PROCLAIM™ CX-2009

Preliminary Results of PROCLAIM-CX-2009, a First-in-Human, Dose-Finding Study of the Probody™ Drug Conjugate CX-2009 in Patients With Advanced Solid Tumors

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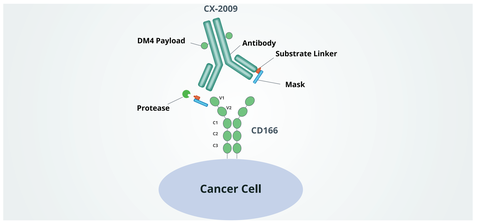
Background

- Activated leukocyte cellular adhesion molecule (CD166) is broadly expressed in normal epithelium and overexpressed in many types of primary and metastatic malignancies, including prostate, breast, non-small cell lung, and endometrial cancers[1-3]
  - Normal tissues expressing CD166 at high levels include lung, pancreas, intestine, prostate, and liver
  - Given its high expression on normal tissues, CD166 has not been considered as a target for therapeutic development due to potential safety concerns
- Probody®* therapeutics are recombinant antibody prodrugs designed to be activated by proteases in the tumor microenvironment and preferentially bind to the tumor rather than to healthy tissue[3]
- CX-2009 is a Probody drug conjugate that consists of a humanized anti-CD166 monoclonal antibody conjugated to DM4, a microtubule inhibitor (**Figure 1**)[3]

Figure 1. CX-2009: A Probody Drug Conjugate Targeting CD166



- Toxicity observed in patients receiving a DM4-conjugated ADC is well described and includes ocular toxicity, peripheral neuropathy, neutropenia, nausea, and liver function test abnormalities[4]
- In preclinical evaluation,[2]
  - CX-2009 resulted in tumor growth inhibition or regression in multiple solid tumor types
  - CX-2009 had a safety profile similar to that previously reported for other DM4-containing ADCs
  - Compared with a corresponding unmasked CD166-targeting antibody-drug conjugate, CX-2009 had extended exposure in animal studies consistent with significantly reduced binding to normal tissues
- Here we report preliminary safety and antitumor activity from the dose-escalation phase (Part A and A2 only) of PROCLAIM-CX-2009 (PRObody CLInical Assessment In Man), an ongoing first-in-human investigational dose-escalation study evaluating CX-2009 in selected tumor types expected to demonstrate high CD166 expression and sensitivity to microtubule inhibition

Objectives

- The objectives of this study are to:
  - Determine the safety, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), dose-limiting toxicities (DLTs), and preliminary antitumor activity of CX-2009 as monotherapy in selected tumor types with high CD166 expression
  - Measure cleavage of CX-2009 in tumor biopsies and peripheral blood in patients with tumors with high CD166 expression (data not shown)

Methods

Study Design

- PROCLAIM-CX-2009 is a first-in-human, open-label, multicenter, proof-of-concept phase 1/2 study (NCT03149549)
- Eligible patients were previously treated and had histologically confirmed metastatic or advanced unresectable breast carcinoma, castration-resistant prostate carcinoma, non-small cell lung carcinoma (NSCLC), epithelial ovarian carcinoma (OC), endometrial carcinoma (EC), head and neck squamous cell carcinoma (HNSCC), or cholangiocarcinoma (**Table 1**)

Table 1. Key Eligibility Criteria

Parts A/A2	Age ≥18 years ECOG performance status 0–1 Histologically confirmed diagnosis of any active metastatic or locally advanced unresectable solid tumor Consented to provide tumor tissue (archival, new, or recent acquisition) 3 to 5 days after first dose of CX-2009 (Part A2) Life expectancy ≥3 months
Breast carcinoma	Patients with ER+ breast carcinoma received antihormone therapy and experienced disease progression Patients with TNBC received ≥2 previous lines of therapy
Castration-resistant prostate cancer	Patients received ≥1 previous line of therapy
Cholangiocarcinoma	Patients experienced progression after ≥1 previous gemcitabine-containing regimen
Endometrial carcinoma	Patients received ≥1 platinum-containing regimen for extrauterine or advanced disease
Epithelial ovarian cancer	Patients with non-BRCA mutation (germline or somatic) and patients with unknown BRCA mutational status must have platinum-resistant or platinum-refractory ovarian carcinoma Patients with BRCA mutation must be refractory to or otherwise ineligible for PARP inhibitors
Head and neck squamous cell carcinoma	Patients received ≥1 platinum-containing regimen and PD-1 inhibitor if approved for indication and locality
Non-small cell lung cancer	Patients received ≥1 platinum-containing regimen Patients received checkpoint inhibitor if approved for indication and locality

BRCA, breast cancer gene; ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor positive; PARP, poly (adenosine diphosphate–ribose) polymerase; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; TNBC, triple-negative breast cancer.

- The study consists of the following parts (**Figure 2**)
  - Part A (ns55) starts with a single-patient cohort (0.25 mg/kg) followed by a standard 3+3 design to determine the MTD (defined as the highest dose tested at which ≤1/6 DLT observed during the first 3 weeks of treatment)
  - Part A2 (ns42) enrolls additional patients with select tumors with high CD166 expression at CX-2009 doses of 4 mg/kg to 10 mg/kg (once each dose level, respectively, is cleared in Part A) for translation assessment (biopsies mandatory)
  - Modified toxicity probability interval-2 (mTPI-2; ns14): enrolls patients with select tumors with high CD166 expression treated at or below the MTD to finalize selection of a RP2D; ocular prophylaxis is mandatory in the mTPI-2 cohort
- Patients receive CX-2009 intravenously every 21 days until disease progression

Figure 2. Study Design

Assessments

- Safety assessments include characterization of DLTs, adverse events (AEs), physical examinations, and clinical laboratory evaluations
- Imaging for tumor response assessment is performed every 8 weeks from the first dose of CX-2009 using Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1)
- All patients undergo complete ophthalmology examination at baseline and during certain points of the study; patients who report treatment-emergent changes in vision or other ocular symptoms undergo repeat examinations before infusion in every other cycle and as clinically indicated
- Serial blood samples are being collected for evaluation of pharmacokinetics by compartmental analysis
- On-treatment tissue biopsies are being collected in Part A2 to assess Probody therapeutic activation in the tumor microenvironment

Preliminary Results

- As of 06 February 2019, 78 patients were enrolled in Parts A and A2, including 30 with breast cancer, 22 with OC, 8 with NSCLC, 8 with HNSCC, 5 with cholangiocarcinoma, 3 with EC, and 2 with castration-resistant prostate cancer
- Patient demographic and baseline characteristics are shown in **Table 2**

Table 2. Baseline Characteristics of Patients Treated With CX-2009

	All Cohorts (n=78)
Median age, (range) years	57.5 (31–79)
Female, n (%)	61 (78)
Race, n (%)	
White	58 (74)
Black	2 (3)
Asian	5 (6)
Other	13 (17)
Cancer type, n (%)	
Breast	30 (39)
Cholangiocarcinoma	5 (6)
CRPC	2 (3)
Endometrial	3 (4)
Head and neck squamous cell	8 (10)
NSCLC	8 (10)
Ovarian	22 (28)
Baseline CD166 status, n (%)	
High	58 (74)
Low	14 (18)
Unknown	6 (8)*
Median prior cancer treatments (range)	6 (1–20)
Prior anti-microtubule or platinum-containing treatment, n (%)	75 (96)
Prior anti-PD-1/PD-L1 treatment, n (%)	25 (32)

CRPC, castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand.
*Reasons for unknown status: non-evaluable results due to insufficient tumor tissues present (n=4), no archived tumor sample collected (n=2).

- High CD166 expression (defined as 3+ membranous staining intensity in ≥50% tumor cells) by immunohistochemistry was found in 58/78 (74%) patients (archival tissue)
  - Patients were heavily pre-treated, with a median of 6 (range 1–20) prior therapies, including anti-microtubule or platinum-containing agents in 96% (75/78) of patients, and anti-PD-1 or anti-PD-L1 agents in 32% (25/78) of patients
- Of 78 enrolled patients, 15 (19%) remained on treatment as of the cut-off date
  - Reasons for discontinuation of treatment (63 patients; 81%) included disease progression (n=35, 45%); symptomatic deterioration (n=10, 13%); AEs, all related to study drug (n=9, 12%); and investigator decision, withdrawal by patient, and death (not related to study drug) (each: n=3 , 4%)

Treatment Duration

- The median number of CX-2009 doses received was 2 (range, 1–13) and median treatment duration was 6.3 weeks (range, 0.3–42.1) (**Table 3**)

Table 3. Duration of CX-2009 Treatment

	CX-2009 dose (mg/kg)					
	<4 (n=10)	4–5 (n=19)	6–7 (n=18)	8–9 (n=23)	10 (n=8)	All Cohorts (n=78)
Median number of doses administered (range)	3 (1–3)	3 (1–13)	2 (1–11)	2 (1–7)	2 (1–3)	2 (1–13)
Median duration of treatment, wk (range)	8.9 (3.0–9.3)	9.0 (3.0–42.1)	6.2 (3.0–33.0)	6.1 (0.3–22.1)	6.0 (2.4–10.4)	6.3 (0.3–42.1)

Safety

- One DLT (vomiting) was observed in 1 patient at 8 mg/kg; the MTD was not reached at the highest dose level tested (10 mg/kg)
- Serious AEs were observed in 27 (35%) patients; those occurring in ≥2 patients included nausea (n=4), vomiting (n=4), abdominal pain (n=3), small intestinal obstruction (n=3), hypokalemia (n=2), hyponatremia (n=2), infusion-related reaction (n=2), and pericardial effusion (n=2)
- Treatment-related AEs (TRAEs) were observed in 69 (89%) patients; most were CTCAE grades 1 and 2
  - The most common (>10%) TRAEs of any grade were nausea (32%), fatigue (24%), decreased appetite (23%), diarrhea (19%), keratitis (19%), infusion-related reaction (18%), blurred vision (17%), vomiting (15%), and increased aspartate aminotransferase (13%)
    - All events were medically manageable, with improvement or resolution following dose delay, discontinuation, and/or dose reduction
  - 18 patients had at least 1 treatment delay; the most common reasons for treatment delays included ocular toxicity (n=12, 67%) and peripheral neuropathy (n=4, 22%)
  - 9 (12%) patients had TRAEs leading to treatment discontinuation (**Table 4**)

Table 4. Most Common TRAEs Leading to Permanent Discontinuation of Study Treatment

	TRAEs Leading to Discontinuation (n=9)
TRAE, n (%)	
Keratitis	6 (67)
Vision blurred	1 (11)
Peripheral neuropathy*	1 (11)
Nausea†	1 (11)

*Patient (4–5 mg/kg) had baseline neuropathy.
†Patient (6–7 mg/kg) had tumor-related small bowel obstruction.

- 3 of the 7 responders experienced grade 3-4 ocular toxicity, which resulted in dose delay or discontinuation of study treatment
- Ocular prophylaxis with steroidal eye drops was not introduced until the top 2 dose levels at the end of dose escalation
- Grade 3–4 TRAEs (in ≥2% of patients; all cohorts) are summarized in **Table 5**; 2 (2.6%) patients had grade 4 TRAEs (1 each: keratitis, gamma-glutamyl transferase increased)

Table 5. Most Common Grade 3+ TRAEs (≥2%; All Cohorts)

	CX-2009 Dose (mg/kg)					
	<4 (n=10)	4–5 (n=19)	6–7 (n=18)	8–9 (n=23)	10 (n=8)	All Cohorts (n=78)
TRAE, n (%)						
Keratitis	0	1 (5)	0	4 (17)*	1 (13)	6 (8)
Increased AST	0	0	0	1 (4)	3 (38)	4 (5)
Increased ALT	0	0	0	1 (4)	2 (25)	3 (4)
Nausea	0	0	1 (6)	2 (9)	1 (13)	4 (5)
Hyponatremia	0	0	2 (11)	1 (4)	0	3 (4)
Anemia	0	1 (5)	1 (6)	0	0	2 (3)
Fatigue	0	1 (5)	0	0	1 (13)	2 (3)
Peripheral sensory neuropathy	0	1 (5)	1 (6)	0	0	2 (3)
Vomiting	0	0	1 (6)	1 (4)	0	2 (3)

TRAEs, treatment-related adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*Including one patient with grade 4 keratitis.

Tumor Response

- Best overall response by RECIST in 71 response-evaluable patients (those with ≥1 post-baseline disease assessment) is shown in **Table 6**
  - Evidence of anti-cancer activity was observed with 7 (10%) unconfirmed objective responses in the intent-to-treat population
- 17 (24%) patients had stable disease and the disease control rate (unconfirmed partial response + SD) across all dose groups was 34%

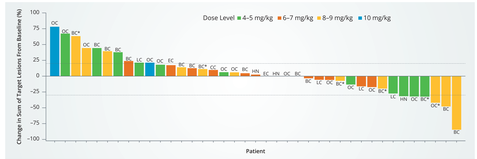
Table 6. Best Tumor Response per RECIST v1.1 (Intent-to-Treat Population†)

	CX-2009 Dose (mg/kg)					
	<4 (n=10)	4–5 (n=19)	6–7 (n=18)	8–9 (n=20)	10 (n=4)	All Cohorts (n=71)
n (%)						
Unconfirmed partial response	3 (16)			3 (15)	1 (25)	7 (10)
Stable disease‡	5 (26)		5 (28)	7 (35)		17 (24)
Progressive disease	7 (70)		7 (37)	6 (33)	7 (35)	3 (75)	30 (42)
Not evaluable§	1 (10)		3 (17)	4 (6)			4 (6)
Early discontinuation#	2 (20)		4 (21)	4 (22)	3 (15)		13 (18)

Note: 7 additional patients are ongoing with no post-baseline tumor assessment prior to data cut date.
*In response-evaluable population with post-baseline disease assessment.
†Patients with at least 1 stable disease assessment ≥7 weeks after the treatment start date (and not qualifying for complete or partial response).
‡Patients with stable disease with only 1 evaluable post-baseline tumor scan <7 weeks from treatment start.
§Patients who discontinued study without providing a post-baseline scan.

- The waterfall plot (**Figure 3**), for all patients who received ≥4 mg/kg of CX-2009 and had at least one post-baseline on-study tumor assessment, demonstrates that 15/39 (38%) achieved tumor shrinkage and 29/39 (74%) achieved stable disease or better at the time of the first on-treatment scan

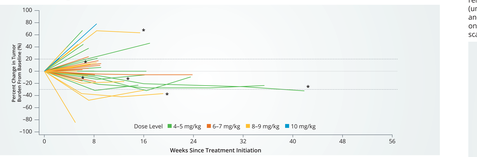
Figure 3. Best Percent Change in Sum of Target Lesion Dimensions From Baseline (N=39)*



*Denotes patient considered to be on treatment, as no end-of-treatment data listed in database as of data cut-off date.
†CX-2009 4- to 10-mg/kg dose levels; response-evaluable population with post-baseline disease assessments.
Patients (n=9) who are evaluable for efficacy but are not presented in the figure as the magnitude of tumor burden change was not in the database at the time of data cut-off. Patients (n=2) with non-measurable disease at baseline who are evaluable for efficacy are not included in the figure. Patients (n=3) with 1 evaluable post-baseline tumor scan <7 weeks from treatment start assessed as stable disease will be considered to have best overall response of not evaluable.
BC=breast carcinoma; EC=non-small cell lung carcinoma; OC=epithelial ovarian carcinoma; EC=endometrial carcinoma; HN=head and neck squamous cell carcinoma; CC=cholangiocarcinoma.

- The spider plot in **Figure 4** demonstrates tumor burden over time for all patients treated with ≥ 4 mg/kg CX-2009

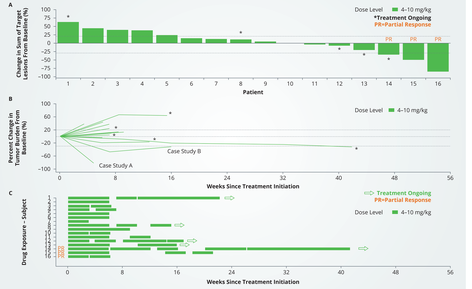
Figure 4. Percent Change in Tumor Burden From Baseline*



*Denotes patient considered to be on treatment, as no end-of-treatment data listed in database as of data cut-off date.
†CX-2009 4- to 10-mg/kg dose levels; response-evaluable population with post-baseline disease assessments.
Patients (n=9) who are evaluable for efficacy but are not presented in the figure as the magnitude of tumor burden change was not in the database at the time of data cut-off. Patients (n=2) with non-measurable disease at baseline who are evaluable for efficacy are not included in the figure. Patients (n=3) with one evaluable post-baseline tumor scan <7 weeks from treatment start assessed as stable disease will be considered to have best overall response of not evaluable.

- Tumor response and time on treatment for patients with breast cancer in the 4- to 10-mg/kg dose groups are shown in **Figure 5**
  - 4/17 (24%) partial responses (2 pending confirmation responses, 2 formally unconfirmed) in response-evaluable patients (eg, those with at least one on-treatment scan)

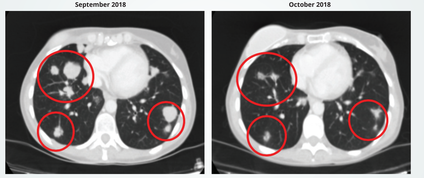
Figure 5. Response and Treatment Exposure for Patients With Breast Cancer. (A) Best Percentage Change From Baseline in Target Lesions; (B) Percent Change in Tumor Burden From Baseline; (C) Time on Treatment by Patient†



*Denotes patient considered to be on treatment, as no end-of-treatment data listed in database as of data cut-off date.
†CX-2009 4- to 10-mg/kg dose levels; response-evaluable population with post-baseline disease assessments.
Patients (n=9) who are evaluable for efficacy but are not presented in the figure as the magnitude of tumor burden change was not in the database at the time of data cut-off. Patient (n=1) with 1 evaluable post-baseline tumor scan <7 weeks from treatment start assessed as stable disease will be considered to have best overall response of not evaluable.

Case Study A: Heavily Pretreated Triple-Negative Breast Cancer Patient Treated With CX-2009 9 mg/kg

Patient A is 45-year-old white female with triple-negative breast cancer based on a 2018 biopsy, with first diagnosis in 2015. She had no relevant medical history. Prior treatment includes mastectomy, lymphadenectomy, and sternum resection; doxorubicin/cyclophosphamide + taxane (with unknown response) + tamoxifen (with progressive disease [PD]), erbulin (with unknown response), abraxane (with PD), gemcitabine + cisplatin (partial response), capecitabine (PD), and canakinumab (PD). At baseline, scans showed metastasis in both lungs and retroperitoneal lymph nodes. At the first on-treatment scan, the patient experienced an 82% reduction in her index lesions. After her second dose and prior to the second on-treatment scan, the patient permanently discontinued study drug due to grade 3 keratitis.



Case Study B: Pembrolizumab-Refractory Triple-Negative Breast Cancer Patient Treated With CX-2099 8 mg/kg

Patient B is a 41-year-old Asian female with first diagnosis of triple-negative breast cancer (*BRCA* status unknown) in 2014. She had no relevant medical history except smoking for 20 years. Prior treatment included neoadjuvant docetaxel/doxorubicin/cyclophosphamide (unknown response), mastectomy + radiation therapy, gemcitabine + carboplatin (unknown response), pembrolizumab + paclitaxel (PD), and sacituzumab govitecan (PD). At baseline, scans showed ulcerating skin lesions on chest wall and nodal metastasis right axilla. At the first on-treatment scan, the patient experienced a 48% reduction in her index lesions. After her third dose and prior to the second on-treatment scan, the patient experienced an extended dose delay due to grade 4 keratitis, which completely resolved.

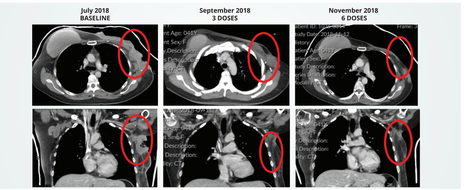
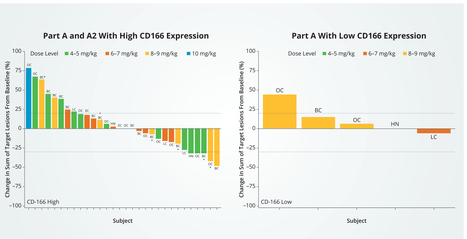


Figure 6. Anti-Cancer Activity Associated with CD166 Expression



Preliminary Conclusions

- **CX-2009, an anti-CD166 Probody drug conjugate, is generally well tolerated with early evidence of biological activity in multiple cancer types over a wide range doses (4–10 mg/kg) in a heavily pretreated population**
- **Preliminary data suggest a potential association between CD166 tumor expression levels and clinical activity; this is consistent with preclinical observations in murine PDX models (see Poster 3948)**
- **DM4-associated ocular toxicity led to early discontinuation and dose delays in 3 of 7 patients with unconfirmed partial response and may have contributed to the short duration of their response**
- **Further dose-ranging is ongoing in the mTPI dose-refinement stage of the study with the addition of mandatory prophylactic measures to manage ocular toxicity and potentially prolong duration of treatment**

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CytomX THERAPEUTICS

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