CytomX Therapeutics

Leveraging Conditional Activation to Localize Antibody Drug Conjugates to the Tumor

Marcia Belvin, CSO

OCTOBER 2023

Antibody Drug Conjugates Have Emerged as a Growing and Potent Modality in Both Solid and Liquid Tumors

Approved Solid Tumor ADCs

tivdak
tisotumab vedotin-tftv
for injection 40 mg

TF1

ENHERTU®
fam-trastuzumab deruxtecan-nxki
20 mg/mL INJECTION FOR INTRAVENOUS USE

HER2

TRODELVY®
sacituzumab govitecan-hziy
180 mg for injection

TROP2

Kadcyla®
ado-trastuzumab emtansine
20 mg/mL INJECTION FOR INTRAVENOUS USE

HER2

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

Nectin4

ELAHERE™
mirvetuximab soravtansine-gynx
injection 100 mg

FRα

Approved Liquid Tumor ADCs

POLIVY™
polatuzumab vedotin-piiq
INJECTION FOR INTRAVENOUS USE 30 MG | 140 MG

CD79b

Zynlonta®
loncastuximab tesirine-lpyl
for injection, for intravenous use • 10mg

CD19

ADCETRIS®
brentuximab vedotin | injection 50 mg

CD30

BESPONSA™
inotuzumab ozogamicin INJECTION FOR IV INFUSION
0.9 mg single-dose vial

CD22

MYLOTARG™
gemtuzumab ozogamicin injection for IV infusion
4.5 mg single-dose vial

CD33

CytomX THERAPEUTICS

What Has Driven the Recent Increase in ADC Approvals?

- **Target Selection**
  - Careful selection of targets with limited expression in normal tissue
- **Payload Selection**
  - Development of next generation linker-payloads with a higher inherent therapeutic index (Enhertu, Trodelvy)
- **Matching payload with tumor type**
  - Heme versus solid tumors, alignment with standard of care

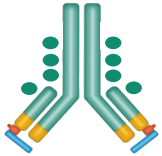
Broad potential for new ADCs expanding to promising cancer targets that are also expressed in normal tissue, such as **EpCAM**

Targeting EpCAM with CX-2051

A conditionally activated ADC with a next-gen camptothecin analog linker-payload

ADC target options are limited by normal tissue expression. Conditional activation can allow ADC technology to be applied to a wider set of targets.

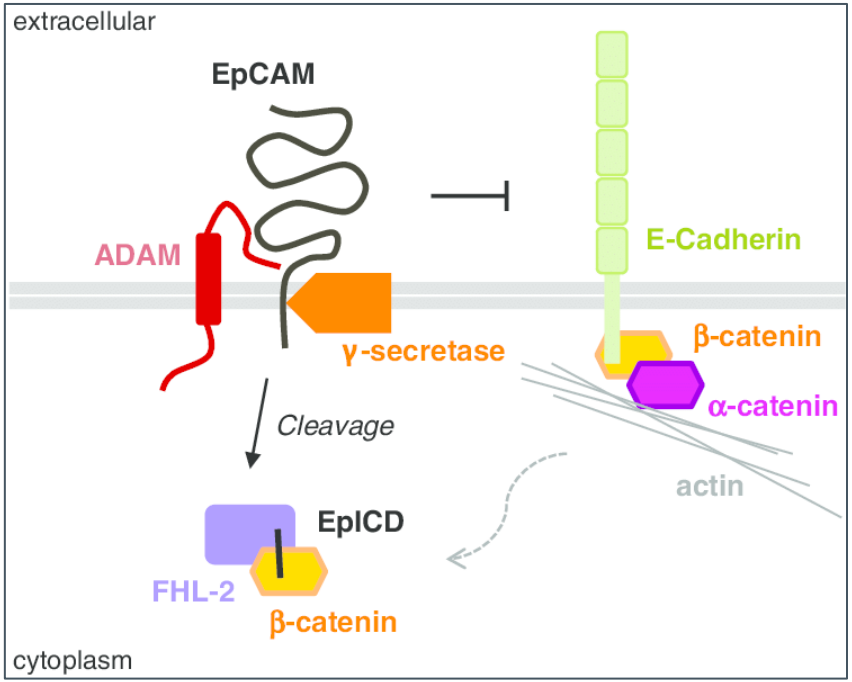
Conditional activation using Probody® Therapeutic technology restricts molecular activity to the site of the tumor.



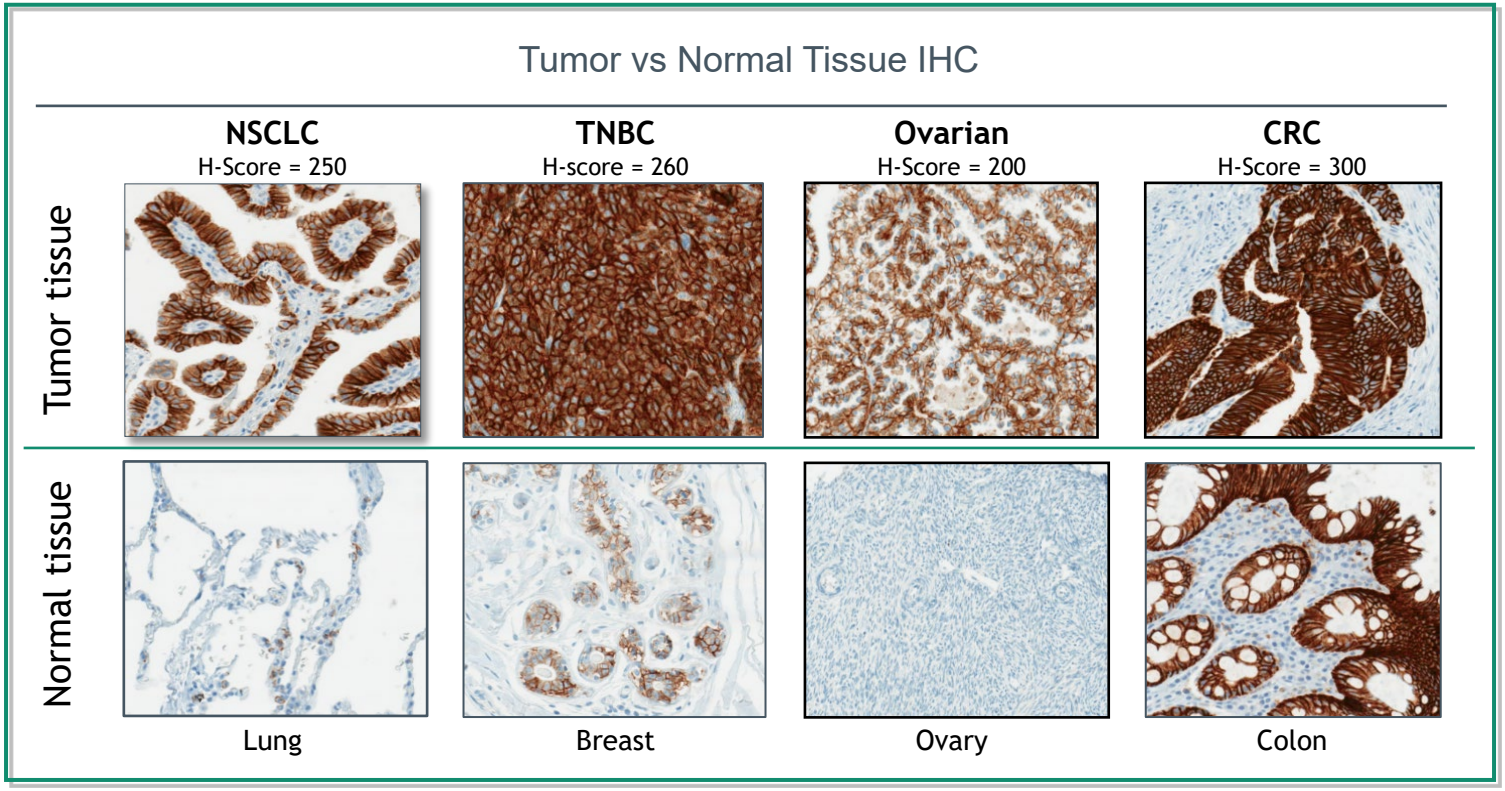
CX-2051 uses Probody® technology to direct an ADC to one of the most promising cancer targets, EpCAM

EpCAM (Epithelial Cell Adhesion Molecule / Trop1) is an Attractive ADC Target

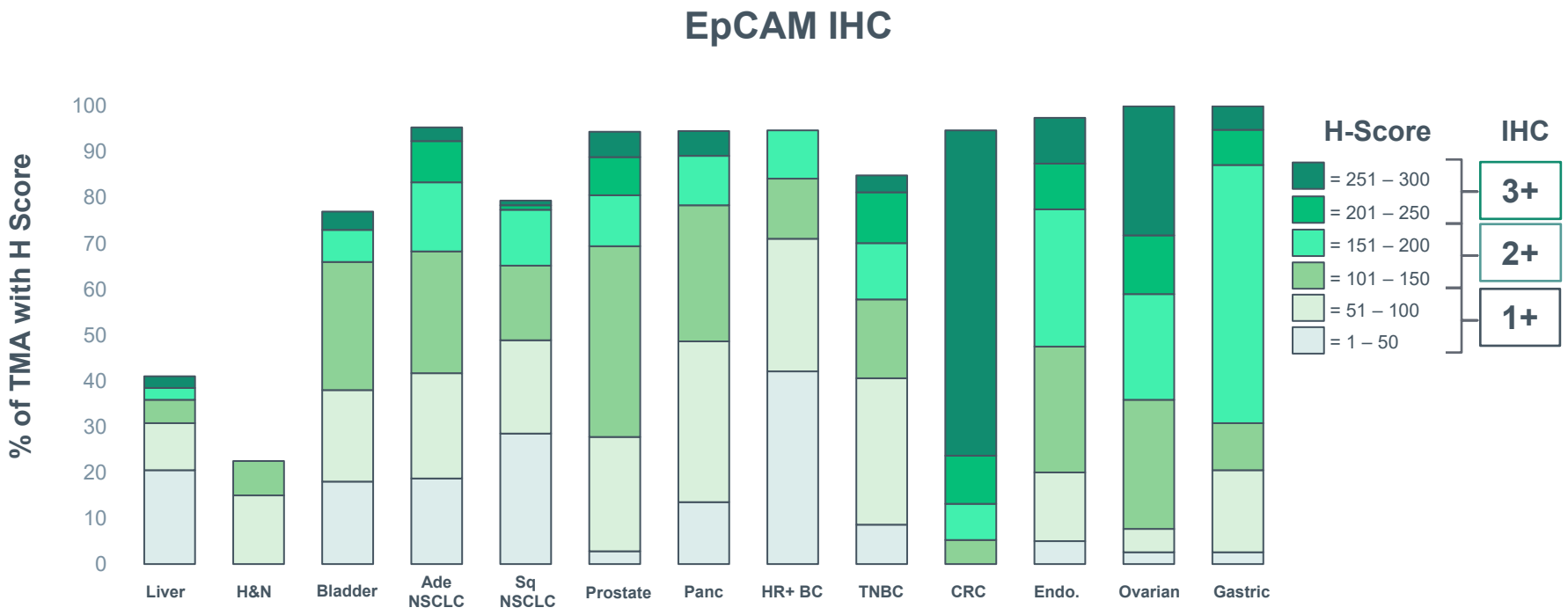
- **Highly expressed on cancer cells**
  - Overexpressed in multiple cancer indications
  - Expressed in both adeno and squamous histologies
- **Functional role in cancer signaling**
  - Internalizes and binds to β-catenin
  - Upregulates c-myc, cyclins
- **Expressed on circulating tumor cells**
  - Associated with cancer stem / progenitor cells



EpCAM: High Expression in Tumors; Moderate Expression in Normal Tissues



EpCAM is Broadly Expressed in Many Cancers

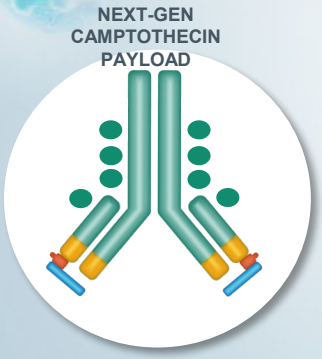


Although EpCAM is an Ideal Cancer Target, it Has Not Been Tractable by Conventional Approaches

EpCAM Has Been Clinically Validated But Only by Local Administration

	Molecule	MOA	Latest Stage of Advancement	Status
Local administration	Catumaxumab	EpCAM/CD3 bispecific	Approved for malignant ascites	Withdrawn
	Vicineum	EpCAM – exotoxin fusion	Ph3 bladder cancer (CR 40%)	Development paused
Systemic administration	Solitomab	EpCAM/CD3 BiTE	Ph1	Discontinued: GI tox
	ING-1	EpCAM mAb	Ph1	Discontinued: pancreatitis
	3622W94	EpCAM mAb	Ph1	Discontinued: pancreatitis

CytomX Therapeutics

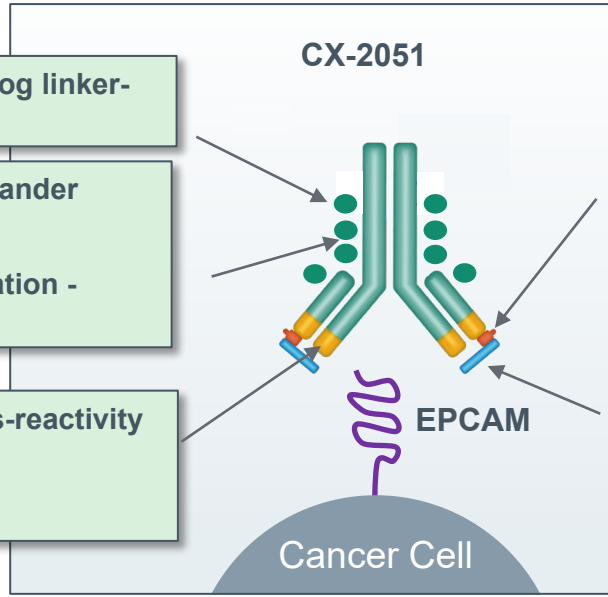


CX-2051: EpCAM ADC

First-in-Class Conditionally Activated ADC With Next Generation Camptothecin Analog Linker-Payload

CX-2051: EpCAM Probody® ADC with Next Generation Camptothecin Analog Linker-Payload

- Next-gen camptothecin analog linker-payload
- Optimized linker drives bystander activity
- Inter-chain cysteine conjugation - DAR8
- Anti-EpCAM MAb with cross-reactivity to cyno
- Single digit nM affinity



- Protease-cleavable substrate with broad cleavability profile across multiple tumor types
- Affinity peptide mask with masking efficiency >100x by ELISA
- Decreases normal tissue binding

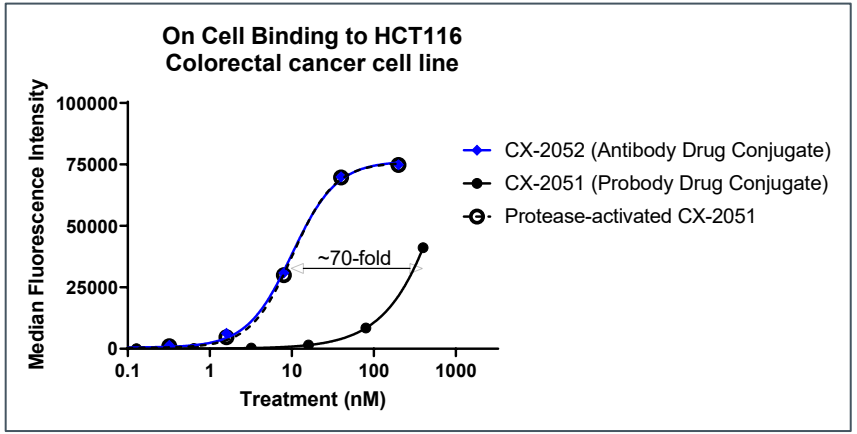
CX-2051 is a conditionally activated EpCAM ADC designed to be active preferentially in the tumor microenvironment with limited activity in normal tissues

Program licensed from immunogen

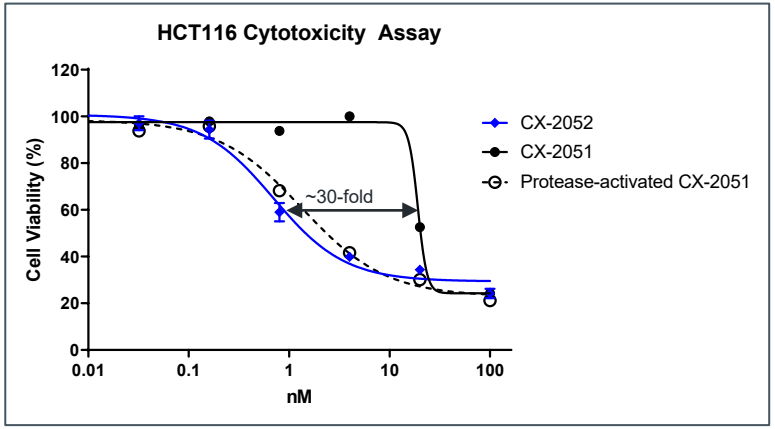
CX-2051 Shows Strong In Vitro Masking Efficiency in Cancer Cell Lines

Potency is fully reversible upon protease activation

On Cell Binding

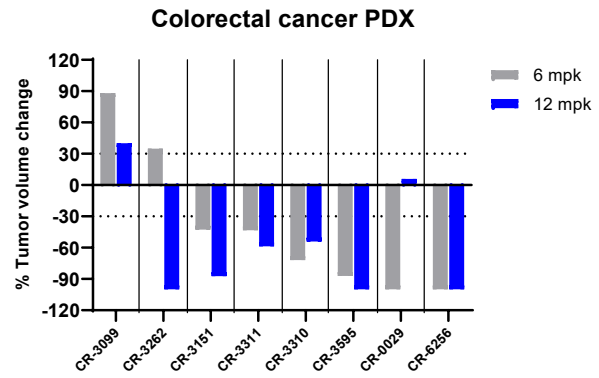


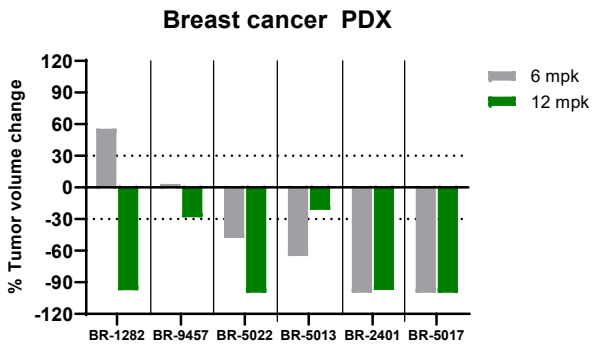
Cytotoxicity

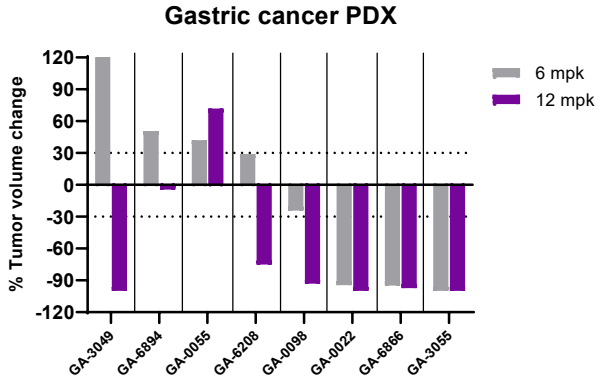


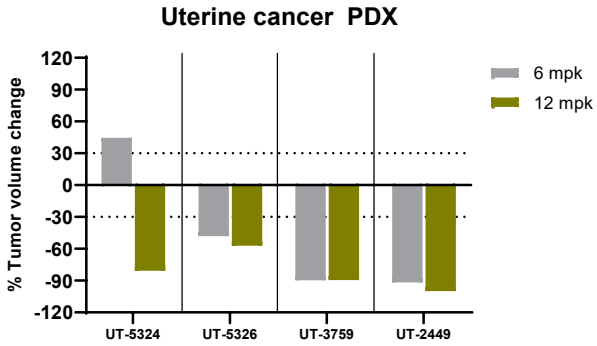
CX-2052: Unmasked EpCAM-ADC
CX-2051: Masked EpCAM-ADC

CX-2051 Shows Broad Preclinical Activity Across Multiple Tumor Types









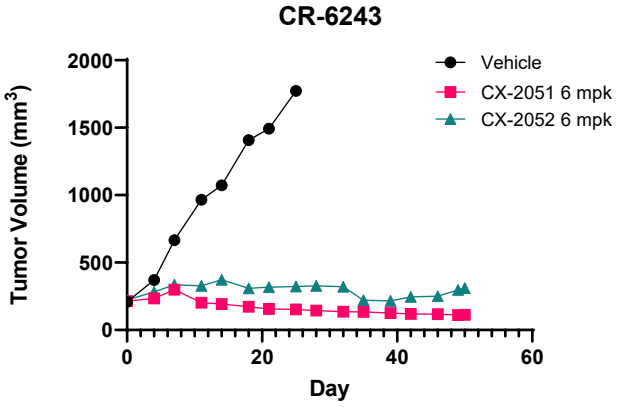
- High percentage of deep regressions across multiple PDX tumor models

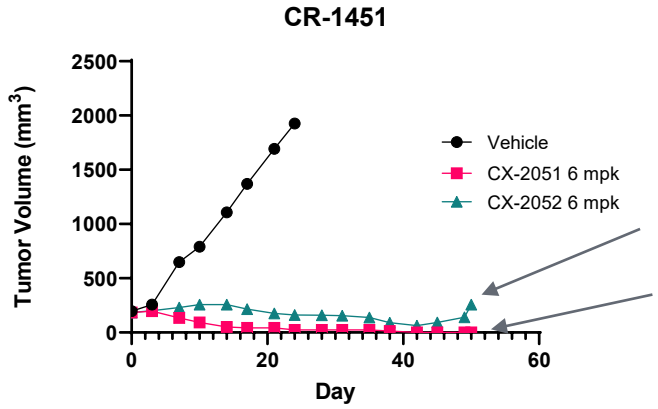
- High percentage of regressions even at lower doses

CX-2051 Shows Equivalent Anti-Tumor Efficacy as Unmasked ADC

CX-2052: Unmasked EpCAM-ADC
CX-2051: Masked EpCAM-ADC

Colorectal Cancer Patient-Derived Xenograft Models



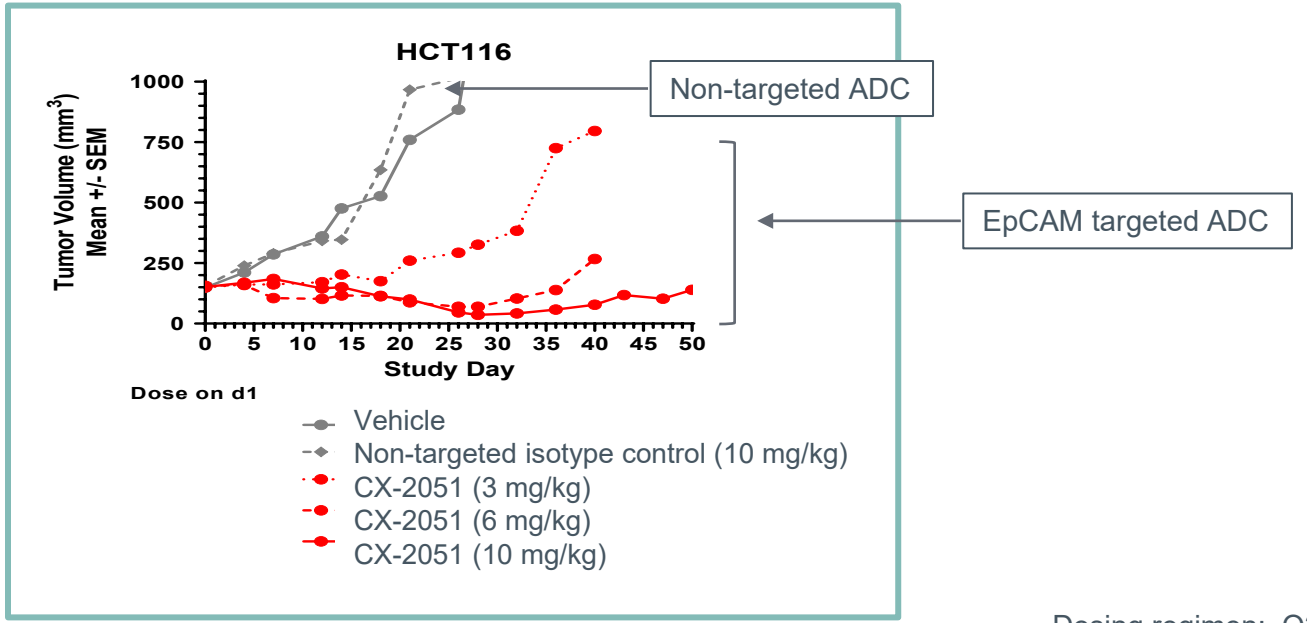


Demonstrates that CX-2051 is efficiently unmasked and activated in the tumor microenvironment

Dosing regimen: Q2W x 3

CX-2051 Efficacy is Dependent on Target Engagement

Colorectal Cancer Cell Line-Derived Model



Dosing regimen: Q2W x 3

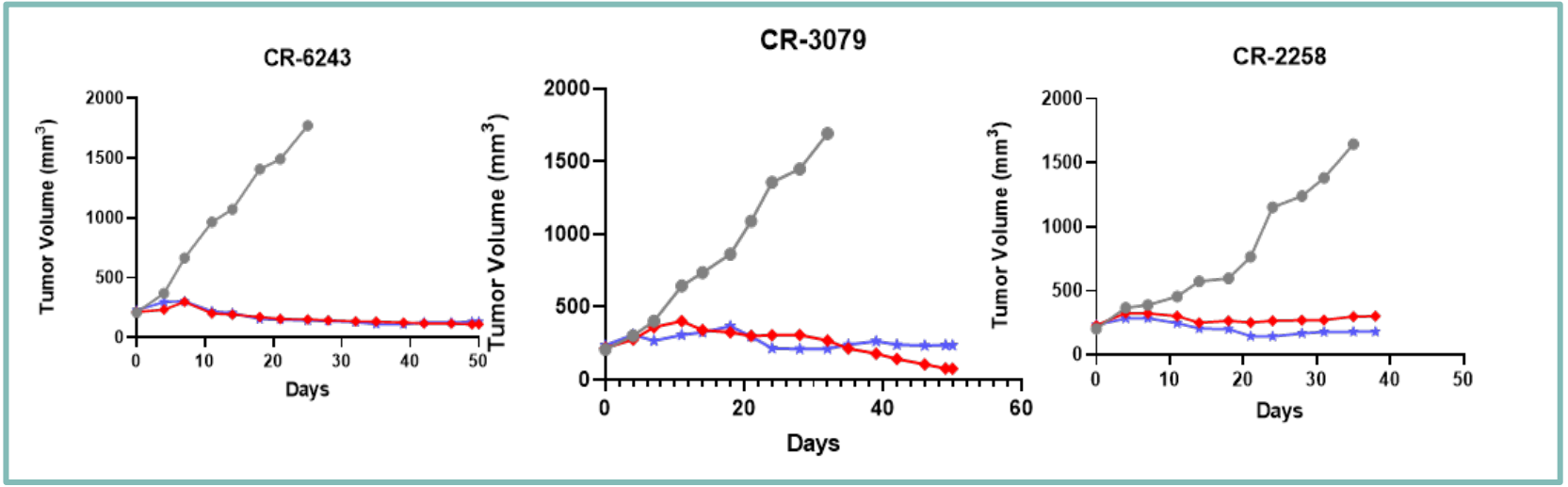
- Nonspecific activity of the linker-payload is not observed
- Payload internalized by EpCAM target

CytomX Therapeutics

Next-Gen Linker-Payload in CX-2051 Is Equally Efficacious as DXd Linker-Payload in Murine Cancer Models

- Vehicle
- CX-2051 6 mk/kg
- EpCAM-DXd 6 mk/kg

Colorectal cancer patient-derived xenograft models

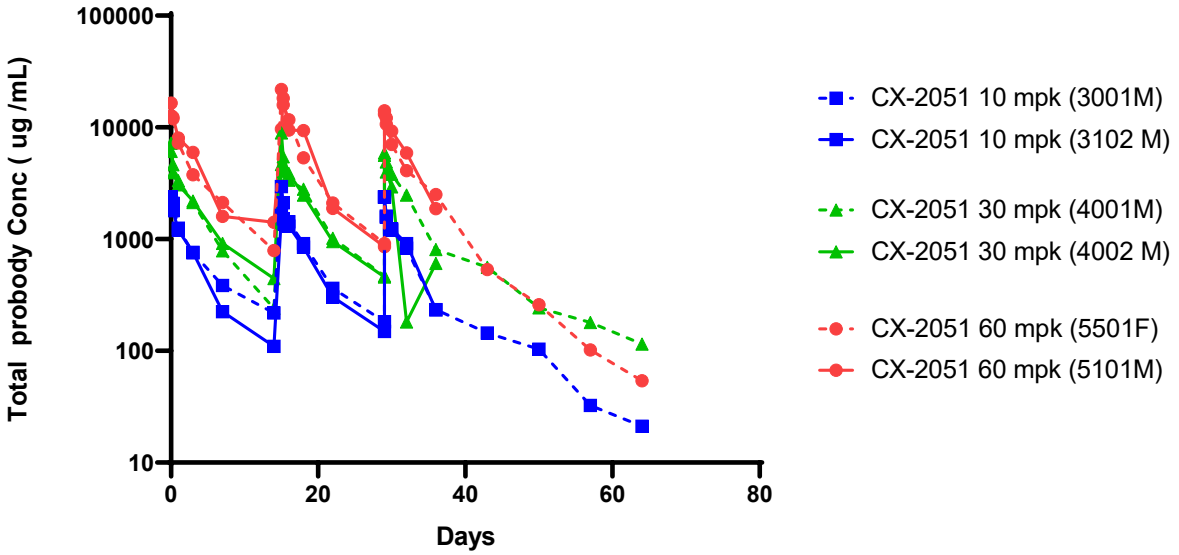


CX-2051 is equally efficacious preclinically as EpCAM-DXd

Dosing regimen: Q2W x 3

CX-2051 Shows Dose Proportional Pharmacokinetics in Non-Human Primates

Pharmacokinetic Profile of CX-2051 in Cyno



- Exposure is maintained after each dose (Q2Wx3)

CX-2051 Is Tolerated in Non-Human Primates at >6x Unmasked EpCAM ADC

Tolerability of CX-2051 in Cyno Pilot Tox Study

Dosing (3 x Q2W)	CX-2051 (Masked)	CX-2052 (Unmasked)
10 mpk	Tolerated	Not tolerated
30 mpk	Tolerated	
60 mpk	Tolerated	
90 mpk	Not Tolerated	

CX-2052: Unmasked EpCAM-ADC

CX-2051: Masked EpCAM-ADC

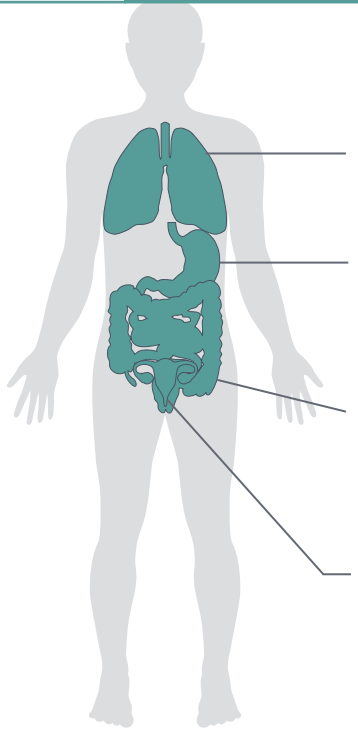
- CX-2051 Shows Substantially Improved Safety Profile Over Unmasked ADC

CytomX Therapeutics

Next Steps For CX-2051

Broad Opportunity Across Multiple Indications

2023 US Metastatic, Drug-Treatable Patients
EpCAM IHC ≥2+



% of Patients with EpCAM IHC ≥2+

NSCLC 85,000 Patients	30%
Gastric 28,000 Patients	80%
Colorectal 106,000 Patients	95%
Ovarian 50,000 Patients	92%
Endometrial 26,000 Patients	80%

>295,000 EpCAM-Treatable Patients

Source: DRG Epidemiology & Forecast Dashboards, 2021 – 2023

CX-2051 Can Address High Unmet Need in Metastatic CRC

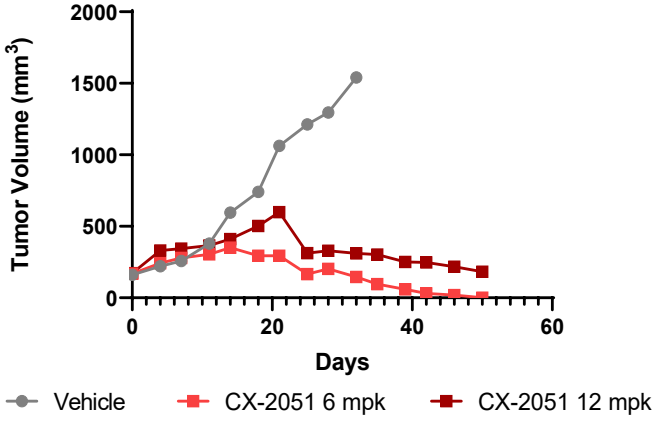
Broad Opportunity for Topo I Based ADCs in CRC

1L	FOLFOX (folinic acid, fluorouracil, oxaliplatin) / FOLF**IRI** (folinic acid, fluorouracil, **irinotecan**) + bevacizumab / cetuximab /panitumumab	53 – 65% ORR 24 – 30 mo. OS
2L	FOLF**IRI** / FOLFOX +/- bevacizumab / aflibercept / ramucirumab / cetuximab / panitumumab	13 – 22% ORR 10 – 14 mo. OS
3L	regorafenib / trifluridine & tipiracil +/- bevacizumab	1 – 6% ORR 6 – 10 mo. OS

Strong preclinical anti-tumor activity even in irinotecan resistant setting

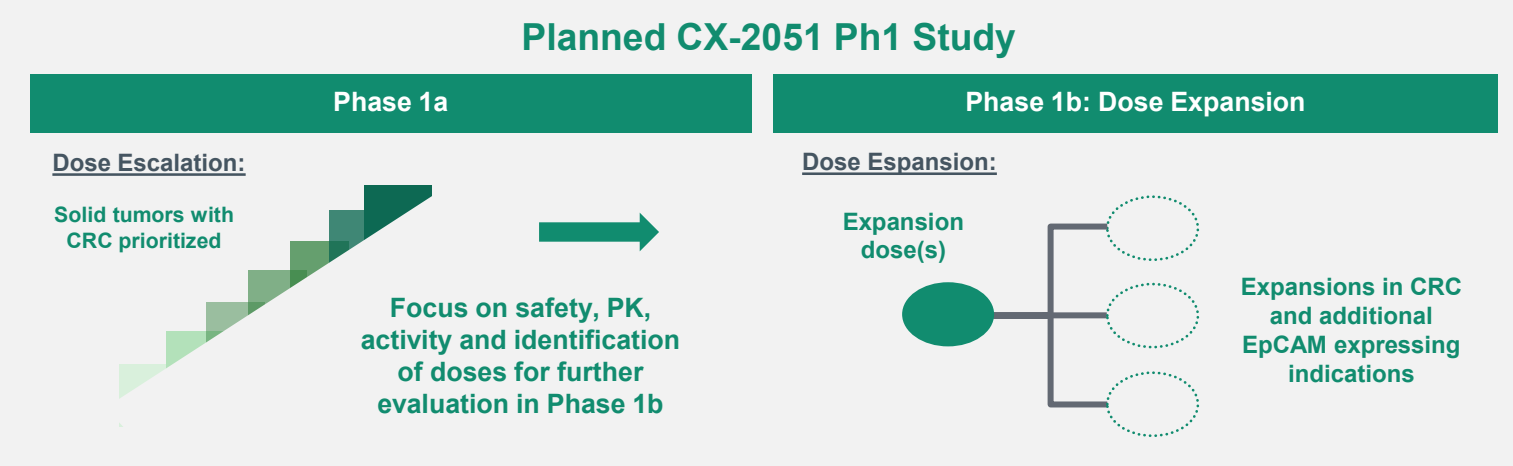
CRC PDX Model (CR-0029)

(Irinotecan resistant model)



CX-2051 Poised for First in Human Studies

- IND filing planned for end of year 2023
- Initiate Ph1a dose escalation to assess safety, tolerability and preliminary activity, with initial focus in CRC
- Robust biomarker and translational science effort to optimize future patient selection strategies



Summary

- CX-2051 is a conditionally activated ADC targeting EpCAM using Probody therapeutic technology
- CX-2051 contains a next generation camptothecin analog payload with a linker that is optimized for potent bystander activity
- CX-2051 demonstrates strong preclinical activity and tolerability in irinotecan-resistant models with a favorable predicted therapeutic index
- EpCAM expression and treatment landscape provides broad opportunity across multiple solid tumors with initial focus towards CRC
- CX-2051 is on track to file an IND by end of 2023

Thank you!