

# Phase 1C Combination Data for Vilastobart (XTX101)

*A tumor-activated, Fc-enhanced, high affinity  
binding anti-CTLA-4*

**November 7, 2024**

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# Today's Agenda



**René Russo, Pharm.D.**  
Chief Executive Officer



**Katarina Luptakova, M.D.**  
Chief Medical Officer



**Aparna Parikh, M.D.**  
MGH Cancer Center

## Introduction

René Russo, Pharm.D.

## Unmet Medical Need in Colorectal Cancer

Aparna Parikh, M.D.

## Phase 1C Combination Data for Vilastobart (XTX101)

Katarina Luptakova, M.D.  
Aparna Parikh, M.D.

## Concluding Remarks

René Russo, Pharm.D.

## Q&A

# Introduction

**René Russo, Pharm. D.**

*President and Chief Executive Officer*

# Immuno-Oncology Therapy is the Key to Curative Potential, But Continues to Be Limited by Systemic Toxicity

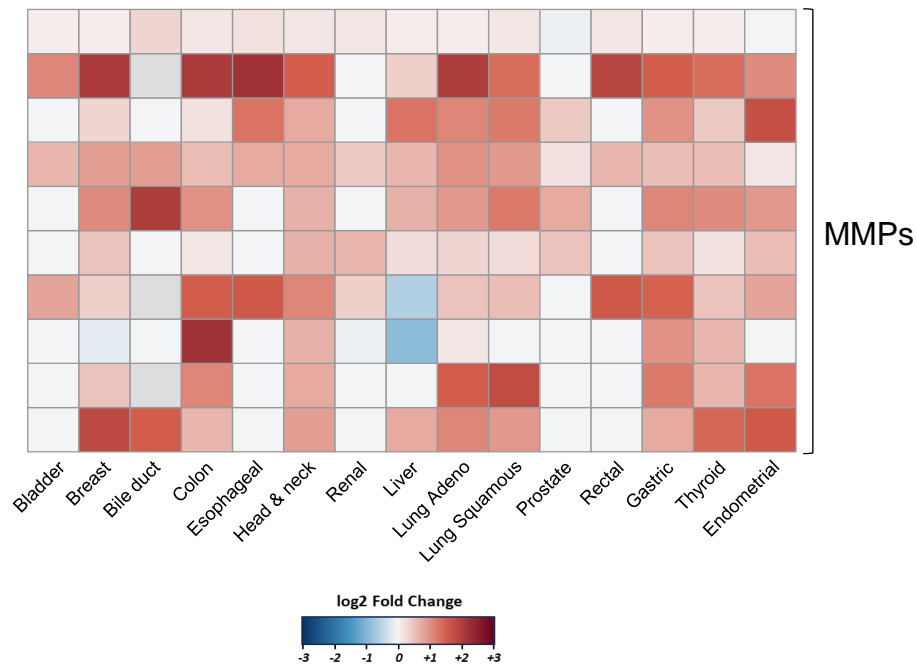
**Xilio** believes the next revolution in I-O therapy will **harness the power of the body's immune system** by **leveraging the dysregulated biology of the tumor against itself**



# Xilio Exploits Dysregulated MMP Activity, a Hallmark of Invasive Cancer Common Across a Wide Range of Solid Tumors, to Activate Molecules in the Tumor

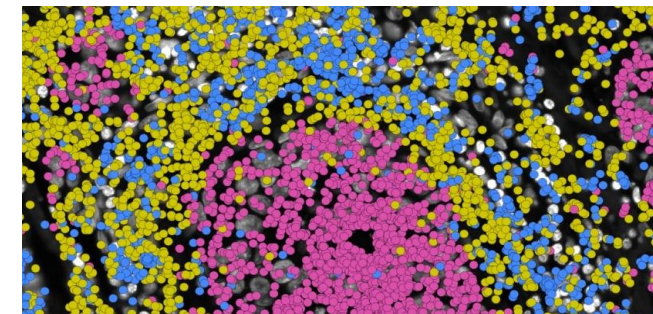
## MMPs are dysregulated broadly across solid tumors

MMP mRNA expression in tumor vs. normal tissue



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

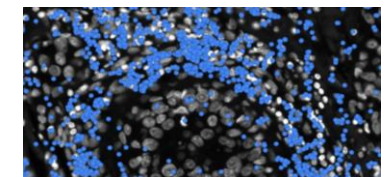
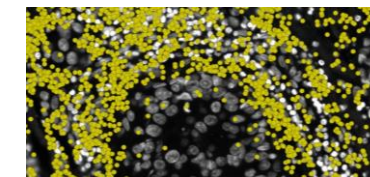
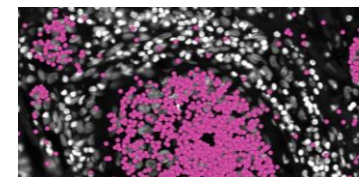
*In situ* mRNA expression in human breast cancer



Tumor cells  
(TROP2)

MMP  
(MMP2)

T cells  
(CD4, CD8A)



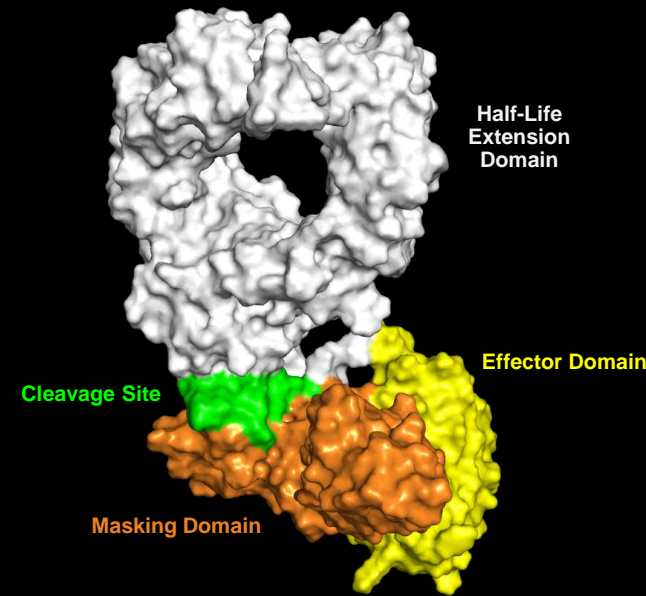
**Left panel:** Heatmap summarizing RNA expression changes of genes encoding for selected MMPs (bottom) in tumor vs. adjacent normal samples from multiple TCGA studies (x-axis). Color intensity tracks with log<sub>2</sub>-transformed fold changes (log<sub>2</sub>FC). Pre-processed TCGA data were obtained 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  
MMP: matrix metalloproteases



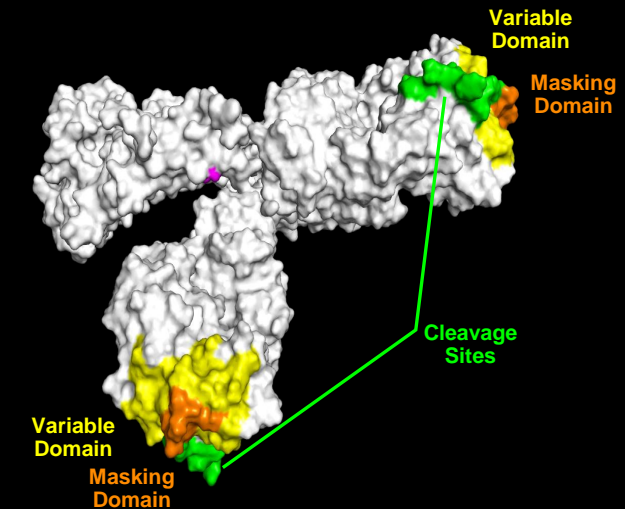
# Xilio's Tumor-Activated Approach Has Been Successfully Applied in the Clinic Across Diverse Molecular Architectures

- Initial clinical validation, with >200 patients enrolled to date across clinical programs
- Molecules designed for tumor-selectivity with a masking domain to block interaction with healthy tissue and cells
- Dysregulated MMPs in the TME activate molecules via the protease cleavage site across a wide range of solid tumors (without the need for biomarkers)
- Bank of >1,000 human solid tumor samples informed design and test molecule activation

## Cytokine Example



## Antibody Example



# Advancing Pipeline of Clinical and Preclinical Tumor-Activated Molecules

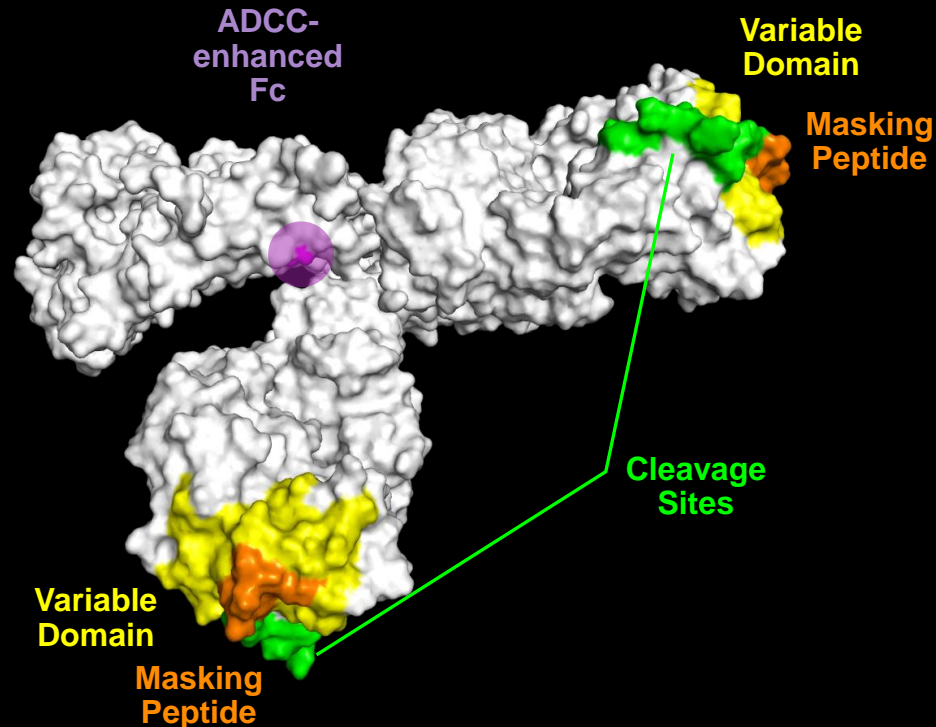
Program	Tumor Types	Mechanism of Action	Discovery	IND-Enabling	Phase 1	Phase 2	Phase 3	Partnerships
Vilastobart (XTX101) in combination with atezolizumab <sup>(1)</sup>	Metastatic MSS CRC	anti-CTLA-4 + PD-L1						Clinical collaboration with Roche (with co-funding)
XTX301 <sup>(2)</sup>	Advanced Solid Tumors	IL-12						Exclusive global license with Gilead
XTX501 <sup>(3)</sup>	Advanced Solid Tumors	PD-1/IL2 bispecific						
Additional research-stage programs	Undisclosed	Tumor-activated cell engagers						

1. Evaluating vilastobart (XTX101) in combination with atezolizumab (Tecentriq®) in patients with metastatic MSS CRC.  
 2. Evaluating XTX301 in Phase 1 monotherapy dose escalation and dose expansion for the treatment of advanced solid tumors.  
 3. Conducting initial IND-enabling activities.  
 CRC: colorectal cancer; MSS: microsatellite stable



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

## Inactive State



## Vilastobart Incorporates Multiple Differentiating Design Features for a Potential Best-in-Class Profile

- High affinity binding, 10x potency of ipilimumab in preclinical studies\*
- Fc mutations for enhanced effector function (ADCC), improved T cell priming and Treg depletion
- On-treatment biopsies in Phase 1 monotherapy demonstrated >70% activated molecule in tumor with <15% activated molecule in periphery
- Generally well-tolerated in Phase 1 monotherapy, consistent with tumor-activated design
- Confirmed PR observed with monotherapy in Phase 1 in a PD-L1 negative NSCLC patient, including resolution of innumerable liver metastases

# Vilastobart (anti-CTLA-4) Advancing in Phase 2 Proof-of-Concept Trial for MSS CRC in Co-Funded Clinical Collaboration with Roche

## ***Phase 2 Combination Proof-of-Concept Trial***

Metastatic MSS CRC patients  
with and without liver metastases

vilastobart at 100 mg Q6W +  
atezolizumab at 1200 mg Q3W

*Currently Enrolling*

## ***Anticipated Near-Term Phase 2 Data Milestones***

- Initial data (n = ~20 total) in MSS CRC in Q4 2024
- Additional data (n = ~40 total) in MSS CRC in Q1 2025

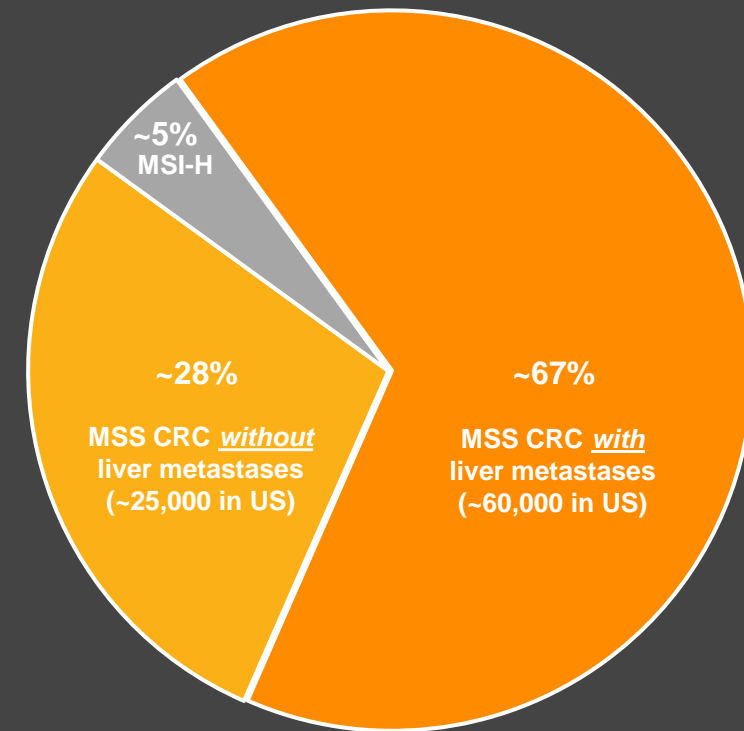
# Unmet Medical Need in Colorectal Cancer

**Aparna Parikh, M.D.**  
*MGH Cancer Center*

# CRC Incidence is Increasing, Particularly In Young Adults: Majority of Patients with Stage 4 MSS CRC Have Liver Metastases

- CRC is 2<sup>nd</sup> in cancer-related deaths in the US and leading cause of cancer-related death in men younger than 50 in the US <sup>(1)</sup>
- CRC is 3<sup>rd</sup> in total annual new cases globally, with ~1.9M new cases and ~900,000 deaths related to CRC globally <sup>(2)</sup>
- >65% of Stage 4 CRC patients present with liver metastases, which are associated with poor outcomes <sup>(3)</sup>

~90,000 new cases of Stage 4 CRC patients estimated in the US per year



# I-O Therapies Have Shown Little to No Efficacy in MSS CRC to Date

- Majority of patients diagnosed with metastatic disease are not eligible for surgery and primary treatment includes chemotherapy and/or radiation <sup>(1)</sup>
- Treatment for advanced MSS CRC typically includes chemotherapy +/- TKI, <sup>(1)</sup> followed by clinical trials or late-line therapies with minimal benefit (OS: ~6-9 months) <sup>(2)</sup>
- Immune checkpoint inhibitors (pembrolizumab/nivolumab) approved in MSI-H CRC have no meaningful efficacy in patients with MSS CRC (0-3% ORR) <sup>(3)</sup>



1. Eng. Lancet. 2024;404:294.

2. Grothey. Lancet. 2013;381:303; Mayer. N Engl J Med. 2015;372:1909; Li. JAMA. 2018;319:2486; Dasari. Lancet. 2023;402:41; Kawazoe. J Clin Oncol. 2024;42:2918.

3. Sahin. Am Soc Clin Oncol Educ Book. 2022:42:1

OS: overall survival; ORR: objective response rate; TKI: tyrosine kinase inhibitor

# Phase 1C Combination Data for Vilastobart (XTX101)

**Katarina Luptakova, M.D.**  
*Chief Medical Officer*



# Vilastobart (anti-CTLA-4) Advancing in Phase 2 Proof-of-Concept Trial for MSS CRC in Co-Funded Clinical Collaboration with Roche

## *Phase 1C Combination Dose Escalation*

### **Advanced solid tumors**

vilastobart at 75, 100 and 150 mg Q6W +  
atezolizumab at 1200 mg Q3W

*Currently enrolling*

## *Phase 2 Combination Proof-of-Concept*

### **Metastatic MSS CRC patients with and without liver metastases**

vilastobart at 100 mg Q6W +  
atezolizumab at 1200 mg Q3W

*Currently enrolling*

# Phase 1C Combination Dose Escalation for Vilastobart (anti-CTLA-4) and Atezolizumab Enrolled Heavily Pre-Treated Patients with Cold Tumors

## Vilastobart Phase 1 Trial Design

Phase 1A  
Monotherapy Dose-Escalation  
Advanced Solid Tumors

Phase 1B  
Monotherapy Expansion

**Phase 1C Combination  
Dose Escalation  
(vilastobart + atezolizumab)**  
  
Advanced Solid Tumors  
(n=17)  
  
Enrollment ongoing at  
vilastobart 150 mg Q6W  
dose level

## Patient Characteristics Total (n=17)

Demographics	
Age, median (range)	69 (39, 77)
Female	6 (35%)
ECOG PS 0	7 (41%)
ECOG PS 1	10 (59%)
Prior Lines of Anti-Cancer Treatment	
	<b>Median 3 (1-12)</b>
1	2 (12%)
2	1 (6%)
3	6 (35%)
4	1 (6%)
5	3 (18%)
6 and more	4 (24%)

Progressed on Prior Treatment with I-O	
≥1	4 (24%)

## Tumor Types Total (n=17)

Colorectal cancer (MSS)	12
Colorectal cancer (MSI-H)	1
Ampullary carcinoma	1
NSCLC	1
Esophageal cancer	1
Abdomen	1

## Treatment Status Total (n=17)

Continuing on Treatment	7
Discontinued Treatment	10
Progressive Disease	1
Adverse Events	2
Consent Withdrawal	4
Death	0
Investigator Decision	3

83% of patients had ≥3 prior lines of treatment

# Combination of Vilastobart (anti-CTLA-4) and Atezolizumab Was Generally Well-Tolerated with Minimal irAEs

AE Category / Term <i>All TRAEs with ≥10% incidence in any category or any Grade 3 TRAE</i>	All Phase 1C Patients (n=17) vilastobart (75, 100 or 150 mg Q6W) + atezolizumab (1200 mg Q3W)	
	Any	Grade 3
ALT increased	3 (18%)	2 (12%)
Blood ALP increased	2 (12%)	1 (6%)
Diarrhea	2 (12%)	1 (6%)
Colitis	1 (6%)	1 (6%)
Infusion related reaction <sup>(1)</sup>	10 (59%)	0
AST increased	3 (18%)	0
Lipase increased	3 (18%)	0
Fatigue	2 (12%)	0
<hr/>		
Dose reduction due to TRAE		1
Treatment discontinuation due to TRAE <sup>(2)</sup>		1

- *No Grade 4 or Grade 5 TRAEs at any dose level*
- *Only 3 patients experienced Grade 3 TRAEs, of these 2 experienced DLTs (150 mg dose level of vilastobart) <sup>(3)</sup>*
- *No endocrine irAEs and limited skin irAEs*
- *Selected initial RP2D of vilastobart (100 mg Q6W) + atezolizumab (1200 mg Q3W)*

Data cutoff date: October 7, 2024

1. Of the 10 patients with infusion related reactions, 4 experienced reactions related to vilastobart, 3 experienced reactions related to atezolizumab and 3 experienced reactions related to the combination.

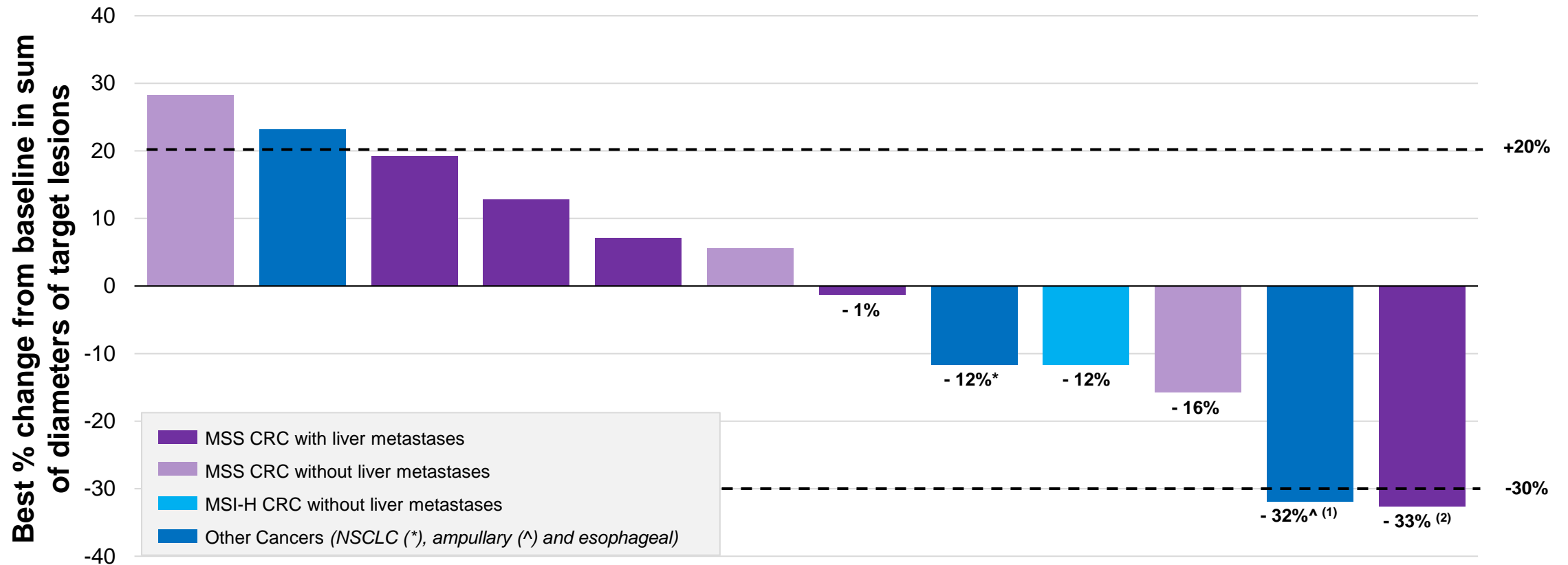
2. Reflects discontinuation of both vilastobart and atezolizumab.

3. DLTs at the 150 mg dose level of vilastobart were experienced by one patient with Grade 3 colitis and diarrhea and one patient with grade 3 ALT and blood ALP elevation.

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate transaminase; DLT: dose-limiting toxicity; irAE: immune-related adverse event; RP2D: recommended Phase 2 dose; TRAE: treatment-related adverse event

# Combination of Vilastobart (anti-CTLA-4) and Atezolizumab Demonstrated Anti-Tumor Activity in Cold Tumors, Including a Sustained Tumor Reduction in a MSS CRC Patient with Metastatic Liver Disease

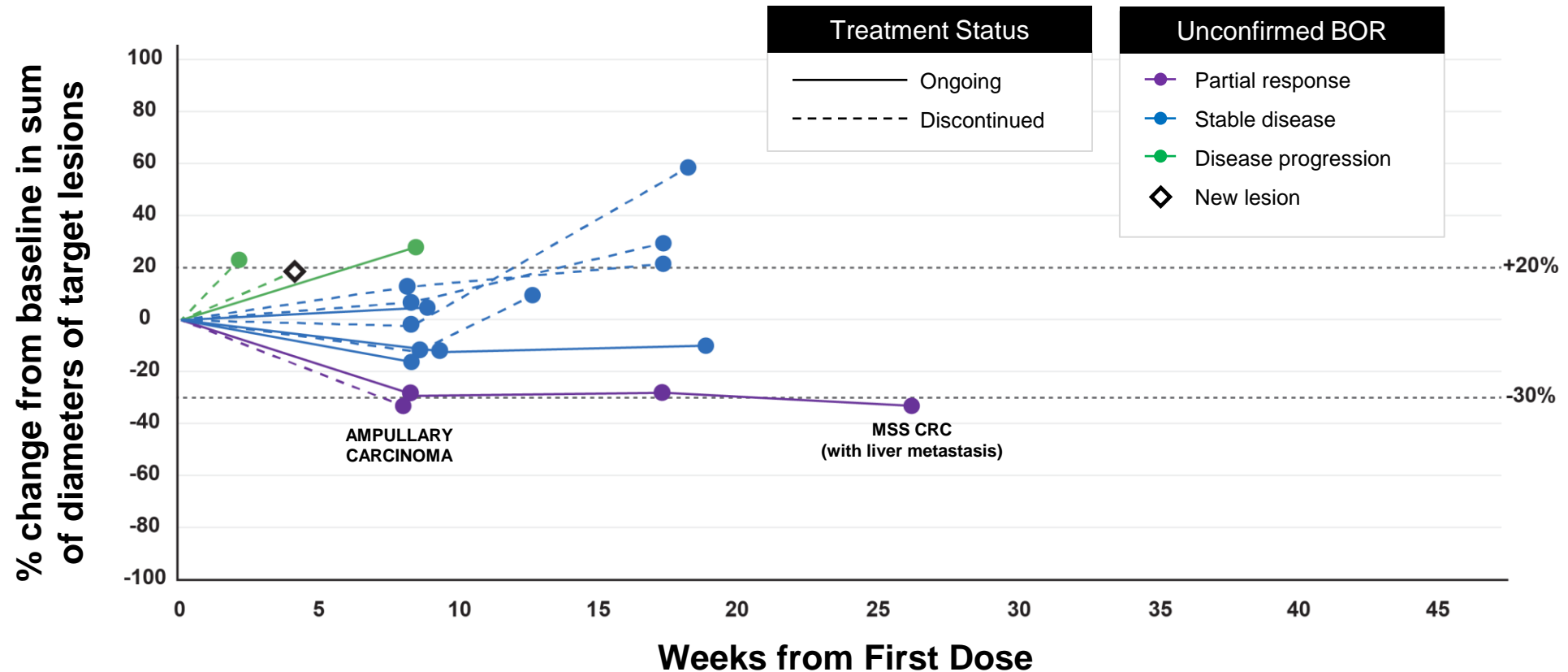
## Patients Treated with the Combination of Vilastobart and Atezolizumab in Phase 1C



Data cutoff date: October 7, 2024. n=12 response-evaluable patients.  
 1. PR (unconfirmed), patient withdrew consent prior to confirmatory scan.  
 2. PR (unconfirmed), awaiting confirmation.

# Combination of Vilastobart (anti-CTLA-4) and Atezolizumab Demonstrated Anti-Tumor Activity in Cold Tumors, Including a Sustained Tumor Reduction in a MSS CRC Patient with Metastatic Liver Disease

## Patients Treated with the Combination of Vilastobart and Atezolizumab in Phase 1C



# PR (Unconfirmed)\* in Patient with Ampullary Carcinoma (Cold Tumor) After Single Cycle of Combination of Vilastobart (anti-CTLA-4) and Atezolizumab

## *Malignant Neoplasm of Ampulla of Vater*

- 76 year-old male
- 2 prior lines of therapy:
  - Gemcitabine + nab-Paclitaxel
  - 5-fluorouracil + Irinotecan Liposome + Leucovorin
- Administered vilastobart (150 mg Q6W) + atezolizumab (1200 mg Q3W)
- Significant CA 19-9 decrease after a single cycle of the combination

	Screening		8 weeks after C1D1
Sum of diameters	60.5 mm		41.2 mm
Change			- 32%
Serum tumor marker	Screening	C1D1	6 weeks after C1D1
CA 19-9 (U/mL)	575.0	700.2	40.8

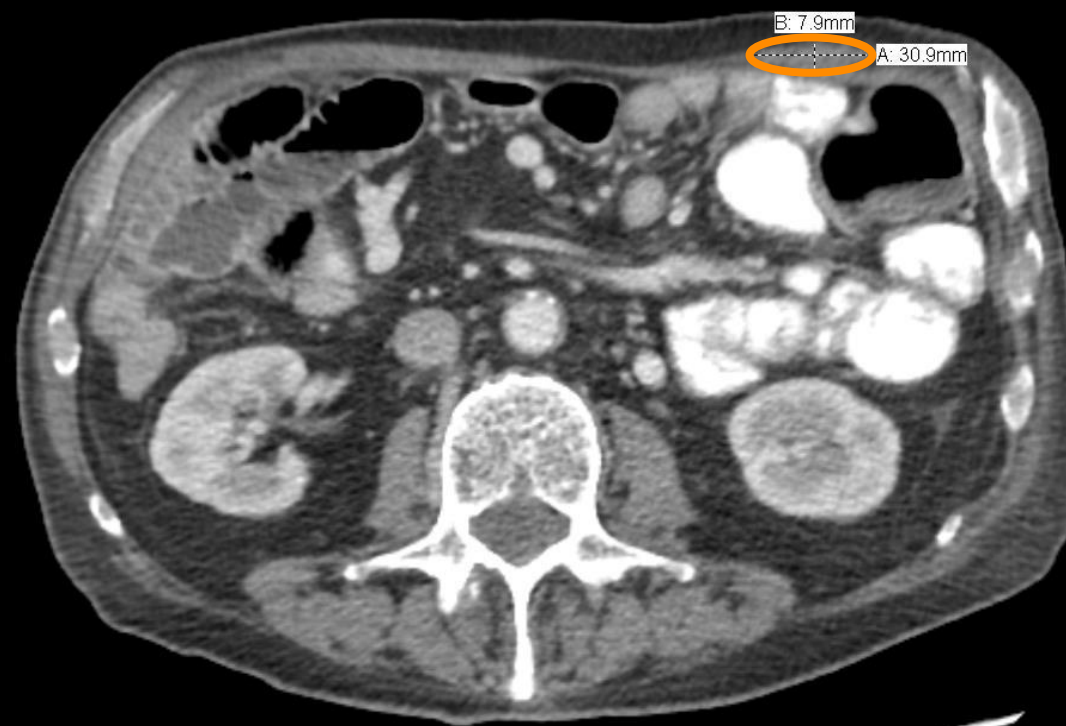


# PR (Unconfirmed)\* in Ampullary Carcinoma After Single Cycle of Combination of Vilastobart (anti-CTLA-4) and Atezolizumab (32% Reduction in Sum of Diameters)

Target Lesion at Screening



Target Lesion After 8 weeks



# PR (Unconfirmed)\* in Patient With MSS CRC, Including Full Resolution of Target Lesion in Liver

## MSS CRC and Liver Metastasis

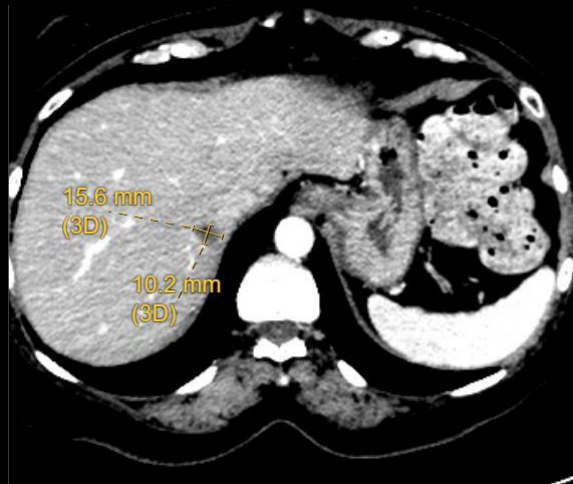
- 69 year-old female
- 5 prior lines of therapy:
  - FOLFOX-Avastin
  - FOLFIRI-Avastin
  - Cetuximab
  - Lonsurf
  - FOLFIRI-Panitumumab
- Administered vilastobart (150 mg Q6W) + atezolizumab (1200 mg Q3W)

	Screening	1st follow-up (9 weeks)	2 <sup>nd</sup> follow-up (18 weeks)	3 <sup>rd</sup> follow-up (27 weeks)
Sum of diameters	98.4 mm	70.5 mm	71.0 mm	66.3 mm
Change		- 28%	- 28%	- 33%

*Including full resolution of target lesion in the liver*

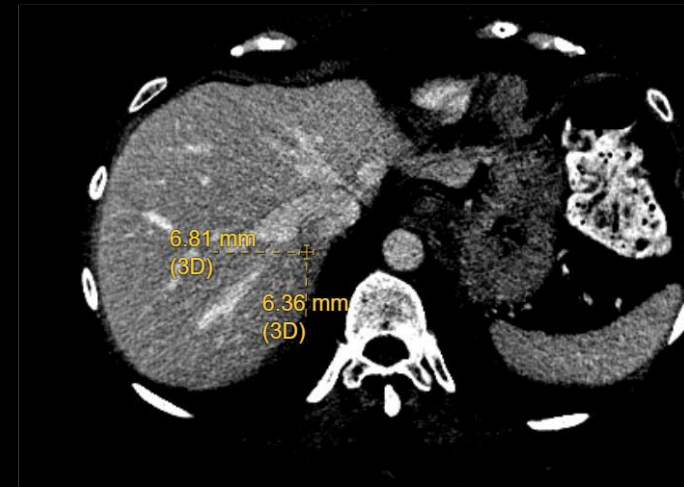
# PR (Unconfirmed)\* Including Resolution of Liver Metastatic Lesion in Patient With MSS CRC (33% Reduction in Sum of Diameters)

Target Liver Lesion – Baseline



15.6 mm

Target Liver Lesion – After 9 weeks



6.8 mm

Target Liver Lesion – After 18 weeks



5.8 mm

Target Liver Lesion – After 27 weeks

No visible lesion

# Encouraging Initial Evidence of Combination Activity Observed in Phase 1C; Anticipate Initial Phase 2 Combination Proof-of-Concept Data in Q4 2024

## *Initial Phase 1C Data for Combination of Vilastobart and Atezolizumab*

- Generally well-tolerated with minimal irAEs
- Initial evidence of anti-tumor activity in cold tumors, including a PR (unconfirmed) in a patient with MSS CRC with complete resolution of liver metastasis

## *Anticipated Near-Term Phase 2 Data Milestones*

- ❑ Initial data (n = ~20 total) in MSS CRC in Q4 2024
- ❑ Additional data (n = ~40 total) in MSS CRC in Q1 2025

# Q&A