PS11-07

Intratumoral Activation and Phase 1/2 Clinical Activity of Praluzatamab Ravtansine (CX-2009), a Probody® Drug Conjugate (PDC) Targeting CD166

San Antonio Breast Cancer Symposium®
December 8-11, 2020

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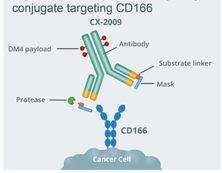
BACKGROUND

- Probody drug conjugates (PDCs) are a new class of recombinant proteolytically activated antibody prodrugs. PDCs consist of 4 molecular components: the antibody, a peptide masking the antigen-binding site of the antibody, a protease-cleavable linker designed to keep the peptide mask in place, and a toxin conjugated to the antibody (**Figure 1**)[1,2]

Figure 1. CX-2009: a Probody drug conjugate targeting CD166



- PDCs remain largely inactive in normal tissue and in circulation until the substrate linker is cleaved by upregulated protease activity in the tumor microenvironment
- The masking of the active antibody allows PDCs to address previously undruggable targets with high expression in both tumor and normal tissue
- CD166 (ALCAM; activated leukocyte cell adhesion molecule), which is widely expressed on normal and malignant cells, is a transmembrane protein that functions as a junctional adhesion molecule and facilitates cell migration, differentiation, and hematopoiesis[3]
- In patients with breast cancer, the incidence of high CD166 expression is >80% for HR+/HER2– (HER2 non-amplified) and ~50% for triple-negative breast cancer (TNBC)[4]
- CX-2009 is an investigational PDC consisting of an anti-CD166 monoclonal antibody conjugated to the microtubule inhibitor DM4, and is designed to largely restrict target engagement to tumors expressing CD166
- Clinical data have been previously presented[4]; here, we present translational data assessing intratumoral CX-2009 activation in patients receiving ≥4 mg/kg every 2 or 3 weeks (Q2W or Q3W), together with updated clinical results from breast cancer patients

METHODS

Objectives

- To determine the safety profile, maximum tolerated dose (MTD), preliminary efficacy, pharmacokinetic, and biologic correlates of response to CX-2009 in this dose-escalation, multi-cohort, multicenter study (NCT03149549)[5]

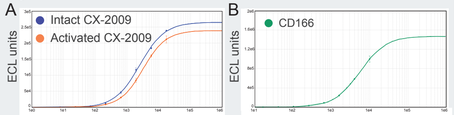
Clinical study design

- CX-2009 was administered at escalating doses Q3W (0.25-10 mg/kg) or Q2W (4-6 mg/kg) in patients with advanced cancer
- Eligible patients with metastatic cancer after ≥2 prior standard treatments were required to submit tumor tissue for CD166 IHC analysis
- On-treatment tumor biopsies were collected 3–5 days after the first dose

Assessment of intratumoral CX-2009 activation and CD166 levels

- Levels of intact/masked and activated/unmasked CX-2009 and of CD166 in biopsy lysates were measured by capillary electrophoresis immunoassays. **Figure 2** shows assay standard curves

Figure 2



Immunoassays used a custom anti-idiotypic antibody to CX-2009 (A) or a commercial antibody to CD166 (B)

RESULTS

Enrollment data

- As of August 31st, 2020, 99 patients (n=89 Q3W dosing, n=10 Q2W dosing) were enrolled and treated at 27 centers. **Table 1** describes the characteristics of enrolled patients with HR+/HER2- breast cancer or TNBC

Table 1: Characteristics of enrolled female patients with breast cancer

(All n=99)	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)

- 98 patients discontinued treatment for the following reasons: disease progression / symptomatic deterioration (n=69), adverse event (n=12), investigator/patient decision (n=11), and death (n=6)

SAFETY

- The Safety profile (**Table 2**) of CX-2009 is related to dose level, with increased frequency of treatment-related adverse events (TRAEs) at doses ≥8 mg/kg, Q3W
- DLTs during Cycle 1 were rare; later onset DLTs were predominantly ocular adverse events
- 14 patients experienced TRAEs resulting in discontinuation: keratitis (n=6), blurred vision (n=1), peripheral neuropathy (n=2), nausea (n=1), sepsis (n=1), back pain (n=1), dyspnea (n=1), urticaria (n=1)
- There were 107 ocular toxicity events reported as related to CX-2009; 90% were Grade 1-2 in severity. Ocular toxicity was both less frequent and less severe in patients treated at ≤7 vs ≥8 mg/kg Q3W
- Ocular adverse events included blurred vision, keratitis (including punctate keratitis and keratopathy), dry eyes, and eye pain. These adverse events were reversible with either temporary interruption of CX-2009 or local treatment for the ocular adverse event
- Ocular prophylaxis (topical vasoconstrictors, ocular corticosteroids, artificial tears, and a cool eye compress during infusion) was not required at the initiation of the trial, but was introduced at 8 mg/kg as optional therapy and subsequently made mandatory

Table 2: Overall summary of safety related to CX-2009

	CX-2009 Dose (mg/kg)									All Cohorts
Number of Patients, n (%)	≤4 (N=20)	5 (N=9)	6 (N=9)	7 (N=12)	8 (N=22)	9 (N=9)	10 (N=8)	4 (Q2W) (N=4)	6 (Q2W) (N=6)	(N=99)
TEAE	14	9	9	12	21	9	7	3	6	90
TEAE ≥G3	1	3	2	4	14	5	4	0	3	36
Causing Discontinuation	0	3	2	1	3	2	1	0	0	12
DLT	0	0	0	0	1	0	0	0	2	3
SAEs	0	0	0	2	6	2	1	0	0	11
Ocular Toxicity	2	6	2	3	13	5	6	1	5	43
Ocular Toxicity ≥G3	0	1	0	0	3	3	1	0	2	10

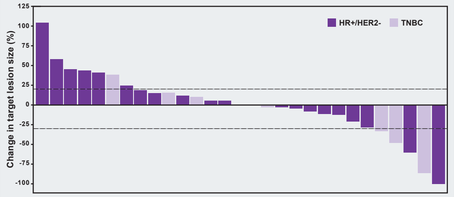
DLTs: 8 mg/kg Q3W: vomiting and increased liver enzymes; 6 mg/kg Q2W: peripheral neuropathy
G3, grade 3; TEAE, treatment emergent adverse event; SAE, serious adverse event

ACTIVITY

Clinical activity in Phase 1

- Patients who were included in the summary of anti-tumor activity were those who had a baseline radiographic assessment, received at least one dose of CX-2009, and had an on study post-treatment assessment
- Tumor volume regression was observed at CX-2009 doses ≥4 mg/kg IV Q3W, in multiple disease types
- Confirmed partial responses and clinically meaningful disease control, as measured by clinical benefit rate at 16 and 24 weeks (CBR16, 41%; CBR24, 28%), were observed in patients with breast cancer (**Figure 3**)
- Two patients with disease control beyond 48 weeks had sustained benefit despite dose reduction from the original dose assignment
  - One patient has a visceral CR with a dose reduction from 6mg/kg Q2W to 4mg/kg Q2W
  - One patient had prolonged stable disease after dose reduction from 8mg/kg Q3W to 7mg/kg Q3W

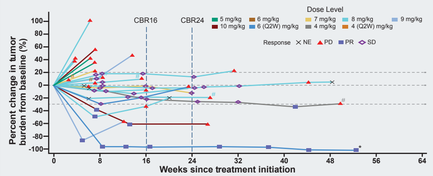
Figure 3: Response data: Percent change in sum of target lesions from baseline



HR+/HER2 negative: hormone-receptor positive/HER2 negative TNBC: Triple-negative breast cancer

	Evaluable Breast Cancer Patients		
	Overall (n=32)	HR+/HER2- (n=22)	TNBC (n=10)
CBR16	13 (41%)	9	4
CBR24	9 (28%)	5	4
SD or Better	16 (50%)	12 (2 cPR)	4 (3 uPR)

cPR, confirmed partial response; uPR, unconfirmed partial response; SD, stable disease

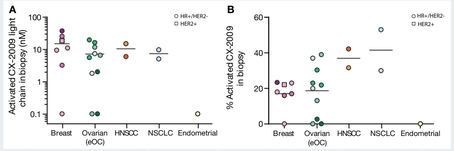


*Denotes a patient who is considered to be on treatment
#Denotes a patient who had progressive disease at the timepoint due to a worsening non-target lesion or the presence of a new lesion

CX-2009 is activated in patient tumor biopsies

- Pharmacokinetic data demonstrated that CX-2009 remained predominantly (median >95%) in the inactive/masked form in circulation[6]
- Intratumoral activated CX-2009 was assessed in 22 biopsies and was quantifiable in 18, including in 6 of 7 biopsies from breast cancer patients
- This assay measures the amount of activated light chain, and results are interpolated against a standard curve of two-arm activated CX-2009
- **Figure 4** shows the concentration (A) and percentage (B) of intratumoral activated CX-2009; the latter ranged from ~3% – 53%
- The median percentage of light chain activation is ~23%, which could indicate that 23% of PDC molecules have both light chains activated, ~46% have one light chain activated, or a mix of these two outcomes
- The extent of CX-2009 activation may be underestimated due to low tumor content in the biopsy, target-mediated drug disposition, or other factors

Figure 4: Intratumoral activation of CX-2009

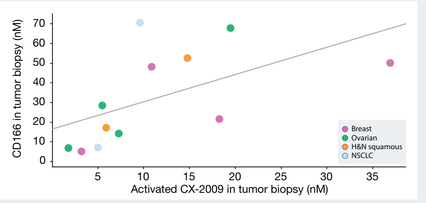


Values below the lower limit of quantification (LLOQ) are plotted as 0.1. The percentage of activated intratumoral CX-2009 was calculated as follows: [nM activated CX-2009] / [nM activated CX-2009 + nM intact CX-2009]
The CX-2009 dose ranged from 4-10 mg/kg; for a given indication, a darker color indicates a higher dose. eOC: epithelial ovarian cancer

CD166 target levels are correlated with CX-2009 activation

- Levels of CD166 in the biopsy lysate were significantly correlated with the intratumoral concentration of activated CX-2009 (r^2=0.59, p=0.004), suggesting a role for target in the process of PDC activation and/or retention in the tumor (**Figure 5**)

Figure 5: Intratumoral levels of CD166 and activated CX-2009 are correlated

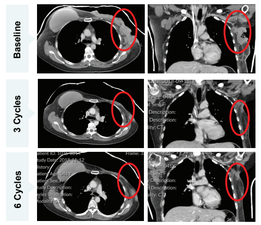


12 of 22 evaluable biopsies had quantifiable values for both activated CX-2009 and for CD166, and are shown in Figure 5

PATIENT CASE

Evidence of benefit in a patient with pembrolizumab and sacituzumab-refractory TNBC

- 41-year-old Asian female treated with 8 mg/kg CX-2009 Q3W
- Prior treatments included: **1.** Neoadjuvant docetaxel + doxorubicin + cyclophosphamide (mastectomy + radiation therapy); **2.** Gemcitabine + carboplatin; **3.** Pembrolizumab + paclitaxel (PD); **4.** Sacituzumab govitecan (PD)
- Baseline: chest wall ulcerating lesions, right axillary lymph node metastases
- First scan (Week 8): 48% reduction in index lesions
- Extended dose delay after third dose (week 9) due to Grade 4 keratitis (completely resolved), PD at 2nd scan (Week 16)



CONCLUSIONS

Clinical activity

- The Probody platform enables administration of CX-2009, an antibody-drug conjugate targeting CD166 (a previously undruggable target) at tolerable doses, with signs of clinical benefit in patients with advanced malignancies
- Evidence of clinical benefit, including partial responses (confirmed and unconfirmed) and disease control (SD or better) was observed at doses ≥4 mg/kg Q3W
- Adverse events at the recommended Phase 2 dose of 7 mg/kg Q3W are manageable

Translational findings

- CX-2009 is activated/unmasked in tumors and is predominantly intact/masked in circulation[6]
- Levels of CD166 are significantly correlated with the concentration of activated intratumoral CX-2009
- Preliminary analyses (not shown) show a trend between CD166 levels and response; future studies will further explore this connection
  - CD166 expression screening could be beneficial for patient selection
- **Taken together, these data support the Phase 2 investigation of CX-2009 in patients with advanced TNBC or HR+/HER2 non-amplified breast cancer**
  - **CX-2009 is also being investigated in combination with CX-072 (pacmilimab), a Probody therapeutic targeting PD-L1, in patients with TNBC[7]**

CX-2009 PHASE 2 TiP PRESENTATION AT SABCS

Poster Number: OT-03-08

Miller KD, et al. A Phase 2, Open-Label Study to Evaluate the Safety and Efficacy of the Probody Therapeutic (Pb-Tx) CX-2009 in Metastatic HR-Positive/HER2-Negative Breast Cancer (mHR+/HER2− BC) and of CX-2009 as Monotherapy and in Combination Therapy With CX-072 in Metastatic Triple-Negative Breast Cancer (TNBC)

Ongoing Trials Posters – Wednesday, December 9, 2020: 8:00 AM CT

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ACKNOWLEDGEMENTS

This study was sponsored by CytomX Therapeutics, Inc. We would like to thank the physicians, patients and their families. Editorial support was provided by Phillips Gilmore Oncology Communications, funded by CytomX Therapeutics, Inc.