PROCLAIM-CX-2009: A First-in-Human Trial to Evaluate CX-2009 in Adults With Metastatic or Locally Advanced Unresectable Solid Tumors

Javier Garcia-Corbacho,[1] Alexander Spira,[2] Valentina Boni,[3] Jaime Feliu,[4] Mark Middleton,[5] Howard Burris,[6] Annie Yang Weaver,[7] Matthias Will,[7] James Harding,[8] Funda Meric-Bernstam,[9] Volker Heinemann[10]

[1]Hospital Clinic Barcelona, Barcelona, Spain; [2]Virginia Cancer Specialists Research Institute, and Oncology Research, Fairfax, VA, USA; [3]START Madrid-CIOCC, Madrid, Spain; [4]Hospital Universitario La Paz, Madrid, Spain; [5]Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford, United Kingdom; [6]Sarah Cannon Research Institute, Nashville, TN, USA; [7]CytomX Therapeutics, South San Francisco, CA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [10]Ludwig-Maximilian-University of Munich, Munich, Germany

BACKGROUND

- Antibody drug conjugates (ADCs) are composed of potent cytotoxins conjugated to tumor-targeting antibodies, which concentrates therapy at tumor cells and allows for the use of more toxic therapies than standard chemotherapeutic regimens[1]
  - However, ADCs still provide a relatively narrow therapeutic window, and adverse events often occur before ADCs can reach their optimal therapeutic dose[2]
  - Additionally, target selection for ADCs can be problematic because expression of the target antigen in healthy tissue has led to on-target toxicity[2,3]
- Probody™ therapeutics are fully recombinant antibody prodrugs that remain relatively inactive systemically and in healthy tissue, thereby avoiding binding to target antigen in healthy tissue. Once a Probody therapeutic reaches the tumor, it is activated by proteases associated with that microenvironment and can freely bind target antigen in the tumor (**Figure 1**)[4,5]
  - Probody drug conjugates (PDCs) are Probody therapeutics that are conjugated to cytotoxic agents and are similar to ADCs except that PDCs preferentially bind to target antigen in the tumor microenvironment
  - This tumor-specific activation allows PDCs to target novel highly and homogeneously expressed tumor antigens while avoiding binding to these same targets on healthy tissue
- CX-2009 is a novel recombinant PDC derived from a humanized monoclonal antibody against CD166 and conjugated to N-succinimidyl 4-(2-pyridyldithio) butanoate-N2′-deacetyl-N2′-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (SPDB-DM4, licensed from ImmunoGen), a potent microtubule inhibitor
  - CD166 (also referred to as activated leukocyte cell adhesion molecule) is highly expressed in multiple cancers but also in healthy tissue[6] (**Figures 2A-B**)
  - Specific activation by tumor-associated proteases allows CX-2009 to target the homogeneously expressed antigen CD166 in tumors and is expected to keep CX-2009 relatively inactive in peripheral tissue, which may prevent on-target toxicity and increase the therapeutic window
- In preclinical studies, CX-2009 exhibited antitumor activity and reduced peripheral binding compared with the corresponding anti–CD166 ADC[7]
  - CX-2009 produced potent antitumor responses in mouse models of human xenograft tumors (**Figure 2C**)[7]; in cynomolgus monkeys, CX-2009 was well tolerated at therapeutically relevant doses (~5 mpk), and exposure was significantly extended compared with the anti-CD166 ADC, consistent with reduced binding in healthy tissue[7]

Figure 1. Probody therapeutics are protease-activatable antibody prodrugs that are preferentially activated in the tumor microenvironment.

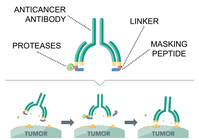
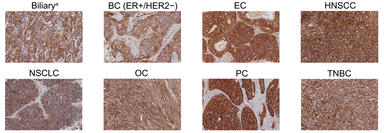


Figure 2. CX-2009 targets the homogeneously expressed antigen CD166 and induces potent antitumor activity in preclinical studies. (A) CD166 is highly expressed in several types of cancer. (B) CD166 is also highly expressed in healthy tissue. (C) CX-2009 produced complete and durable responses in mouse models of human xenograft tumors.

A

CD166 expression in human tumor samples by IHC



Cancer Type	Prevalence of CD166 Expression (IHC ≥2+), %	Prevalence of CD166-negativity (IHC <1+), %	No. of cases examined
Biliary[a]	56.5	11.9	177
Breast	87.1	1.7	533
Endometrial	75.2	6.0	315
Head and neck	81.1	0.8	122
Lung	71.0	8.2	465
Prostate	98.3	0.8	119
Ovarian	70.5	3.9	129

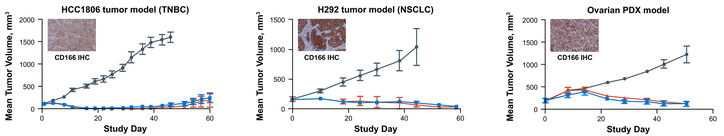
B

CD166 Expression in Healthy Human Tissue by IHC

Adrenal gland (−/+)	Cervix (+/++)	Kidney (+/+++)	Ovary (−/++)	Spleen (+/++)	Thymus (+)
Bone marrow (−/+)	Colon (++)	Larynx (+/++)	Pancreas (++/+++)	Stomach (+++)	Uterus (+/+++)
Breast (+/++)	Esophagus (+/++)	Liver (++)	Prostate (++/+++)	Striated/skeletal muscle (−/+)	
Brain, cerebrum (−/+)	Eye (+)	Lung (+/++)	Skin (+/++)	Testis (−/++)	
Brain, cerebellum (−/+)	Heart (+)	Nerve (+/++)	Small intestine (+/+++)	Thyroid (++/+++)	

C

IV Dosing on Days 0 and 7



ADC, antibody drug conjugate; BC, breast carcinoma; DM4, maytansine derivative; EC, endometrial carcinoma; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; NSCLC, non–small cell lung carcinoma; OC, ovarian carcinoma; PC, prostate carcinoma; PDX, patient-derived xenograft; TNBC, triple-negative breast cancer.
IHC staining was performed with an anti–CD166 rabbit monoclonal antibody, clone EPR2759. CD166 expression levels are based on IHC staining.
[a]Biliary carcinoma (cholangiocarcinoma).

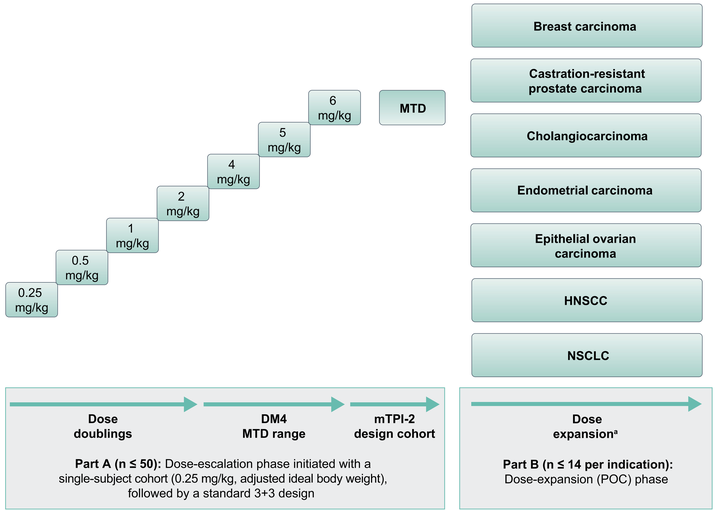
OBJECTIVES

- The objectives of the ongoing PROCLAIM-CX-2009 (**PRO**body **CL**inical **A**ssessment **I**n **M**an) trial are to determine the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), dose-limiting toxicities, and preliminary antitumor activity of CX-2009 as monotherapy in the following 7 selected tumor types with high CD166 expression: breast carcinoma, castration-resistant prostate carcinoma (CRPC), cholangiocarcinoma, endometrial carcinoma, epithelial ovarian carcinoma, head and neck squamous cell carcinoma (HNSCC), and non–small cell lung carcinoma (NSCLC)

STUDY DESIGN

- This is a first-in-human, open-label, multicenter, dose-escalation, proof-of-concept phase 1/2 study of CX-2009
- The study is to include patients with breast carcinoma, CRPC, cholangiocarcinoma, endometrial carcinoma, epithelial ovarian carcinoma, HNSCC, and NSCLC
- Patients are to be treated with CX-2009 monotherapy intravenously every 21 days
- The study consists of 2 parts (**Figure 3**)
  - Part A (n ≤ 50) will begin with accelerated dose titration, followed by a standard 3+3 design to determine the MTD, and will end in a modified toxicity probability interval 2 design cohort treated at the MTD to determine the RP2D[8]
  - Part B will be a dose-expansion (proof-of-concept) phase testing CX-2009 administered at the RP2D for the 7 tumor types (up to 14 patients per type; n ≤ 98)
- Patients will be treated until disease progression; duration of treatment is estimated at approximately 6 months, with follow-up contact every 3 to 6 months for another 1 to 2 years or as long as the patient is alive

Figure 3. PROCLAIM-CX-2009 phase 1/2 study design.



DM4, maytansine derivative; HNSCC, head and neck squamous cell carcinoma; MTD, maximum tolerated dose; mTPI-2; modified toxicity probability interval 2; NSCLC, non–small cell lung carcinoma; POC, proof-of-concept; RP2D, recommended phase 2 dose.
[a]Additional cohorts may be implemented to further refine the RP2D.

Patients

- Up to 150 patients will be enrolled in the study in both the dose-escalation and dose-expansion cohorts
- Key eligibility criteria are shown in **Table 1**

Table 1. Key Eligibility Criteria by Study Part and Indications

Part A	• Age ≥18 years • ECOG performance status 0-1 • Histologically confirmed diagnosis of any active metastatic or locally advanced unresectable solid tumor • Consent that tumor tissue (archival, new, or recent acquisition) be provided before initiation of study drug • Life expectancy ≥3 months
Part B	• Consent from ≥7 patients, 1 for each tumor type, to provide a baseline and an on-study tumor biopsy sample (if safe to perform biopsy) and a peripheral blood sample
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 carcinoma	• Received ≥1 previous line of therapy
Cholangiocarcinoma	• ≥1 previous gemcitabine-containing regimen failed
Endometrial carcinoma	• Received ≥1 platinum-containing regimen for extrauterine or advanced disease
Epithelial ovarian carcinoma	• 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
HNSCC	• Received ≥1 platinum-containing regimen and PD-1/PD-L1 inhibitor if approved for patient's indication and locality
NSCLC	• Received ≥1 platinum-containing regimen • Checkpoint inhibitor should have been administered if approved for the patient's indication in the patient's locality

BRCA, breast carcinoma; ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor–positive; HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small cell lung carcinoma; PARP, poly (adenosine diphosphate-ribose) polymerase; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TNBC, triple-negative breast cancer.

END POINTS

Primary End Points

- Determine the safety, MTD/RP2D, and dose-limiting toxicities of CX-2009

Secondary End Points

- Objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or tumor-specific criteria, as applicable
- Time to response
- Duration of response
- Progression-free survival
- Overall survival
- Pharmacokinetic profile of CX-2009 including analyzing intact CX-2009, total CX-2009, total CX-2009–conjugated DM4, free DM4, and S-methyl DM4
- Incidence of antidrug antibody formation

Exploratory Objectives

- Explore potential predictive markers associated with CX-2009 clinical activity, such as CD166 expression and mitotic markers (eg, Ki-67), in tumor specimens before and during treatment
- Characterize the protease activity and activation of CX-2009 in on-treatment tumor biopsy samples and peripheral blood, respectively

SPECIFIC ASSESSMENTS

- All patients will undergo complete ophthalmology examination at screening and during certain points of the study; patients who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations before infusion in every other cycle and as clinically indicated
- In Part A and Part B, pretreatment and on-treatment biopsy samples will be mandatory for 7 of the 14 patients for each tumor type
- Imaging for tumor response assessment will be performed every 8 weeks from the first dose of CX-2009
- After the last dose of study medication, patients will be evaluated every 3 months for the first year and then every 6 months or until death

Translational Analyses

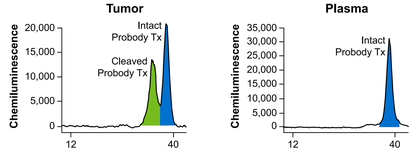
- Several translational strategies will be used to investigate Probody therapeutic activation and CX-2009 activity (**Table 2, Figure 4**)

Table 2. Translational Analyses Included in PROCLAIM-CX-2009

Goal	Sample(s)	Assay	Description
Determine activation of Probody therapeutic	Biopsy, plasma	WES™ assay	Capillary electrophoresis with immunodetection to identify masked and activated CX-2009
	Biopsy	QZ™ assay	Protease activity detection
Correlation of markers with CX-2009 activity	Biopsy	IHC	CD166 expression, Ki-67

IHC, immunohistochemistry.

Figure 4. General preclinical example of how WES technology works to measure cleaved (green) and intact (blue) Probody therapeutic in tumor and plasma.



kDa, kilodalton; Tx, therapeutic.

STUDY PROGRESS

- The study started in June 2017; sites for Part A are open in the United States and will open in Europe later in 2017. Enrollment in Part B will open after completion of the dose-escalation phase
- This study is registered with ClinicalTrials.gov, number NCT03149549 (https://clinicaltrials.gov/ct2/show/NCT03149549)
- For more information, please contact: clinicaltrials@cytomx.com or garcia33@clinic.ub.es

REFERENCES

1. De Goeij BE, Lambert JM. *Curr Opin Immunol*. 2016;40:14-23.
2. Donaghy H. *mAbs*. 2016;4:659-671.
3. Tijink BM et al. *Clin Cancer Res*. 2006;12(part 1):6064-6072.
4. Desnoyers LR et al. *Sci Transl Med*. 2013;5:207ra144.
5. Polu KR et al. *Expert Opin Biol Ther*. 2014;14:1049-1053.
6. Wiedle UH et al. *Cancer Genomics Proteomics*. 2010;5:231-243.
7. Weaver AY et al. Presented at: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; November 5-9, 2015; Boston, MA.
8. Ji Y et al. *Clin Trials*. 2007;3:235-244.

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