Range of Tumor Types and a DCR Rate > 50% at 4 mg/kg

Dose Level [1] (mg/kg)	# Patients Treated (Phase 1 & 2)	# EOT Without Response Assessment	# Ongoing Before 1st Response Assessment	# Response Evaluable	# SD for 9+ Weeks as BOR	DCR (% of evaluable)
<1.4	16	2	0	14	2	14%
1.4	22	1	0	21	8	38%
2.8	13	6	0	7	3	43%
4	44	5	8	31	16	52%
All	**95**	**14**	**8**	**73**	**29**	**40%**

Phase 2 DCR in Evaluable Patients by Tumor Type



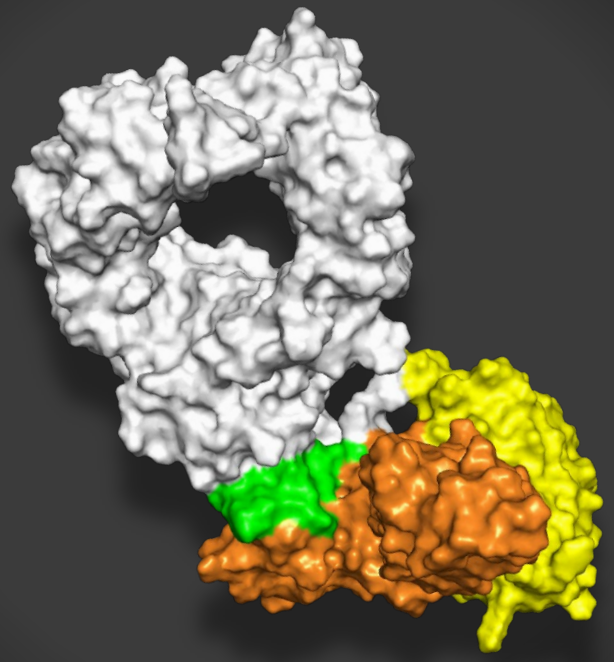
- 37 patients treated in Phase 2 at dose level of 1.4 mg/kg or 4 mg/kg
- Best overall response reported by investigators is stable disease (SD)
- Generally well-tolerated with safety profile consistent with previously report data[2]

Best response: long-term stable disease (> 18 months) in Stage IV MSS CRC patient with liver metastases

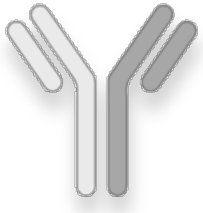
Data cutoff date: March 6, 2024.
1. All dose levels are Q3W outpatient administration. Patients are categorized based on their highest administered dose.
2. Initial Phase 1/2 data reported in November 2023 at Society for Immunotherapy of Cancer (SITC) 38th Annual Meeting.
EOT: end of treatment; SD: stable disease; BOR: best overall response; DCR: disease control rate (defined as SD or PR at 9+ weeks)

Combination with IL-2 Required for Many Modalities to Pursue Maximum Potential and XTX202 Well-Suited for Broad Applications

XTX202's novel design has potential to enable wide range of combination modalities

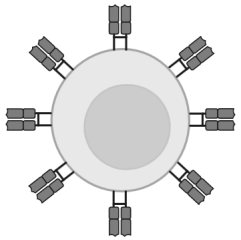


XTX202 (IL-2)



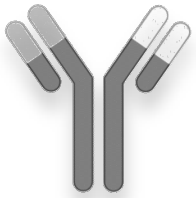
Cell Engagers

- Increased quantity and quality of effector cells induced by XTX202 benefits T cell engagers, as well as NK engagers
- Demonstrated combination benefit preclinically (internal data on file)



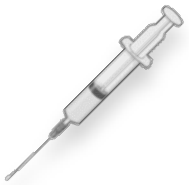
Cell Therapies

- TIL-based therapies require co-administration with IL-2 to engraft and expand T cells
- IL-2 co-administration limited by poor aldesleukin tolerability[1]



Checkpoint Inhibitors

- Preclinical data supportive of IL-2 combination with checkpoint inhibitors including CTLA-4[2,3]



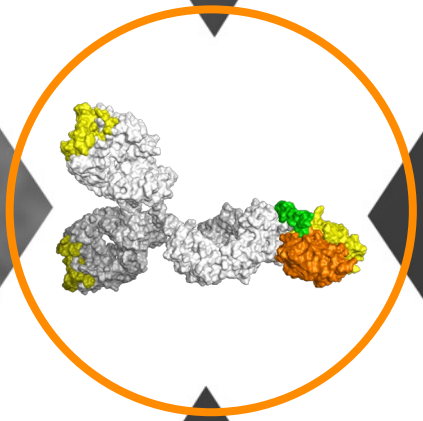
Cancer Vaccines

- IL-2 addition key to vaccination regimen enabled eradication of large tumors in preclinical studies[4]

1.Chesney and Lewis, JITC, 2022
2. Broucek et al., JITC, 2013
3. Caudana et al., Cancer Immunology Research, 2019
4. Moynihan et al., Nature Medicine, 2016

XTX501

PD1/IL2 bispecific



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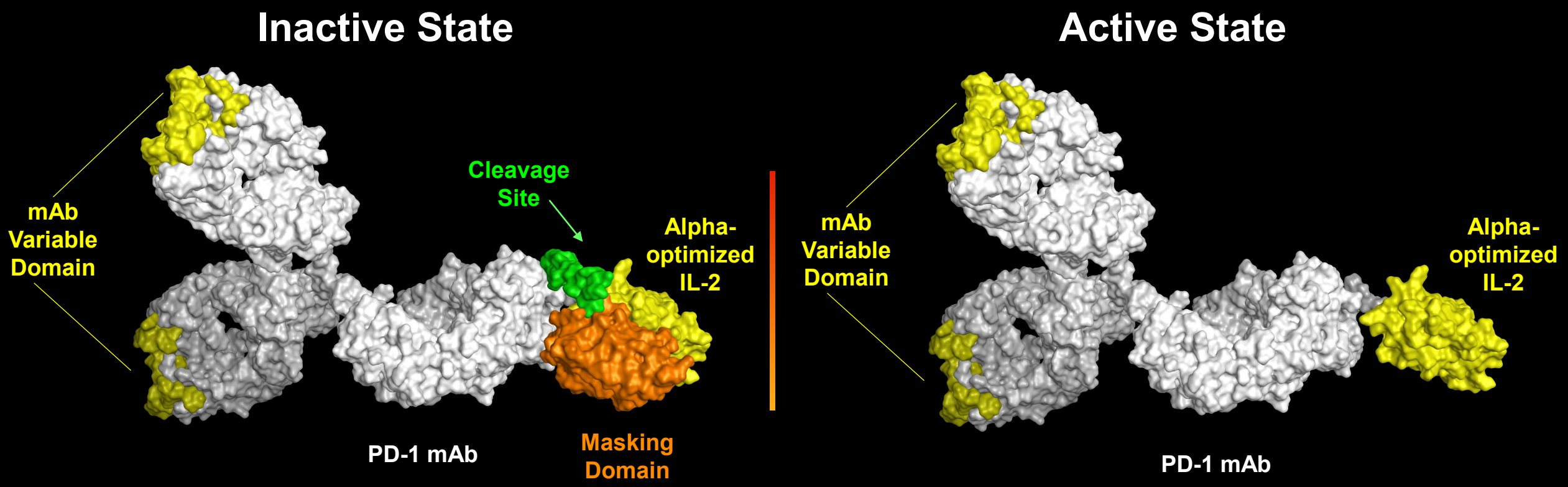
XTX501: Xilio's Clinically Validated Technology Extended to Create Tumor-Activated PD1/IL2 Bispecific



- Affinity-tuned, VHH-based mask
- Alpha-optimized IL-2
- Non-masked PD1 in Fc-silenced heterodimeric IgG1 backbone
- XTX501 designed to direct IL-2 to PD1+ T cells

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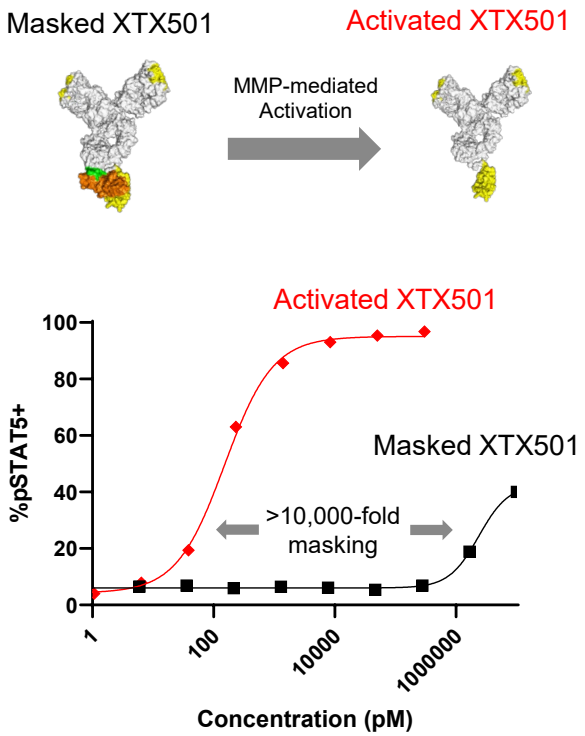
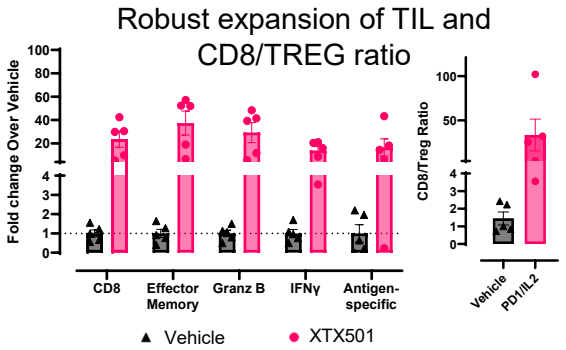
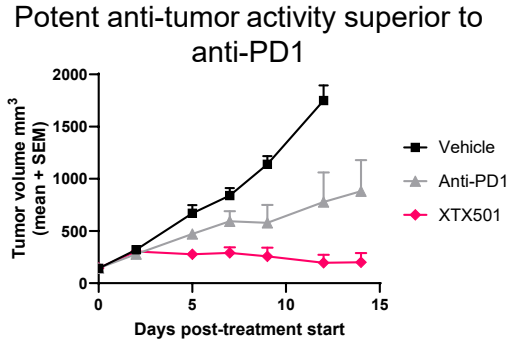
XTX501: Tumor-Activated PD1/IL2 Bispecific Demonstrated Synergistic Anti-Tumor Activity, Antibody-Like PK and Favorable Tolerability in NHP

Effective masking in vitro

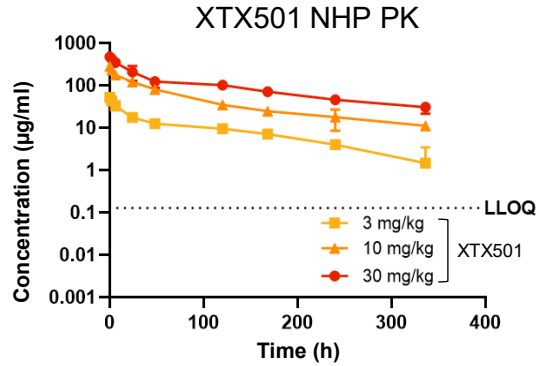


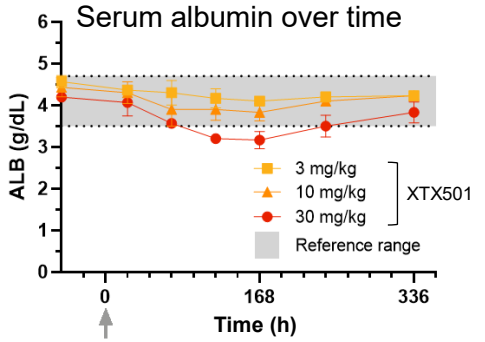
Potent in vivo pharmacology as monotherapy





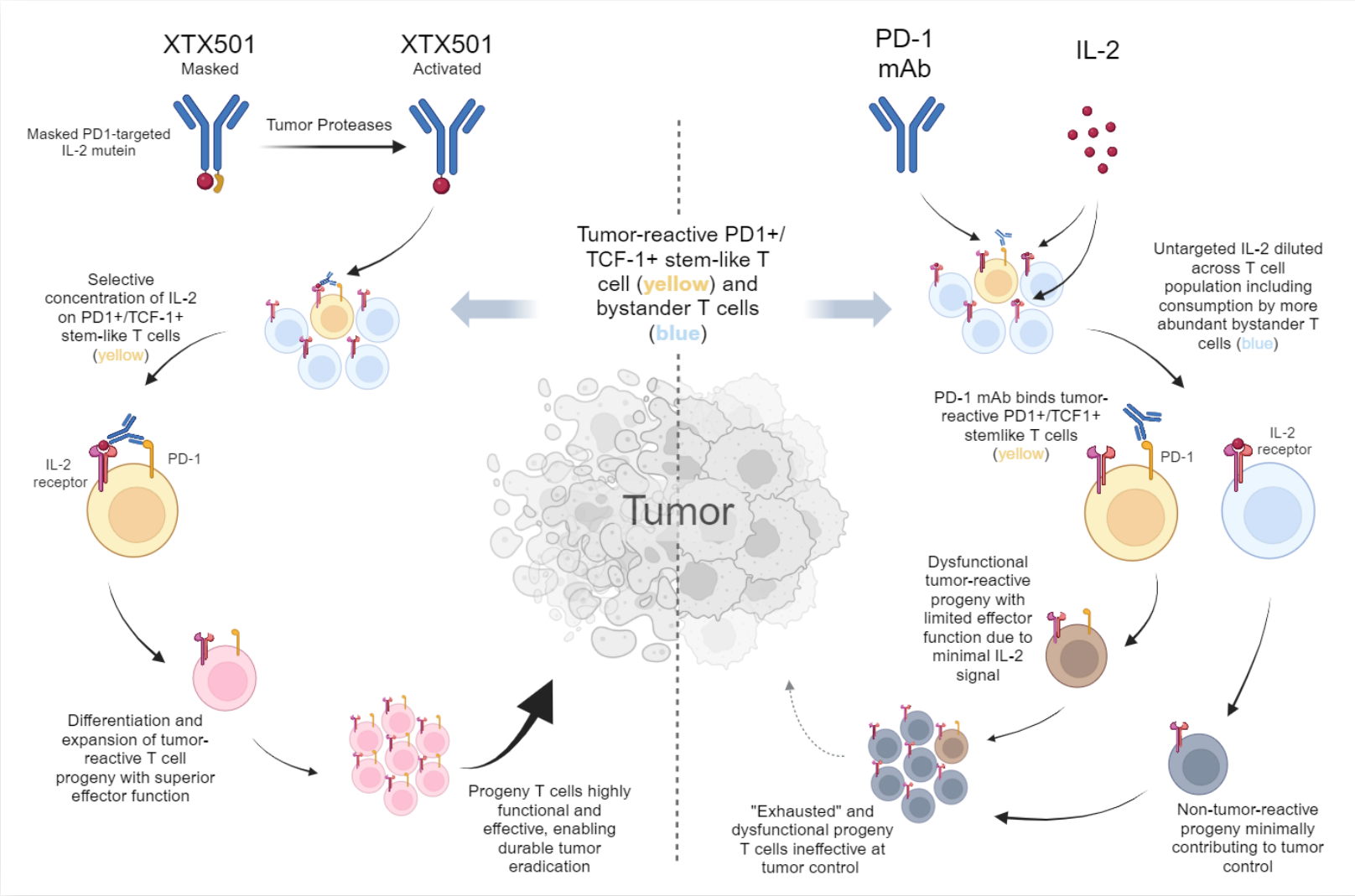
Antibody-like half-life and tolerability in NHP





First Panel: Preactivated PBMCs were incubated with varying concentrations of XTX501 or MMP-activated XTX501 for 12 minutes followed by evaluation for STAT5 phosphorylation. **Second Panel (top):** Female C57BL/6 hPD-1 mice (n=5 in each treatment group) were inoculated with MC38 tumor cells. On day 0, 3 mice received 7.5 mg/kg of XTX501 or vehicle. The percentage of cells for each immune phenotype was calculated as percentage of live CD45+ cells and the ratio of percent cells after XTX501 treatment to vehicle treatment is presented as mean ± SEM. Effector memory (CD44+CD62L-), Antigen-Specific (p15E-Pentamer). **Second Panel (bottom):** In the same mouse model as above, in anti-tumor activity of XTX501 at 7.5 mg/kg Q3Dx2 was compared to vehicle or equimolar doses of PD1 antibody. **Third panel (top):** Concentration over time profile (PK) for XTX501 following single dose administration in non-human primate (NHP). **Third panel (bottom):** Serum albumin measurements over time following single dose administration of XTX501 in NHP. VHH: Variable Heavy domain of Heavy chain. Data generated with analog of XTX501 with minimal variance in amino acid sequence.

XTX501 Designed to Induce a Differentiated, Enhanced Immune Response to Cancer Compared to PD-(L)1 Monotherapy or PD-(L)1 + IL-2 Combination

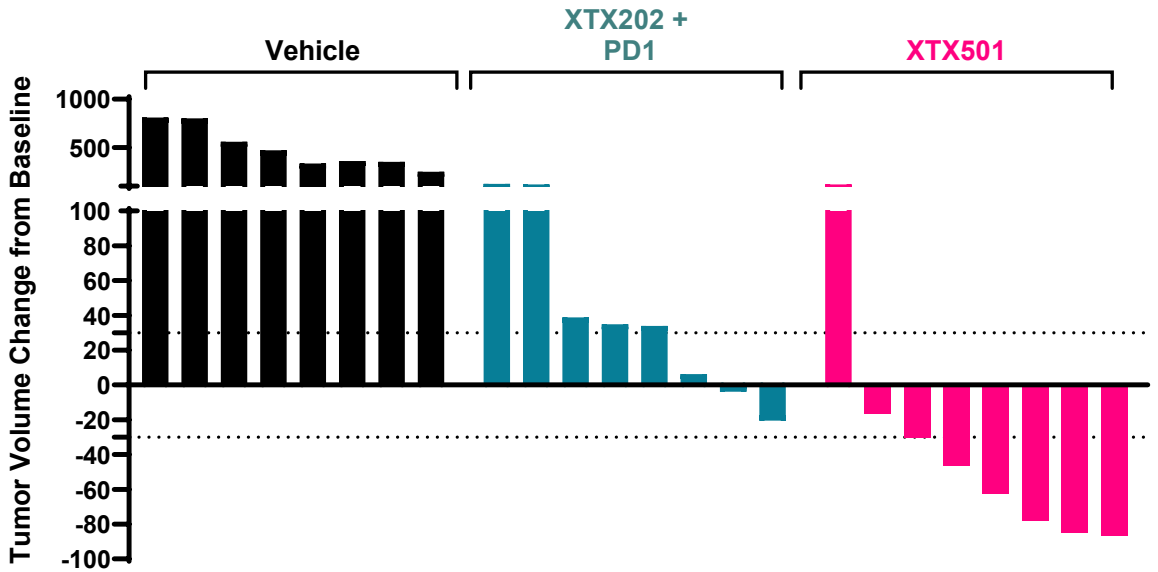


- Targeted delivery of IL-2 to PD1+ cells selectively enhances IL-2 signaling on tumor-reactive, stem-like T cells
- Drives unique differentiation program in progeny effector T cells endowing them with superior effector function and anti-tumor activity
- Not achievable with PD-(L)1 monotherapy or IL-2 combo since no concurrent selective targeting of tumor-reactive cells

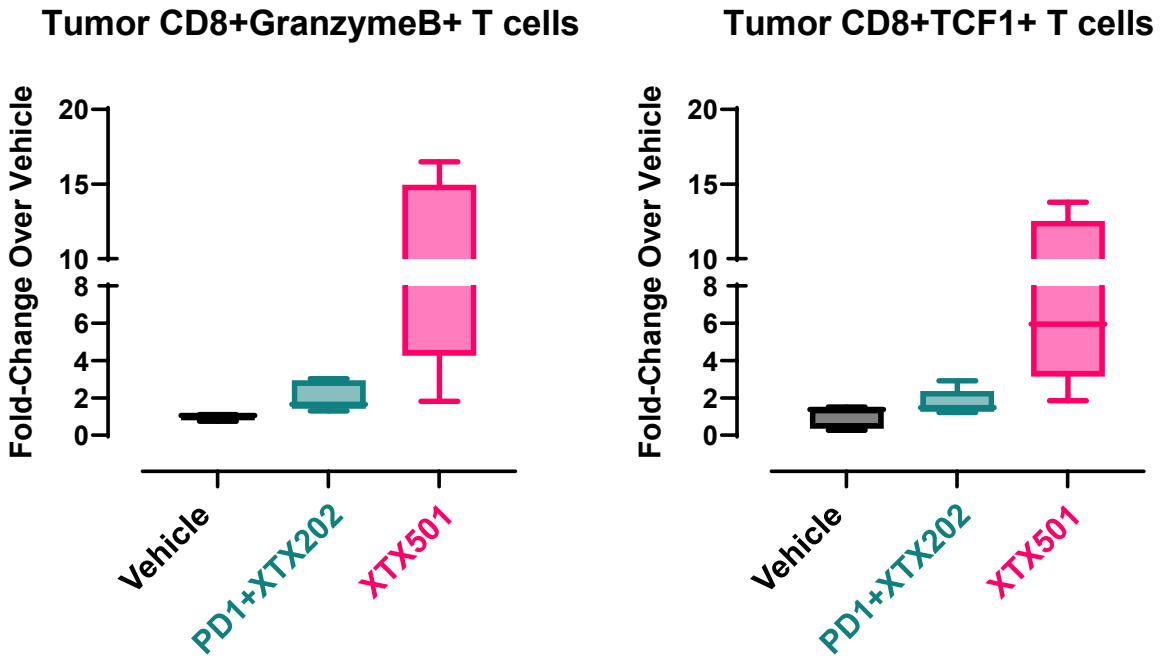
Figure adapted from Deak et al., OncoImmunology, 2023. Figure generated using BioRender.com.

XTX501 Demonstrated Differentiated Pharmacology vs PD1 or PD1+XTX202 Indicative of Enhanced Anti-Tumor Immunity

Robust Preclinical Monotherapy Activity Beyond XTX202 + PD1 Combination

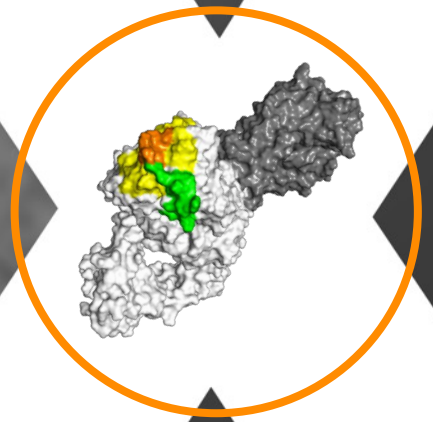


XTX501 Increased Intra-tumoral Cytotoxic and TCF1+ Stem-like T cells



Left panel: Female C57BL/6 hPD-1 mice (n=8 in each treatment group) were inoculated with MB49 tumor cells. On day 0, 5 mice received vehicle or equimolar doses of anti-PD1 antibody (pembrolizumab) plus XTX202 (Masked βγIL-2), or XTX501. Tumor volume change on day 12 post treatment relative to baseline is shown as a waterfall plot. **Right panel:** Female C57BL/6 hPD-1 mice (n=5 in each treatment group)) were inoculated with MB49 tumor cells. On day 0, 5 mice received vehicle or equimolar doses of anti-PD1 antibody (pembrolizumab) plus XTX202 (Masked βγIL-2), or XTX501. Tumors were harvested on day 7 post initial treatment and tumor infiltrating lymphocytes were phenotyped using flow cytometry. Fold-over mean vehicle is shown for the treatment arms for CD8+/GranzymeB positive and CD8+/TCF1+ T cells. Data generated with analog of XTX501 with minimal variance in amino acid sequence.

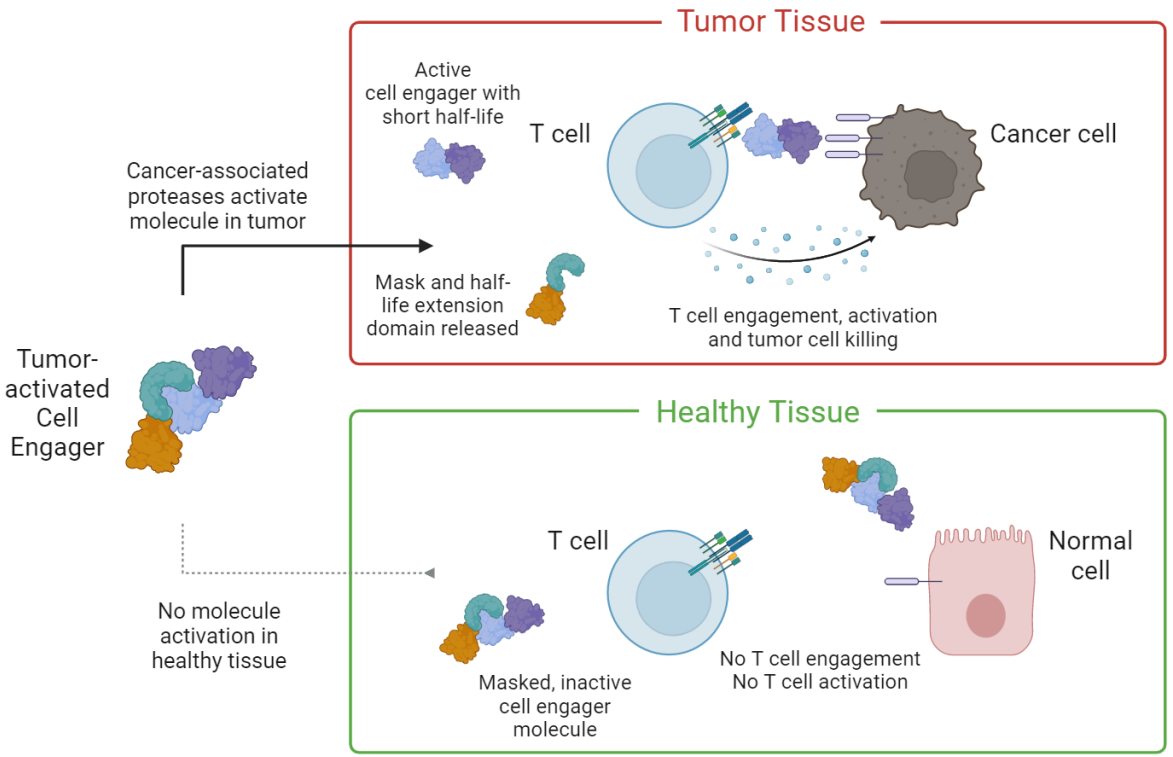
Cell Engager Programs



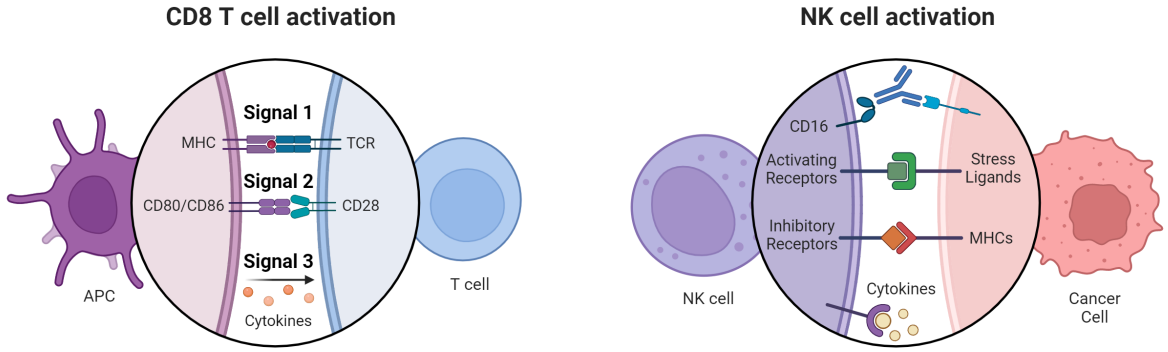
x·ilio THERAPEUTICS®

Xilio is Developing Tumor-Activated Cell Engagers Built on Our Validated Masking Approach and Conditional Half-Life Optimization

Advanced Tumor-Activated Cell EngageRs (ATACRs)



Selective Effector-Enhanced Cell EngageRs (SEECRs)

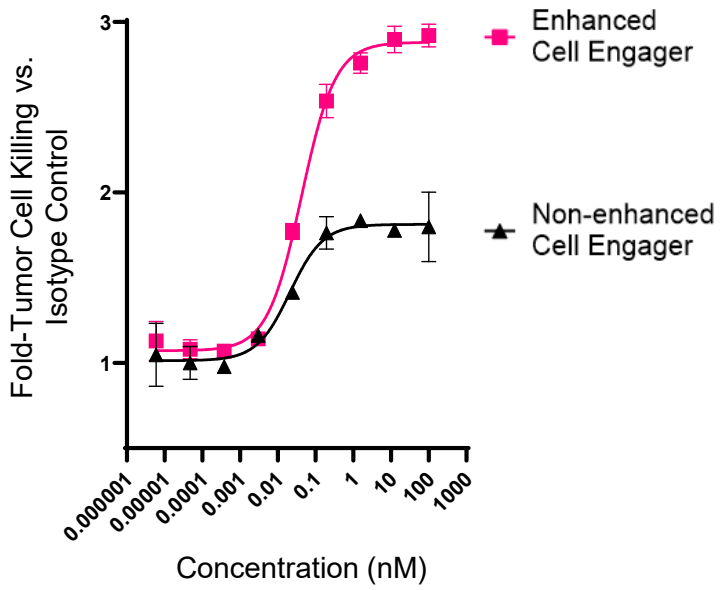


- Designed to provide multiple stimulatory signals in a tumor-selective manner
- Uniquely enabled by Xilio's masking approach, keeping individual components masked until activated in the tumor microenvironment

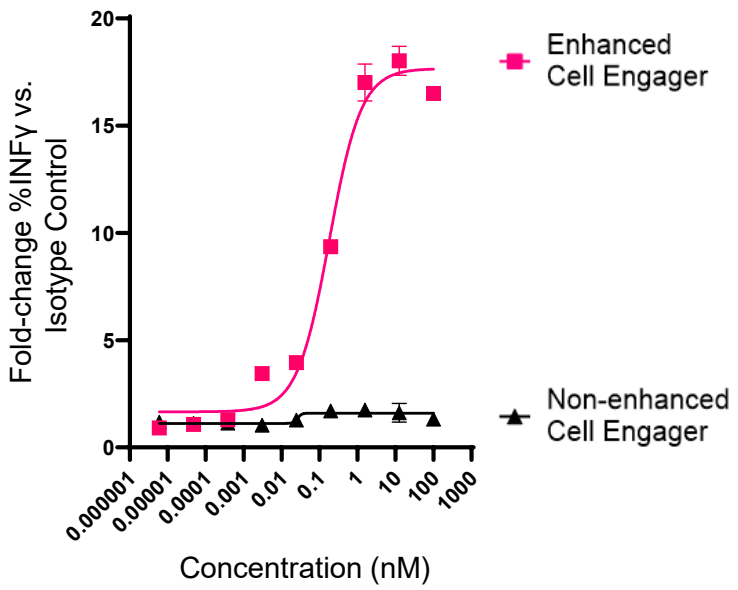
Illustrations generated using Biorender.com

SEECR Format Demonstrated Enhanced Functionality Compared to Established Cell Engager Format

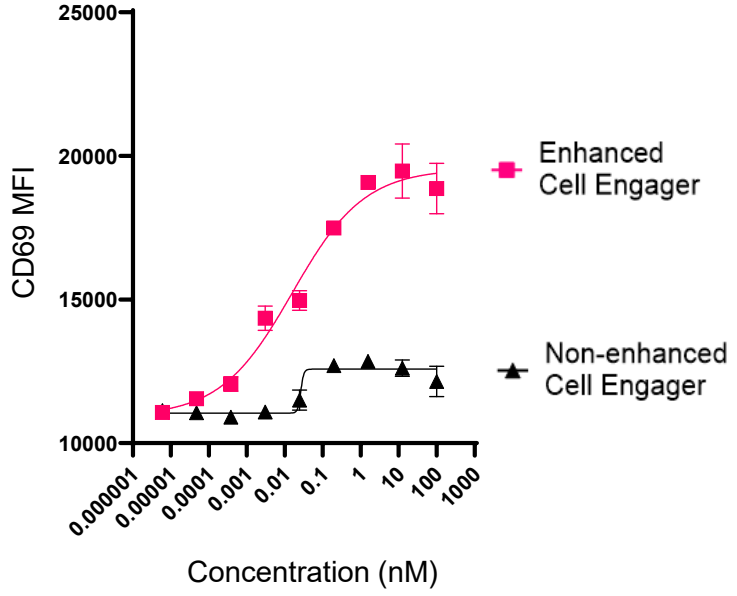
Enhanced Tumor Cell Killing



Potent IFNγ Induction



Increased Expression of CD69 Activation Marker



Co-culture assay using human primary immune cells and luciferized A375 cancer cells. Tumor cell killing was assessed by luciferase readout. Interferon gamma (IFNγ) readout and CD69 mean fluorescence intensity (MFI) were determinedby by flow cytometry.

Positioned for Multiple Anticipated Key Clinical Milestones in 2H 2024
Anticipate Cash Runway Into Q2 2025

XTX301 (IL-12)
Announced Partnership with Gilead
Exclusive global license for IL-12 program

XTX202 (IL-2)
Reported Additional Phase 2 Data [1]
Plan to explore strategic opportunities to continue to develop XTX202 in combinations

XTX501 (PD-1/IL2 bispecific)
Preclinical Poster Presentation
Presented data at AACR demonstrating initial preclinical proof-of-concept

XTX101 (anti-CTLA-4) [2]
RP2D in Combination Dose Escalation
Plan to select RP2D for XTX101 + atezolizumab

Initiate Phase 2 Combination Trial
Plan to initiate Phase 2 trial for XTX101 + atezolizumab in MSS CRC

XTX101 (anti-CTLA-4) [2]
Report Initial Phase 2 Combination Data
Plan to report initial Phase 2 data for XTX101 + atezolizumab in ~20 patients with MSS CRC

XTX301 (IL-12)
Report Phase 1 Data
Plan to report Phase 1 safety and PK/PD data for XTX301 in patients with advanced solid tumors

1. In March 2024, announced plans to discontinue further investment in XTX202 as a monotherapy.
2. Evaluating XTX101 in combination with atezolizumab (Tecentriq®) under co-funded clinical collaboration with Roche in Phase 1 combination dose escalation trial and planned Phase 2 combination trial in MSS CRC.

Q1 2024 Financial Results
Anticipate Cash Runway Into Q2 2025

Balance Sheet

	March 31, 2024 (1)	December 31, 2023
Cash and Cash Equivalents	$34.0M	$44.7M

Received ~$44.6M in additional gross proceeds in April 2024 (2)

Statement of Operations

	Three Months Ended March 31	
	2024 (1)	2023 (1)
Research & Development Expenses	$10.4M	$16.1M
General & Administrative Expenses	$6.1M	$7.4M
Net Loss	$(17.2M)	$(22.6M)

1. Unaudited
2. Consists of $30.0M upfront payment under license agreement with Gilead and ~$14.6M in gross proceeds from private placements with certain existing investors and Gilead, which closed in April 2024.

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