CytomX Therapeutics

Conditionally Activated Therapeutics for the Treatment of Cancer

Investor Event

APRIL 7, 2021

Forward-Looking Statements

This presentation may contain projections and other forward-looking statements regarding future events. All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, technology platform, development strategy, prospective products, preclinical and clinical pipeline and milestones, regulatory objectives, expected payments from and outcomes of collaborations, and likelihood of success, are forward-looking statements. Such statements are predictions only and involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These risks and uncertainties include, among others, the costs, timing and results of preclinical studies and clinical trials and other development activities; the uncertainties inherent in the initiation and enrollment of clinical trials; the uncertainties associated with the COVD-19 pandemic; expectations of expanding on-going clinical trials; availability and timing of data from clinical trials; the unpredictability of the duration and results of regulatory review; market acceptance for approved products and innovative therapeutic treatments; competition; the potential not to receive partnership milestone, profit sharing or royalty payments; the possible impairment of, inability to obtain and costs of obtaining intellectual property rights; and possible safety or efficacy concerns, general business, financial and accounting risks and litigation. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. More information concerning us and such risks and uncertainties is available on our website and in our press releases and in our public filings with the U.S. Securities and Exchange Commission. We are providing this information as of its date and do not undertake any obligation to update or revise it, whether as a result of new information, future events or circumstances or otherwise. Additional information may be available in press releases or other public announcements and public filings made after the date of this presentation.

This presentation concerns products that have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). No representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

CytomX Therapeutics

Welcome and Opening Remarks

Sean A. McCarthy, D.Phil.
President, Chief Executive Officer and Chairman

Company Snapshot

Clinical-Stage Oncology Focused Biopharma Company

Conditionally Activated Antibodies

- Probody Therapeutic™ Platform
- Leverages tumor microenvironment
- Opens previously undruggable target space

Key 2021 Milestones

- CX-2009 initial Phase 2 data in breast cancer
- CX-2029 initial Phase 2 expansion cohort data
- Next IND filings

Foundational Partnerships

- AbbVie, Amgen, Astellas & BMS
- Retained certain US rights

Strong Balance Sheet

- $316M cash at end of Q4 2020
- Additional $108M from equity offering Jan 2021

Agenda

10:00 am – 10:10 am	Welcome and Opening Remarks *Sean A. McCarthy, D. Phil., President, Chief Executive Officer, and Chairman*	
10:10 am – 10:30 am	Probody Platform Design, Optimization, and Versatility *Marcia P. Belvin, Ph.D., Senior Vice President, Head of Research*	
10:30 am – 10:50 am	Addressing Novel Oncology Targets with Probody Drug Conjugates *John Lambert, Ph.D., Former CSO, ImmunoGen Inc.*	
10:50 am – 10:55 am	Clinical Pipeline Overview *Amy C. Peterson, M.D., Executive Vice President, Chief Development Officer*	
10:55 am – 11:15 am	Praluzatamab Ravtansine (CX-2009) – anti-CD166 Conditional ADC *Sara M. Tolaney, M.D., Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*	
11:15 am – 11:35 am	CX-2029 – anti-CD71 Conditional ADC *Melissa L. Johnson, M.D., Sarah Cannon Research Institute, Nashville, TN*	
11:35 am – 11:45 am	Closing Remarks and Future Outlook *Sean A. McCarthy, D. Phil., President, Chief Executive Officer, and Chairman*	
11:45 am – 12:00 pm	Q&A Session	

CytomX Therapeutics

Probody Platform Design, Optimization and Versatility

Marcia P. Belvin, Ph.D.

Senior Vice President and Head of Research

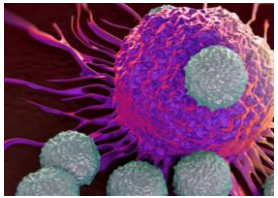
The Promise of Conditionally Activated Cancer Therapy

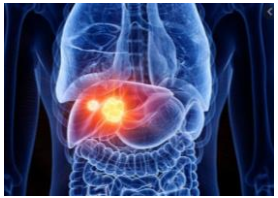
Traditional Chemotherapy

Targeted Therapy

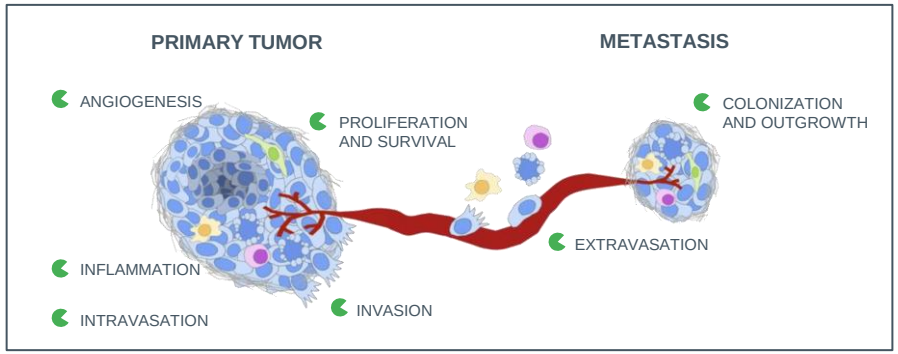
I/O Therapy

Conditionally Activated Therapy



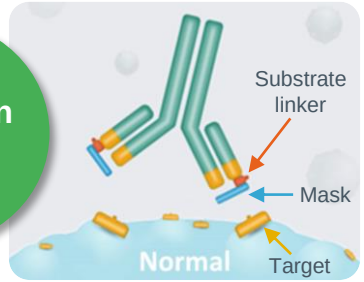


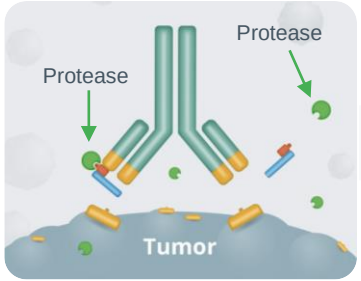
The Probody® Therapeutic Platform

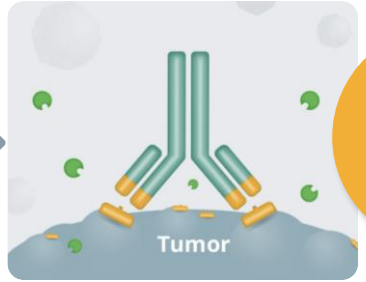


Upregulated protease activity is a hallmark of cancer

Less Binding in Normal Tissues







More Binding in Tumors

"Masking" limits ability of conditionally activated antibody to bind to healthy tissues

Proteases in tumor microenvironment "unmask" conditionally activated antibody, allowing more binding to tumor cells

CytomX Therapeutics

PROBODY is a U.S. registered trademark of CytomX Therapeutics, Inc. All other brands and trademarks referenced herein are the property of their respective owners.

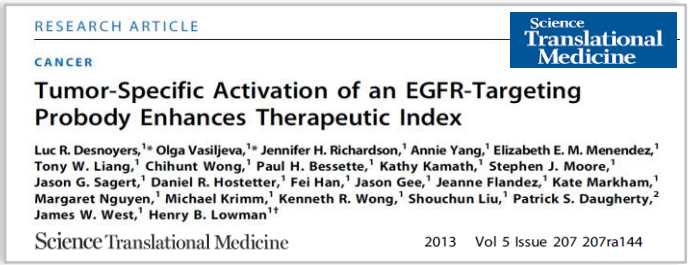
CytomX is Leading Research in the Field of Tumor Protease Biology

DE GRUYTER Biol. Chem. 2019; 400(8): 965–977

Review

Olga Vasiljeva*, Daniel R. Hostetter, Stephen J. Moore and Michael B. Winter

The multifaceted roles of tumor-associated proteases and harnessing their activity for prodrug activation



RESEARCH ARTICLE

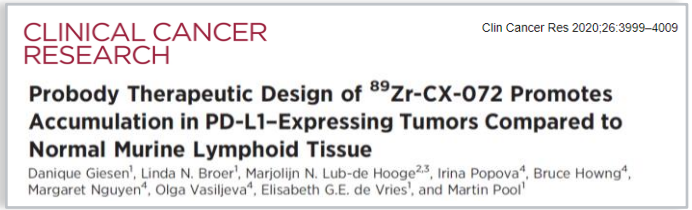
Science Translational Medicine

CANCER

Tumor-Specific Activation of an EGFR-Targeting Probody Enhances Therapeutic Index

Luc R. Desnoyers,[1]* Olga Vasiljeva,[1]* Jennifer H. Richardson,[1] Annie Yang,[1] Elizabeth E. M. Menendez,[1] Tony W. Liang,[1] Chihunt Wong,[1] Paul H. Bessette,[1] Kathy Kamath,[1] Stephen J. Moore,[1] Jason G. Sagert,[1] Daniel R. Hostetter,[1] Fei Han,[1] Jason Gee,[1] Jeanne Flandez,[1] Kate Markham,[1] Margaret Nguyen,[1] Michael Krimm,[1] Kenneth R. Wong,[1] Shouchun Liu,[1] Patrick S. Daugherty,[2] James W. West,[1] Henry B. Lowman[1†]

Science Translational Medicine 2013 Vol 5 Issue 207 207ra144



CLINICAL CANCER RESEARCH

Clin Cancer Res 2020;26:3999–4009

Probody Therapeutic Design of ^{89}Zr-CX-072 Promotes Accumulation in PD-L1–Expressing Tumors Compared to Normal Murine Lymphoid Tissue

Danique Giesen[1], Linda N. Broer[1], Marjolijn N. Lub-de Hooge[2,3], Irina Popova[4], Bruce Howng[4], Margaret Nguyen[4], Olga Vasiljeva[4], Elisabeth G.E. de Vries[1], and Martin Pool[1]

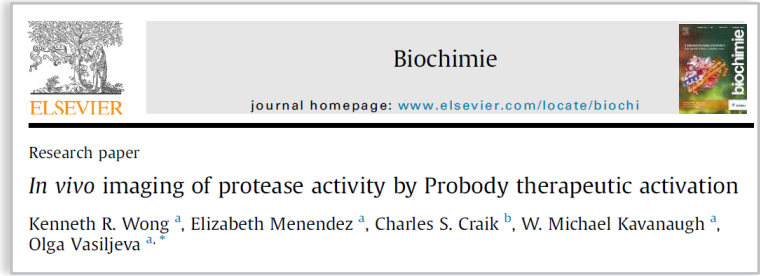
Monitoring protease activity in biological tissues using antibody prodrugs as sensing probes

SCIENTIFIC REPORTS nature research

Olga Vasiljeva[1*], Elizabeth Menendez[1], Margaret Nguyen[1], Charles S. Craik[2] & W. Michael Kavanaugh[1]

nature publishing group npg

SCIENTIFIC REPORTS | (2020) 10:5894 | https://doi.org/10.1038/s41598-020-62339-7



ELSEVIER

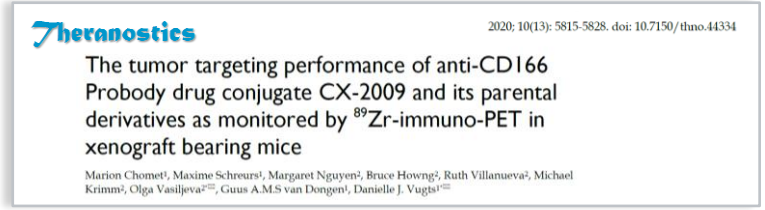
Biochimie

journal homepage: www.elsevier.com/locate/biochi

Research paper

In vivo imaging of protease activity by Probody therapeutic activation

Kenneth R. Wong [a], Elizabeth Menendez [a], Charles S. Craik [b], W. Michael Kavanaugh [a], Olga Vasiljeva [a, *]

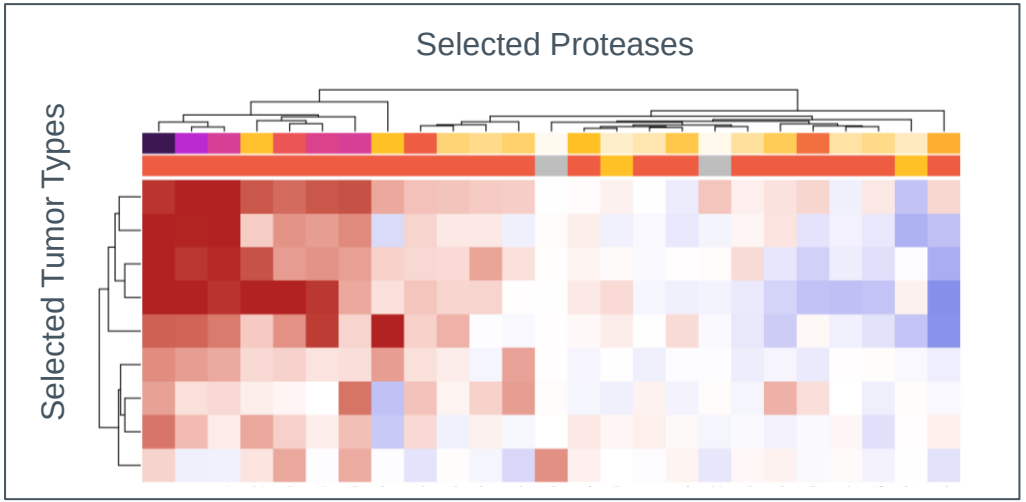


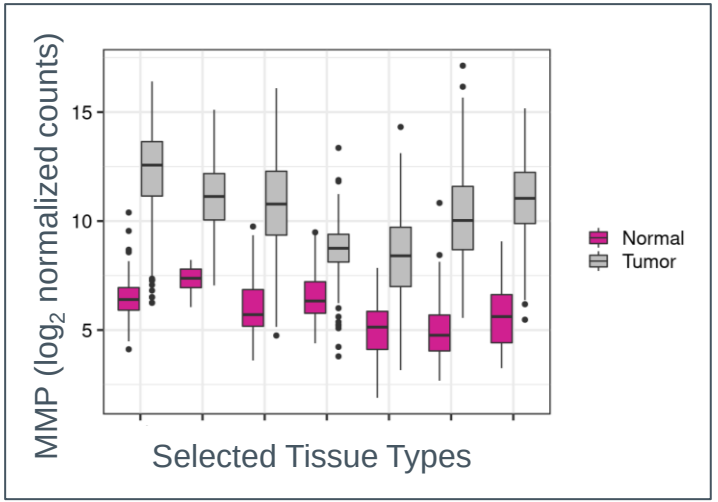
Theranostics 2020; 10(13): 5815-5828. doi: 10.7150/thno.44334

The tumor targeting performance of anti-CD166 Probody drug conjugate CX-2009 and its parental derivatives as monitored by ^{89}Zr-immuno-PET in xenograft bearing mice

Marion Chomet[1], Maxime Schreurs[1], Margaret Nguyen[2], Bruce Howng[2], Ruth Villanueva[2], Michael Krimm[2], Olga Vasiljeva[2✉], Guus A.M.S van Dongen[1], Danielle J. Vugts[1✉]

Systems Biology Provides Insights into Protease Differences in Tumors vs. Normal Tissue





- Specific proteases are up-regulated in tumor vs. normal in multiple tumor types
- Common and unique signatures inform protease substrate design

CytomX Therapeutics

Development of Multi-Selective Protease Substrates for Anti-Cancer Probody Therapy

CytomX has Developed Novel Methods to Measure Protease Activity in Tumors

Monitoring protease activity in biological tissues using antibody prodrugs as sensing probes

SCIENTIFIC REPORTS
nature research

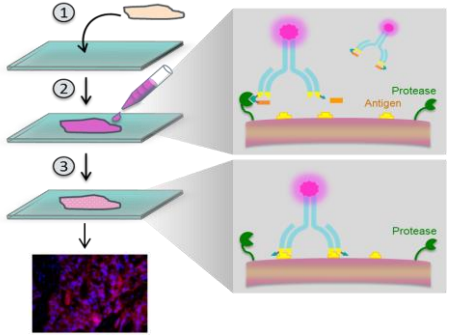
Olga Vasiljeva[1*], Elizabeth Menendez[1], Margaret Nguyen[1], Charles S. Craik[2] & W. Michael Kavanaugh[1]

nature publishing group npg

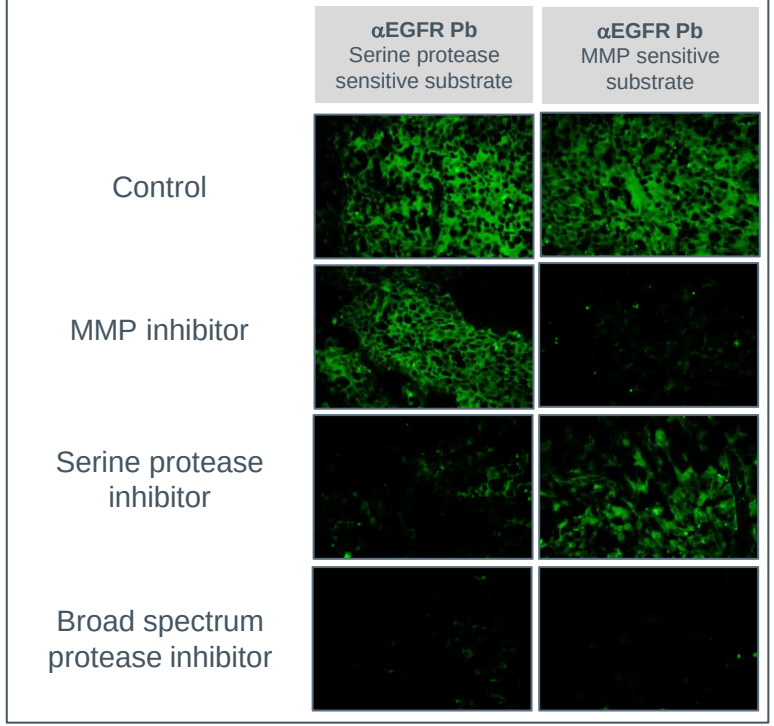
SCIENTIFIC REPORTS | (2020) 10:5894 | https://doi.org/10.1038/s41598-020-62339-7

Immunohistozymography (IHZ™) measures protease activity in situ

IHZ Assay



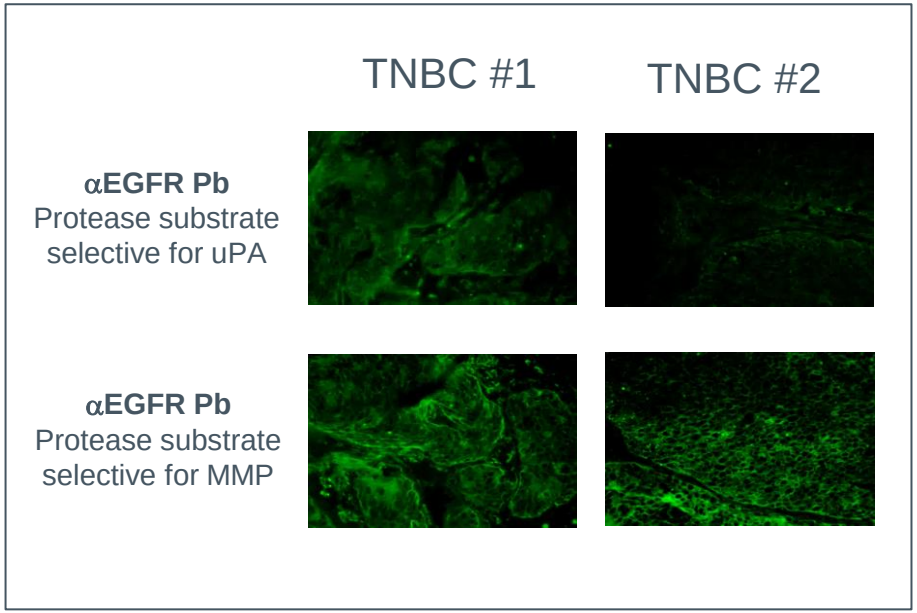
Anti-EGFR Probodies staining H292 NSCLC xenograft tissue



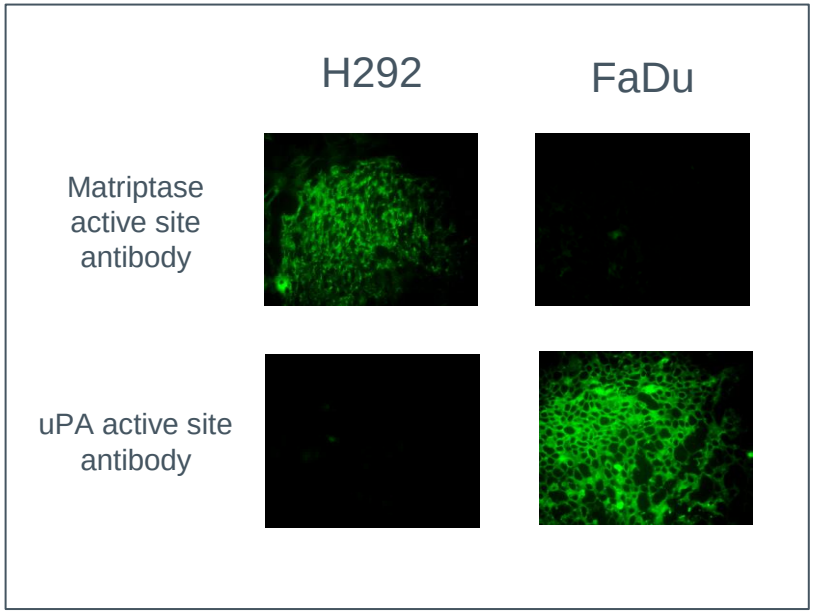
Vasiljeva et al., Sci. Rep. 2020, 10(1) 5894

Tumors Display Distinct Profiles of Protease Activity

Human TNBC Tumors



Xenograft Tumors

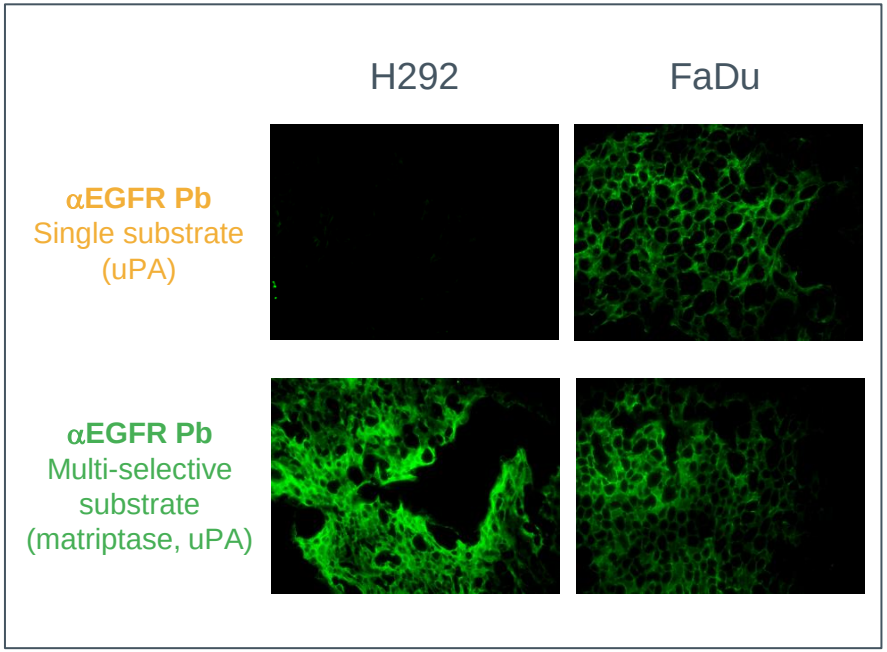


H292: Mucoepidermoid lung cancer; FaDu: HNSCC
uPA: urokinase plasminogen activator

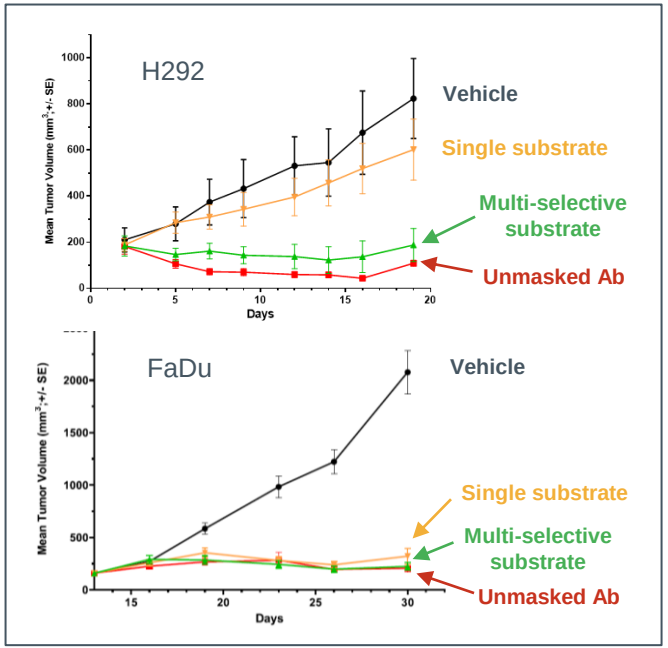
Vasiljeva et al., Sci. Rep. 2020, 10(1) 5894

Multi-Selective Substrates Broaden the Activity of Protease-Activated Agents

Activity ex vivo (IHZ)



Activity in vivo

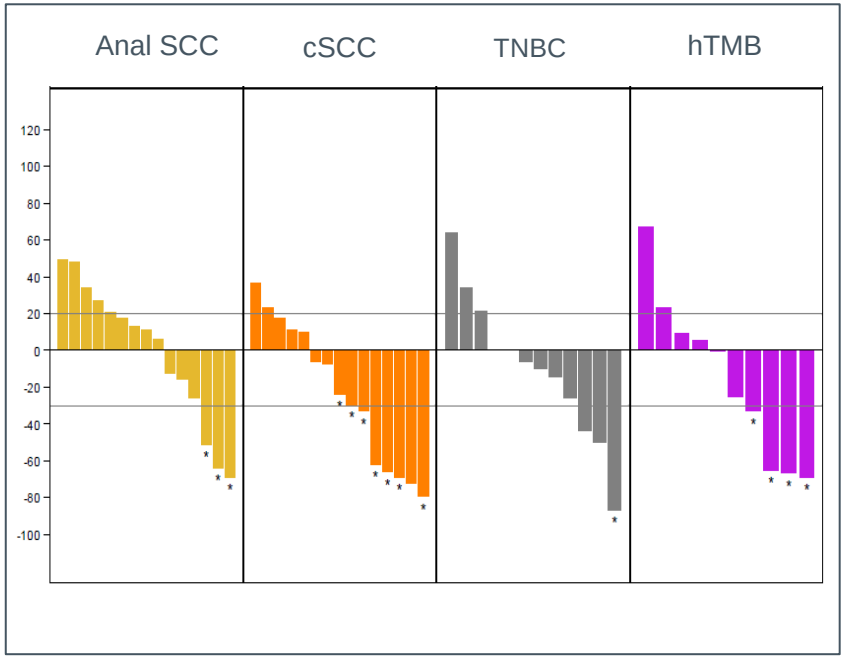


Vasiljeva et al., Sci. Rep. 2020, 10(1) 5894

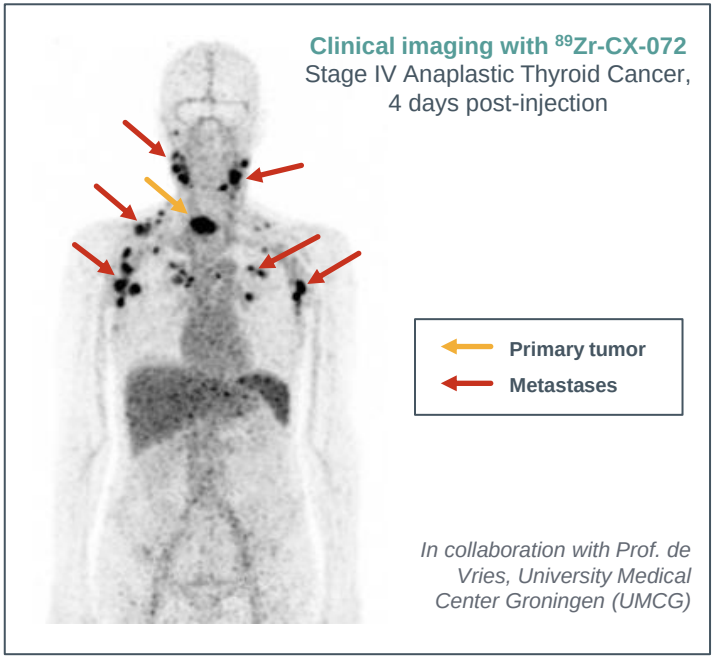
Multi-Selective Protease Substrate Strategy Translation to the Clinic

Broad Anti-Cancer Activity of First Probody Therapeutic Evaluated in Phase 1/2

Clinical activity of Pacmilimab (CX-072, Anti-PD-L1 Pb)



Uptake in primary and metastatic lesions



* Denotes patient on treatment as of data cut-off date 20 April 2020. Includes all evaluable patients from dose escalation at 10 mg/kg (n=2, TNBC and anal SCC) and dose expansion. aSCC: anal squamous cell carcinoma, cSCC: cutaneous squamous cell carcinoma, TNBC: triple-negative breast cancer, hTMB: high tumor mutational burden. **Thistlethwaite et al.** *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) Abstract 3005

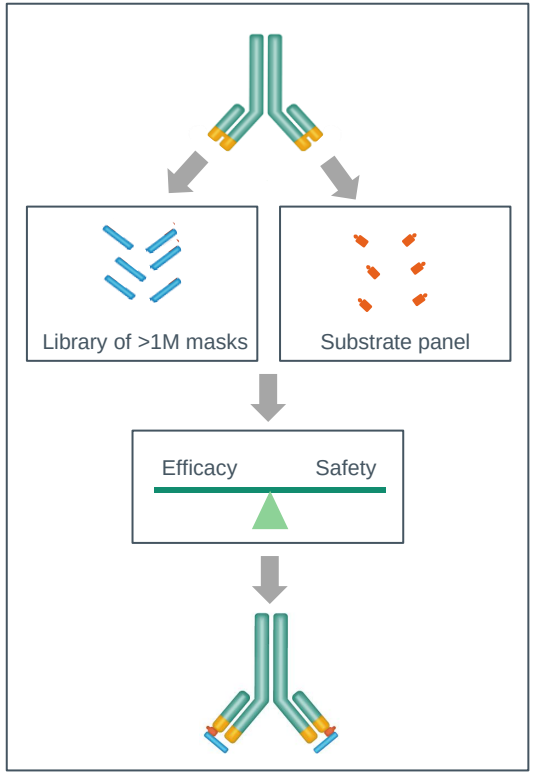
CytomX Therapeutics

CytomX Therapeutics

Probody Platform Versatility

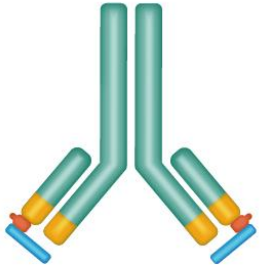
The Probody Platform is Versatile and Tunable

- Affinity based masking enables choice of masking efficiency
- Protease substrate panel enables choice of cleavability
- Ability to optimize therapeutic index based on target and modality



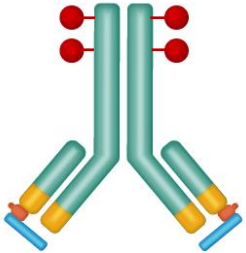
Probody Platform Versatility Extends to Multiple Biologic Formats

IMMUNE MODULATORS/ CHECKPOINT INHIBITORS



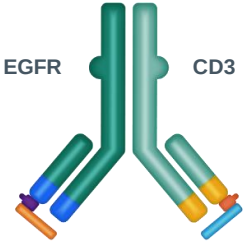
PD-L1 (CX-072)
PD-1 (CX-188)
CTLA-4 (BMS-986249, 986288)

ANTIBODY-DRUG CONJUGATES



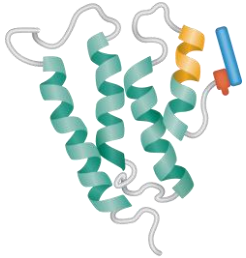
CD166 (CX-2009)
CD71 (CX-2029)
EpCAM (CX-2043)

T-CELL BISPECIFICS



EGFR-CD3 (CX-904)

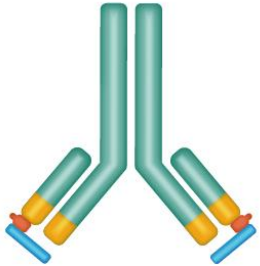
CYTOKINES



IFNα-2b
Additional discovery stage programs

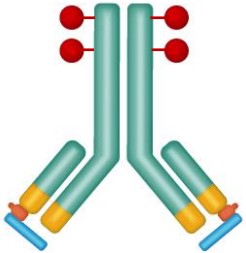
Focus on Conditionally Activated Antibody-Drug Conjugates

IMMUNE MODULATORS/ CHECKPOINT INHIBITORS



PD-L1 (CX-072)
PD-1 (CX-188)
CTLA-4 (BMS-986249, 986288)

ANTIBODY-DRUG CONJUGATES



CD166 (CX-2009)
CD71 (CX-2029)
EpCAM (CX-2043)

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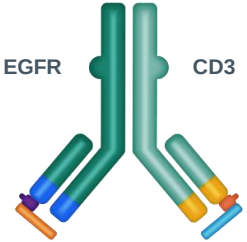
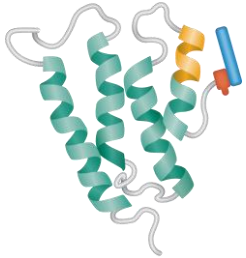


EGFR-CD3 (CX-904)

CYTOKINES



IFNα-2b
Additional discovery stage programs

CytomX Therapeutics

Addressing Novel Oncology Targets with Probody Drug Conjugates

John Lambert, Ph.D.

Former CSO, ImmunoGen Inc.

Honorary Professor, Queen's University, Belfast, UK

Member of CytomX Scientific Advisory Board

The Basic Components of an ADC

Antibody

- Stable, non-immunogenic IgG
- Target antigen - Highly expressed on surface of all target cells
- Internalized efficiently
- Target largely absent from all other normal cells

Conjugate/Linker

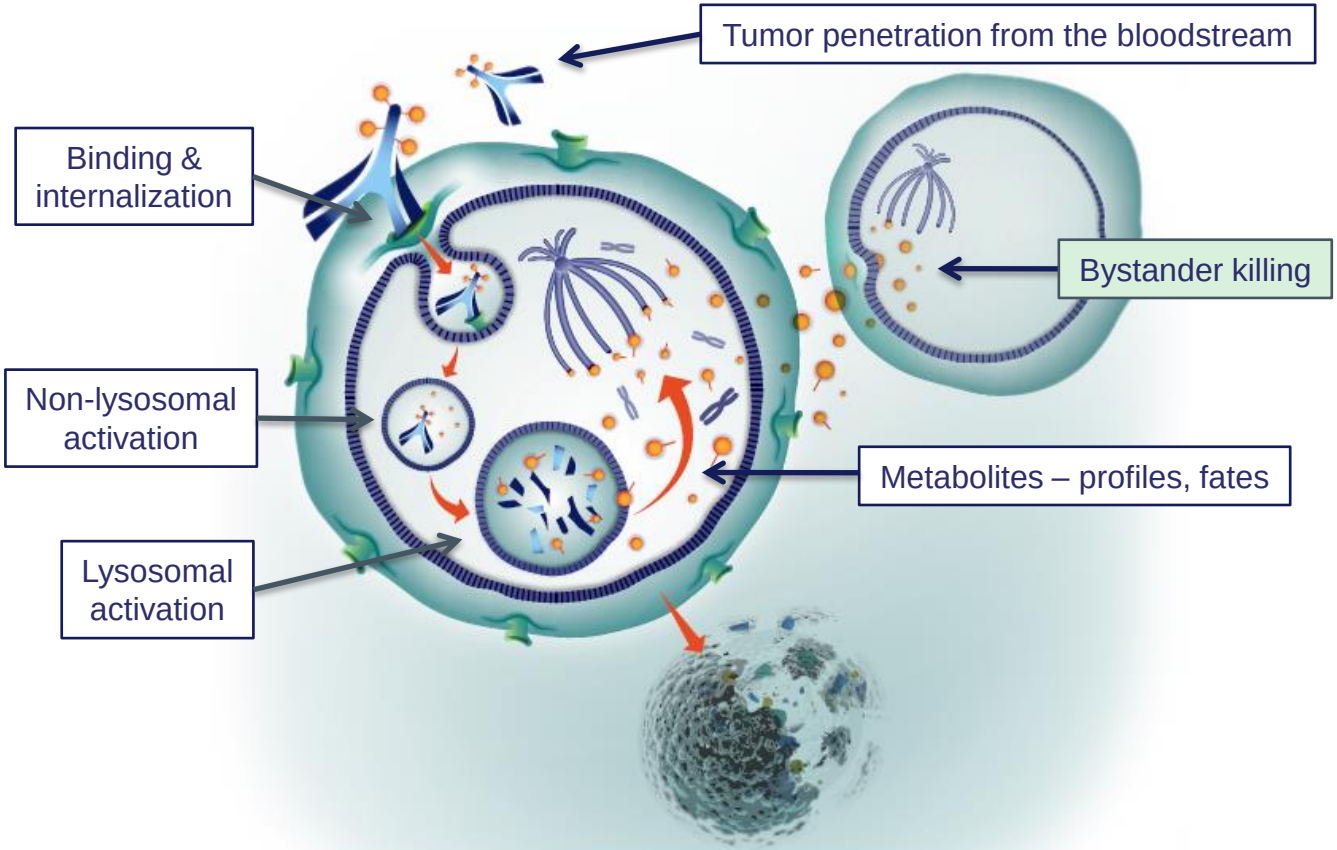
- Stable linkage
- Release triggered ***only*** in target cells

Drug/Payload

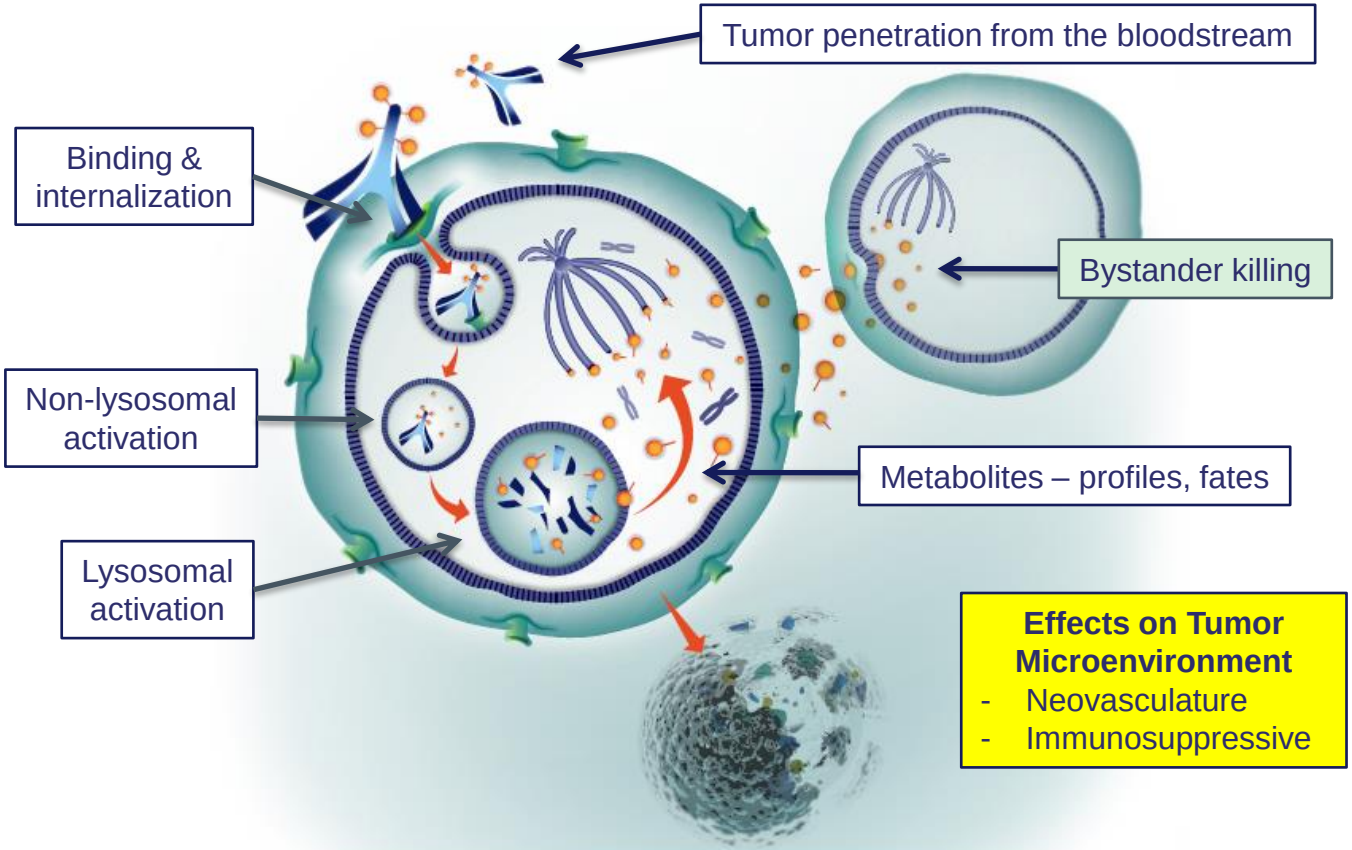
- Highly cytotoxic drug (pM)
- Kills tumor cells rapidly
- Rapidly de-toxified after release
- Soluble for conjugation to proteins
- Active in the targeted cancer indication

Adapted from P. Polakis *Pharmacological Reviews* 2015

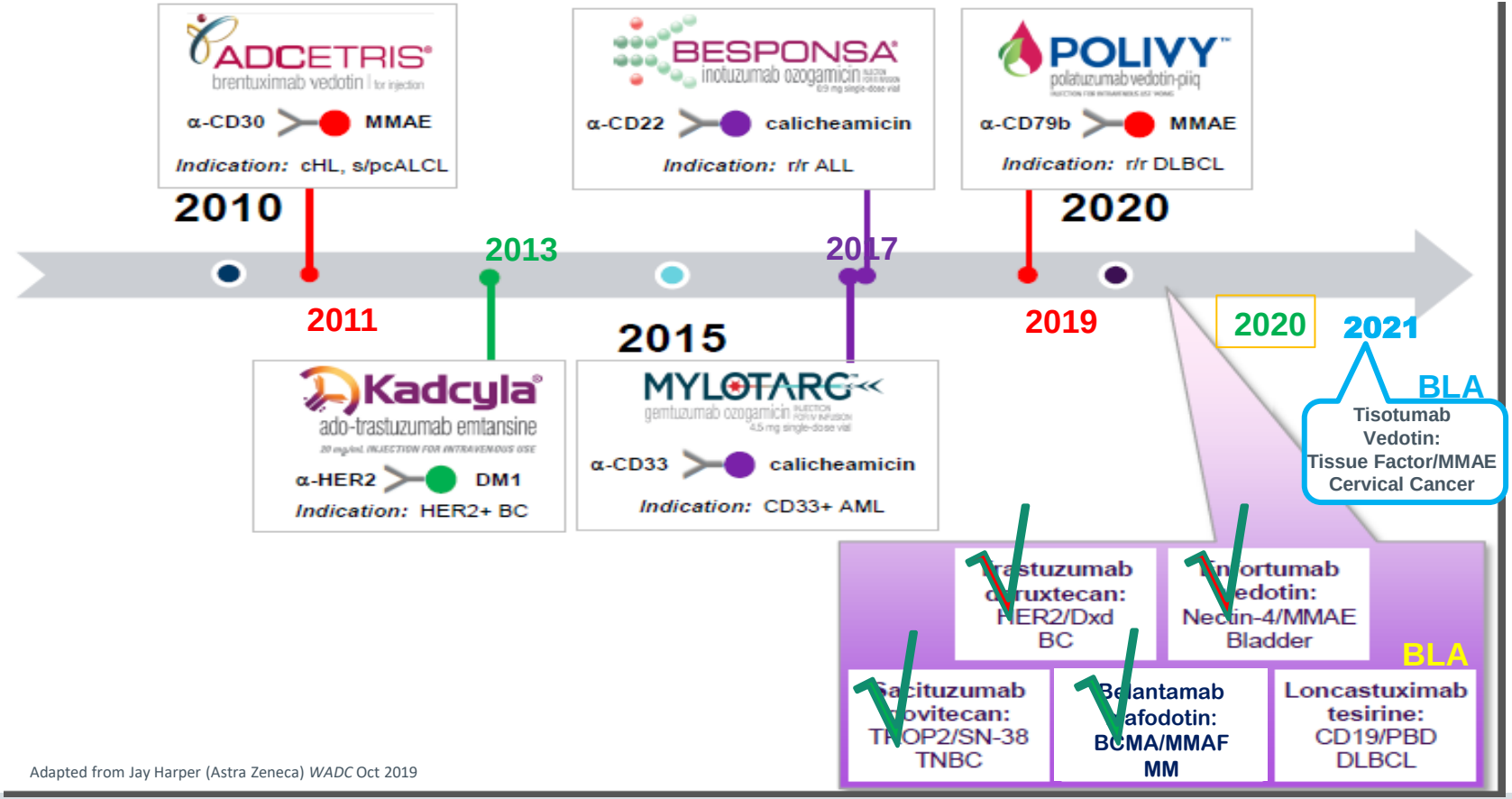
ADCs – The Challenge and the Opportunity: Using Antibodies to Provide Specificity to Cytotoxic Compounds



ADCs – The Challenge and the Opportunity: Using Antibodies to Provide Specificity to Cytotoxic Compounds



Approved ADCs and Those Close to Launch

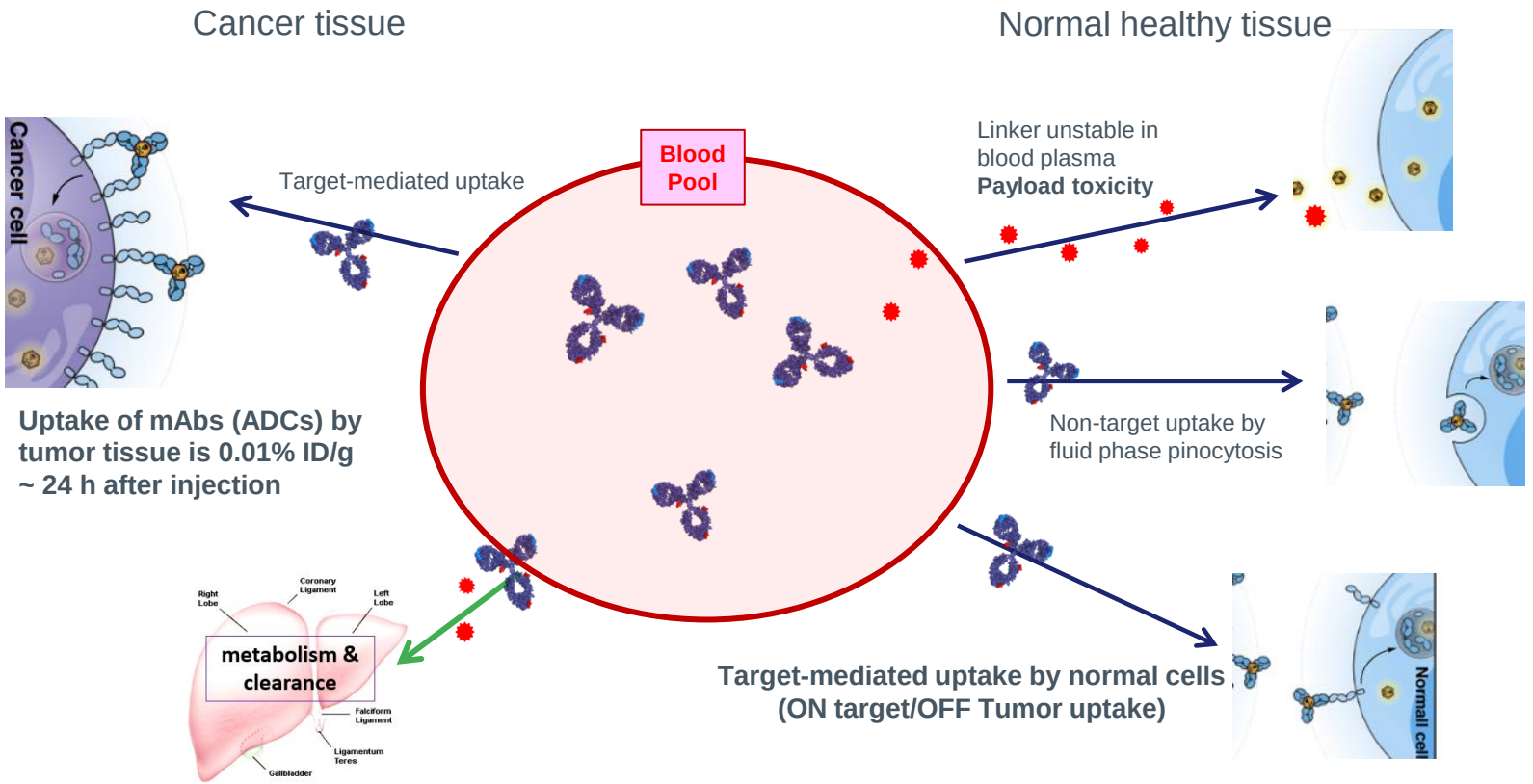


Adapted from Jay Harper (Astra Zeneca) *WADC* Oct 2019

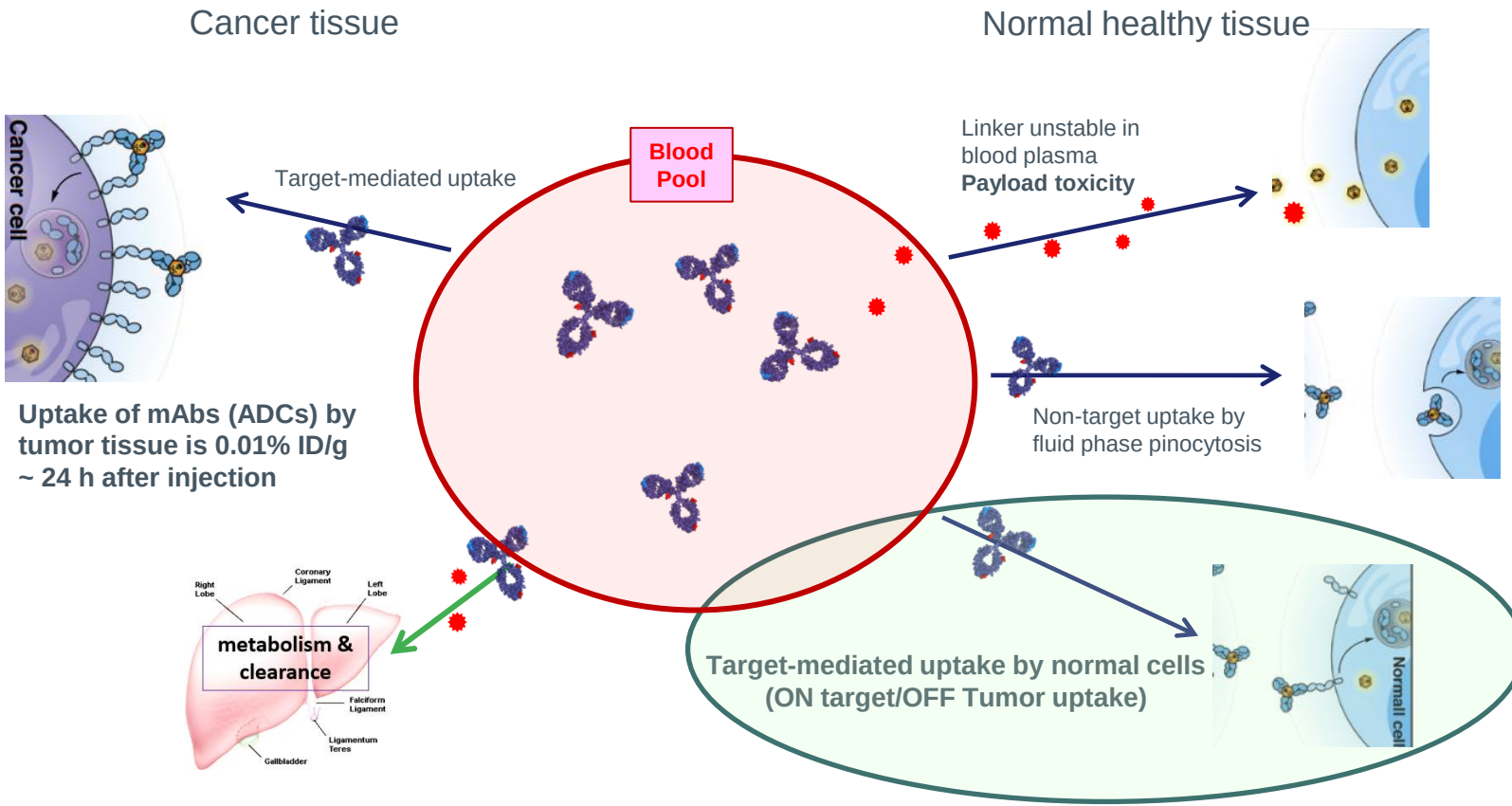
CytomX Therapeutics

Payload Considerations for Antibody-Drug Conjugates

ADC Catabolism – Multiple Mechanisms of Payload Toxicity



Non-specific Uptake Independent of Target is a Mediator of ADC Toxicity



MMAE and DM4 are Well-Validated Payloads With Predictable Toxicity Profiles

Payload	Targets	Indication	MTD (Q3W)	DLT
MMAE	MSLN CD22 CD79b NaPi2b STEAP1	Pancreatic NHL NHL Ovarian Prostate	~2.5 mg/kg	• Neutropenia • Anemia • Neuropathy
DM4	FRα CD19 CanAg CA6 MSLN CEACAM5	Ovarian NHL Colon, Gastric Breast Mesothelioma Colon, Lung	~ 6 mg/kg	• Reversible blurred vision and associated corneal keratopathy

ADC platform-associated toxicity

- Independent of target
- Reflects ADC payload
- Familiar to clinicians

CytomX has selected clinically-validated payloads for its lead conditional ADC programs

- ❑ CX-2009: DM4
- ❑ CX-2029: MMAE

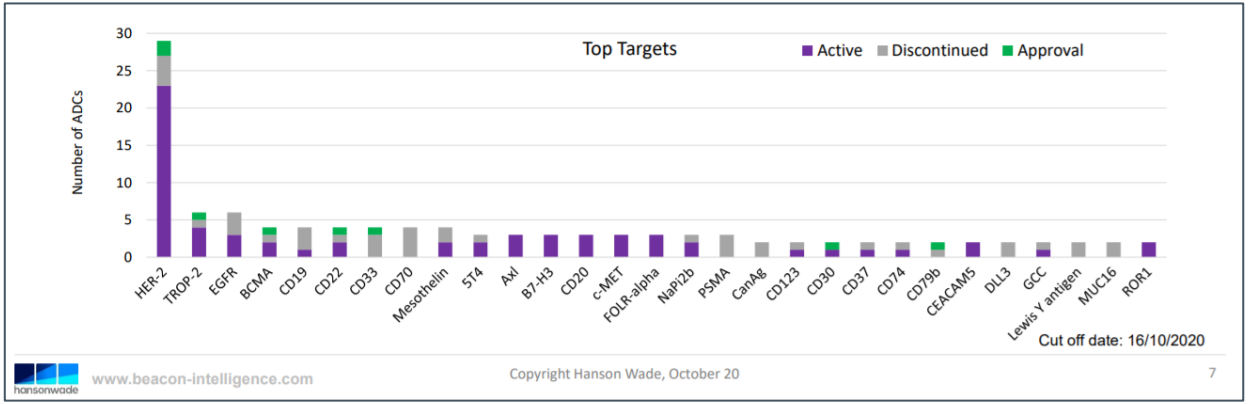
CytomX Therapeutics

Conditional Technology Expands the Target Landscape

Targets that Meet the Criteria for Successful ADCs are Limited

- Target antigen
  - Tumor specific
  - Minimal normal tissue expression
  - High expression on tumor cells
  - Uniform expression on all cancer cells in tumor tissue
  - High prevalence in cancer
  - Internalizing

- Examples of target antigens that fit most of the criteria
  - HER2 on HER2+ breast cancer
  - Lineage-specific markers in hematologic cancers



New Targets for Conventional ADCs are a Challenge

- There are many targets that would meet all criteria, except for having minimal normal tissue expression
- Such targets are considered undruggable by ordinary ADCs
  - Normal tissue removes ADC from circulation, the rapid clearance thus compromising delivery to tumor tissue
  - Delivery of payload to normal tissue may result in unwanted target-mediated toxicity
- Rationale for conditional activation of ADCs binding only within the tumor microenvironment

Conditional Activation Broadens Target Landscape for ADCs

Targets for traditional ADCs

Targets with no/low expression on normal tissue

Traditional ADC targets

High Expression on Tumors

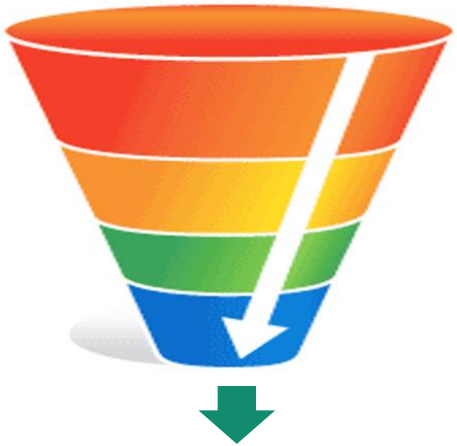
Internalization and trafficking to lysosome

Cytotoxicity, Efficacy

Tolerability

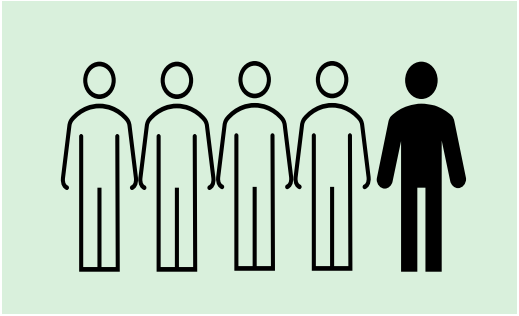
Targets for **conditional** ADCs

Targets agnostic to expression on normal tissue

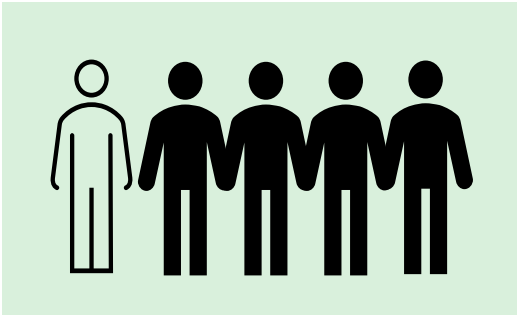


Conditional ADC targets

A Broader Target Landscape Brings the Potential of ADC Therapy to Previously Underserved Patient Populations



Patients eligible for conventional ADC's



Patients eligible for **conditional** ADC's

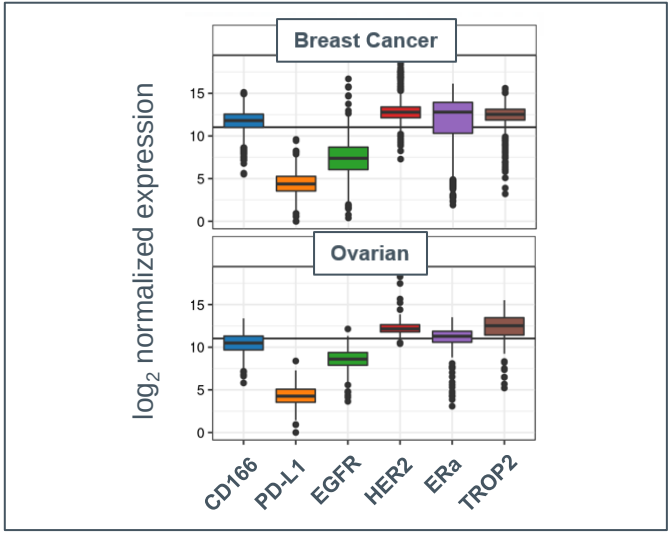
The value of the Probody Drug Conjugate (PDC) platform is unlocking novel, broadly expressed targets to treat a wider range of patients

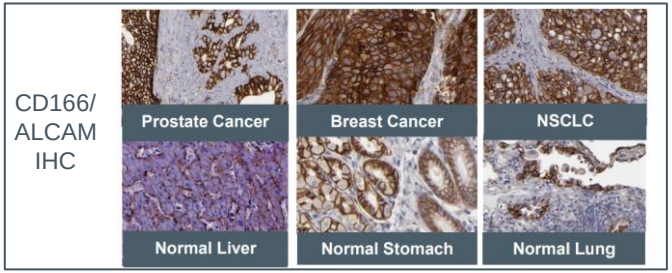
CX-2009 Targets CD166/ALCAM: A Novel, Undruggable Cancer Target

High Expression on Tumors

- CD166/ALCAM is an IgSF cell adhesion molecule highly expressed on multiple tumor types
- Pleiotropic protein that plays a role in cell growth, motility, tumor invasion, metastasis, and breast cancer cell survival
- High expression in multiple normal tissues limits development of CD166 as a traditional ADC target

CD166 is a highly desirable ADC target due to its high tumor expression, but requires a conditional approach due to its expression on normal tissues





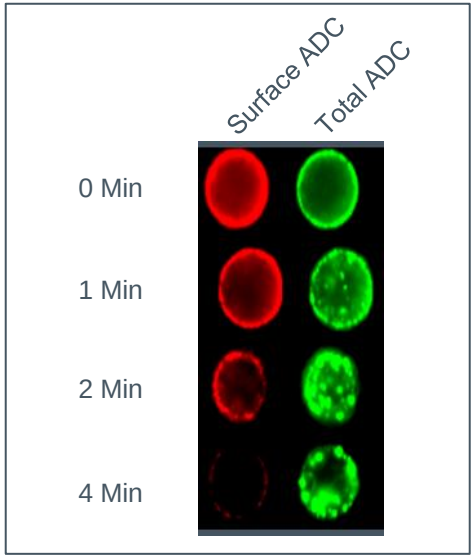
Von Lersner et al., *Clin Exp Met 2019 36(2)*; Dana et al., *J Stem Cell Res, 2016 6(226)*; Goncalves et al, *Front Immunol 2018 9(2994)*

CX-2029 Targets CD71 (TfR): A Previously Undruggable Target

Internalization and trafficking to lysosome

- CD71 is a transmembrane glycoprotein that efficiently internalizes iron-bound transferrin
- Highly expressed on malignant cells
- Also expressed in healthy tissue with high iron requirements (rapidly dividing cells; erythrocyte precursors)
- Unmasked CD71 ADC has potent preclinical efficacy, but no therapeutic index

CD71 Internalization



CD71 is a highly desirable ADC target due to its high internalization rate, but cannot be targeted by traditional approaches

Couch et al. *Sci Trans Med 2013: 5(183)*

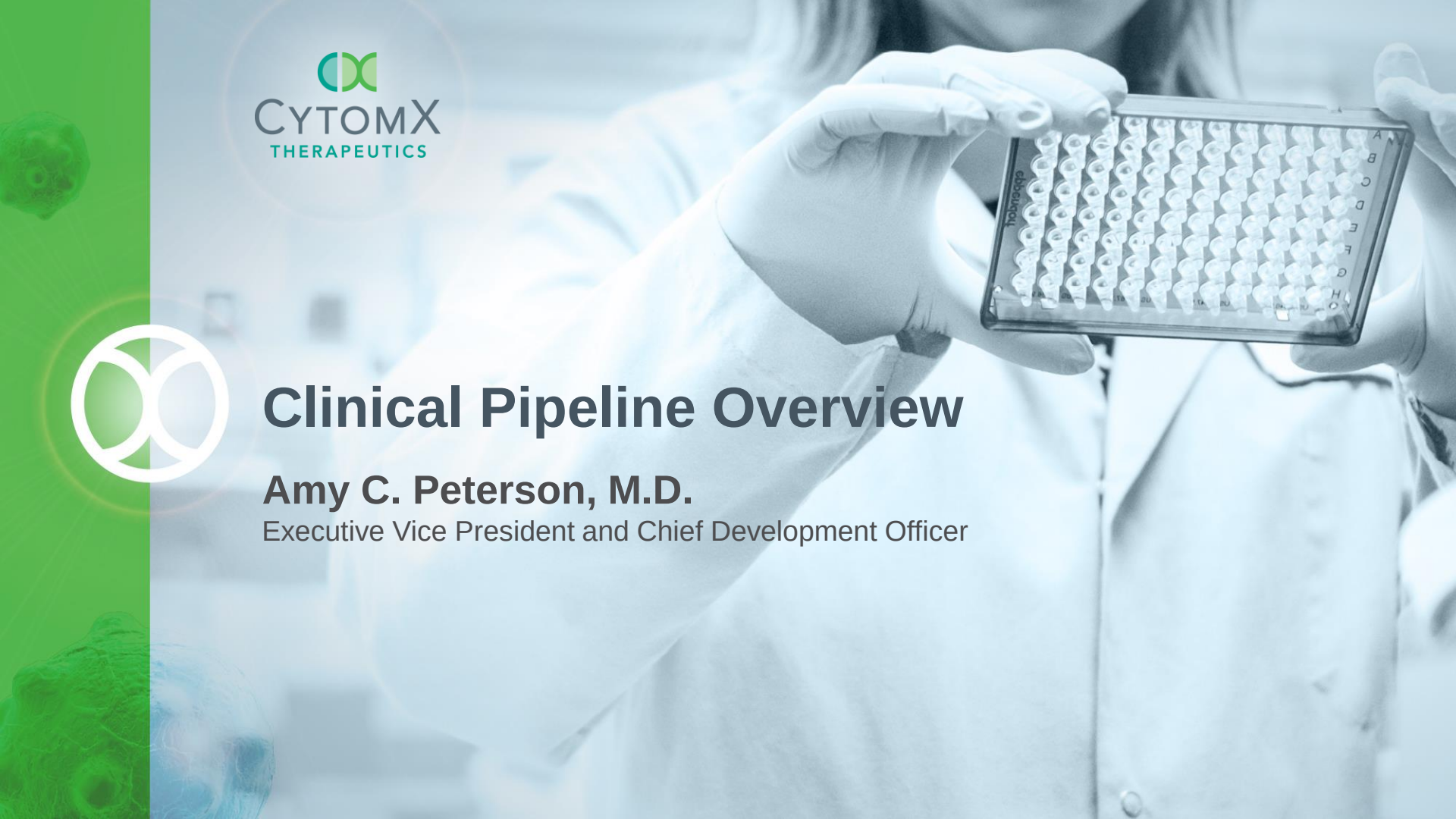
Summary

- The pace of ADC approvals has accelerated rapidly in recent years
- ADC technology has advanced dramatically with respect to novel linker/payload technology
- However, ADC target space remains limited to heme targets and a few, select solid tumor targets
- Conditional activation technology broadens the target space for ADCs
- CytomX is advancing two conditionally-activated ADCs against novel targets in Phase 2 studies

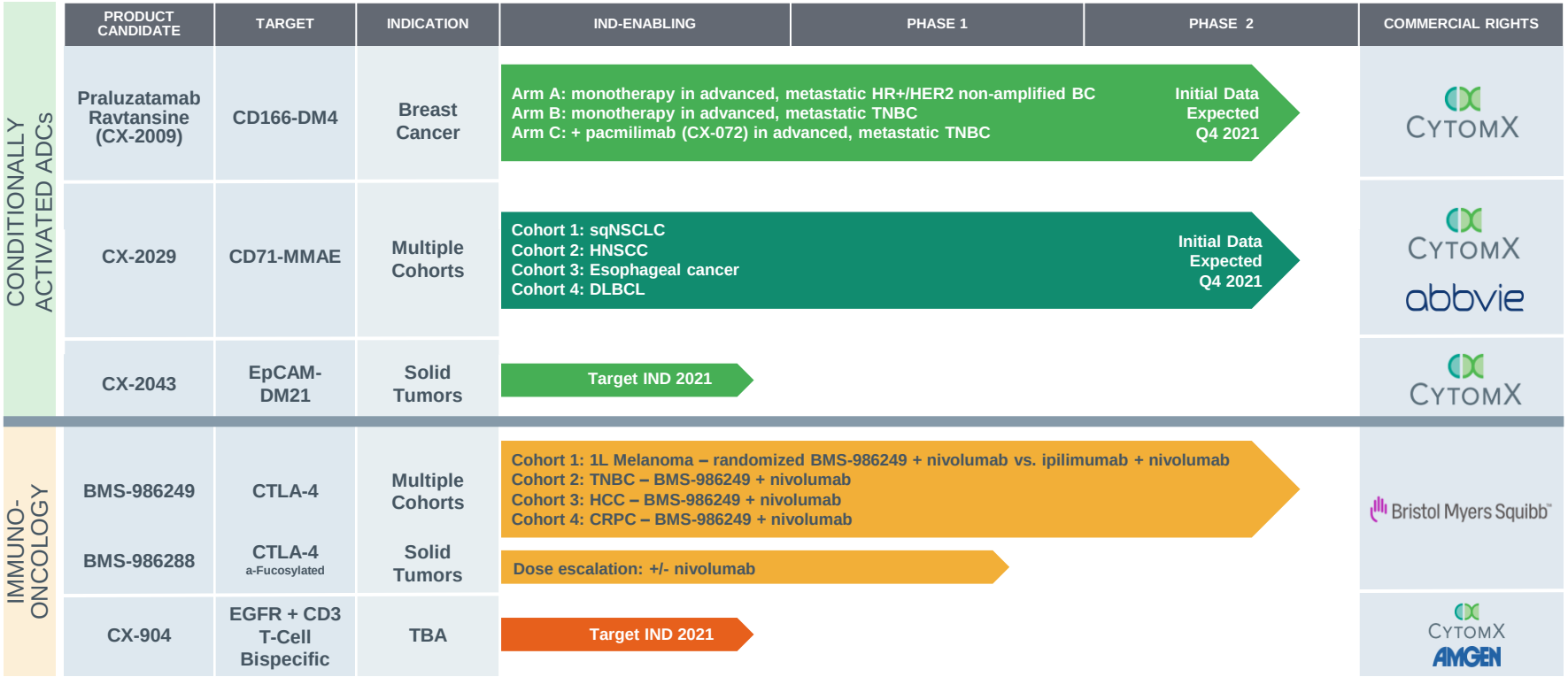
CytomX Therapeutics

Clinical Pipeline Overview

Amy C. Peterson, M.D.
Executive Vice President and Chief Development Officer



Broad Clinical and Preclinical Pipeline with Multiple Phase 2 Readouts 2021+



CytomX Therapeutics

Praluzatamab ravtansine (CX-2009)

Anti-CD166 Conditional ADC for HER2 non-Amplified Breast Cancer

Sara M. Tolaney, M.D., MPH
Associate Director, Susan F. Smith Center for Women's Cancers
Director, Clinical Trials, Breast Oncology
Dana-Farber Cancer Institute, Boston MA
Associate Professor of Medicine, Harvard Medical School

Substantial Unmet Need Remains in Breast Cancer

30% of all cancer in females with an estimated **~276k** new cases and **~42k** deaths in the United States in 2020

Breast cancer is the 2nd leading cause of cancer deaths in women[1]

- **~80% of breast cancer is HER2 non-amplified**
- **Despite recent advances, new therapies are needed, especially in the metastatic setting**
- **CD166 is broadly and highly expressed in HER2 non-amplified breast cancer**

1. Cancer Statistics, 2020; Siegel CA Cancer J Clin 2020;70:7-30

ADCs in Breast Cancer

CD166: a novel target for the treatment of patients with HER2-non amplified breast cancer

Current competitive landscape for ADCs in breast cancer

- Two approved ADCs: TNBC and HER2+ BC
  - TROP-2 and HER2 targeted
- Two ADCs in phase 3 clinical trials for HR+ BC
  - HR+/ HER2-low BC (HER2 targeted)
  - HR+/ HER2-negative BC (TROP-2 targeted)
- Other targets in BC under investigation
  - PD-L1, HER3, LIV1

Current Therapies

Trastuzumab emtansine (Kadcyla®)
- Target: HER2

Sacituzumab govitecan-hziy (Trodelvy®)
- Target: TROP-2 in TNBC after 2+ prior therapies

Fam-Trastuzumab-deruxtecan-nxki (Enhertu®)
- Target: HER2 in pts after 2+ prior anti-HER2 treatments

Emerging Therapies

Sacituzumab govitecan-hziy (Trodelvy®)
- HR+/HER2neg BC (TROPICS-02)

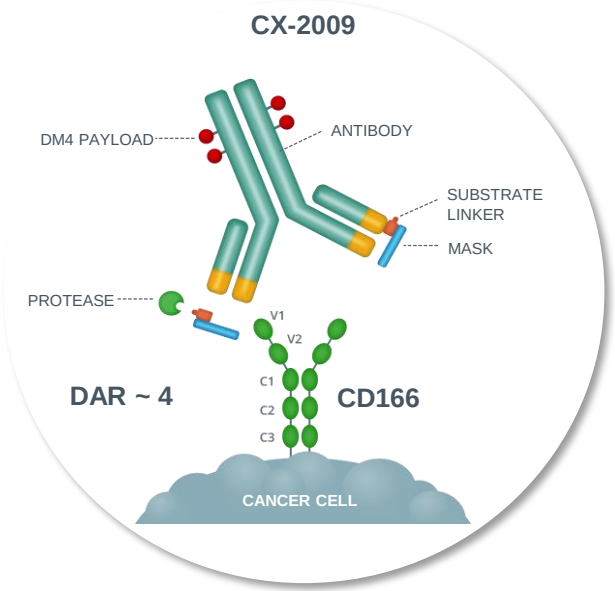
Fam-Trastuzumab-deruxtecan-nxki (Enhertu®)
- HR+/HER2 low (DESTINY-06) and
- HER2 low (DESTINY-04)

SYD985 (Trastuzumab duocarmazine)
- HER2+ BC (TULIP Phase 3 study)

Early-Stage Therapies

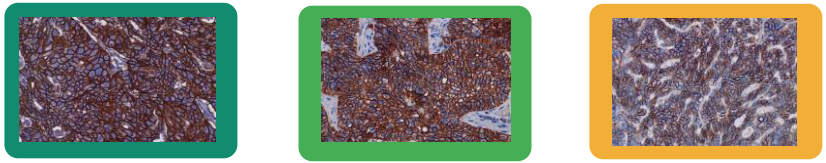
HER2+	BAT8001 BioTherapy solutions
	Disitamab vedotin (RC48-ADC) RemeGen
PD-L1+	Serplulimab (HLX10) Shanghai Henlius
	TQB2450, CBT-502 CPT Pharmaceuticals
HER3	U3-1402 Daiichi
TROP-2	DS-1062 (TNBC) Daiichi
LIV1	Ladiratuzumab vedotin (TNBC, HR+) Seagen/Merck

CX-2009: A Probody Drug Conjugate Targeting CD166 (ALCAM*)



- CX-2009 is a first-in-class anti-CD166 Probody conjugated to the maytansinoid cytotoxic payload DM4, designed to target CD166 towards tumor tissue, away from healthy tissue
- CD166: an adhesion molecule with a role in the cell growth, survival and motility, contributing to tumor invasion and progression[1-3] with a specific role noted in the survival of breast cancer cells[4,5]
- CD166 expression in normal cells limits development of a conventional ADC
- CD166 expressed on many other cancer types: ovarian, NSCLC, and HNSCC (anti-tumor activity in patients with these malignancies seen in CX-2009 phase 1 clinical trial)

CD166 Expression by IHC



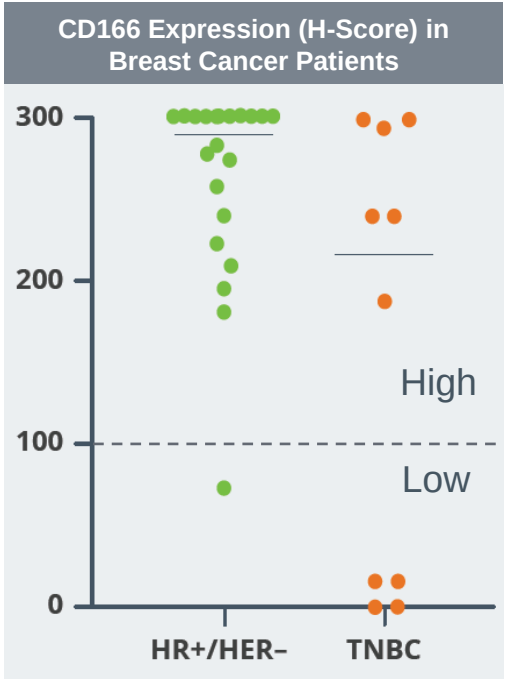
1. Jiang WG, et al. *Br J Surg.* 1994;81:1576–1590.
2. Degen WG, et al. *Am J Pathol.* 1998;152:805–813.
3. von Lersner A, et al. *Clin Exp Metastasis*. 2019;36:87-95.
4. King JA, et al. *Breast Cancer Res*. 2004;6:478–487.
5. Jezierska A, et al. *Med Sci Monit*. 2006;12:245–256.

* ALCAM - Activated Leukocyte Cell Adhesion Molecule

Phase 1 Enrolled 39 Patients with Breast Cancer at Doses 0.25-10 mg/kg

	Overall (n=39)	HR+/HER2- (n=28)	TNBC (n=11)
Median age, years (range)	53 (31-77)	54 (37-77)	45 (31-68)
White/Asian/Hawaiian/Unk/Other, n	30/1/1/5/2	21/0/1/5/1	9/1/0/0/1
ECOG PS 0/1	17/22	12/16	5/6
Median no. of prior regimens, (range)	7.5 (3-16)	8 (4-16)	7 (3-11)
Prior platinum, n (%)	15 (38.5%)	6 (21.4%)	9 (81.8%)
Prior microtubule inhibitor, n (%)	37 (94.9%)	26 (92.9%)	11 (100%)
Prior CDK4/6 inhibitor, n (%)	17 (43.6%)	17 (60.7%)	0
Prior anti-PD-l or PD-L1, n (%)	6 (15.4%)	2 (7.1%)	4 (36.4%)
CD166 High/Low/Unknown	32/5/2	26/1/1	6/4/1
Median no. of CX-2009 doses (range)	2 (1-25)	2.5 (1-25)	2 (1-14)

HR+/HER2- : Hormone Receptor positive and HER2 non-amplified breast cancer;
TNBC: Triple negative breast cancer



CX-2009: Phase 1 Tolerability Supports Phase 2 Dose of 7 mg/kg

	≤ 6 mg/kg (n=38)	7 mg/kg (n=12)	8 mg/kg (n=22)	9 mg/kg (n=9)	10 mg/kg (n=8)
		RP2D			
TRAE (Grade 3+)	16%	33%	64%	56%	50%
TRAE leading to Discontinuation	13%	8%	14%	22%	13%
Cycle 1 DLT (n)	0	0	1	0	0
Ocular Toxicity (All / Grade 3+)	26%/3%	25%/0%	59%/14%	56%/33%	75%/13%
Neuropathy (All / Grade 3+)	24%/5%	25%/8%	32%/0%	33%/11%	13%/0%
Hepatic Toxicity (All / Grade 3+)	8%/0%	8%/0%	41%/18%	33%/0%	38%/38%

- CX-2009 was generally well tolerated at doses ≤ 7 mg/kg; Toxicity profile consistent with payload: ocular, neuropathic and hepatic
- Ocular toxicities appeared dose dependent in frequency and severity; ocular prophylaxis appears effective
- Selection of 7 mg/kg Q3W as RP2D is supported by activity, tolerability and PK/PD modeling

RP2D= Recommended Phase 2 Dose
*Ocular prophylaxis became mandatory at doses of 9-10 mg/kg; future studies will incorporate mandatory ocular prophylaxis

Clinical Toxicity of ADC Payloads

Masters JC, et al. Inv New Drugs 2018

Qualitative comparison of toxicities within/across select payloads and cancers

	MMAE		MMAF[a]		DM1		DM4	
	Solid	Heme	Solid	Heme	Solid	Heme	Solid	Heme
AE: Grade ≥ 3 (≥ 10% reported)								
Anemia	N	Y	N	N	Y	N	N	Y
Neutropenia	Y	Y	N	N	N	Y	N	Y
Thrombocytopenia	N	Y	Y	Y	Y	N	N	N
Leukopenia	N	Y	N	N	N	N	N	N
Hepatic toxicity	N	N	N	N	Y	N	N	N
AE: any Grade / Grade ≥ 3 (≥ 10% reported)								
Peripheral neuropathy	Y/Y	Y/Y	Y/N	Y/N	Y/N	N	Y/N	Y/N
Ocular toxicity	N	N	Y/Y	Y/Y	Y/N	N	Y/N	Y/Y

[a] MMAF reported safety included mix of solid tumor and hematologic malignancy patients, therefore these cannot be differentiated

Masters JC, et al. *Invest New Drugs*. 2018;36:121-135.

DM4-Associated Adverse Events

Ocular toxicity is the most common AE associated with DM4-conjugated ADCs in patients

- Ocular DLTs are observed for ADCs that use DM4 as the payload (e.g., mirvetuximab)
- The shared toxicity profile across ADCs that target different antigens suggests ocular toxicity is an off-target (antigen-independent) toxicity
- Mechanism presumed to be due to pinocytosis of DM4 by the epithelial layer of the cornea[1]

Common symptoms: Blurred vision, keratitis, dry eye, and microcystic epithelial damage

- Grade 1-2: patients asymptomatic or mild symptoms; intervention may be limited to artificial tears
- Grade 3: changes in visual acuity, limits self care activities of daily living; treatment required

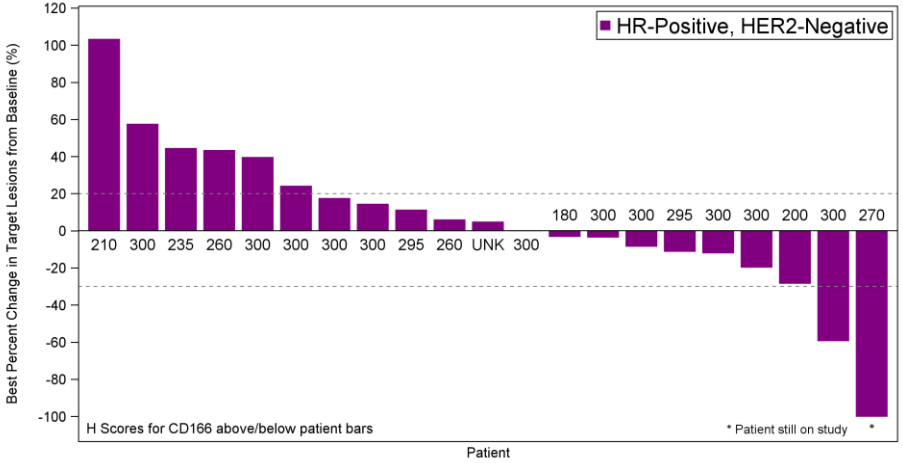
Dose-related: ≤7 mg/kg, most ADC-related ocular AEs are not severe (≤ grade 2) and are reversible

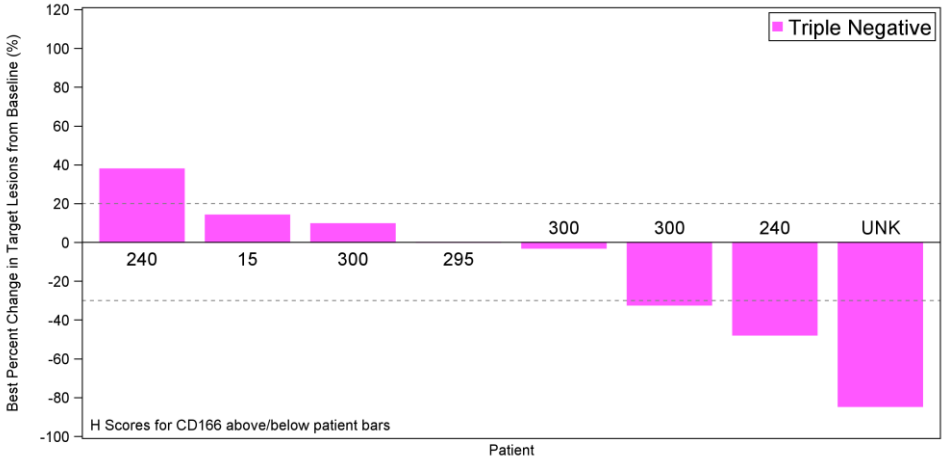
Ocular prophylaxis: steroids drops, vasoconstrictor drops on day of infusion and cold compresses as tolerated during the infusion

1. Matulonis UA, et al. *Clin Cancer Res*. 2019;25:1727-1736.

Observed Clinical Activity in Breast Cancer with CX-2009 at Doses ≥4 mg/kg Q3W

Breast cancer patients with measurable disease who received ≥ 4 mg/kg CX-2009 and had a post-baseline assessment





Parameter	Evaluable* Breast Cancer Patients		
	Overall (n=32)	HR+/HER2- (n=22)	TNBC (n=10)
CBR16	13 (41%)	9	4
CBR24	9 (28%)	5 (2 cPR)	4 (3 uPR)

*Includes those with non-measurable but evaluable (e.g. bone-only) disease

CBR= clinical benefit rate (CR, PR or SD for 16 or 24 wks);
cPR= confirmed partial response;
uPR= unconfirmed Partial Response
UNK = Unknown

CytomX Therapeutics

Data presented SABCS 2020

Observed Clinical Activity in Breast Cancer with CX-2009 at Doses ≥4 mg/kg Q3W

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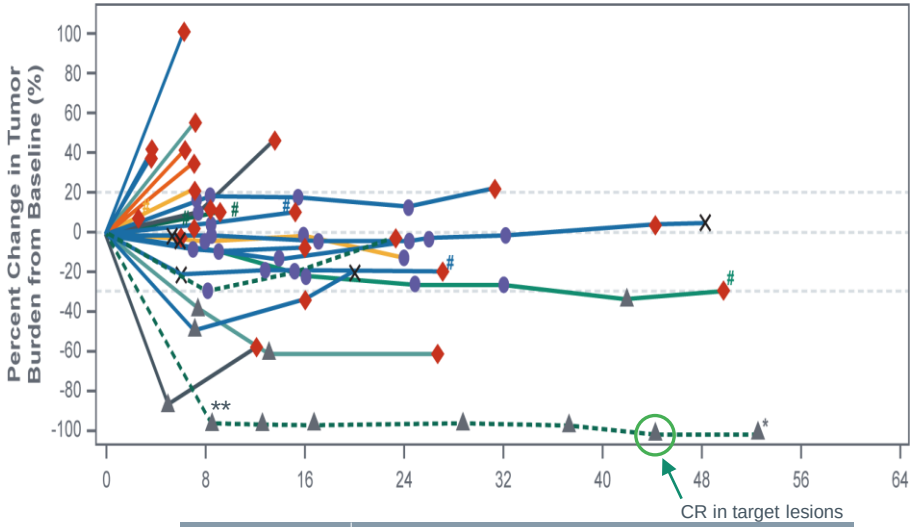

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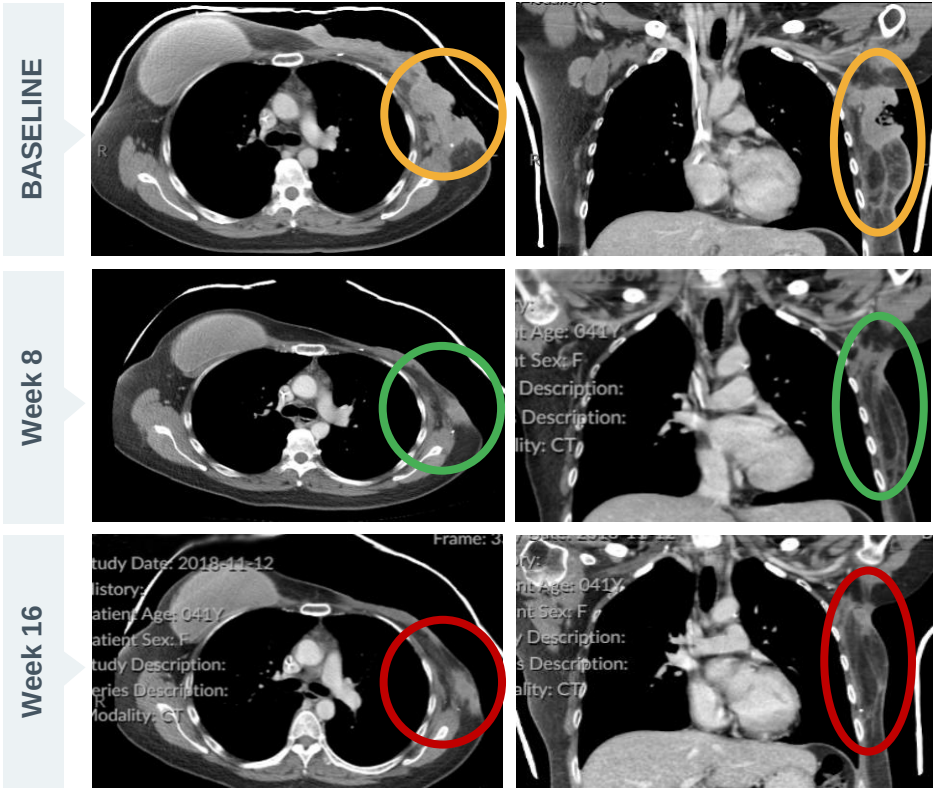
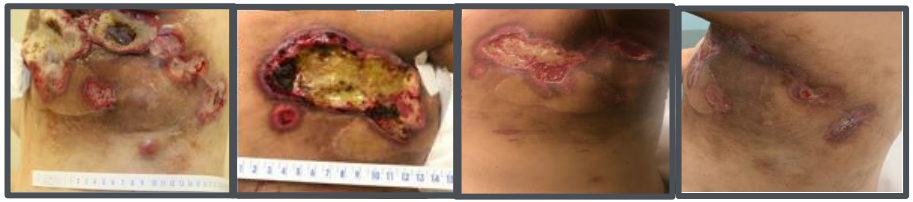
Patient with TNBC Refractory to Pembrolizumab + Paclitaxel and Sacituzumab Govitecan





Week 1 Week 5 Week 10 Week 13

- 41-year-old treated at 8 mg/kg
- Disease progression after
  - Pembrolizumab + Paclitaxel
  - Sacituzumab govitecan
- Baseline: **ulcerating lesions** chest wall, axilla
- First scan: 48% reduction in **target lesions**
- Dose interruption for keratitis (resolved), **disease progressed** before treatment could be re-initiated

Baseline

CX-2009 Breast Cancer Phase 2 Study Design

Monotherapy (7 mg/kg Q3W) and Combination with Pacmilimab (CX-072; anti-PD-L1) In Advanced, HER2 non-Amplified Breast Cancer

Key Eligibility

Ocular prophylaxis required
- Treated/stable brain metastases allowed
- No active corneal disease
- Measurable disease required

HR+/HER2 non-amplified
- 0 – 2 prior cytotoxics for advanced disease
- Prior CDK4/6i required

TNBC
- CD166 High
- ≥ 1 and ≤ 3 priors for advanced 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

Readout: Initial data expected Q4 2021

*Evaluable, **https://meetinglibrary.asco.org/record/186711/abstract

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Arm A
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CX-2009

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CX-2009

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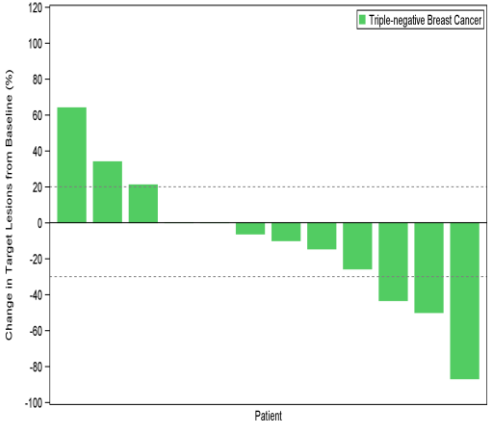
PROCLAIM CX-072

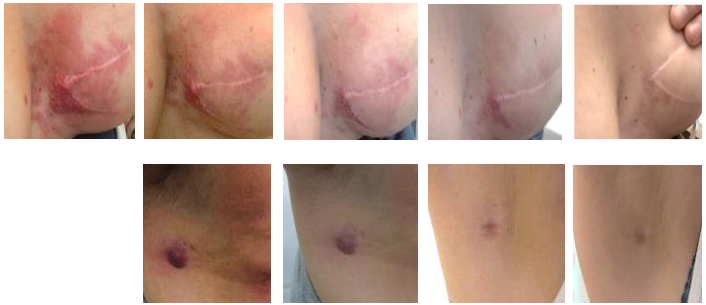
CytomX Checkpoint Inhibitor: Pacmilimab (CX-072) with Single-Agent Anti-Tumor Activity in TNBC

Monotherapy CX-072 in TNBC

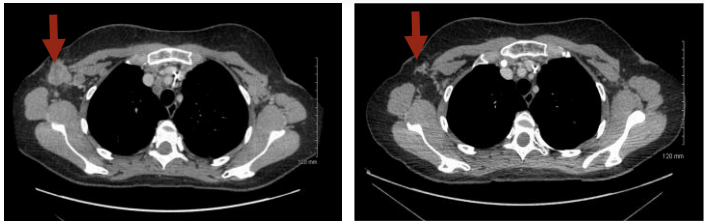


PATIENT A: TNBC WITH SKIN LESIONS (PR); TREATMENT DURATION 72+ WEEKS; PD-L1 Low

Aug 30, 2017 **Baseline**
Sept 25, 2017 **After 2 doses**
Oct 9, 2017 **After 4 doses**
Nov 7, 2017 **After 6 doses**
Jan 2, 2018 **After 9 doses**

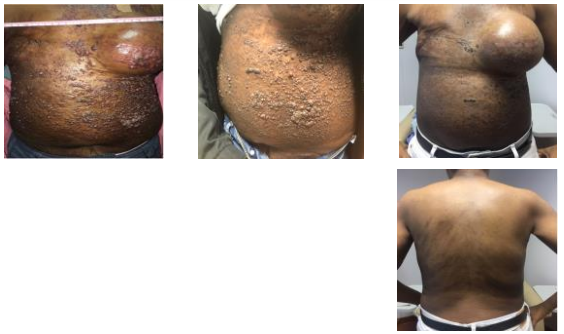


August 14, 2017 **Screening Scan**
December 5, 2017 **Staging Scan**



PATIENT B: TNBC WITH SKIN LESIONS (UPR); TREATMENT DURATION 20+ WEEKS; PD-L1 Neg

August 9, 2018 **Baseline**
September 5, 2018 **After 1 dose**
October 3, 2018 **After 3 doses**



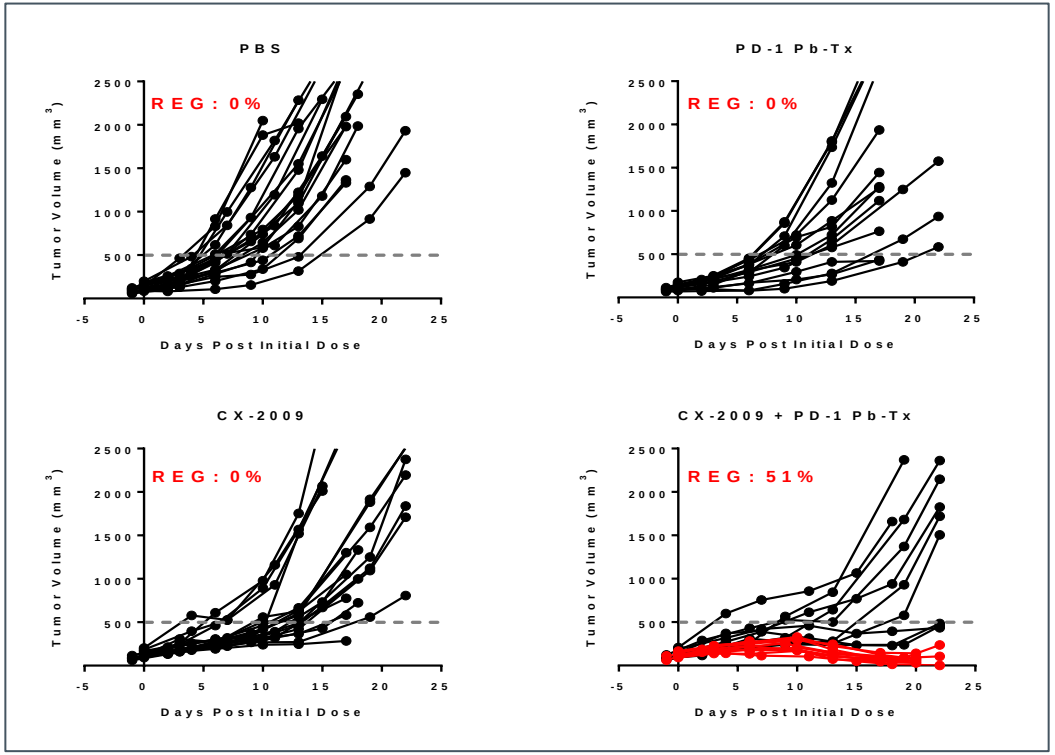
CytomX Therapeutics

Rationale for Combining CX-2009 and CX-072

- ADCs capable of killing cancer cells AND modulate the immune response
  - Cytotoxic payloads/ADCs have been shown to induce immunogenic cell death in vitro and in vivo[1]
  - Immunologic cell death: the release of damage-associated molecular patterns that elevate the immunogenic potential of dying cells[2]
  - Cytotoxic payloads also provoke phenotypic and functional dendritic cell maturation and activation[3]
- Cytotoxic payloads may therefore have both cytotoxic effects **and** potentiate an immune response
- The activity of CX-2009 in combination with a Probody Checkpoint Inhibitor (CPI) therapeutic to mouse PD-1 was investigated in a subcutaneous mouse cell line cancer model[4]
  - Neither CX-2009 nor anti-PD-1 Probody therapeutic monotherapy result in regressions in mice with established CT26-hCD166 tumors
  - The combination produced tumor regressions in 51% of mice (highlighted in red)

1. Rios-Doria J, et al. *Cancer Res*. 2017;77:2686-2698 2. Garg AD, et al. *Immunol Rev*. 2017;280:126-148.
3. Müller P, et al. *Oncoimmunology*. 2014;3:e954460. 4. Liu B, et al. Cancer Res 2019;79(13 Suppl):Abstract # 212 \

Mouse Anti-PD-1 CPI Plus CX-2009 (CT26 HuCD166 Syngeneic Model)



Clinical Data Combining CPIs with Chemotherapy

- Data are available from clinical studies of maytansinoid-based ADCs in combination with CPIs which support the benefit of this type of combination therapy in breast cancer patients

- Phase 2 randomized KATE2 trial: atezolizumab + trastuzumab emtansine (T-DM1) vs placebo + T-DM1 in previously-treated HER2-positive advanced BC patients[1]
  - In the PD-L1+ subgroups, the combination of T-DM1 + atezolizumab improved the ORR from 54% compared to 33% in the T-DM1 + placebo arm
  - In the PD-L1+ subgroups, PFS was extended to 8.5 months in the T-DM1 + atezolizumab group compared to 4.1 months in the T-DM1 + placebo group (stratified hazard ratio, 0.60)

- These data indicate a potential durable clinical benefit for combination of an anti-PD-L1 antibody and a maytansinoid ADC in a PD-L1+ patient population
  - Other combinations are underway (e.g., sacituzumab govitecan + pembrolizumab in TNBC)

1. Emens EA, et al. 2019;79[4Suppl]: *Cancer Res* 2019;79(4 Suppl):Abstract nr PD3-01

CD166: A Previously Undruggable ADC Target

- CD166: validated as a viable first-in-class therapeutic target in cancer
  - Probody technology enables administration of a CD166-directed antibody drug conjugate at tolerable doses with signs of clinical benefit at doses ≥ 4 mg/kg Q3W
  - Confirmed activity were observed in patients with HER2 non-amplified breast cancer
- Recommended Phase 2 dose: 7 mg/kg Q3W
  - Supported by activity, tolerability, PK modeling and nonclinical data[1]
  - CX-2009 produces dose-dependent ocular toxicities consistent with DM4 payload
- Optimization of a CD166 IHC assay is ongoing to support a potential selection strategy
- CX-2009 is under active investigation
  - Arm A: monotherapy in patients with HR+/HER2- breast cancer
  - Arm B: monotherapy in patients with TNBC
  - Arm C: CX-2009 in combination with CX-072 (an anti-PD-L1 Probody) in patients with TNBC

1. Stroh M, et al. *J Clin Oncol*. 2020;38[15suppl]:abstract 3599

CytomX Therapeutics

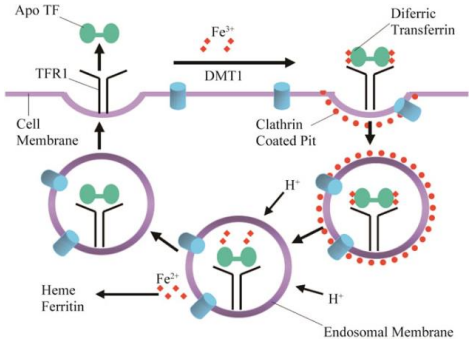
CX-2029

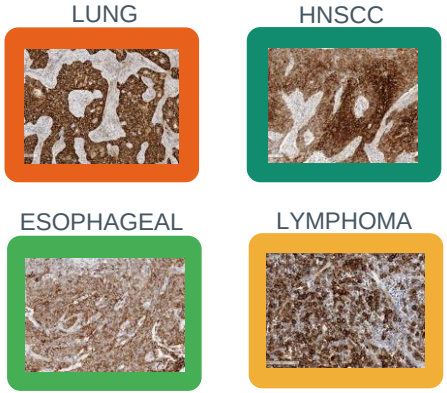
Anti-CD71 (Transferrin Receptor) Conditional ADC

Melissa L. Johnson, M.D.
Director, Lung Cancer Research
Sarah Cannon Research Institute, Nashville, TN

CD71 (Transferrin Receptor)

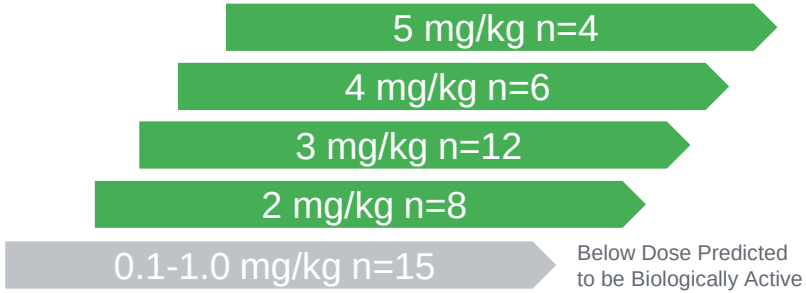
- Highly expressed tumor antigen
- “Professional internalizer” ideally suited to delivery of cytotoxic payloads to cancer cells
- Undruggable target with conventional antibody approaches due to normal tissue biology
- Probody strategy – open therapeutic window by limiting normal tissue binding
  - Masked ADC is tolerated at biologically active doses; the unmasked is lethal (neutropenic sepsis)
  - Broad in vivo activity in 30 out of 36 PDX models
- Potentially paradigm shifting anti-cancer agent with first in class potential





CD71 Expression by IHC

Phase 1 Dose Escalation Study Evaluated CX-2029 Q 3 Weeks in 45 Patients with Solid Tumors



Key Eligibility Criteria
- Metastatic or locally advanced unresectable solid tumor
- Archival tissue or biopsy available for tissue analyses
- Stable brain metastases permitted

Exclusions:
- Transfusion-dependent anemia or iron metabolism disorders
- Grade 2 or higher neuropathy

Key Patient Demographics	All Cohorts (n=45)
Age, median (min, max)	60 (31, 75)
Baseline ECOG 0 / 1, %	29 / 71
CD71 IHC staining, n (%)	
High expression [2+/3+]	15 (33)
Low expression [0/1+]	16 (36)
Unknown	14 (31)
Tumor types, n (%)	
NSCLC	9 (20)
Squamous NSCLC	4 (9)
HNSCC	8 (18)
Colorectal cancer	7 (16)
Other*	21 (46)
Median priors (min, max)	3 (1, 16)

*Other tumor types include sarcoma (4), Prostate (3), parotid gland (3); ovarian (2); melanoma (n=1); endometrial (1); hepatocellular (1); mesothelioma (1); ocular melanoma (1); pancreatic (1); perivascular epithelioid (1); thymoma (1); thyroid (1).

CX-2029 Phase 1 Tolerability Supports Phase 2 Dose of 3 mg/kg

Generally Well Tolerated to 3 mg/kg with Manageable Adverse Events

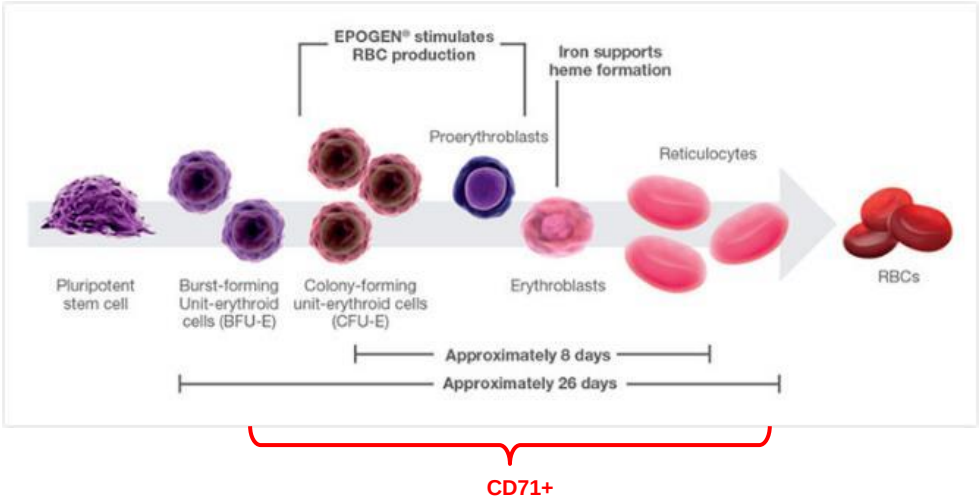
Treatment-Related Grade 3+ AEs (≥2 patients)	1.0 mg/kg (n=3)	2.0 mg/kg (n=8)	RP2D 3.0 mg/kg (n=12)	4.0 mg/kg (n=6)	5.0 mg/kg (n=4)
Anemia	33%	63%	58%	83%	100%
Neutropenia	0	0	33%	50%	75%
Infusion-related reaction	0	13%	0	17%	0
Any Grade TRAE => Discont	0	0	0	0	0
Cycle 1 DLT	0	0	0	33%[1,2]	50%[3,4]

1. Grade 3 infusion-related reaction >6 hours; 2. Grade 4 neutropenia; cycle 2 delayed 23 days for grade 3 anemia; ↓ ECOG to 2
3. Grade 3 pancytopenia >7 days; 4. Grade 3 febrile neutropenia

- > 90% masking maintained in circulation
- Most frequent Grade 3+ AE was anemia
  - Managed with red blood cell transfusions, growth factor support and/or dose delays/reductions
  - Likely multi-factorial including CD71 biology and MMAE payload
- 3 mg/kg Q3W selected as Phase 2 dose

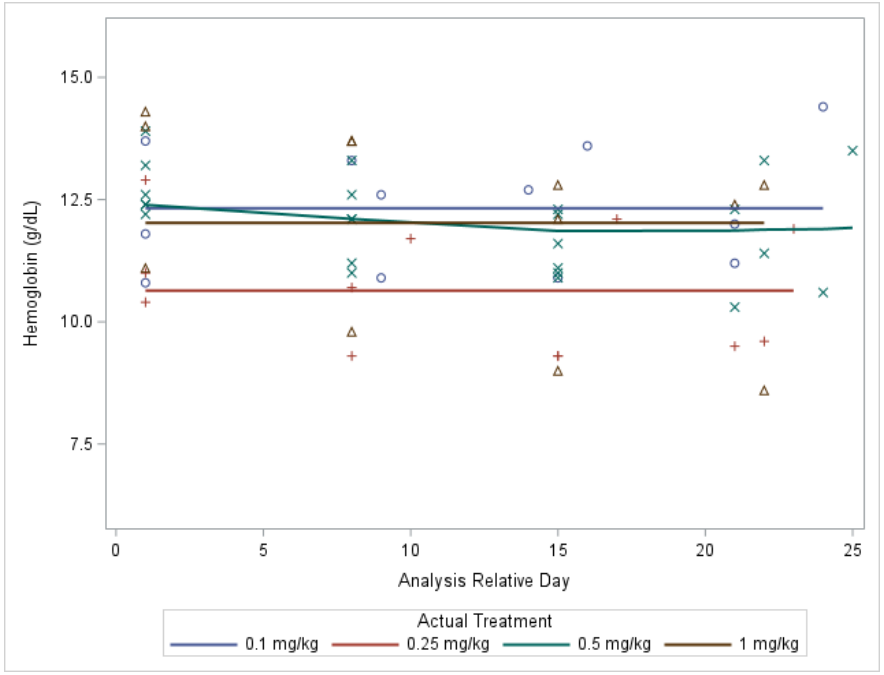
Mechanism of Anemia

- CD71 expression on red blood cell (RBC) progenitors in the bone marrow is high
- Normal response to anemia would lead to increase in progenitor activity and peripheral reticulocyte count
  - Significant decreases in peripheral reticulocyte count (in the setting of anemia) are seen in patients at doses >2 mpk (consistent with on-target toxicity against RBC progenitors)
- Other mechanisms of anemia ruled out:
  - Decreased production (disorders of iron metabolism)
  - Increased destruction (hemolysis, RBC apoptosis, splenic sequestration)
  - Blood loss

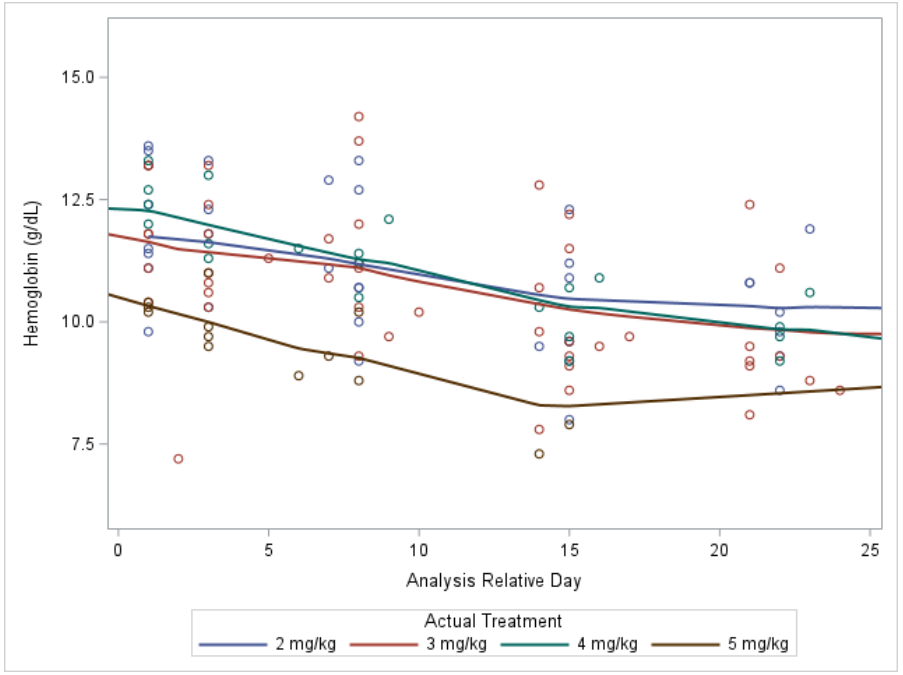


Higher Doses of CX-2029 Associated with Steeper Decline in Hemoglobin

Hemoglobin (g/dL)
0.1 – 1 mg/kg dose groups



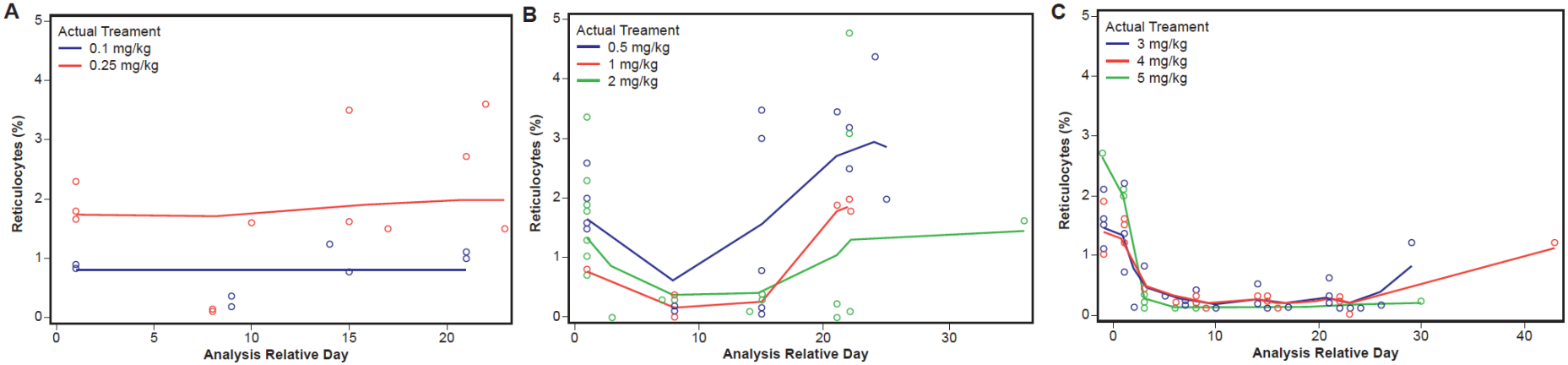
Hemoglobin (g/dL)
2 – 5 mg/kg dose groups



* 1 patient received transfusion after C1D15, and data from C2D1 excluded from this figure

Dose Dependent Effect of CX-2029 on Reticulocytes

CX-2029 Dose



Hemoglobin does not drop at doses < 0.5 mg/kg

- HGB drops and reticulocytes rise at 0.5 - 2 mg/kg
- HGB drops and reticulocytes do not compensate at doses ≥3 mg/kg

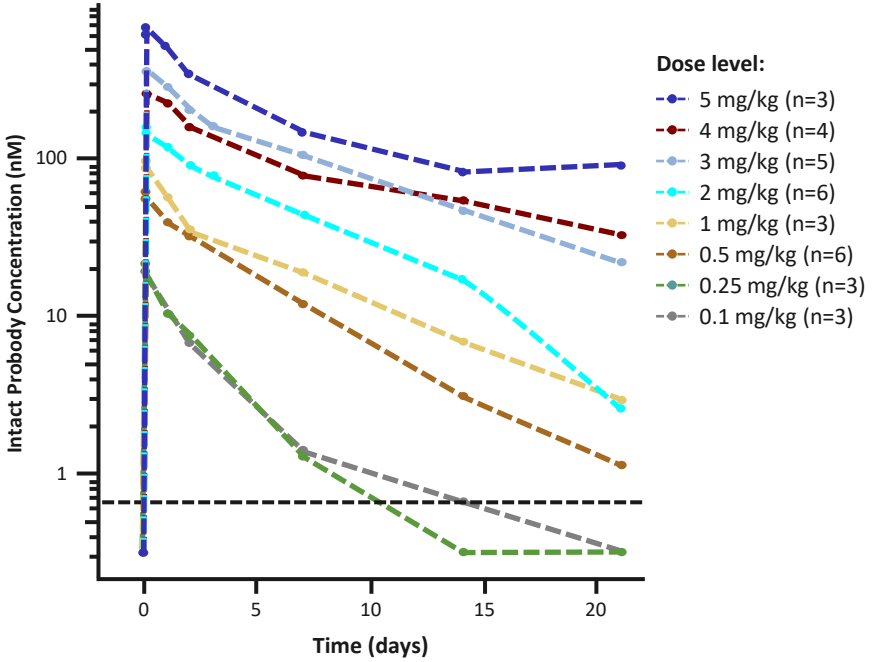
The lack of reticulocytosis in a setting of anemia: multifactorial

- CX-2029 effects on RBC precursors and MMAE/payload toxicity

Johnson et al. *Clin Cancer Res* accepted for publication 2021

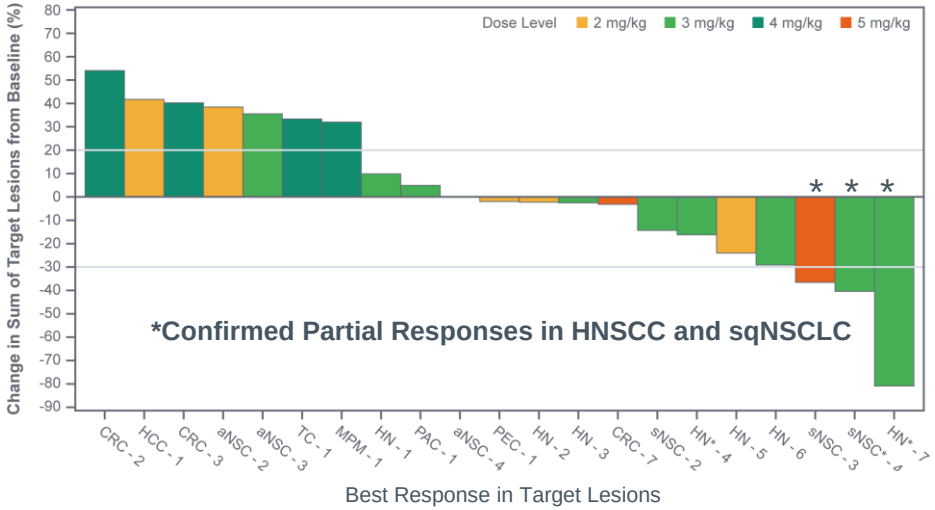
Pharmacokinetics

- Following 0.25–5.0 mg/kg, CX-2029 circulates predominantly as intact CX-2029 (>90%)
- For intact CX-2029:
  - No trends from dose-proportionality
  - Clearance 0.55–2.7 L/day
  - Volume of distribution 3.2–10.6 L
  - Terminal half-life 2.3–9.8 days
- Free MMAE circulates <4.3% of Total CX-2029



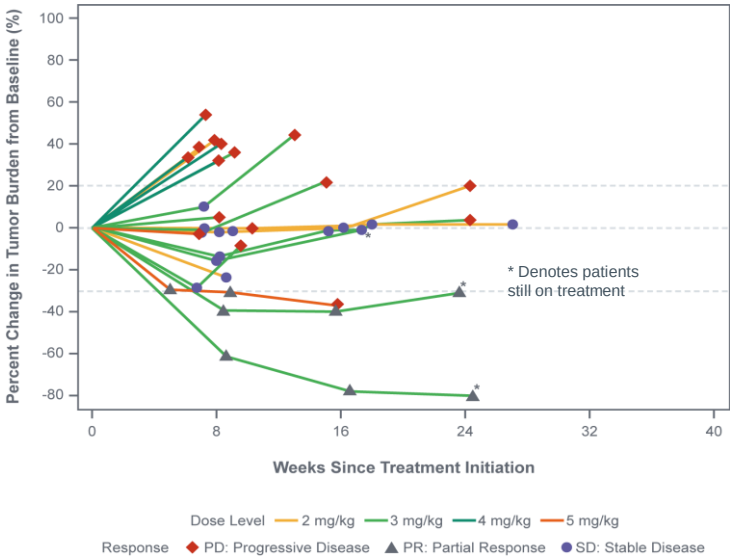
Observed Clinical Activity with CX-2029 at Doses ≥2 mg/kg Q 3 Weeks

Patients with measurable disease who received ≥ 2 mg/kg CX-2029 and had a post-baseline assessment



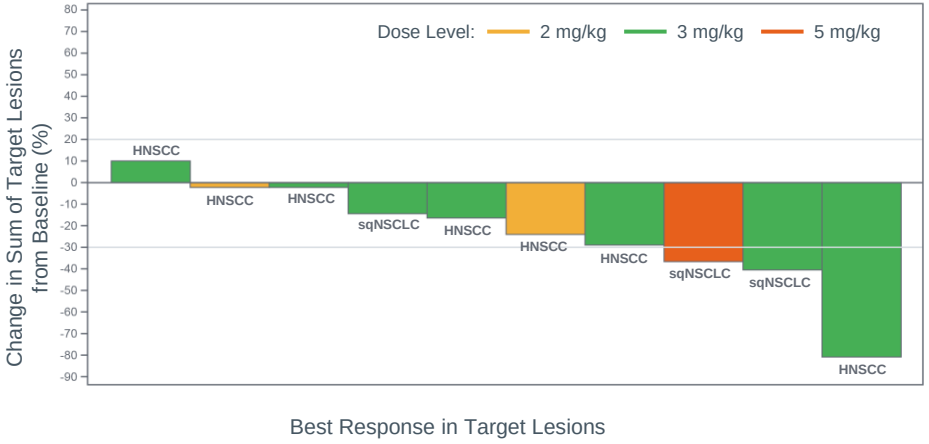
Best Response in Target Lesions

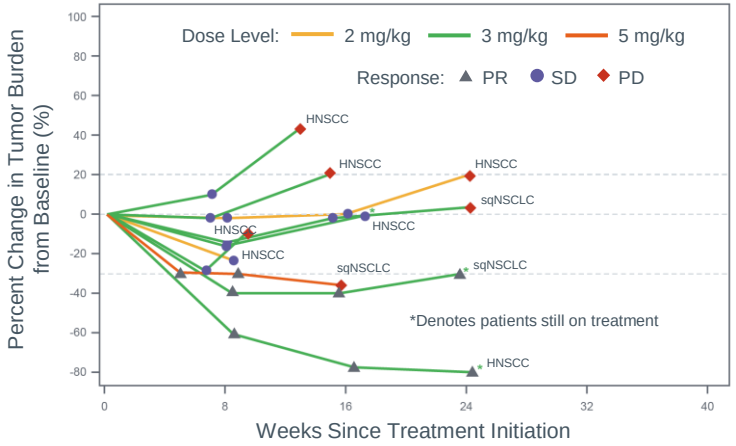
CRC=Colorectal Cancer, HCC=Hepatocellular carcinoma, aNSC=Non-small cell lung adenocarcinoma, TC=Thyroid carcinoma MPM=Malignant pleural mesothelioma, HN=Head and neck squamous cell carcinoma, PAC=Pancreatic cancer, PEC=Perivascular epithelioid cell tumor, sNSC=Non-small cell lung squamous carcinoma



Observed Clinical Activity in sqNSCLC and HNSCC with CX-2029 at Doses ≥2 mg/kg Q 3 Weeks

sqNSCLC or HNSCC patients with measurable disease, received ≥ 2 mg/kg CX-2029, and had a post-baseline assessment



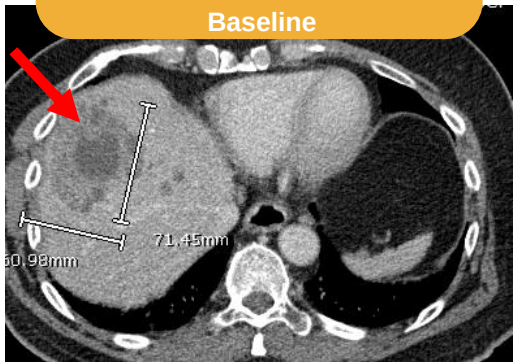


1 patient with sqNSCLC was dosed at 1 mg/kg; 1 patient with HNSCC came off study without a post-baseline assessment

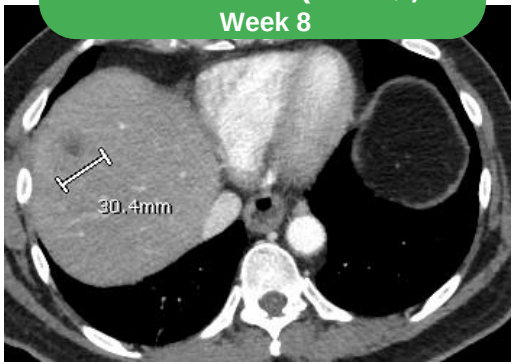
CX-2029 Case Study #1: 66 Y/O Patient with HNSCC

- Nasopharyngeal carcinoma (Diagnosed in February 2018)
- Prior therapies: Docetaxel/5FU/cisplatin with radiation (3mos) + high-dose cisplatin (1mos); Investigational agent (sEphB4-HSA) + pembrolizumab (3mos, PD)
- CX-2029 (3mg/kg) initiated January 2020, dose reduced for anemia to 2 mg/kg Mar 2020
- Partial response at Week 8 (Mar 2020) confirmed 8 weeks later. Continued shrinkage of target lesions on 2mg/kg

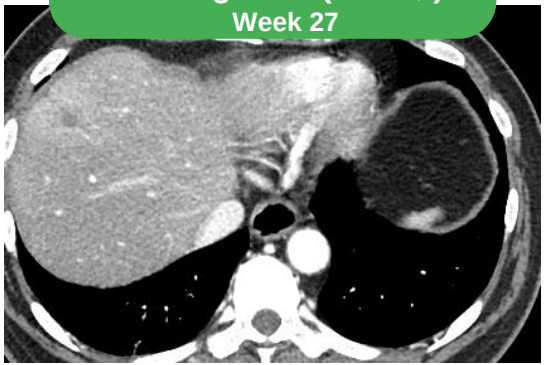
18 Dec 2019
Baseline



13 Mar 2020 (43% ↓)
Week 8



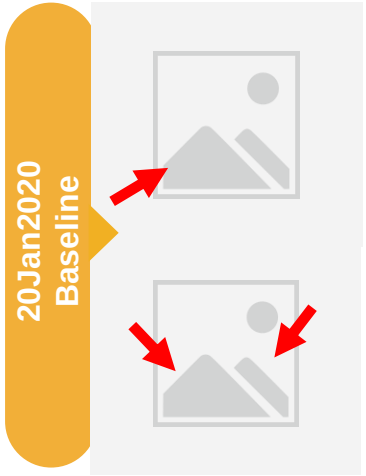
28 Aug 2020 (84% ↓)
Week 27

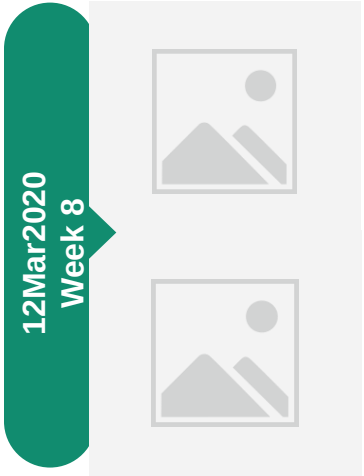


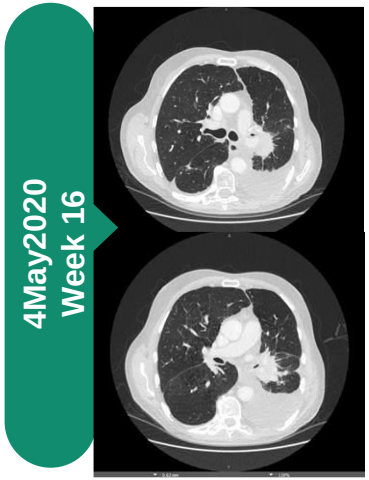
Data cut-off: August 2020.

Case Study #2: 75-Year-Old Patient with Squamous NSCLC

- Stage III squamous NSCLC diagnosed in August 2017
- Prior therapy: Carboplatin/paclitaxel with radiation (2 mo); durvalumab (10 mo); gemcitabine (2 mo); docetaxel/ramucirumab (8 mo; SD then PD)
- CX-2029, 3mg/kg, initiated Jan2020, received pRBCs and darbopoeitin, dose reduced to 2mg/kg Apr2020
- Partial response at Week 8 (Mar2020) confirmed Week 16 (May2020)







Near resolution of R perifissural target lesion

Decrease in LLL target lesion
Decrease in RLL nodular (Non-target) lesions

Johnson et al. ASCO 2020. Abstract 3502

(Images are courtesy of Navid Hafez, MD)

Phase 2 Expansion Underway to Evaluate CX-2029 in Four Cohorts

Monotherapy at 3 mg/kg Q3W

Eligibility

sqNSCLC, HNSCC and esophageal

- Prior therapy must include prior platinum and a checkpoint inhibitor (alone or in combination; if approved by the local Health Authority).
- For esophageal: squamous, adenocarcinoma or GE junction; prior HER2-targeted therapy if tumor is HER2+
- Documented progression after at least one prior regimen for advanced disease

DLBCL

- Progression after at least 2 prior regimens (one of which must be anti-CD20 based therapy); not a candidate for stem cell transplant

Cancer Type

sqNSCLC
n~25*

HNSCC
n~25*

Esophageal/GEJ
n~25*

DLBCL
n~25*

*Evaluable

Endpoints

Primary: Overall Response Rate (ORR) by local investigator

Secondary: PFS, DCR, CBR24, DoR, OS, Safety, PK, ADA, TTR

Exploratory: Biomarker correlation with outcome

Readout: Initial data expected Q4 2021

Summary of Phase 1 Results

- Safety:
  - CX-2029 produces dose-dependent hematologic toxicities consistent with MMAE payload
  - Anemia: most common hematologic toxicity, also seen in non-clinical species
- CX-2029 at 3 mg/kg will be studied in the dose-expansion phase
  - No Cycle 1 DLT; no discontinuation for toxicity
  - Manageable Grade 3 anemia: frequently assessed by routine labs and can be managed with standard supportive care (ESA, transfusions), dose reduction / dose delays
- Clinical activity: observed at doses of 2 mg/kg and higher; consistent with PK predictions
  (activity to date was observed in squamous histologies: head and neck; NSCLC)

Conclusions

- The results of first-in-human trial validates CD71 (transferrin receptor 1) as a viable therapeutic target in cancer
- Probody technology enables administration of a CD71-directed antibody-drug conjugate at tolerable doses with clinical anti-tumor activity
  - CD71: a previously undruggable ADC target
- Safety profile and clinical activity support dose-expansion, including cohorts of HNSCC, squamous NSCLC, esophageal carcinoma and DLBCL
  - Work ongoing regarding CD71 expression *vs* tumor regression

Closing Remarks and Future Outlook

Sean McCarthy, D.Phil.
President, Chief Executive Officer and Chairman

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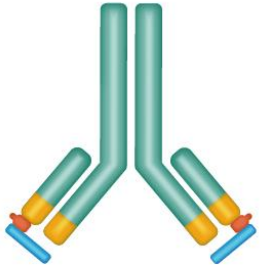
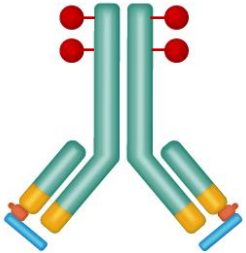
Probody Platform Versatility Extends to Multiple Biologic Formats

IMMUNE MODULATORS/ CHECKPOINT INHIBITORS



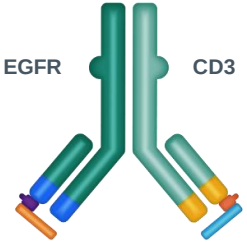
PD-L1 (CX-072)
PD-1 (CX-188)
CTLA-4 (BMS-986249, 986288)

ANTIBODY-DRUG CONJUGATES



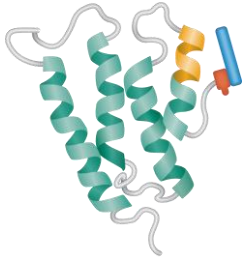
CD166 (CX-2009)
CD71 (CX-2029)
EpCAM (CX-2043)

T-CELL BISPECIFICS



EGFR-CD3 (CX-904)

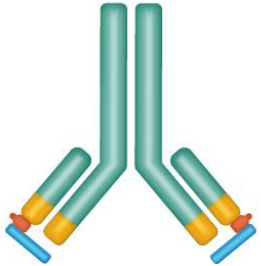
CYTOKINES



IFNα-2b
Additional discovery stage programs

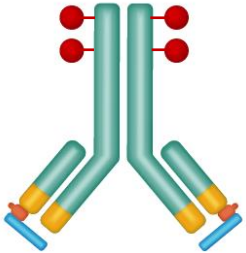
Applying the Probody Platform to Localized Cytokine Therapeutics

IMMUNE MODULATORS/ CHECKPOINT INHIBITORS



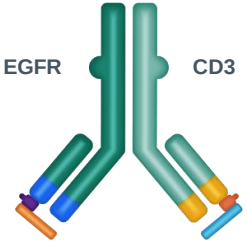
PD-L1 (CX-072)
PD-1 (CX-188)
CTLA-4 (BMS-986249, 986288)

ANTIBODY-DRUG CONJUGATES



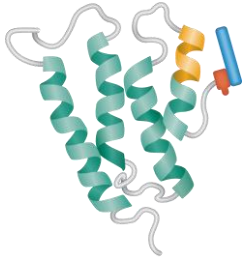
CD166 (CX-2009)
CD71 (CX-2029)
EpCAM (CX-2043)

T-CELL BISPECIFICS



EGFR-CD3 (CX-904)

CYTOKINES



IFNα-2b
Additional discovery stage programs

Cytokine Therapeutics are Potent Immune Modulators, but Therapeutic Window is Limiting

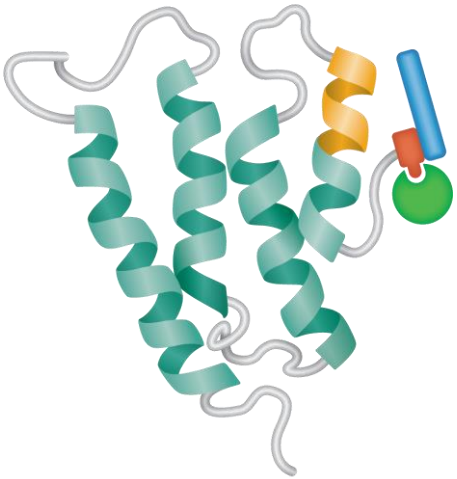
Cytokines and Cytokine Therapeutics

- Major regulators of innate and adaptive immune system
- Broad preclinical anti-tumor activity
- Clinical success limited by systemic toxicity and poor exposure

Potential advantages for Conditional Cytokine Therapeutics

- Reduced systemic toxicity
- Improved exposure (reduced TMDD)
- Systemic delivery versus intra-tumoral injection
- Increased therapeutic index
- Improved potential for combination therapy

Conditional Cytokines



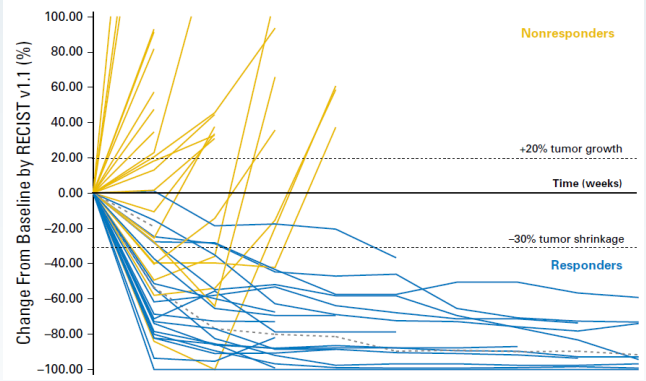
Target Biology and Opportunity for Localized Interferon-Alpha Therapy

TARGET BACKGROUND

- Pleiotropic immune activities:
  - Antiviral
  - Immunomodulatory
  - Antiproliferative/Pro-apoptotic
- Widespread expression of IFNα/β receptors
- Approved for antiviral and cancer therapy
- Systemic administration is accompanied by dose dependent toxicities
- Local delivery is safe and effective in BCG unresponsive bladder cancer

CONDITIONAL IFNα-2b OPPORTUNITY

peginterferon + PD-1 in Melanoma



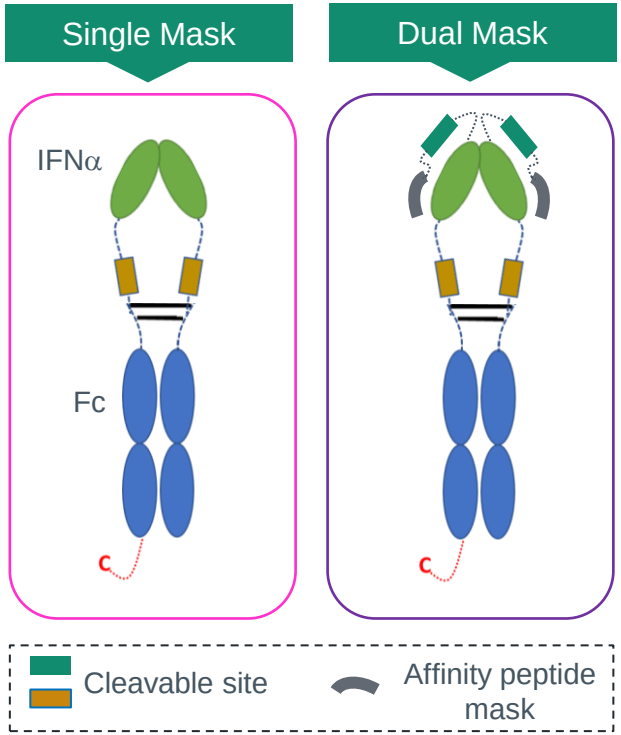
peginterferon: 1-3μg/kg Pembro: 2mg/kg

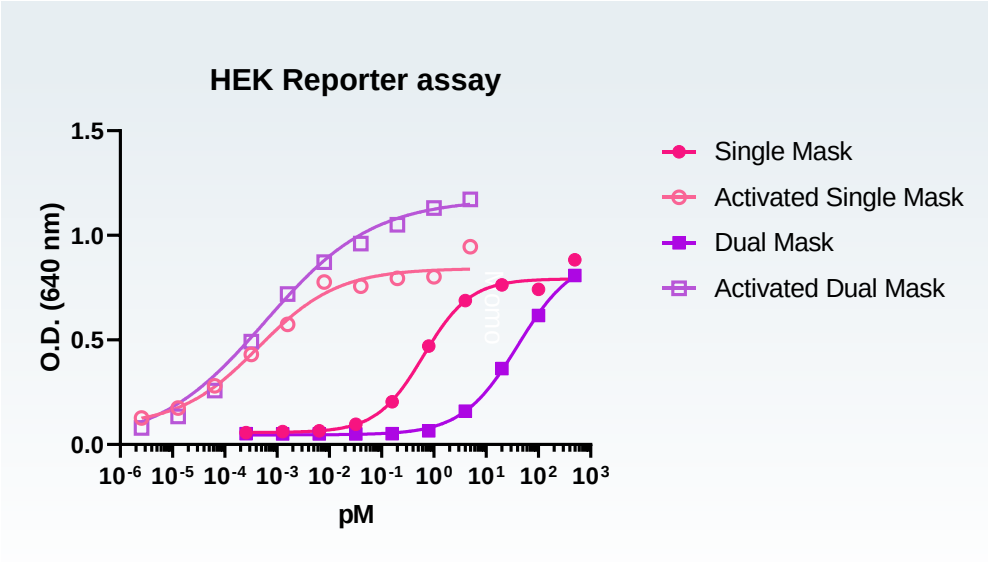
- ORR: 60.5%
- 49% G3/4 AEs

- Room to improve therapeutic index
- Potential for tumor localized activity

(Davar et al., J Clin. Onc., 2018)

Successful Application of Probody Technology to Generate a Conditionally Active IFNα2b

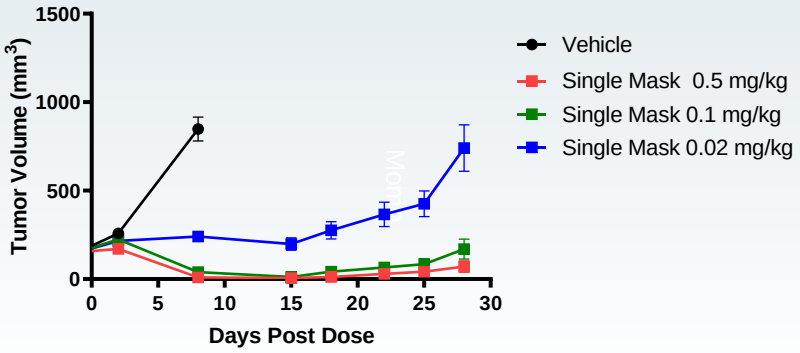




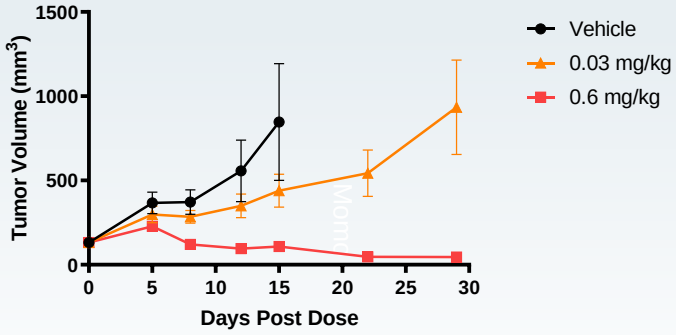
	Single Mask	Dual Mask
Masking strategy	Steric	Steric + Affinity
Masking efficiency	~1,000X	>5,000X

Masked IFNα-2b Shows Strong Anti-Cancer Activity

Single Masked IFNα-2b/Fc



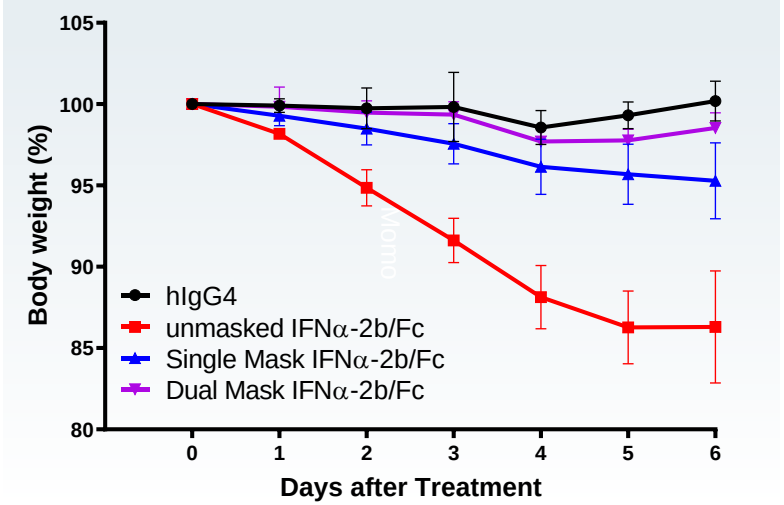
peginterferon



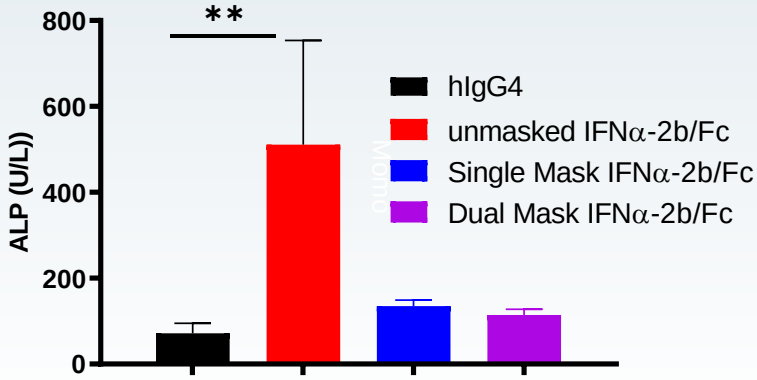
- Daudi Tumor Mouse Model
- Single Masked IFNα-2b/Fc induces tumor regression at dose as low at 0.1mg/kg
- Single Masked IFNα-2b/Fc is as active as peginterferon

Masked IFNα-2b Demonstrates Improved Therapeutic Window

Body weight (15mpk dose)



ALP (15mpk dose)



- Evidence of INFα-2b mediated toxicity in animals dosed with unmasked IFNα-2b/Fc (Increased ALP detected at 0.4mpk)
- Increased therapeutic index for dual and single masked IFNα-2b

Summary and Future Outlook

- CytomX is the leading innovator in protease-activated, conditional biologics
- Uniquely positioned to leverage platform across multiple modalities and cancer types
- Ongoing clinical studies of five Probody Therapeutics
- Four Phase 2 programs spanning across 9 cancer types; Initial readouts from CX-2009 and CX-2029 in Q4 2021
- Multiple emerging preclinical programs including conditional cytokines

CytomX Therapeutics

Questions and Answers