Tailoring the Selection of Target, Payload, and Tumor Type to Maximize the Therapeutic Index of Conditionally Activated ADCs

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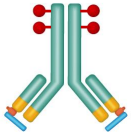
After Decades of R&D, ADCs Have Come of Age

However, actionable novel targets are limited

12+ Over a dozen ADCs are now approved, the majority in the last three years

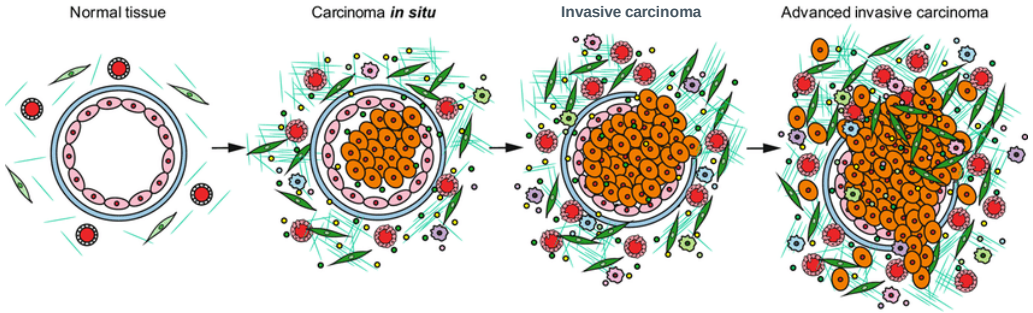
ADCs are becoming an increasingly important therapeutic class for the treatment of cancer

Target space is limited, especially in solid tumors. To further expand the potential of ADCs, we need more targets



Probody® Therapeutics are conditionally activated therapeutics that can open up new target space

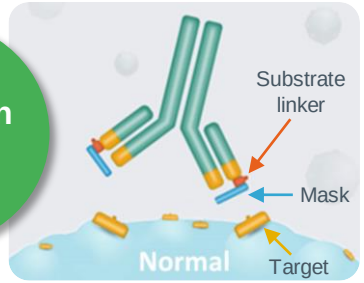
The Probody® Therapeutic Platform – Exploiting Cancer's Achilles' Heel to Make Conditionally Active Therapeutics

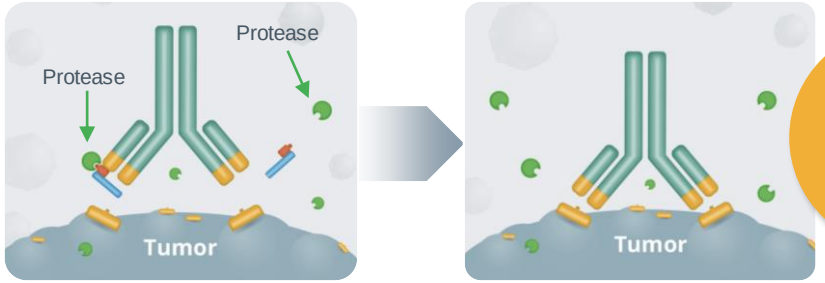


Adapted from Santi et al., Proteomics 2018

Upregulated protease activity is a hallmark of cancer

Less Binding in Normal Tissues



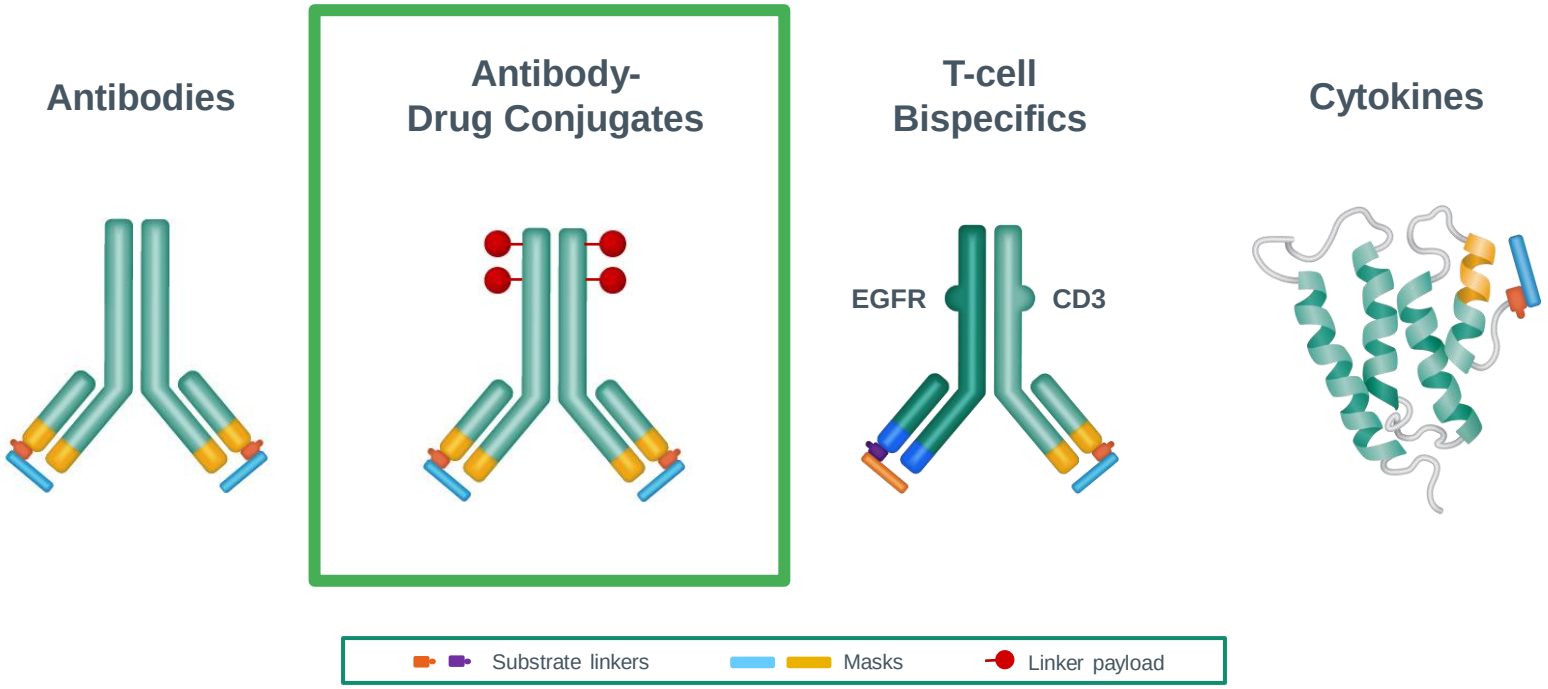


More Binding in Tumors

"Masking" limits ability of Probody therapeutics to bind to healthy tissues

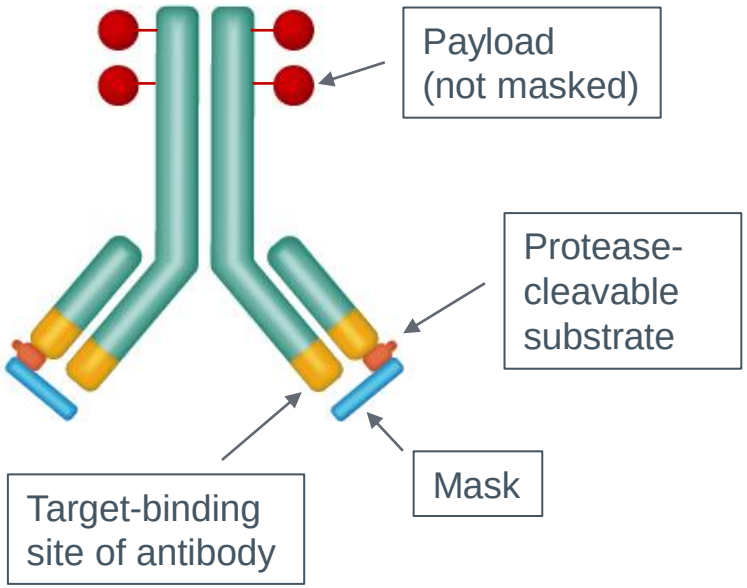
Proteases in tumor microenvironment "unmask" Probody therapeutics, allowing more binding to tumor cells

CytomX has Pioneered a Multi-Modality Platform for Conditional Activation of Potent Biologic Drug Candidates



Probody® Therapeutic ADC Design

Probody® Therapeutic Drug Conjugates



- A Probody® Therapeutic ADC contains a mask that attenuates target binding in the periphery
- The payload is not masked
- Therefore, payload-associated toxicities should be expected
- Payload selection is ***critical***

Conditional Activation Broadens Target Landscape for ADCs

Targets for Traditional ADCs

Targets with minimal normal tissue expression

Traditional ADC Targets

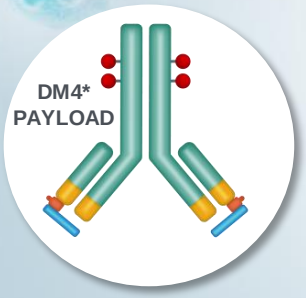
Targets for **Conditional** ADCs

Targets **agnostic** to expression on normal tissue

Conditional ADC Targets

CytomX Therapeutics

Target 1: CD166/ALCAM



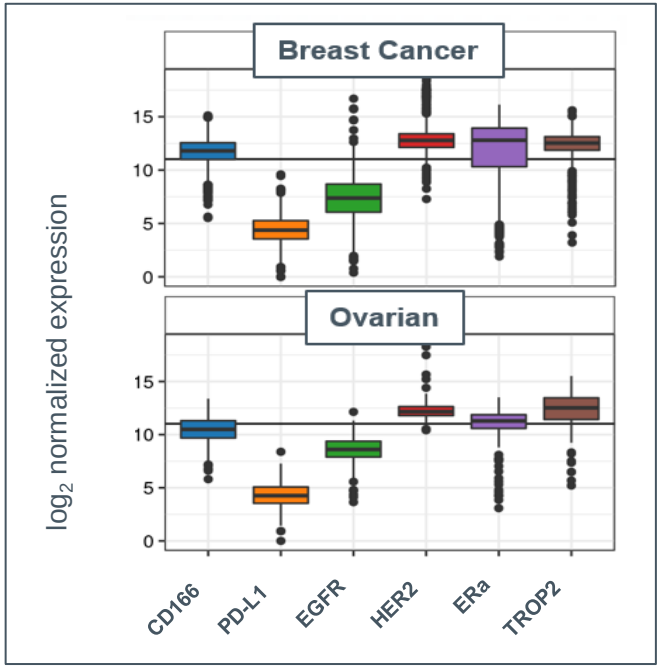
Praluzatamab Ravtansine (CX-2009)

First-in-Class ADC for HER2-non-Amplified Advanced Breast Cancer

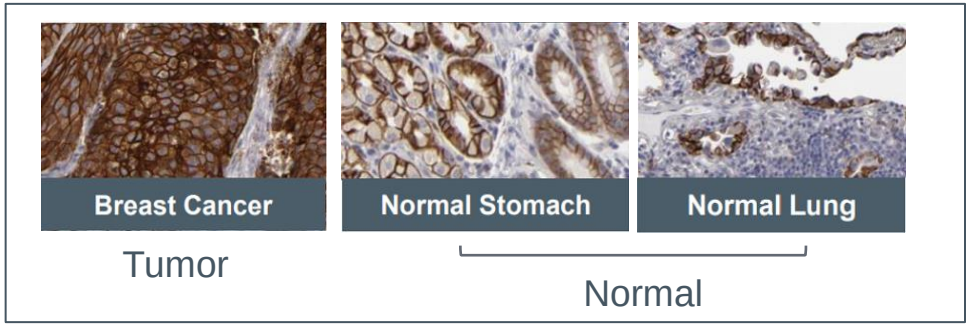
*Microtubule inhibitor (maytansinoid) (DAR~4)

CD166/ALCAM is a Novel ADC Target with High Tumor Expression
Undruggable Using Conventional ADC Because of High Expression on Normal Tissue

High Expression on Tumors



High CD166 Expression by IHC in Normal Tissue



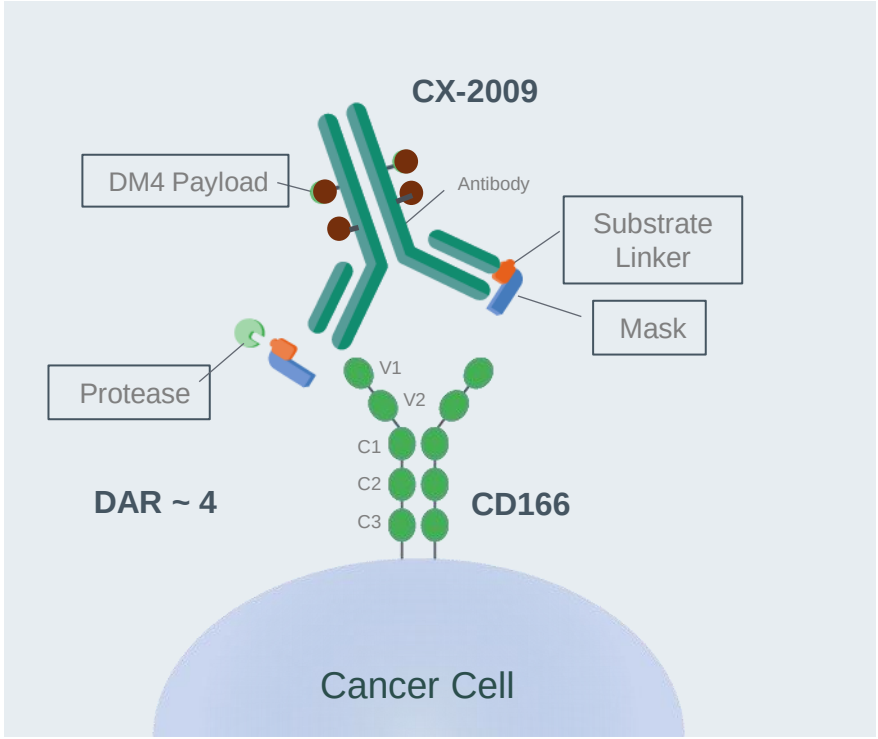
- Cell adhesion molecule expressed on multiple tumor types
- Functions in cell growth, motility, invasion, metastasis, breast cancer cell survival

Source: Lui J. et al SABCS 2020; PS 11-07

Praluzatamab Ravtansine (CX-2009)

First-in-Class ADC Directed Toward CD166/ALCAM

- Masked form of a proprietary anti-CD166 IgG1 antibody
- Linker-payload: SPDB-DM4 (DAR~4)
- Microtubule inhibitor (maytansinoid)
- Linker-payload clinically validated; used in ImmunoGen's mirvetuximab soravtansine



Linker-payload licensed from ImmunoGen

Multi-Arm Breast Cancer Phase 2 Study Design

Monotherapy and Combination with Pacmilimab (CX-072; anti-PD-L1) In Advanced, HER2-non-Amplified Breast Cancer

Key Eligibility

Ocular prophylaxis required

HR+/HER2 non-amplified
- 0 – 2 prior cytotoxics for advanced disease
- Measurable disease required
- No active corneal disease

TNBC
- CD166 High
- ≥ 1 and ≤ 3 priors for advanced disease
- Measurable disease required
- Treated/stable brain metastases allowed
- No active corneal disease
- **Arm C exclusion criteria:**
  - PD-L1 negative/unknown
  - I/O refractory
  - History of or active autoimmune condition

Breast Cancer SubType

Arm A
HR+/HER2 non-amp (n~40*)
CX-2009

Arm B
TNBC (n~40*)
CX-2009

Arm C
TNBC (n~40*)
CX-2009 + CX-072**

Endpoints

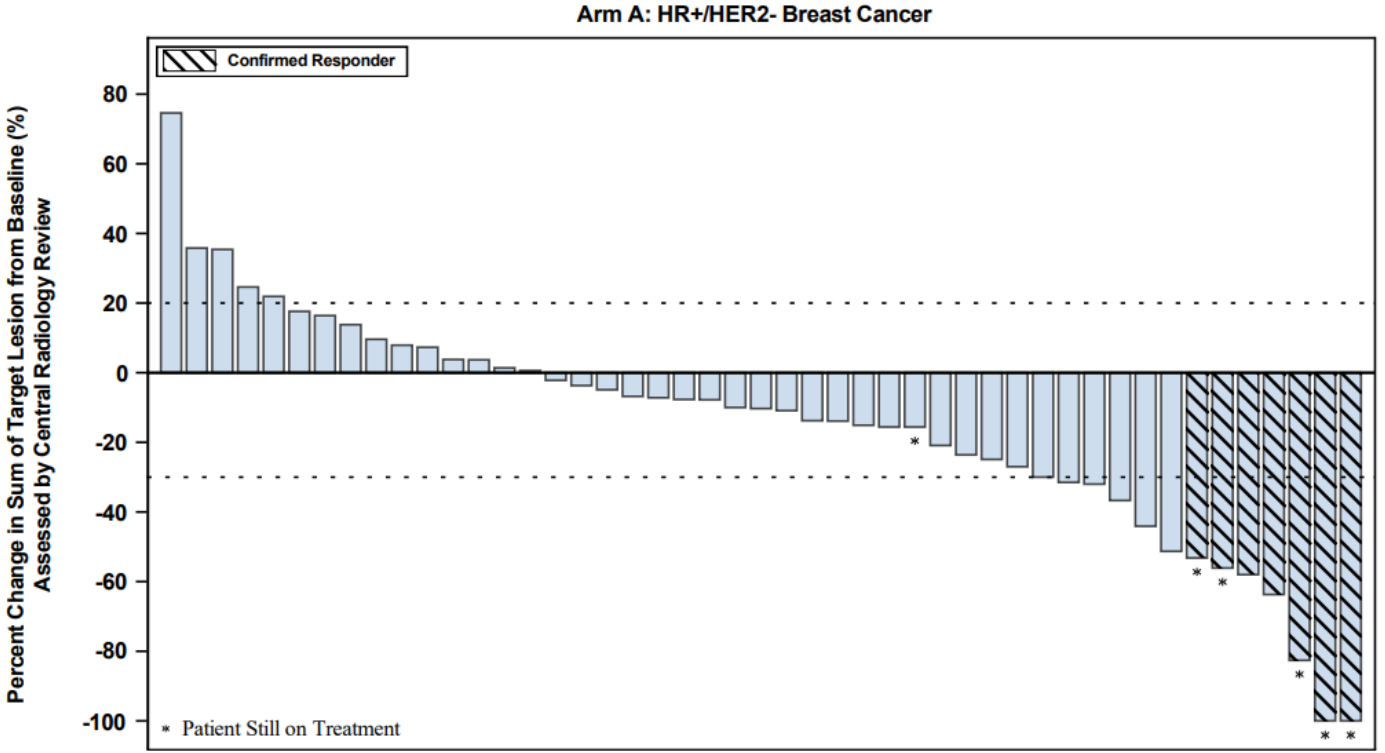
Primary:
Overall Response Rate (ORR) by central review

Secondary:
ORR (Inv), PFS, DCR, CBR24, DoR, OS, Safety, PK, ADA

Exploratory:
Biomarker correlation with outcome

*Efficacy evaluable, ** Naing, A. et al. J Immunother Cancer 2021;9:e002447

CX-2009 Demonstrates Single Agent Activity in HR+/HER2-non-Amplified Breast Cancer(1)



(1) As of the data cutoff on May 13, 2022; Unselected for CD166 expression

Phase 2 CX-2009 Results[1] Support Single-Agent Activity in HR+ BC

Seeking Partnership to Further Develop Program

Arm A – HR+/HER2-non-amplified breast cancer

- Confirmed ORR at 15% met primary efficacy endpoint
- 47 primary efficacy evaluable patients [2]
- 40% CBR24[3], clinical benefit rate at 24 weeks
- 2.6 months median progression-free survival (mPFS)
- All patients treated at initial Phase 2 starting dose of 7 mg/kg, Q3W
- 30% patients discontinued treatment for an adverse event
  - grade 3+ ocular and neuropathic toxicities 15% and 10%, respectively

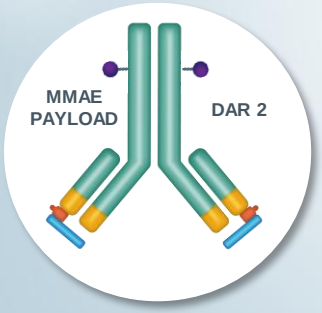
Arm B - triple-negative breast cancer (TNBC)

- Did not pass futility boundary (ORR<10%); enrollment discontinued
- Evaluated 7 mg/kg and 6 mg/kg starting doses
- Toxicity profile of 7 mg/kg starting dose consistent with Arm A
- No patients discontinued treatment for an AE in 6 mg/kg cohort
  - 3% Grade 3+ ocular and neuropathic events 3% and 0%, respectively

- mPFS does not support further evaluation at 7 mg/kg
- Encouraged by the emerging safety profile of 6 mg/kg

(1) As of the data cutoff on May 13, 2022 | (2) Unselected for CD166 expression | (3) Per protocol, any response (confirmed or unconfirmed) or stable disease for 24 weeks

CytomX Therapeutics



Target 2: CD71/Transferrin Receptor

CX-2029

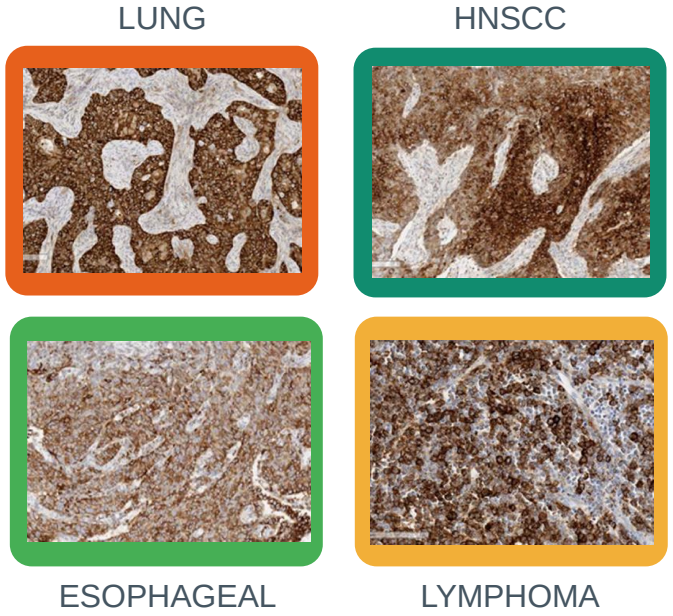
First-in-Class ADC for Multiple Cancer Types

CytomX Therapeutics abbvie

CD71 is a High Potential ADC Target With High Tumor Expression

- CD71 (transferrin receptor): transmembrane glycoprotein responsible for internalization of iron-bound transferrin; highly expressed on malignant cells
- Undruggable target with conventional ADC due to central role in iron metabolism in normal cells
- CX-2029 is a CD71-directed MMAE conjugated conditionally activated ADC
- Anti-cancer agent with first-in-class potential

CD71 Expression by IHC



Data generated by CytomX

Ongoing Multi-Cohort CX-2029 Phase 2 Expansion Study
sqNSCLC, HNSCC and esophageal/GEJ

Patient Enrollment Met Objectives in All Three Indications

Key Eligibility	Cancer Type	Endpoints
• Prior platinum and checkpoint inhibitor required • Documented progression after at least one systemic regimen for advanced disease	**sqNSCLC** n~25* **HNSCC** n~25* **Esophageal/GEJ** n~25*	**Primary:** Overall Response Rate (ORR) by local investigator **Secondary**: PFS, DCR, CBR24, DoR, OS, Safety, PK, ADA, TTR **Exploratory:** Biomarker correlation with outcome **Readout:** Preliminary data for sqNSCLC and HNSCC reported Dec 2021

*Efficacy evaluable

CX-2029 Preliminary Phase 2 ORR of 18.8% in 3L+ SqNSCLC

Enrollment Complete – Data Update Expected in Fourth Quarter 2022

No Current Standard-of-Care in 3L+ Post-Checkpoint Inhibitor Setting

Study	Treatment	Phase	Line	N	Sq NSCLC ORR (%)
CX-2029[1]	**CX-2029**	**2**	**3rd**	**16**	**18.8**
CheckMate 063[2]	Nivolumab	2	3rd	117	14.5
REVEL[3]	Docetaxel	3	2nd	171	10.5
CheckMate 017[4]	Nivolumab	3	2nd	135	20.0
	Docetaxel			137	8.8
OAK[5,6]	Atezolizumab	3	2nd	112	11.6
	Docetaxel			110	8.2

Sources: 1) CytomX press release, 12/20/2021; 2) Rizvi NA, Lancet Oncol 2015; 3) Garon EB, Lancet 2014; 4) Brahmer J, NEJM 2015; 5) Rittmeyer A, Lancet 2017; 6) Cortinovis D, Annals Oncol 2017 Supplement 2, ii32

Preliminary Takeaways from Ongoing Phase 2 Expansion Study

- Heavily-pretreated and unselected sqNSCLC patients (n=16*)
  - Median # prior therapies = 2
  - All received prior checkpoint inhibition
  - Response durability: 5.6 months for 1 PR and two PRs still on therapy**
- HNSCC cohort fully enrolled (n=25*)
  - 4% ORR
- Safety profile consistent with Phase 1 observations
  - No new safety signals identified
  - Anemia most common Grade 3+ adverse event (67%)
  - Low TRAE discontinuation rate, all due to anemia (5.8%)

* Efficacy Evaluable; ** As of data cut off on October 29, 2021

CytomX Therapeutics

Learnings From the Clinical Evaluation of Conditional ADCs

- We have obtained single agent activity against previously undruggable targets using our Probody therapeutic conditional activation platform
- Conditional activation can protect against target-mediated toxicity, but payload toxicity remains a consideration
- The FDA Project Optimus initiative to reform the dose optimization/selection paradigm in oncology is particularly relevant for ADCs and can be informed by QSP modeling
- In order to drive the widest possible therapeutic index, it is important to **tailor the selection of target, payload, and tumor type** for conditionally activated ADCs
- Our next generation of conditionally activated ADCs employs that strategy

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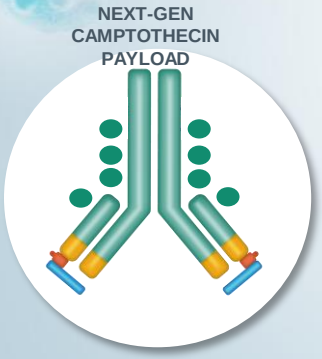


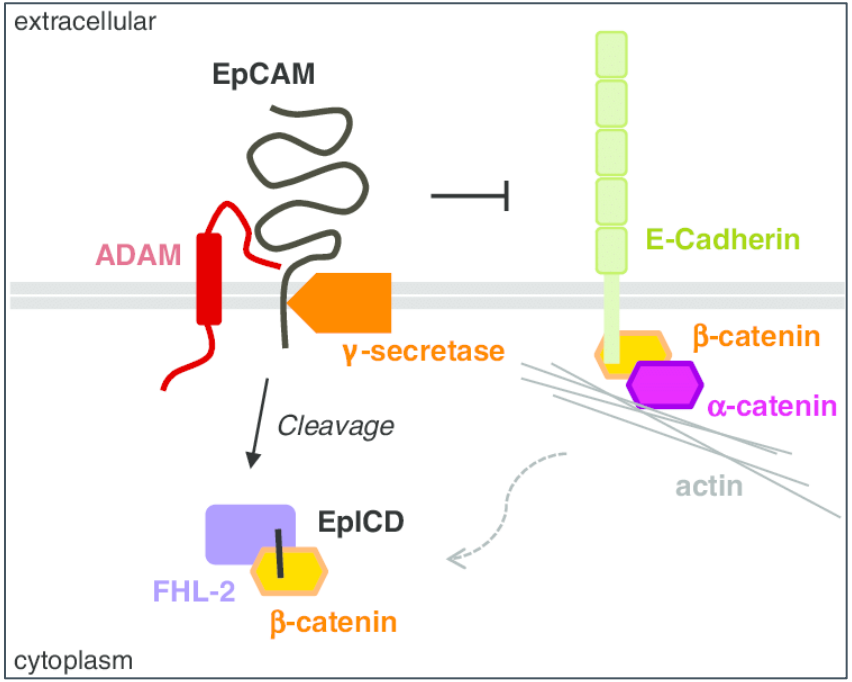
Target 3: EpCAM

CX-2051

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

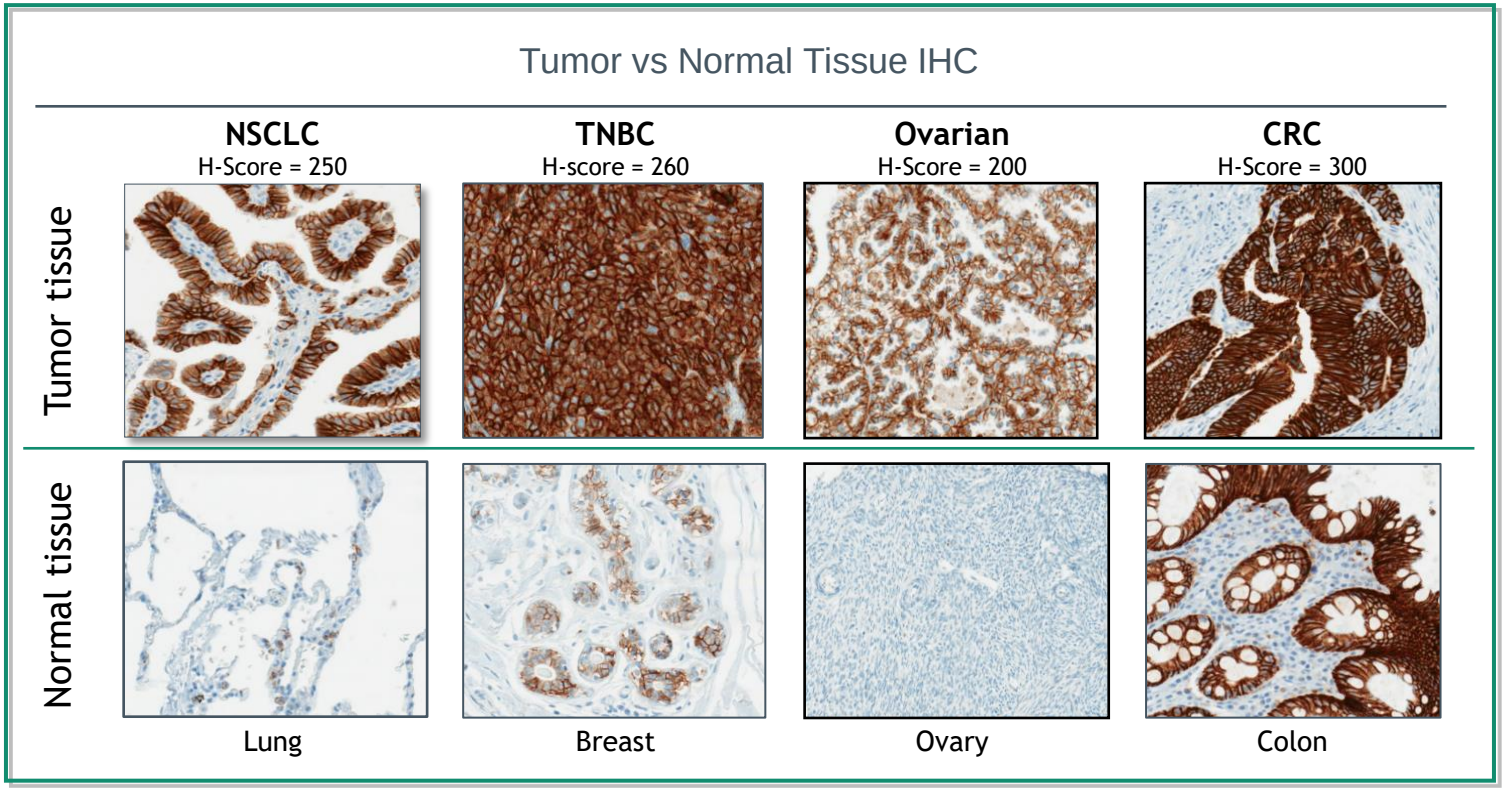
EpCAM (Epithelial Cell Adhesion Molecule) is an Attractive ADC Target
High expression on multiple solid tumors

- **Highly expressed on cancer cells**
  - Both adeno and squamous histologies
- **Functional role in cancer signaling**
  - Involved in tumor progression and cell cycle via WNT/EGFR
- **Expressed on circulating tumor cells**
  - Associated with stem / progenitor cells
  - Prognostic value varies by tumor type



EpCAM: A Compelling Target for a Conditionally Activated ADC

High expression in tumors; moderate expression in normal tissues



EpCAM Has Been Clinically Validated But Not As a Systemic Therapy

Locally administered EpCAM therapies have demonstrated impressive efficacy

- Removab (catumaxomab): EpCAM x CD3 bispecific
- Delivered by intraperitoneal infusion
- Approved for treatment of malignant ascites (but later withdrawn for commercial reasons)

Insys Therapeutics

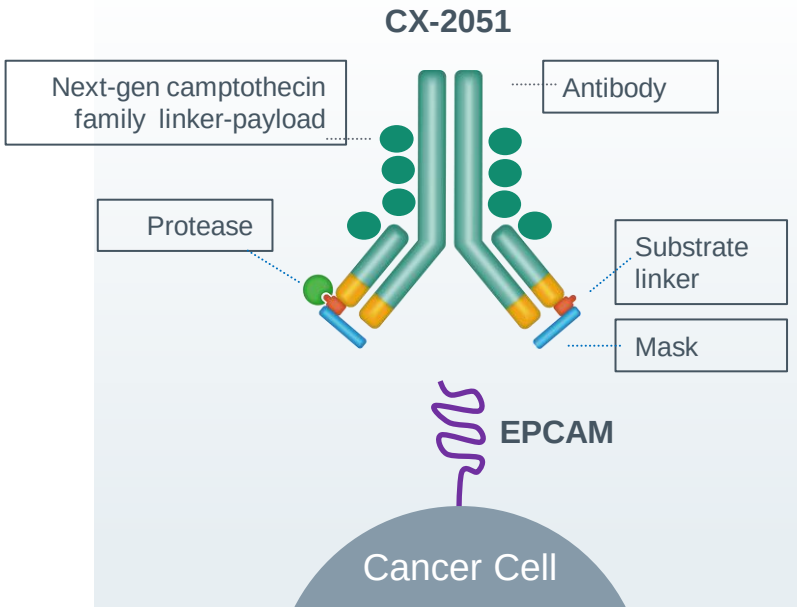
- Vicineum fusion protein: anti-EpCAM scFv linked to a truncated form of Pseudomonas exotoxin A
- Delivered by intravesical administration
- Phase 3 in bladder cancer

Sesen Bio

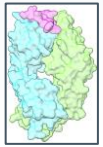
Systemic EpCAM therapies have demonstrated clinical toxicity

Asset	Company	MOA	Stage	Status
Solitomab	Amgen	EpCAM x CD3 BiTE	Ph 1	GI tox reported; discontinued
ING-1	XOMA	EpCAM mAb	Ph 1	Pancreatitis reported; discontinued
3622W94	GSK	EpCAM mAb	Ph 1	Pancreatitis reported; discontinued

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



- Anti-EpCAM MAb with cross-reactivity to cynomolgus monkey
- Probody peptide mask with >60X masking efficiency (by ELISA)
- Protease-cleavable substrate with broad cleavability profile across multiple tumor types
- Next-gen camptothecin linker-payload (licensed from Immunogen)
- Optimized linker drives large bystander effect
- Inter-chain cysteine conjugation DAR8
- Crystal structure of mask interaction with antibody has been solved



Program licensed from ImmunoGen

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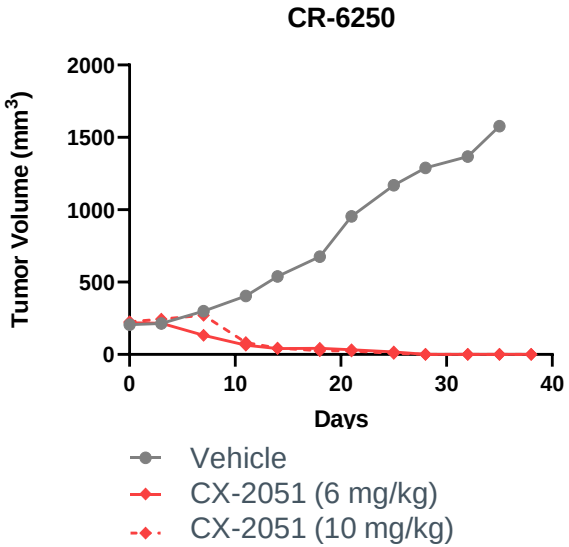
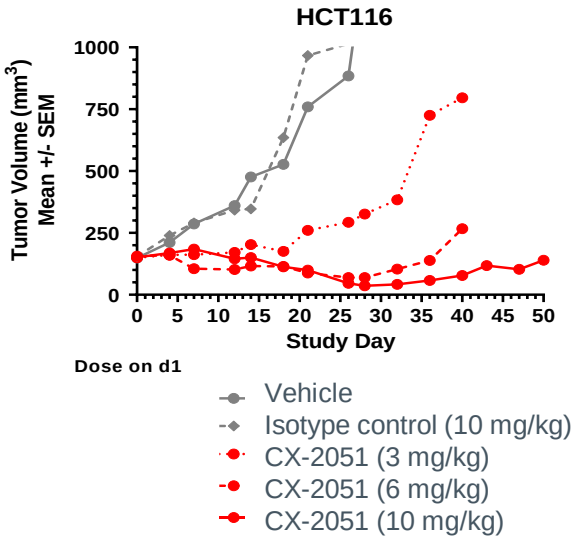
CX-2051 Demonstrates Strong Activity in Preclinical Models





PDX: Patient derived xenograft; CDX: Cell derived xenograft
CR-6250 and HCT116: Colorectal cancer models

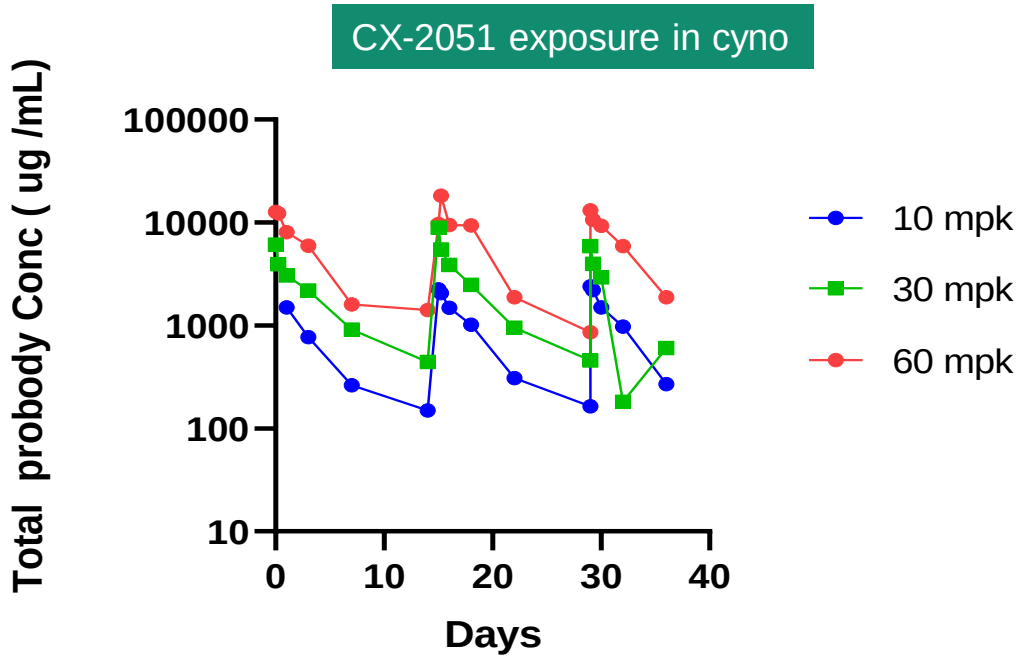
Dosing regimen: Q2W x 3

- **Regression observed in multiple preclinical models**
- **Efficacy is dependent on target engagement**

CytomX Therapeutics

CX-2051 Shows Dose Proportional Pharmacokinetics in Cynomolgus Monkey

Exposure is maintained after each dose (Q2W x3)



- Consistent exposure across individuals
- Well-behaved pharmacokinetic profile
- Increased exposure with increase dose
- No evidence of decreased exposure upon repeat dosing

CX-2051 is Well Tolerated in Cynomolgus Monkey Up To 60mpk

Multidose Exploratory Toxicology Study (3 x Q2W)

Tolerability Summary

Dosing (3 x Q2W)	CX-2051	Isotype
10 mpk	Tolerated (2/2)	
30 mpk	Tolerated (2/2)	
60 mpk	Tolerated (3/3)	Tolerated (2/2)
90 mpk	Not Tolerated (1/2)	

✓ No Evidence of Pulmonary Tox (including post-recovery)

CX-2051 Summary and Next Steps

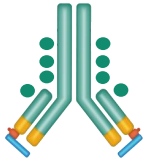
- CX-2051 is a conditionally activated ADC targeting EpCAM using Probody therapeutic technology
- CX-2051 contains a next generation camptothecin payload with a linker that is optimized for potent bystander activity
- CX-2051 demonstrates strong preclinical activity and tolerability, with a favorable predicted therapeutic index
- EpCAM expression and tecan sensitive tumor types provide a clear path forward
- CX-2051 is on track to file an IND in the second half of 2023

Conclusions

ADCs are an increasingly successful therapeutic modality in oncology with a high number of approvals in recent years, but with limited target space

Conditional activation, using Probody therapeutic technology, widens the target space for ADCs

Tailoring the target, payload, and tumor type maximizes the potential therapeutic index



CX-2051 is a next generation conditionally active EpCAM Probody® ADC targeting IND in 2H 2023

CytomX Therapeutics

Thank you!