Harnessing the Power of CytomX's Probody® Technology to Drug the Undruggable

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WORLD ADC 2020

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Presentation Overview

Introduction: Probody® Technology	Probody Drug Conjugate Mechanism of Action
CX-2009	CD166 (ALCAM) Probody Drug Conjugate
CX-2029	CD71 (transferrin receptor 1) Probody Drug Conjugate
Questions & Answers	

Probody Therapeutics are Designed to be Activated in the Tumor Microenvironment (TME)

ON TARGET TOXICITY LIMITS THE DEVELOPMENT OF POTENTIALLY ATTRACTIVE ANTIBODY THERAPEUTICS

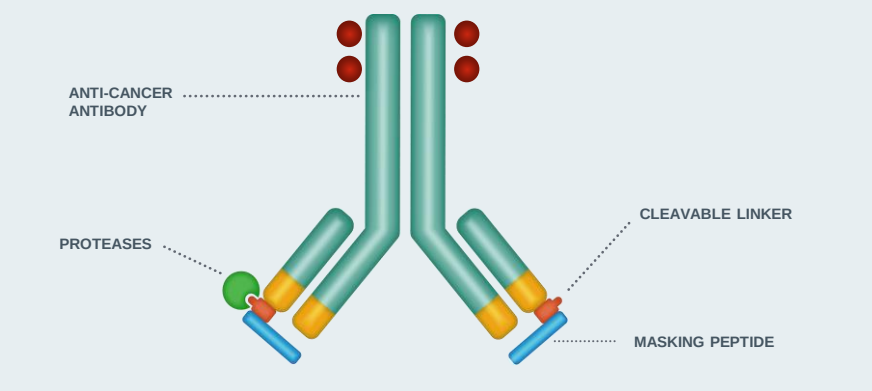
- "Masked" to limit binding to normal tissue
- "Un-masked" by tumor-associated proteases
- Linkers cleaved by multiple proteases for utility across tumor types

CYTOMX PROBODY PLATFORM IS DESIGNED TO LOCALIZE TARGET BINDING TO TUMOR

- Maintaining potency
- Reducing side effects
- Enabling new target opportunities

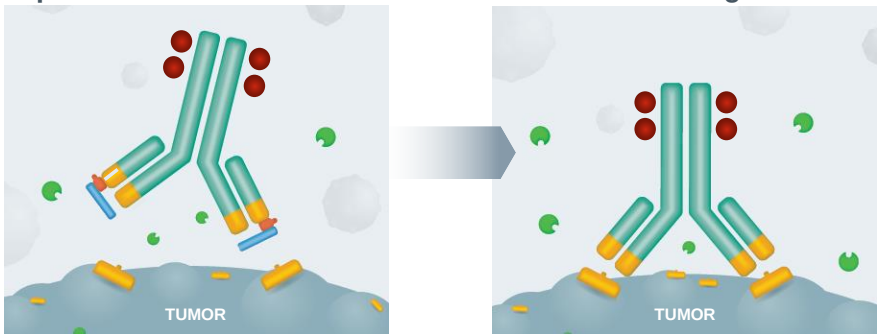
PROBODY PLATFORM IS APPLICABLE ACROSS MULTIPLE TARGETS AND MODALITIES

- Improve therapeutic window for validated targets
- Create therapeutic window for difficult-to-drug targets
- Applicable to multiple binding modalities



Enters TME, proteases remove mask

Antibody binds target



CytomX Therapeutics

Overview

First-in-human trial results for CX-2009 and CX-2029: presented Virtual ASCO 2020

Phase 1 and PK Data for CX-2009 Targeting Undruggable Target CD166

PROCLAIM CX-2009

CX-2009, A CD166-Directed PROBODY Drug Conjugate (PDC):
Results From the First-in-Human Study in Patients With Advanced Cancer Including Breast Cancer

Preliminary Clinical Pharmacokinetics and Dose-Response to Support a Phase 2 Dose Selection for CX-2009:
A Masked PROBODY Drug Conjugate to CD166

Clinical Data for CX-2029 Targeting Undruggable Target CD71

PROCLAIM CX-2029

CX-2029, a PROBODY Drug Conjugate Targeting CD71 (Transferrin Receptor):
Results from a First-in-Human Study (PROCLAIM-CX-2029) in Patients (Pts) With Advanced Cancer (Oral Presentation)

abbvie

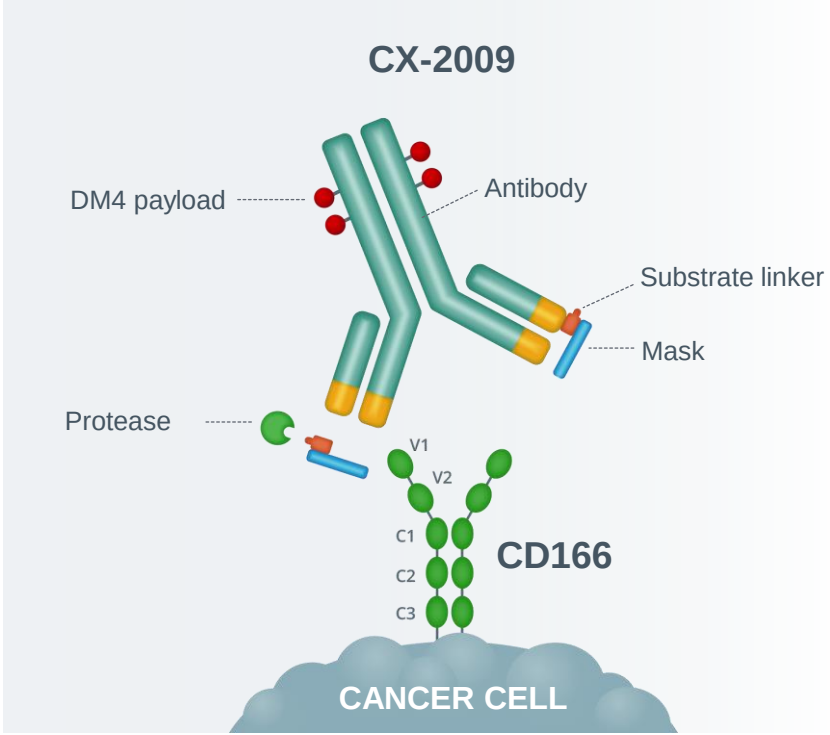
PROCLAIM CX-2009

Phase 1, first-in-human, multi-part, dose-escalation study of CX-2009 in patients with advanced solid tumors (NCT03149549)

CX-2009: A Probody Drug Conjugate Targeting CD166

TARGET: CD166

- Transmembrane protein
- Facilitates cell migration
- Widely expressed on normal tissues and in circulation
- Highly expressed on multiple tumor types



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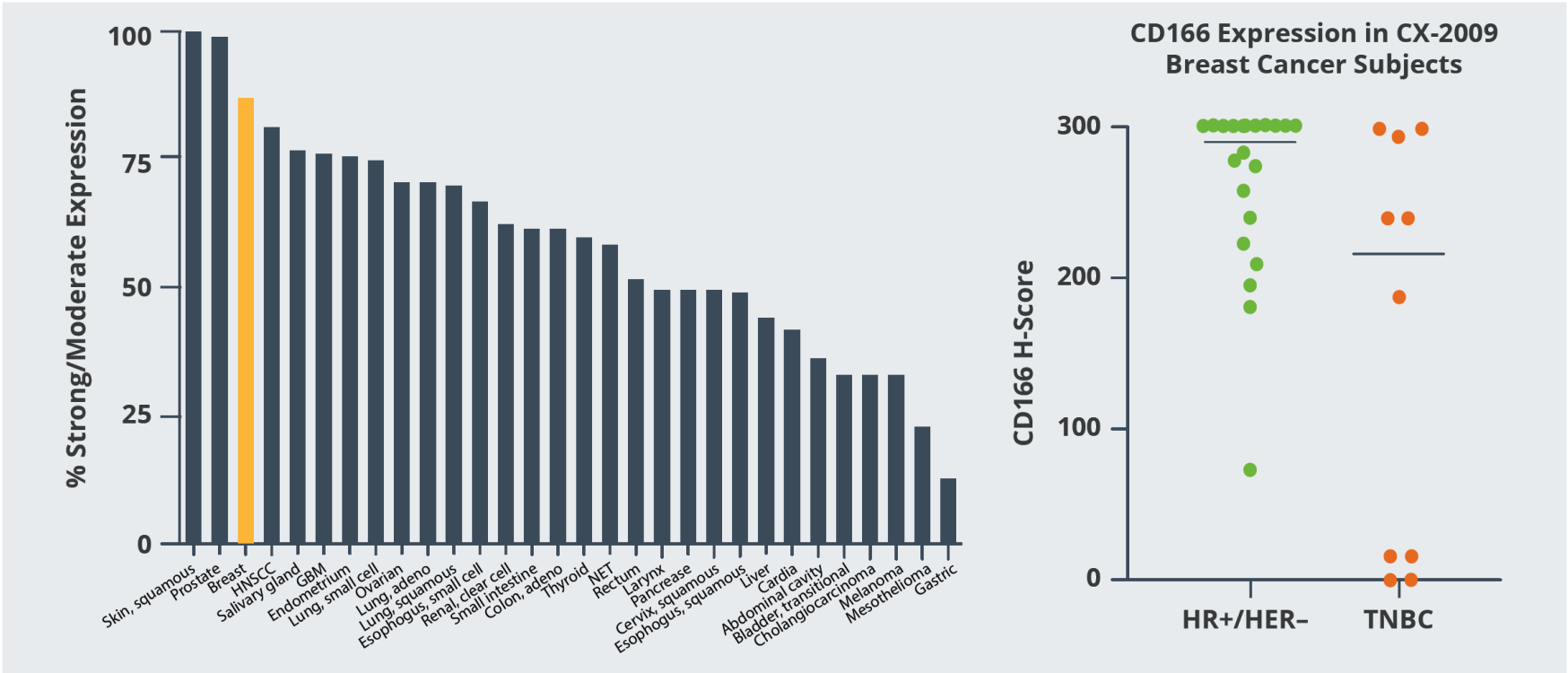
CD166 Expression in Multiple Cancers



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Demographics and Exposure

Phase 1 Dose Escalating Trial

- Two schedules investigated (every 2 and 3 weeks)

Key Eligibility

- Advanced cancer with disease progression after standard treatments
- Available tumor tissue for CD166 IHC analysis
- Prior maytansinoid treatment and neuropathy >Gr 1 exclusionary

Disposition

- Q3W Cohort (Part A) – all off treatment
  - PD/ Deterioration (n=61)
  - Adverse events (n=11)
  - Subject Withdrawal/PI Decision (n=9)
  - Death (n=5)

	Total N=96
Median age (range)	58.5 (31–79)
Male/female, n	21/75
White/Asian/African American/Other, n	78/5/2/11
ECOG PS 0/1, n	31/65
Cancer type, n (%)	
Breast cancer	42 (44)
Epithelial ovarian cancer	22 (23)
Non–small cell lung cancer	13 (14)
Head and neck squamous cell carcinoma	9 (9)
Cholangiocarcinoma	5 (5)
Endometrial carcinoma	3 (3)
Castration-resistant prostate cancer	2 (2)
CD166 Status by IHC (3+ in ≥50% tumor cells), n	
High	77
Low/Unknown	13/6
Median no. prior treatments (range)	5 (1–9)
Median no. CX-2009 doses (range)	2 (1–15)

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Demographics, Cancer Characteristics, and CX-2009 Exposure in Patients With Advanced Breast Cancer

	TNBC (n=11)	HR+/HER2– (n=25)	Overall (n=36)
Median age, range	45 (31–68)	54 (37–77)	53 (31–77)
ECOG PS 0/1, n	4/7	11/14	15/21
CD166 by IHC, high/low/unknown, n	6/4/1	23/1/1	29/5/2
Median no. prior treatments (range)	7 (3–11)	8 (4–16)	7 (3–16)
Platinum, n	9	4	13
Microtubule inhibitor, n	11	24	35
PD-L1/PD-1 inhibitor, n	4	1	5
CDK 4/6 inhibitor, n	0	16	16
Median no. CX-2009 doses (range)	2 (1–16)	2 (1–16)	2 (1–14)

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Grade 3/4 Treatment-Related Adverse Events Overview

Category, n	CX-2009 Dose (mg/kg)							
	≤4 Q3W (n=20)	5 Q3W (n=9)	6 Q3W (n=9)	7 Q3W (n=9)	8 Q3W (n=22)	9 Q3W (n=9)	6 Q2W (n=6)	10 Q3W (n=8)
TRAE	14	9	9	9	21	9	6	7
Grade 3+	1	3	2	2	14	5	3	4
Causing discontinuation	0	3	2	0	3	2	0	1
DLT	0	0	0	0	1	0	2	0
TRAE death	0	0	0	0	1*	0	0	0
Ocular AE	2	6	2	3	13	5	5	6
Grade 3+	0	1	0	0	3	3	2	1
Neuropathy	1	6	2	2	8	3	3	2
Grade 3+	0	1	1	1	0	1	1	0
Hepatic disorder	1	0	2	1	9	3	2	3
Grade 3+	0	0	0	0	4	0	1	3
Blood/lymphatic system disorders	1	0	0	1	6	0	1	0
Grade 3+	1	0	0	0	4	0	0	0

*A 60-year-old man with grade 5 sepsis, related per investigator and complicated by pancytopenia, died 11 days after receiving his first and only dose of CX-2009 (sepsis and hematopoietic toxicity are infrequent with CX-2009)

Recommended Phase 2 Dose = 7 mg/kg Q3W

- No DLTs were reported at doses up to 7 mg/kg Q3W
  - DLTs: 8mg/kg Q3W vomiting, ↑ LFTs
    6mg/kg Q2W: peripheral neuropathy
- Non-specific DM4 payload toxicities seen with other DM4 ADCs (ocular, neuropathic and hepatic toxic)
  - Occur with lower frequency at ≤ 7 mg/kg Q3W
  - Ocular AEs were dose dependent (Grade 3+ in 2% of patients treated with ≤ 7 mg/kg Q3W)
  - Ophthalmic vasoconstricting agents and corticosteroids: mandatory prophylaxis at doses of 8 mg/kg Q3W and 6 mg/kg Q2W.
- Phase 2 monotherapy study in HR+/HER2- breast cancer initiated with **mandatory ocular prophylaxis**

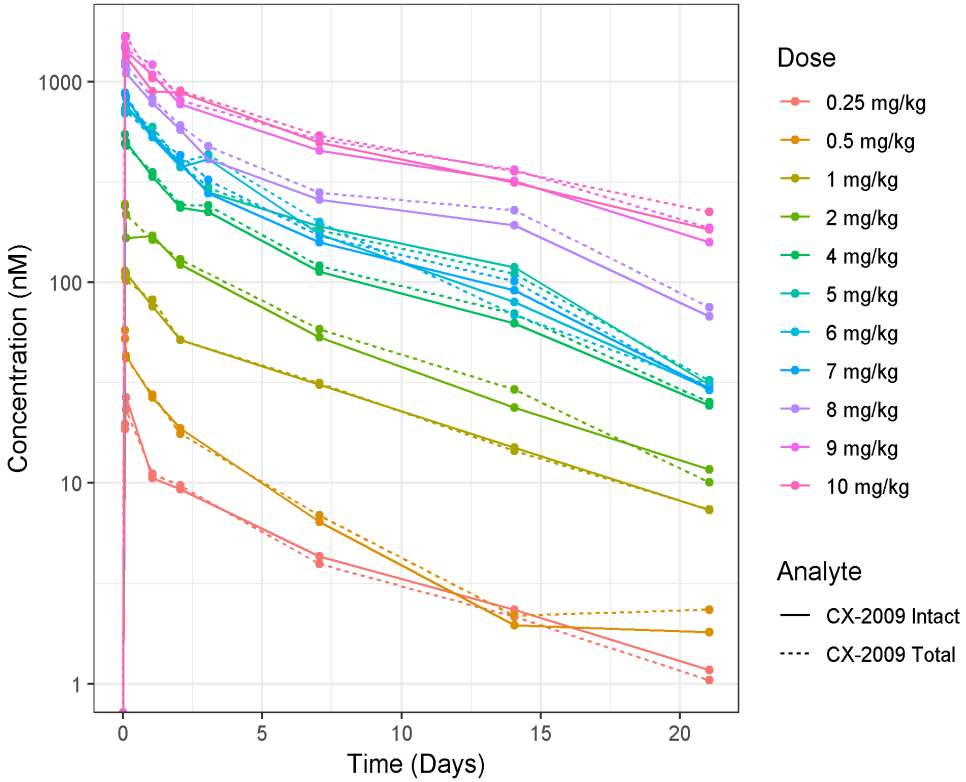
CytomX Therapeutics

Data cut-off: April 20, 2020
Boni et al. ASCO 2020. Abstract 526

CX-2009 PK is Consistent With Effective Peripheral Masking

- CX-2009 circulates predominantly as the intact (masked) prodrug species
- POPPK simulations support selection of 7 mg/kg dose for future study:

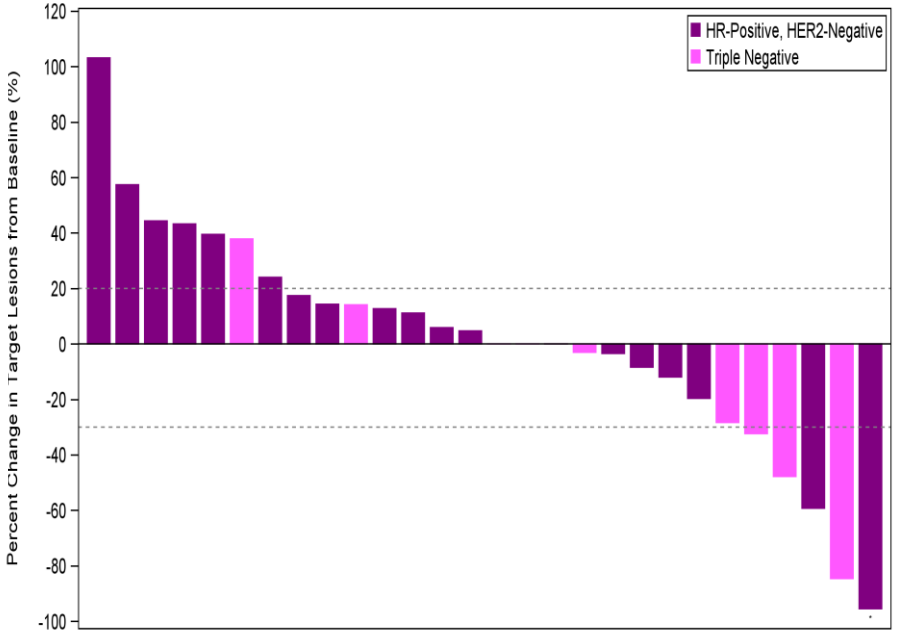
Target 90 nM trough concentration (generated from nonclinical data using systems pharmacology[1]) is contained within the 90% prediction interval of CX-2009 Intact levels following dosing[1]



1. Stroh et al. ASCO 2020; Abstract 3599. Boni et al. ASCO 2020. Abstract 526

Activity in Breast Cancer

	Evaluable Breast Cancer Patients		
	TNBC (n=8)	HR+/HER2– (n=18)	All (n=26)
Response, n			
Confirmed PR	0	2	2
Unconfirmed PR	3	0	3
SD	1	8	9
PD	4	8	12
CBR16	4	6	10 (39%)
CBR24	4	5	9 (35%)



HR+/HER2-: 40% and ->90% reduction in tumor volume
TNBC: 32% - 59% reduction in tumor volume

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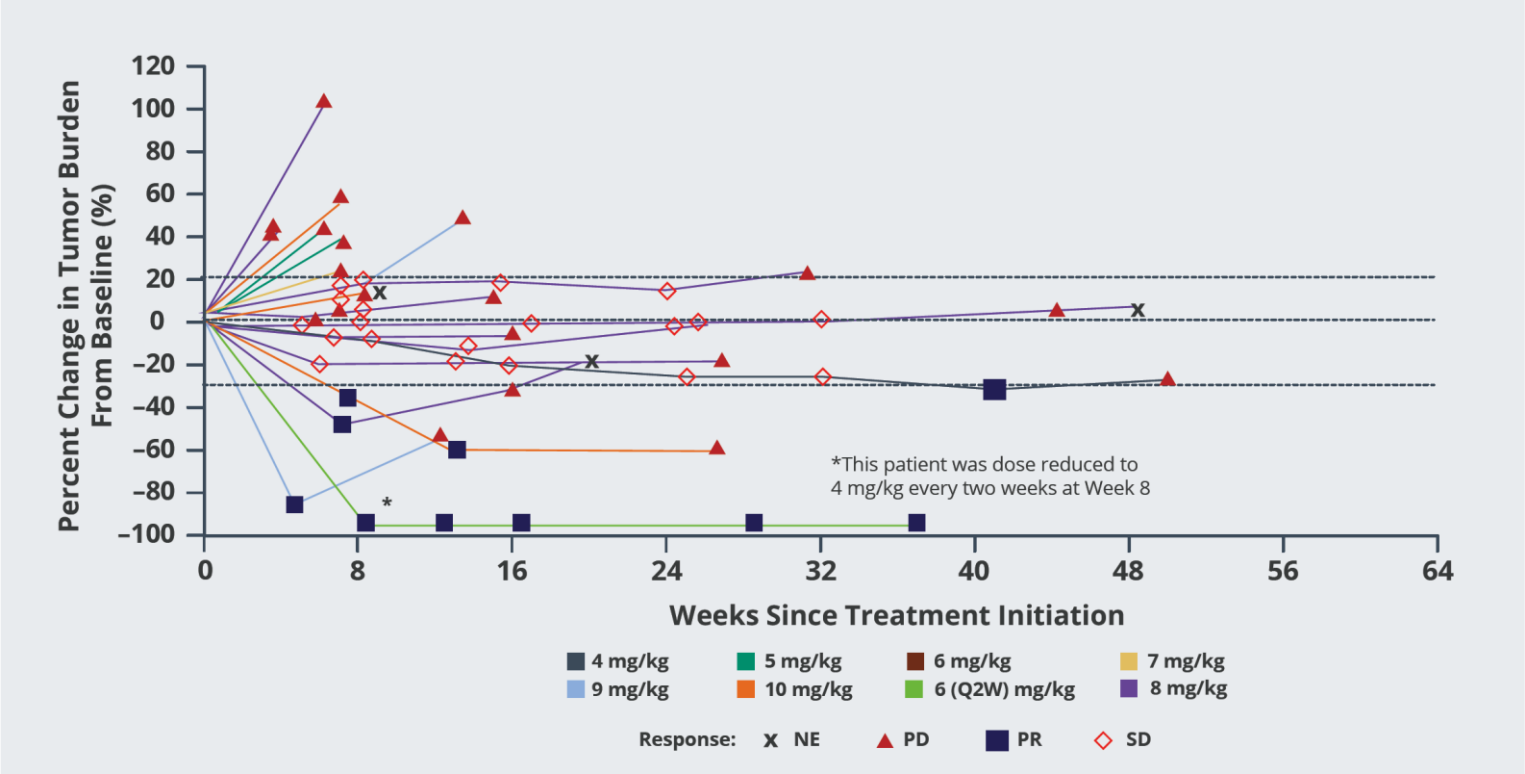
Tumor Burden Reduction by Dose: Efficacy Evaluable Patients; CX-2009 ≥ 4 mg/kg Q3W



Data cut-off: April 20, 2020

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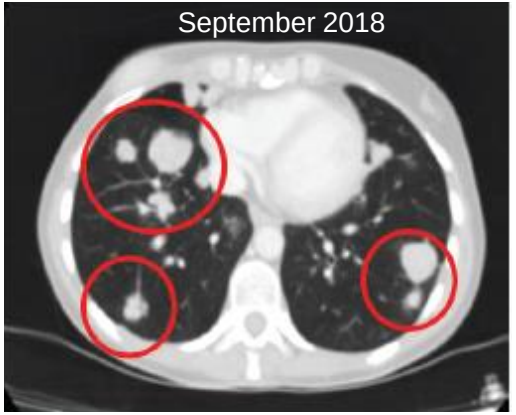
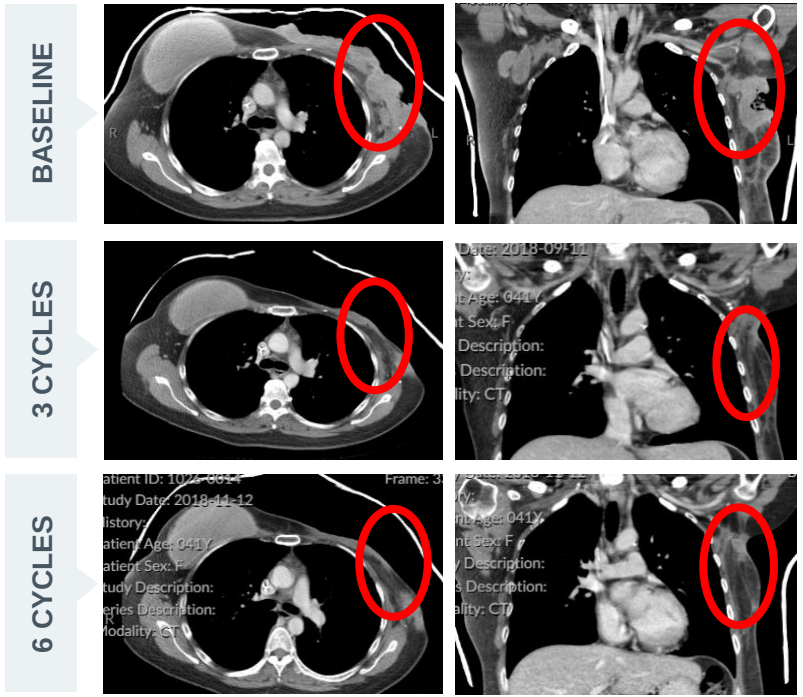
Case Study: Heavily Pretreated Patient with TNBC Treated with CX-2009 9 mg/kg

- 45-year-old white female with TNBC
- No relevant medical history
- Prior treatment included:
  - Mastectomy, lymphadenectomy, and sternum resection
  - Doxorubicin/cyclophosphamide + taxane (with unknown response) + tamoxifen (with progressive disease [PD])
- Baseline: metastases in both lungs and retroperitoneal lymph nodes
- First on-treatment scan: 82% reduction in index lesions
- After second dose and prior to the second on-treatment scan, the patient permanently discontinued study drug due to grade 3 keratitis

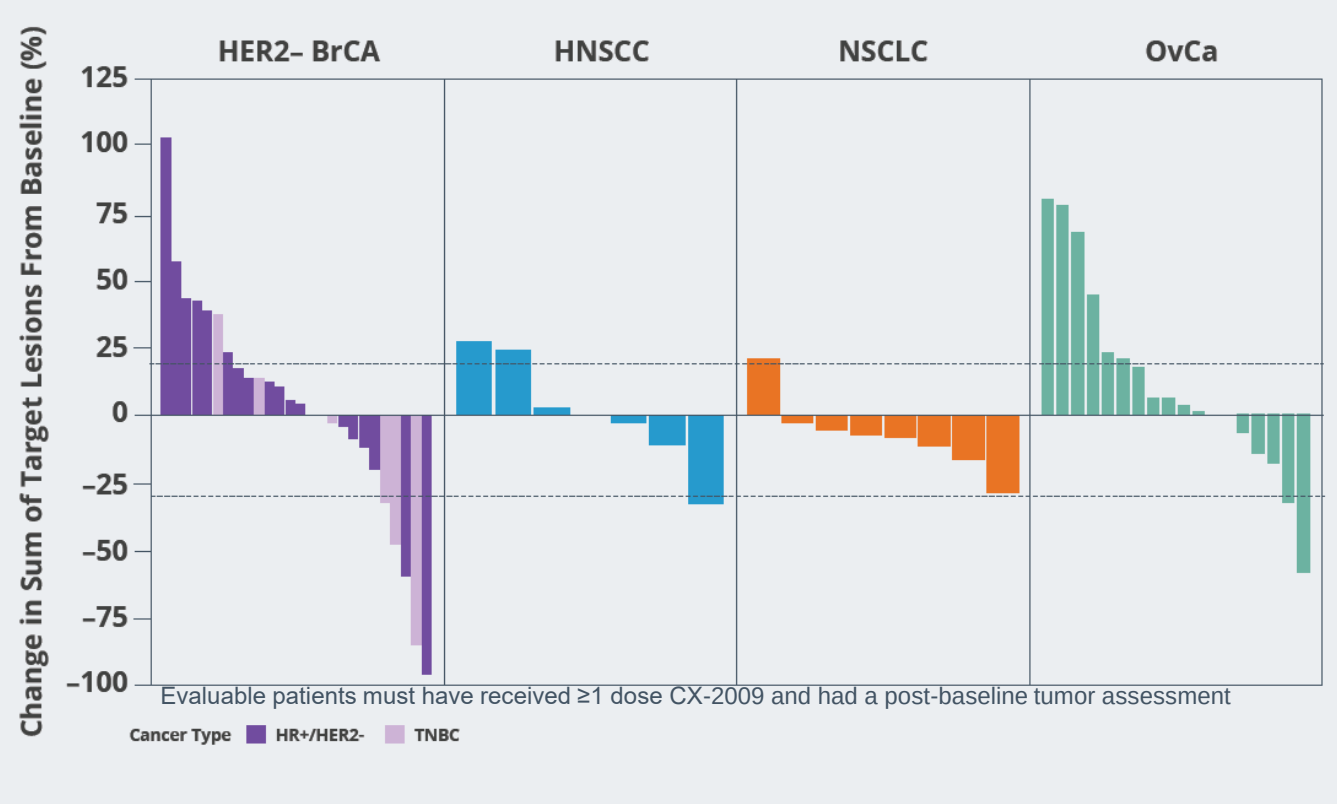


Case Study: Pembrolizumab-Refractory Patient With TNBC Treated with CX-2009 8 mg/kg

- 41-year-old Asian female with TNBC
- No relevant medical history except smoking for 20 yrs
- Prior treatments included:
  - Neoadjuvant docetaxel + doxorubicin + cyclophosphamide (unknown response)
  - Mastectomy + radiation therapy, Gemcitabine + carboplatin (unknown response)
  - Pembrolizumab + paclitaxel (PD)
  - Sacituzumab govitecan (PD)
- Baseline: ulcerating skin lesions on chest wall and nodal metastasis right axilla
- First scan: 48% reduction in index lesions
- After third dose and prior to the 2nd on-treatment scan patient experienced an extended dose delay due to grade 4 keratitis, which completely resolved



CX-2009 Single Agent Activity in Multiple Cancer Types; ≥ 4 mg/kg Q3W Dosing



Data cut-off: April 20, 2020

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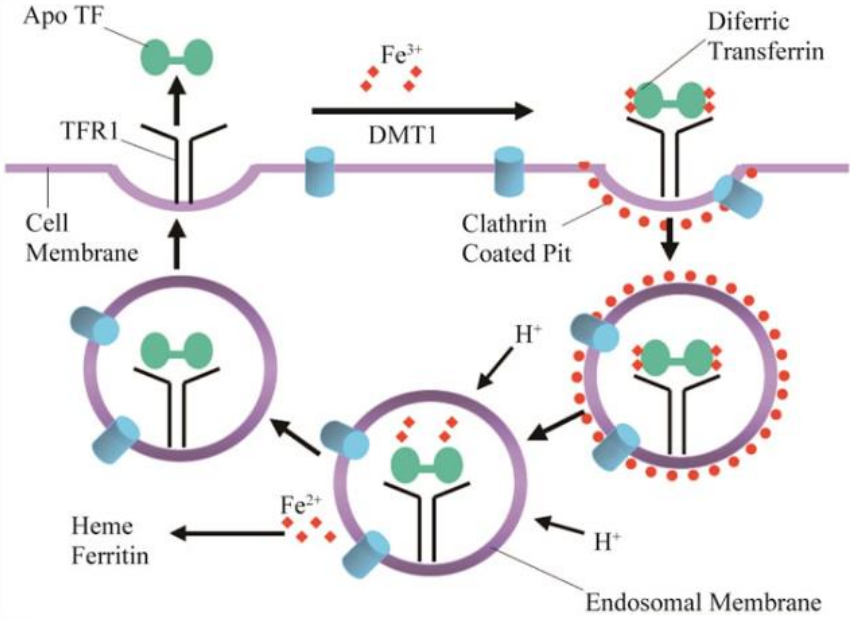
Conclusions

- The results of this trial validate CD166 as a viable first-in-class therapeutic target
- Confirmed PRs and clinically meaningful disease control, as measured by CBR16 (39%) and CBR24 (35%)
- Based on activity, tolerability and pharmacology, the RP2D of CX-2009 is 7 mg/kg Q3W
- Optimization of a CD166 IHC assay is ongoing to support a potential selection strategy
- CX-2009 is being further explored in patients with breast cancer:
  - HR+/HER2- breast cancer: CX-2009 monotherapy
  - TNBC:
    - CX-2009 monotherapy
    - CX-2009 in combination with CX-072 (anti-PD-L1 Probody therapeutic)

Phase 1/2 first-in-human study of CX-2029 in advanced solid tumors (NCT03543813)

Probody Therapeutics: Investigating Undruggable Targets

- CD71 (transferrin receptor 1): attractive target for a Probody drug conjugate
  - CD71 is a transmembrane glycoprotein that efficiently internalizes iron-bound transferrin
  - Highly expressed on malignant cells
  - Expressed in healthy tissue with high iron requirements (eg, rapidly dividing cells; hematopoietic precursors)
- CD71 expression in normal cells prohibits development of a traditional antibody drug conjugate (ADC) due to lethal on-target toxicity



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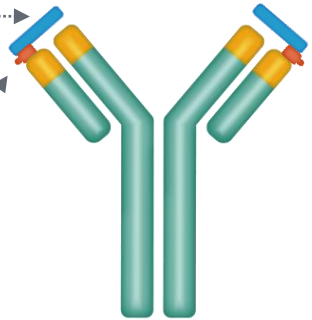
CX-2029: Probody Drug Conjugate Against CD71 With MMAE Payload

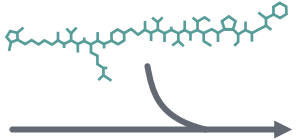
MONOMETHYL AURISTATIN E (MMAE):
Potent Cytotoxic Microtubule Inhibitor,
Blocking Cell Division

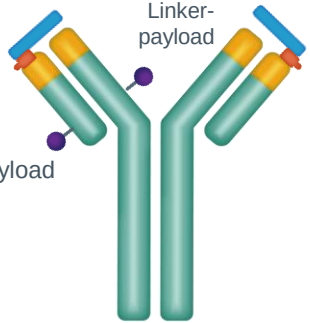
Mask prevents/ significantly reduces binding in normal tissue

Proteases cleave **substrate,** remove mask and allow target engagement in the TME



Linker-payload
mc-vc-PAB-MMAE





CD71- DIRECTED PROBODY

CX-2029 PDC

TME, tumor microenvironment.

Johnson et al. ASCO 2020. Abstract 3502

Phase 1 Dose-Escalating Clinical Trial

Starting Dose

- Given nonclinical toxicity, broad expression of CD71, and novelty of target and platform, the starting dose was ~1/20 the HNSTD in the monkey
- Predicted toxicities (based on MMAE payload): hematopoietic suppression, neuropathy
- Nonclinical PK and toxicology predicted dose range of 2–4 mg/kg in patients

Key Eligibility Criteria

- Metastatic or locally advanced unresectable solid tumor
- ECOG 0 or 1
- 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

Intravenous Dose (every 3 weeks)	TOTAL (n)
0.1 mg/kg	3
0.25 mg/kg	3
0.5 mg/kg	6
1.0 mg/kg	3
2.0 mg/kg	**8**
3.0 mg/kg	**12**
4.0 mg/kg	**6**
5.0 mg/kg	4

HNSTD: Highest non severely toxic dose.
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Demographics and Exposure

	All Cohorts (n=45)
Age, median (min, max)	60 (31, 75)
Sex, male / female (%)	62 / 38
Number of prior cancer treatments, median (min, max)	3 (1, 16)
Baseline ECOG 0 / 1, %	29 / 71
CD71 staining,* n (%)	
High expression [2+/3+ by IHC]	15 (33)
Low expression [0/1+ by IHC]	16 (36)
Unknown	14 (31)
Tumor types, n (%)	
NSCLC	9 (20)
HNSCC	8 (18)
Colorectal cancer	7 (16)
Soft tissue sarcoma	4 (9)
Prostate cancer	3 (7)
Other**	14 (31)
Number of CX-2029 doses administered, median (min, max)	3 (1, 12)
Duration of exposure in weeks, median (min, max)	9 (3, 36)

*CD71 expression was defined by overall tumor staining using a proprietary antibody.
**Other tumor types include adenoid cystic carcinoma of parotid gland (n=2); ovarian cancer (n=2); cutaneous melanoma (n=1); endometrial cancer (n=1); hepatocellular carcinoma (n=1); mesothelioma (n=1); ocular melanoma (n=1); oncocytic carcinoma of parotid gland (n=1); pancreatic cancer (n=1); perivascular epithelioid cell tumor (n=1); thymoma/thymic cancer (n=1); thyroid cancer (n=1).

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Adverse Event Overview

	Patients, n (%)				
	CX-2029 0.1–1.0 mg/kg (n=15)	CX-2029 2.0 mg/kg (n=8)	CX-2029 3.0 mg/kg (n=12)	CX-2029 4.0 mg/kg (n=6)	CX-2029 5.0 mg/kg (n=4)
Any TEAE, n (%)	15 (100)	8 (100)	12 (100)	6 (100)	4 (100)
Related to CX-2029	14 (93.3)	8 (100)	12 (100)	6 (100)	4 (100)
TEAE grade 3+	6 (40)	6 (75)	11 (92)	6 (100)	4 (100)
Related to CX-2029	4 (27)	5 (63)	8 (67)	5 (83)	4 (100)
Grade 3 anemia	1 (7)	5 (63)	7 (58)	5 (83)	4 (100)
Grade 3 neutropenia	1 (7)	0	4 (33)	3 (50)	3 (75)
TEAE leading to CX-2029 discontinuation	2 (13)	0	0	0	0
Related to CX-2029	1 (7)*	0	0	0	0
Cycle 1 dose-limiting toxicity	0	0	0	2 (33)[1,2]	2 (50)[3,4]
Late-onset dose-limiting toxicity**	3/15 (20)	2/7 (29)	3/12 (25)	4/5 (80)	1/2 (50)
Serious TEAE	3 (20)	2 (25)	5 (42)	3 (50)	4 (100)
Related to CX-2029	2 (13)	0	1 (8)	2 (33)	3 (75)
TEAE leading to death	0	0	0	0	0

*One patient with hypoxia treated at a dose of 0.1 mg/kg.
**Percentages are based on number of subjects who had received at least 2 infusions

1. Grade 3 infusion-related reaction >6 hours
2. Grade 4 neutropenia; cycle 2 delayed 23 days due to persistent grade 3 anemia; ECOG status declined to 2
3. Grade 3 pancytopenia (thrombocytopenia, anemia, neutropenia) >7 days
4. Grade 3 febrile neutropenia

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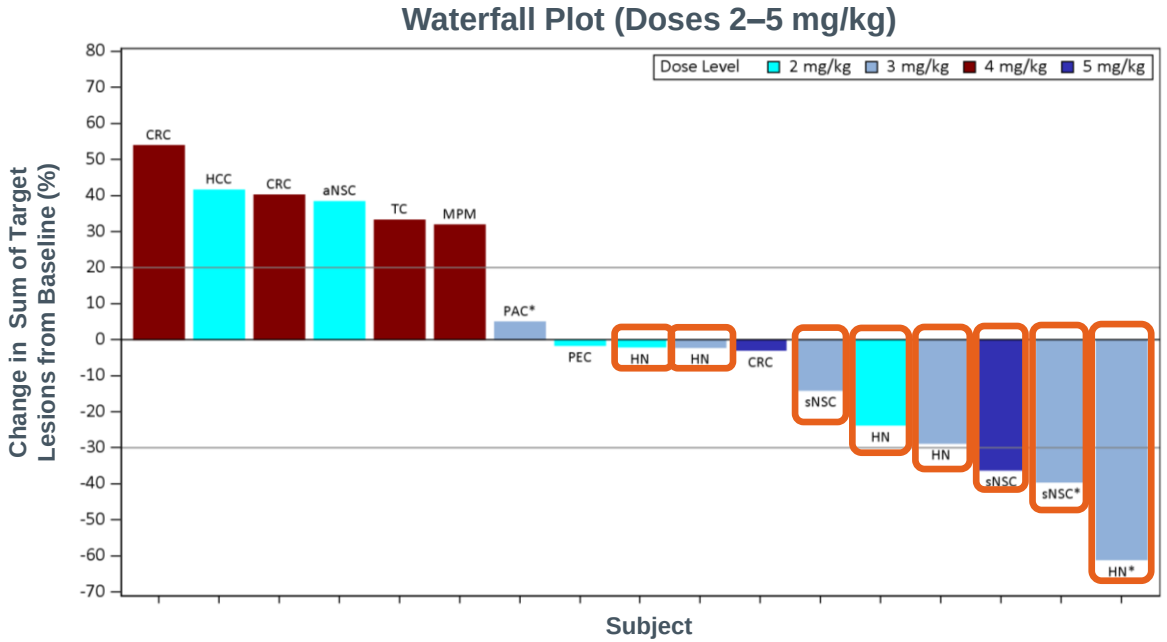
Activity Predominantly Seen in Patients with Tumors of Squamous Histology



aNSC = non–small cell lung cancer (adenocarcinoma), CRC = colorectal cancer, HCC = hepatocellular carcinoma, HN = head and neck squamous cell carcinoma, MPM = malignant pleural mesothelioma, PAC = pancreatic cancer, PEC = perivascular epithelioid cell tumor, sNSC=non–small cell lung cancer (squamous cell carcinoma), TC = thyroid carcinoma.

*Denotes subjects still on treatment.

13 patients not included due to (a) 5 patients ongoing without first on-study scan; (b) 6 patients discontinued without on-study scan; (c) 1 patient without measurable disease at baseline, and (d) 1 patient diagnosed with new lesion without target lesion(s) assessed.

All 3 patients with Target Lesions Shrinkage >30% are confirmed partial responses

Data cut-off: April 20, 2020

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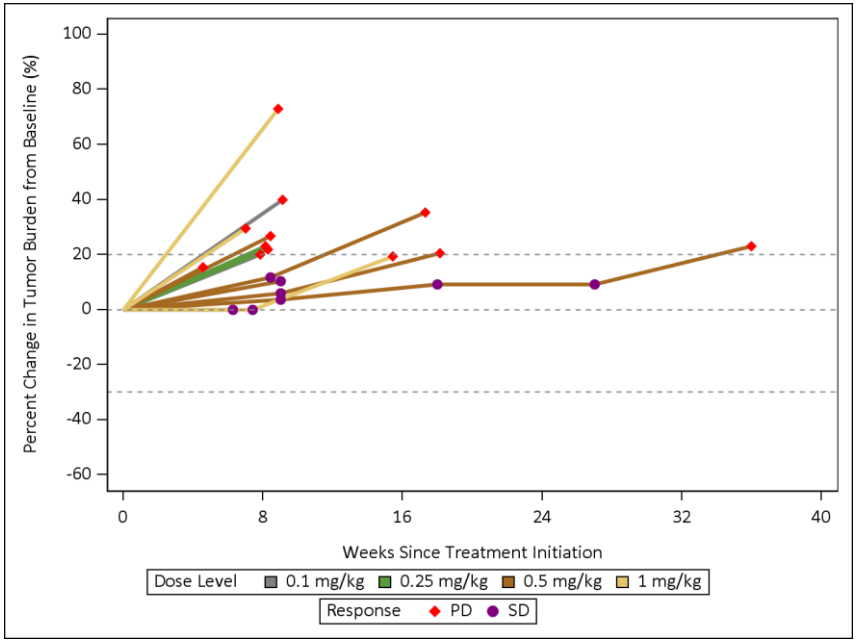
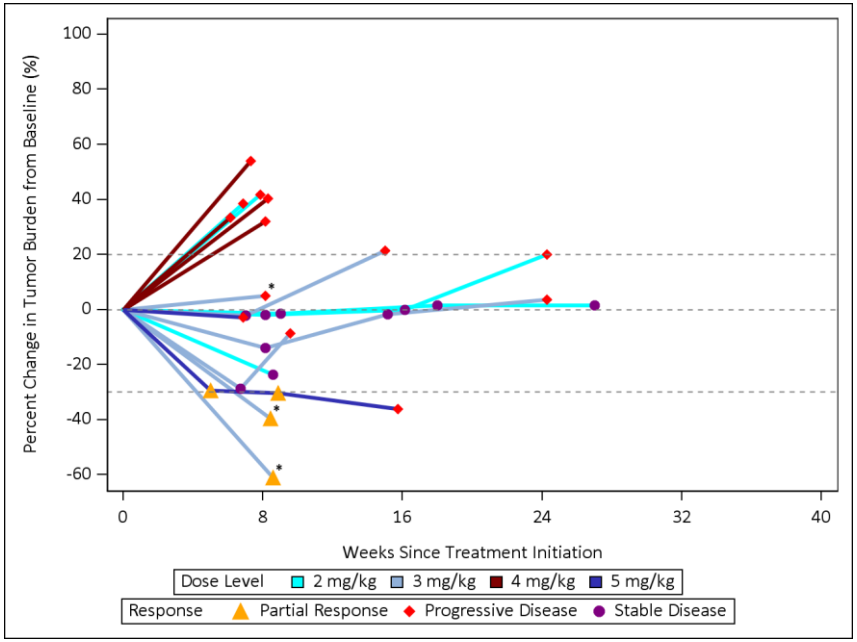
Clinical Activity at CX-2029 Doses ≥ 2 mg/kg

Spider Plot (Doses 0.1–1 and 2-5 mg/kg)





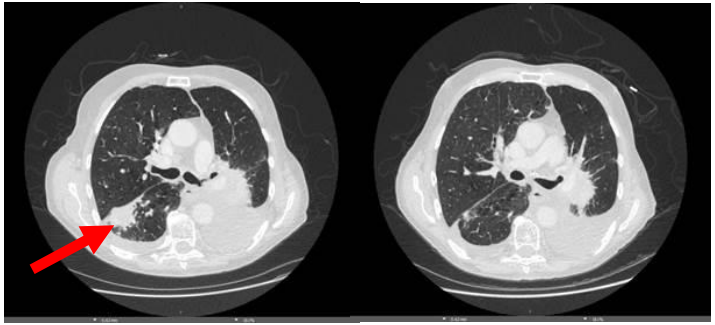
PD, progressive disease; PR, partial response; SD, stable disease.
*Patient on treatment as of data cut-off.

75-Year-Old Patient With Squamous NSCLC (3 mg/kg)

- **Patient:** diagnosed with stage III squamous NSCLC in August 2017
- **Prior therapy:** Carboplatin/paclitaxel with radiation (2 mo); durvalumab (10 mo); gemcitabine (2 mo); docetaxel/ramucirumab (8 mo; SD then PD)
- **Toxicity:** Cycle 2 and cycle 3 grade 3 anemia
- **Response:** confirmed partial response seen on Week 8 (12Mar10) and Week 16 (4May20) scans

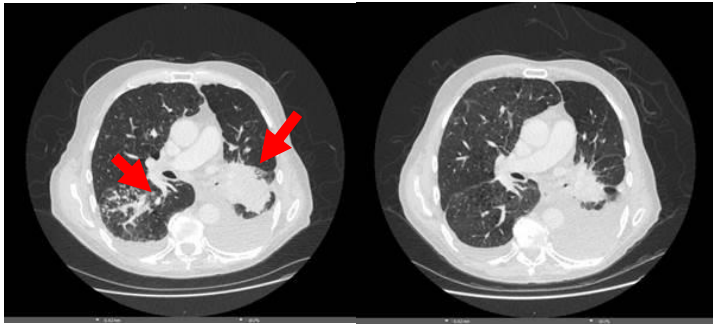
20Jan2020 **12Mar2020**

Near-resolution of right perifissural lesion (target lesion #2)



20Jan2020 **12Mar2020**

Improvement in LLL lesion (target lesion #1),
with marked improvement in RLL nodular lesions (nontarget lesions)



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(Images are courtesy of Navid Hafez, MD)
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66-Year-Old Patient With Squamous Head and Neck Carcinoma (3 mg/kg)

Cancer History

- Diagnosed with nasopharyngeal carcinoma in February 2018
- Prior therapy included: docetaxel/5FU/cisplatin with radiation (3 mo.); high-dose cisplatin (1 mo.); investigational agent (sEPHB4-HAS) + pembrolizumab (3 mo.; PD)

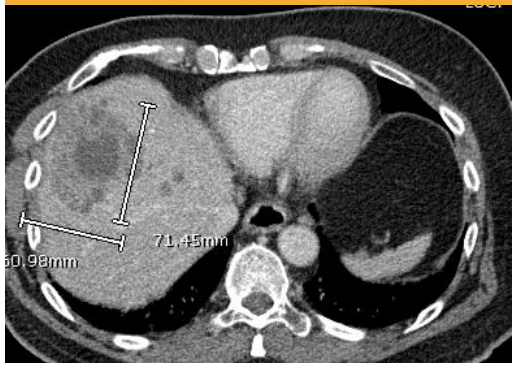
Relevant Past Medical History:

Anemia, increased LFTs, HTN, neuropathy, dyspnea

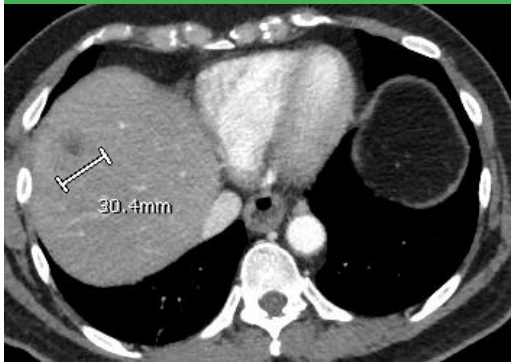
Initiated CX-2029: [14 Jan 2020]

- **Toxicity:** Cycle 1 grade 4 neutropenia (Neulasta) and grade 2 anemia; Cycles 2-4 grade 3 anemia managed with PRBCs, transfusions and **dose reduction to 2 mg/kg**; darbepoetin initiated Cycle 6
- **Response**: Partial response at Week 8 (13 Mar 2020) confirmed 8 weeks later (8 May 2020)

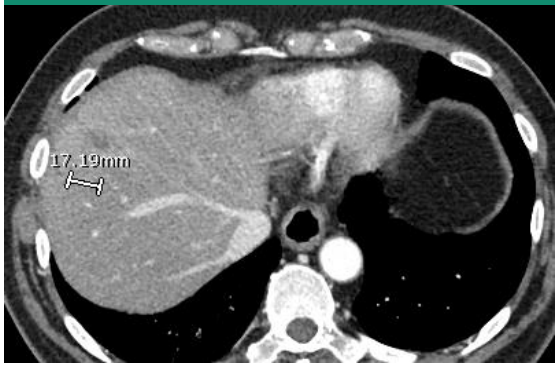
18 Dec 2019



13 Mar 2020 (43% ↓)



8 May 2020 (78% ↓)



PROCLAIM®

Summary and Conclusions

First-in-human trial results of both CX-2009 and CX-2029 validate previously undruggable targets as viable therapeutic targets in cancer

Probody technology enables administration of these antibody drug conjugates at tolerable doses with clinical anti-tumor activity

Toxicities consistent with payload

- CX-2009: ocular toxicity (DM4 payload)
- CX-2029: anemia (multifactorial, secondary to MMAE & effects on RBC precursors → under evaluation)

Clinical activity was observed after single-agent administration

- CX-2009 (at ≥ 4 mg/kg): HR+ breast cancer, TNBC, ovarian, HNSCC, NSCLC
- CX-2029 (at ≥ 2 mg/kg): squamous NSCLC, HNSCC

Future clinical trials:

- CX-2009 at 7 mg/kg Q3W: HR+ BC, TNBC
- CX-2029 at 3 mg/kg Q3W: squamous NSCLC, HNSCC, esophageal/GEJ and DLBCL