Vilastobart (anti-CTLA-4) in MSS mCRC Patients with High Plasma TMB

November 10, 2025

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Today's Agenda

René Russo, Pharm.D.
President and Chief Executive Officer

Katarina Luptakova, M.D.
Chief Medical Officer

Chris Frankenfield
Chief Financial and Operating Officer

Aparna Parikh, M.D.
Associate Professor of Medicine, Harvard Medical School
Program Director, GI Medical Oncology, Colorectal, Anal, and Neuroendocrine; Director of the MGB Global Cancer Care Program Mass General Brigham Cancer Institute, Boston, MA

Diwakar Davar, M.D.
Associate Professor of Medicine
Clinical Director of the Melanoma Program and Medical Oncologist/Hematologist
UPMC Hillman Cancer Center, Pittsburgh, PA

Introduction
René Russo, Pharm.D.

Vilastobart Data in Patients with MSS mCRC and High Plasma TMB
Katarina Luptakova, M.D.

Clinical Perspectives on Plasma TMB Data and Opportunity in MSS mCRC
Aparna Parikh, M.D. and Diwakar Davar, M.D.

Concluding Remarks
Chris Frankenfield

Q&A
Management, Dr. Parikh, and Dr. Davar

Introduction

René Russo, Pharm.D.

President and Chief Executive Officer

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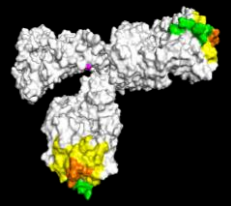
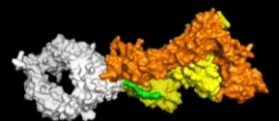
Xilio's Clinically-Validated Platform Technology is Being Applied Across Diverse Mechanisms and Architectures



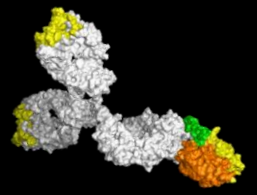
Antibodies

Vilastobart
Tumor-activated
Fc-enhanced anti-CTLA-4



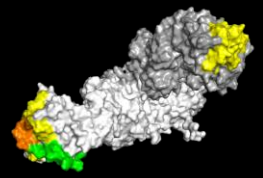
Cytokines

Efarindodekin Alfa (XTX301)
Tumor-activated IL-12



Bispecifics

XTX501
Bispecific PD-1 / masked IL-2



T Cell Engagers

Masked T Cell Engagers
PSMA, CLDN18.2, STEAP1
and AbbVie program

Clinically Validated Platform Technology and Capabilities

- ✓ Proprietary masking libraries and custom computational design workflows
- ✓ Clinically validated protease cleavage elements showing tumor-selective activation of molecules (~300 patients to date across clinical programs)
- ✓ Proprietary preclinical and clinical translational models
- ✓ Highly developable architectures with low immunogenicity in clinic and excellent stability

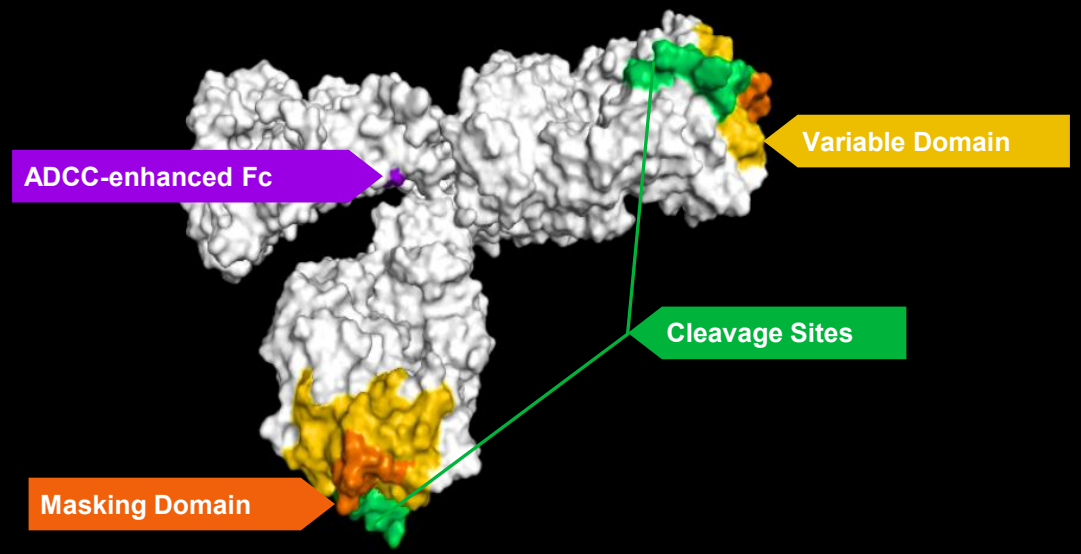
Top-Tier Pharma Partnerships and Collaborations

Roche	*Co-funding plus clinical supply for Phase 1/2 trial of vilastobart in combination with atezolizumab*
GILEAD	*Option to license IL-12*
abbvie	*Multi-program collaboration and option to license masked cell engagers*

PSMA: prostate-specific membrane antigen; CLDN18.2: claudin 18.2; STEAP1: six-transmembrane epithelial antigen of prostate 1

Vilastobart's Differentiated Clinical Activity and Safety Profile in Combination Supports Significant Opportunity in MSS CRC and a Range of Other Tumor Types

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



Inactive (Masked) State

High affinity binding, 10x potency of ipilimumab in preclinical studies [1]

Fc mutations for enhanced effector function (ADCC), improved T cell priming and Treg depletion

- ✓ **Phase 1 monotherapy activity and demonstrated tumor-selective activation** with >70% activated molecule in tumor and <15% activated molecule in periphery
- ✓ **26% ORR** in Phase 2 for combination of vilastobart and atezolizumab in **MSS mCRC without liver metastases**
  - **Heavily pre-treated patients** (80% of patients 3L+)
  - **Deep and durable responses**
- ✓ **Differentiated safety and tolerability profile** as a monotherapy and in combination in Phase 1/2, consistent with tumor-activated design
- ✓ **Low incidence of colitis and other imAEs**, which have limited the potential for administration of other anti-CTLA-4 agents in combination

Data cutoff date: May 12, 2025
1. Ipilimumab analog used for preclinical studies.
3L: third-line; ADCC: antibody-dependent cell-mediated cytotoxicity; AE: adverse event; imAE: immune-mediated adverse event; mCRC: metastatic colorectal cancer; MSS: microsatellite stable; ORR: overall response rate; Treg: regulatory T cells

Presented in poster presentation at ASCO on May 31, 2025

Approved I-O Therapies Have Minimal Efficacy in MSS mCRC, While Next Generation anti-CTLA-4 Combinations Show Promising Clinical Efficacy

Incidence of Colon Cancer is Increasing; Nearly All Colon Cancer is MSS CRC

- ~1.9M new CRC cases globally per yr.
- CRC is currently 2nd in cancer-related deaths in the US
- By 2028, CRC is projected to be the leading cause of cancer-related deaths in men and women <50 yrs. old in the US
- ~95% of mCRC patients are MSS

Approved Therapies Have Minimal Efficacy in MSS mCRC

In patients with MSS mCRC:

- Standard of care in 3L+ provides minimal benefit (1-6% ORR) (1)
- Immune checkpoint inhibitors approved in MSI-H CRC have no meaningful efficacy in MSS mCRC (0-3% ORR) (2)
- Atezolizumab (PD-1) monotherapy demonstrated no meaningful efficacy in MSS mCRC (2% ORR) (3)

0-6% ORR

Next Generation anti-CTLA-4 Agents in Development Show Promising Clinical Efficacy in MSS mCRC

In patients with MSS mCRC without liver metastases:

Program	ORR	Discontinuation due to AEs
Vilastobart Masked, Fc-enhanced anti-CTLA-4 (4)	**26%**	**5%**
Bot/Bal Non-masked, Fc-enhanced anti-CTLA-4 (5)	8-19%	Up to ~30%
Muzastotug Masked anti-CTLA-4 (6)	17-29%	Up to ~10%

26% ORR

1. Current standard of care for approved therapies includes regorafenib, fruquintinib, lonsurf, lonsurf + avastin. 2. Sahin et al, Immunotherapy for Microsatellite Stable Colorectal Cancers: Challenges and Novel Therapeutic Avenue. Am Soc Clin Oncol Educ Book. 2022: Apr:42:1-12. 3. Eng et al, Lancet Oncol. 2019 Jun;20(6):849-861. 4. Data presented in poster presentation at ASCO on May 31, 2025. Data cutoff date: May 12, 2025. 5. Phase 2 response data and Phase 1 safety data reported by Agenus Inc. for the combination of botensilimab (anti-CTLA-4) and balstilimab (PD-1). 6. Phase 2 data reported by Adagene Inc. for the combination of muzastotug (anti-CTLA-4) and pembrolizumab (PD-1).
I-O: immuno-oncology; MSI-H: microsatellite instability-high

Plasma-Based TMB Assays Provide Meaningful Opportunity to Enrich for Response in Patients With MSS mCRC

Tissue-Based TMB Assays

- Historical data for tissue-based TMB assays have suggested <10% of patients with MSS mCRC have high TMB tumors (≥10 mutations/Mb)
- TMB has demonstrated potential as a biomarker predictive of response to immunotherapy, but tissue-based TMB has not demonstrated predictive utility in MSS mCRC

Plasma-Based TMB Assays

- Real-word plasma-based TMB data from Guardant indicate ~55% of patients with MSS mCRC have high plasma TMB tumors (>10 mutations/Mb) (1)
- New Phase 2 data for vilastobart support potential for plasma-based TMB as a biomarker predictive of response in MSS mCRC

1. ~55% of non-MSI-H CRC patients were plasma TMB high (>10 mut/Mb) based on an analysis of the GuardantINFORM real-world clinical-genomic database in ~8,000 patients who received the Guardant360 Liquid (Infinity) assay and who had non-MSI-H disease and a reportable TMB result.

Mb: megabase; TMB: tumor mutational burden

Plasma TMB Data for Vilastobart (anti-CTLA-4) in MSS mCRC

Presented in Late-Breaking Presentation
at SITC Annual Conference on November 7, 2025

Katarina Luptakova, M.D.
Chief Medical Officer

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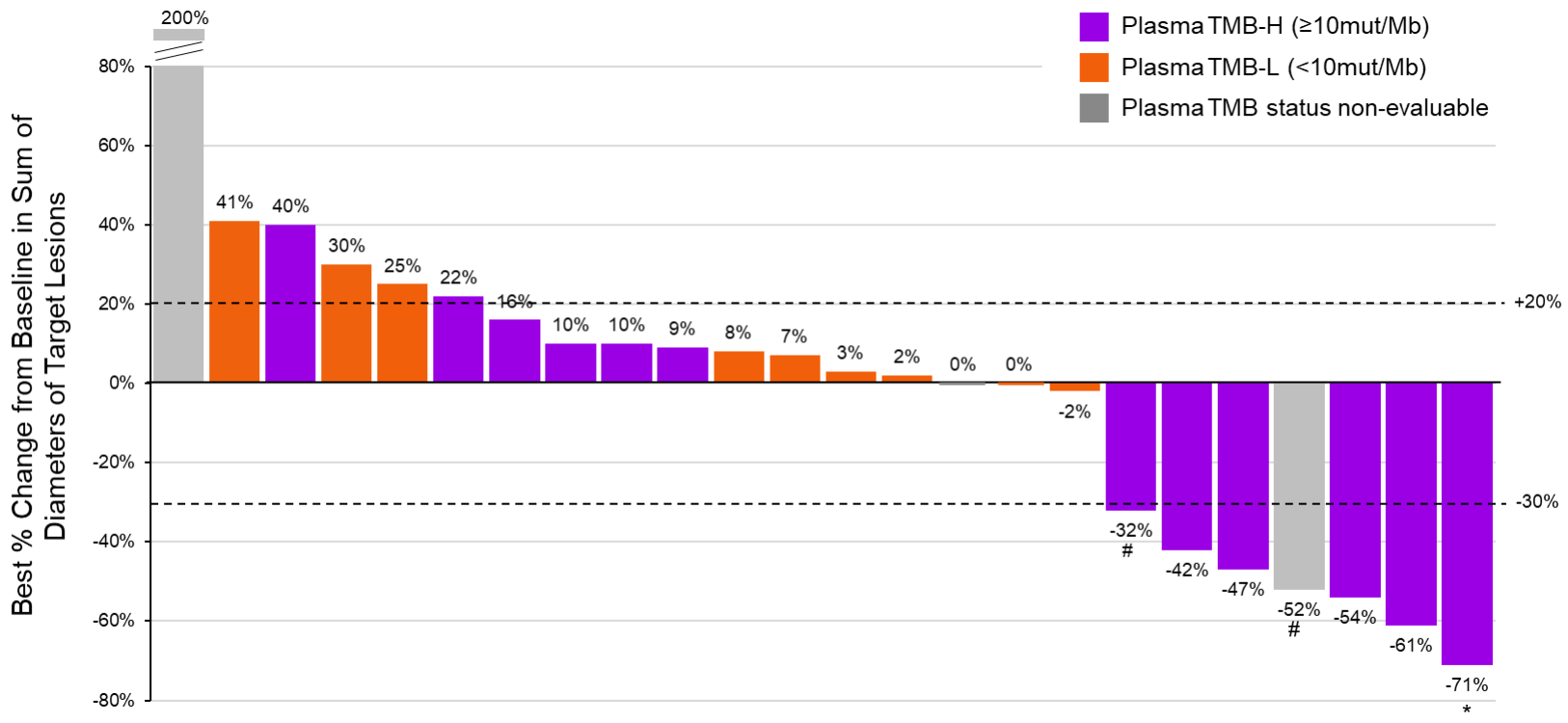
40% ORR for Combination of Vilastobart and Atezolizumab in Patients with MSS mCRC Without Liver Metastases and High Plasma TMB



	MSS mCRC Without Liver Metastases		
	Total n (%) (n=27)	PR (n=7)	Non-PR (n=20)
Plasma TMB-evaluable	24	6	18
High Plasma TMB-H *(≥10 mut/Mb)*	15 (63%)	6	9
Low Plasma TMB *(<10 mut/Mb)*	9 (38%)	0	9
Plasma TMB non-evaluable	3	1	2

- To be eligible to enroll in the Phase 2 trial, patients were required to be MSS based on local assessment (1)
- MSS status for each patient was centrally confirmed using the Guardant-Infinity Liquid Assay to assess baseline plasma samples

- ***63% (n=15) of plasma TMB-evaluable patients had high plasma TMB (≥ 10 mutations/Mb), including all TMB-evaluable responders***
- ***Correlation between plasma TMB status and response was statistically significant (p=0.05)***

Data cutoff date: May 12, 2025. Waterfall plot showing plasma TMB status for all patients with MSS mCRC without liver metastases.
6 confirmed PRs, 2 of which were confirmed after the data cutoff date (#), and 1 unconfirmed PR (*).
1. Patients with MSI-H and deficient mismatch repair (dMMR) tumors were excluded from enrollment in the Phase 2 trial.

Presented in late-breaking presentation at SITC on November 7, 2025

Combination of Vilastobart and Atezolizumab Demonstrated Meaningfully Differentiated Safety and Tolerability Compared to Other Anti-CTLA-4 Agents

TRAEs ≥10% incidence (any Grade) or Grade 3/4 TRAEs with ≥ 5% incidence	All Phase 2 Patients (*n=44*)	
	Any grade n (%)	Grade 3 n (%)
Fatigue	13 (30)	0
Infusion related reaction	10 (23)	2 (5)
related to vilastobart	9 (21)	2 (5)
related to atezolizumab	2 (5)	0
Diarrhea or colitis	9 (20)	2 (5)
Diarrhea	8 (18)	0
Colitis	3 (7)	2 (5)
AST increased	6 (14)	2 (5)
ALT increased	5 (11)	2 (5)
Pruritus	5 (11)	0
Pyrexia	5 (11)	0
WBC decreased	3 (7)	2 (5)

TRAEs are related to vilastobart or atezolizumab

Dose Reduction and Treatment Discontinuation	
Vilastobart dose reduction due to TRAE⁺	1 (2%)
Treatment discontinuation due to TRAE‡	2 (5%)

+ Dose reduction of atezolizumab is not permitted per protocol
‡ Reflects discontinuation of both vilastobart and atezolizumab

- No Grade 5 TRAEs and 2 Grade 4 TRAEs (reversible laboratory abnormalities)
- 3 patients (7%) experienced colitis
- 11 patients (25%) required steroids or other immunosuppression for imAEs

Data cutoff date: May 12, 2025
ALT: alanine aminotransferase; AST: aspartate aminotransferase; TRAE: treatment-related AE; WBC: white blood cell count

Presented in late-breaking presentation at SITC on November 7, 2025

Clinical Perspectives on Plasma TMB Data and Opportunity in MSS mCRC

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Diwakar Davar, M.D.
Associate Professor of Medicine
Clinical Director of the Melanoma Program and Medical Oncologist/Hematologist
UPMC Hillman Cancer Center, Pittsburgh, PA

Significant Opportunity for Vilastobart in Combination with PD-(L)1 and/or PD1-VEGF in Patients with MSS CRC and Other Tumor Types with High Plasma TMB

Promising clinical efficacy in patients with high plasma TMB	• **40% ORR** for vilastobart in combination with atezolizumab in **patients with MSS mCRC without liver metastases and high plasma TMB**, including deep and durable responses
Plasma-based TMB as a biomarker predictive of response	• **Statistically significant correlation** (p=0.05) between **plasma TMB status and response** • **63% of plasma TMB-evaluable patients had high plasma TMB** in Phase 2 trial for vilastobart in combination with atezolizumab, **including all TMB-evaluable responders** • **Real-word data** show **~55% of patients with MSS CRC have high plasma TMB**(1), substantially higher than historically reported with tissue-based TMB assays
Differentiated and well-tolerated safety profile	• **Treatment-related AEs primarily Grade 1 or 2, consistent with the tumor-activated design for vilastobart** • Low discontinuation rate (5%) and only 7% of patients experienced colitis of any grade

Based on the differentiated profile demonstrated by vilastobart as a combination therapy, Xilio is actively seeking a partner to continue to develop vilastobart in combination with PD-(L)1 and/or PD1-VEGF in MSS CRC and other tumor types

Data cutoff date: May 12, 2025. Phase 2 data presented for vilastobart in combination with atezolizumab in late-breaking presentation at SITC on November 7, 2025.
High plasma TMB = ≥10 mutations/Mb

1. ~55% of non-MSI-H CRC patients were plasma TMB high (>10 mut/Mb) based on an analysis of the GuardantINFORM real-world clinical-genomic database in ~8,000 patients who received the Guardant360 Liquid (Infinity) assay and who had non-MSI-H disease and a reportable TMB result.

Additional Data Presented at SITC

Highlighting Breadth and Depth of Xilio's Leadership in Masked Immunotherapies

Chris Frankenfield
Chief Financial and Operating Officer

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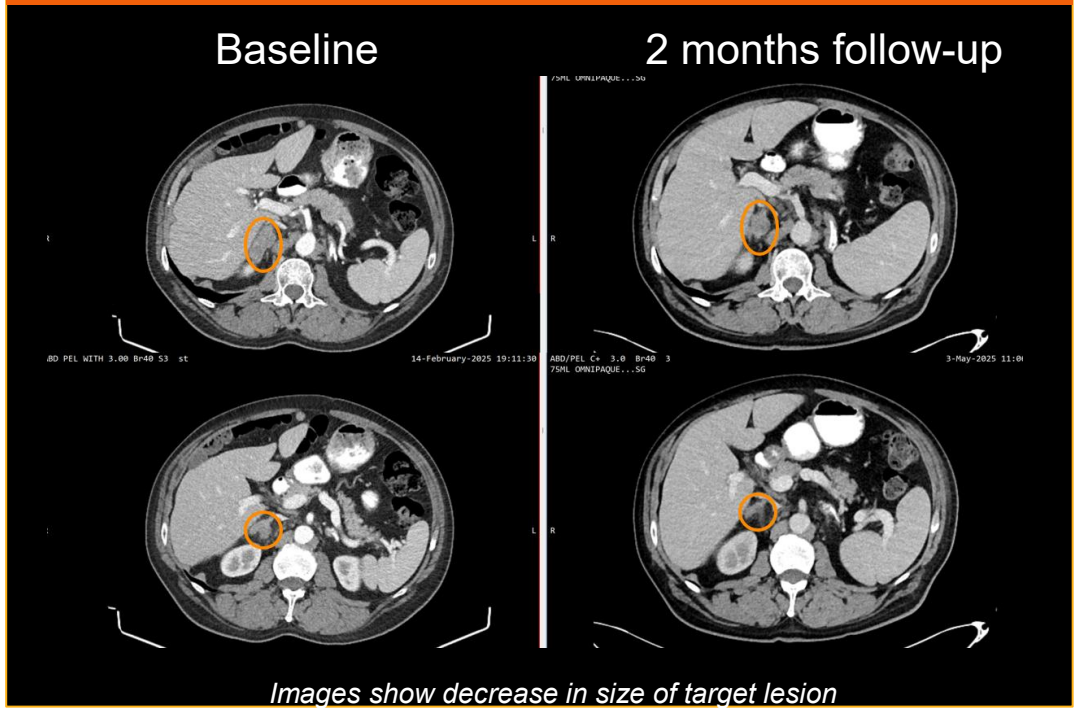
Efarindodekin Alfa (Tumor-Activated IL-12) Demonstrated Promising Clinical Efficacy with Generally Well-Tolerated Safety Profile in Phase 1 in Patients with Advanced Solid Tumors

Promising clinical efficacy	• Two PRs in patients with advanced solid tumors (1 confirmed, 1 unconfirmed) • Translational data demonstrated robust immune cell infiltration and PD-1, PD-L1 upregulation in patient tumors
Sustained dose dependent IFNɣ signaling	• Induced sustained, dose-dependent interferon gamma (IFNɣ) signaling without evidence of tachyphylaxis throughout treatment cycles
Well-tolerated safety profile	• Administered at doses more than 100-fold greater than the MTD of (rh)IL-12 • Generally well-tolerated at dose levels up to RP2D, with treatment-related AEs primarily Grade 1 or 2

66-year-old male with HPV-negative HNSCC

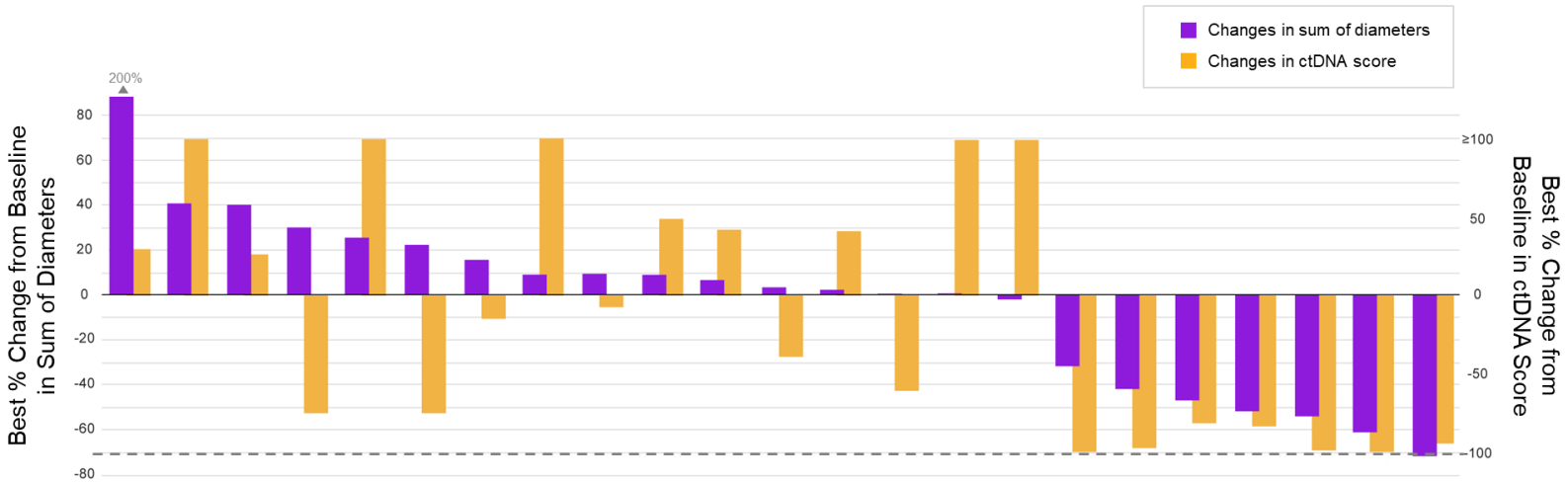


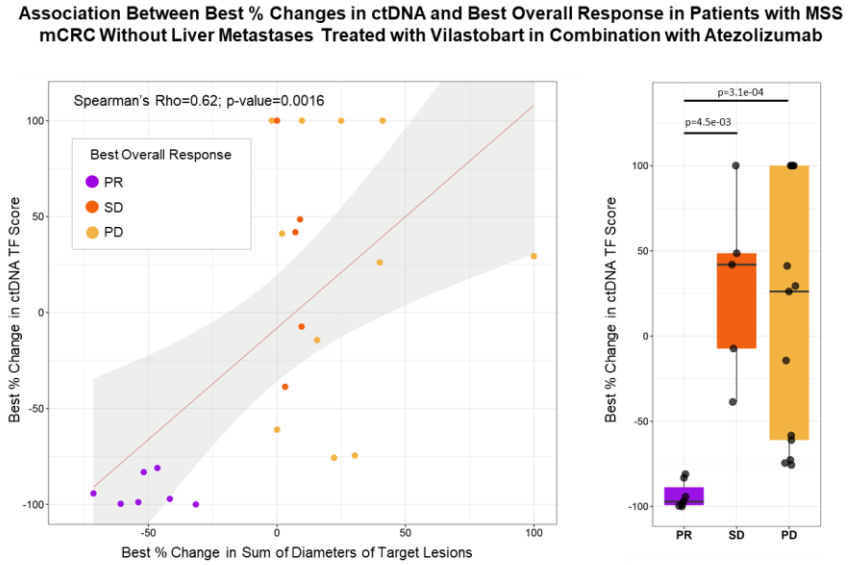
Images show decrease in size of target lesion

Data cutoff date: September 2, 2025.
HPV: human papillomavirus; HNSCC: head and neck squamous cell carcinoma; MTD: maximum tolerated dose; (rh): recombinant human; PR: partial response; RP2D: recommended Phase 2 dose

Presented in poster presentation at SITC on November 7, 2025

Radiographic Responses to Treatment With Combination of Vilastobart and Atezolizumab Were Accompanied by Deep Reductions in ctDNA





- Demonstrated potential for ctDNA as a biomarker predictive of early response to treatment with vilastobart in combination with atezolizumab
- ctDNA reductions were significantly associated with best overall response
- Two patients with endoscopic complete responses (CRs) and reductions in ctDNA to undetectable levels

Data cutoff date: May 12, 2025. In Phase 2, among 27 patients with MSS mCRC without liver metastases, 25 had evaluable ctDNA kinetics and response data for association analysis, and 23 had post-baseline target lesion and ctDNA data for correlation analysis.
Left: Dodged waterfall plot showing best % change from baseline in the sum of diameters of target lesions (left y-axis; purple bars) and best % change from baseline in ctDNA score (right y-axis; yellow bars). Each pair of bars corresponds to the same patient (x-axis).
ctDNA: circulating tumor DNA

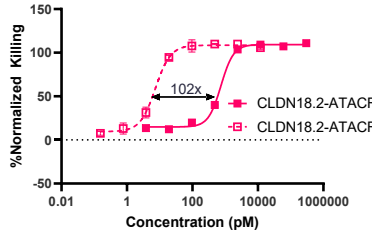
Presented in poster presentation at SITC on November 7, 2025

Potential Best-in-Class Masked T Cell Engager Programs and Platform Technology Drive Potent Anti-Tumor Activity with Favorable Tolerability Across a Diverse Range of Targets

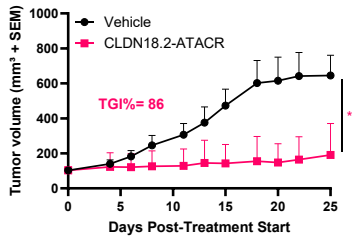
- Xilio's masked T cell engager molecules **demonstrated potent anti-tumor activity with evidence of reduced systemic toxicity** and potential to **significantly expand the therapeutic window** in murine models
- **Incorporation of co-stimulatory signaling in SEECR format enhanced anti-tumor activity** compared with T cell engager molecules that lacked co-stimulation

ATACR

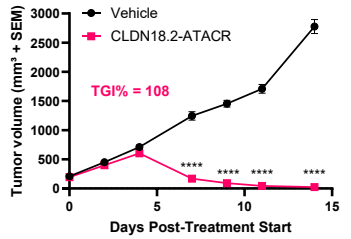
CLDN18.2-ATACR Demonstrated Protease-Dependent Activity in Primary T Cell Assay



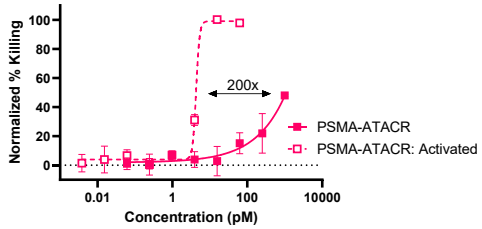
CLDN18.2-ATACR Elicited Significant Anti-Tumor Activity in GSU *In Vivo* Model



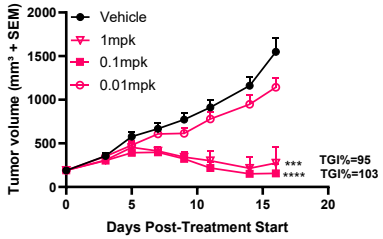
CLDN18.2-ATACR Elicited Significant Anti-Tumor Activity in OE19 *In Vivo* Model



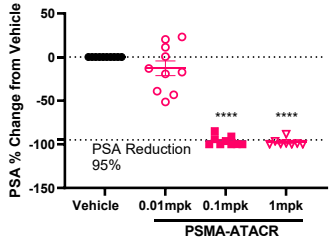
PSMA-ATACR Demonstrated Protease-Dependent Activity in Primary T Cell Assay



PSMA-ATACR Demonstrated Dose-Dependent Anti-Tumor Activity

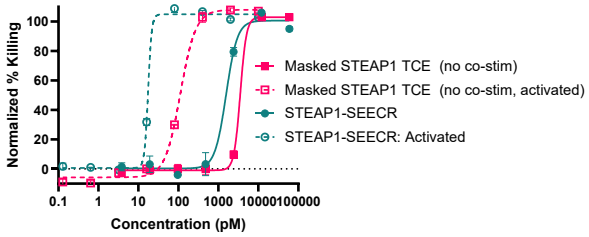


PSMA-ATACR Induced 95% Reduction in Plasma PSA, a Clinically Relevant Biomarker

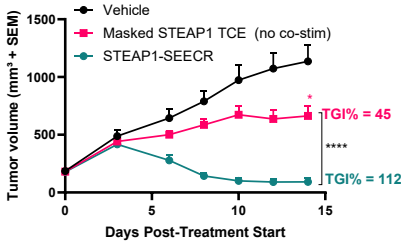


SEECR

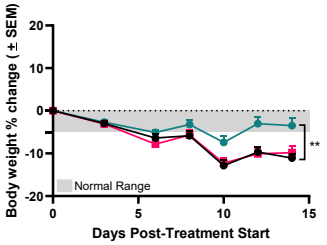
STEAP1-SEECR Confirmed Protease-Dependent Activity in Primary T Cell Assay



STEAP1-SEECR Drove Complete Tumor Regressions *In Vivo*



STEAP1-SEECR Elicited Significant Recovery from Cachexia *In Vivo*



ATACR: advanced tumor-activated cell engager; SEECR: selective effector-enhanced cell engager

Presented in poster presentation at SITC on November 8, 2025

Anticipated Milestones

Milestone	Anticipated Timing
Vilastobart (tumor-activated anti-CTLA-4)	
Report updated Phase 2 data in combination with atezolizumab in metastatic MSS mCRC	1H 2026
XTX301 (tumor-activated IL-12)	
Deliver Phase 1/2 data package for potential opt-in by Gilead (n=40 Phase 2 patients)	Undisclosed
XTX501 (bispecific PD-1 / masked IL-2)	
IND submission	Mid 2026
Masked T cell engager programs	
Nominated development candidate for PSMA	Q3 2025
Nominate development candidate for CLDN18.2	Q4 2025
Nominate development candidate for STEAP1	1H 2026
IND submissions for at least two masked T cell engager programs	2027

Anticipate cash runway into Q1 2027. Estimated cash runway includes $17.5 million development milestone received under Gilead license in Q4 2025 and does not include (i) any potential future contingent payments under AbbVie and Gilead agreements or (ii) up to $100.0 million in additional gross proceeds by 2H 2026 if all common stock warrants issued in connection with June 2025 equity financing are exercised in cash at their initial exercise price of $0.75 per warrant.
IND: investigational new drug application

Q&A

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