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

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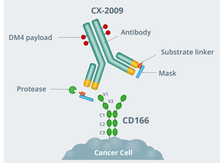
BACKGROUND

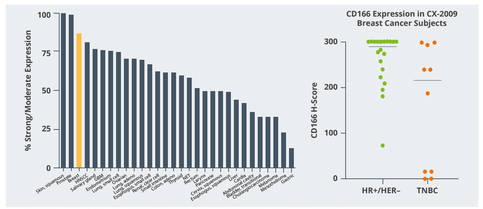
- Probody drug conjugates are a new class of recombinant proteolytically activated antibody prodrugs consisting of 4 molecular components: the antibody; a peptide masking the antigen-binding site of the antibody; a protease cleavable linker designed to keep the peptide mask in place; and a toxin conjugated to the antibody (**Figure 1**)[1]
- Upregulated tumor protease activity, a hallmark of cancer, cleaves the substrate linker and releases the masking peptide, which allows the antibody to bind to its target.[2]

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



- CX-2009 is a Probody drug conjugate that consists of a humanized anti-CD166 monoclonal antibody conjugated to DM4, a potent microtubule inhibitor known to be active against multiple cancer types (**Figure 1**)
- CD166 (activated leukocyte cell adhesion molecule) is a transmembrane protein that functions as a junctional adhesion molecule, and facilitates cell migration, differentiation, and hematopoiesis. It is widely expressed on dividing, normal, and malignant cells (**Figure 2**)[3]
- The incidence of high CD166 expression is >80% for ER+/HER2– breast cancer and ~50% for triple-negative breast cancer (TNBC) (**Figure 2**)

Figure 2. CD166 expression among different tumor types.



GBM, glioblastoma; HNSCC, squamous cell carcinoma of the head and neck; NET, neuroendocrine tumor; TNBC, triple-negative breast cancer.

- As designed, CX-2009 should restrict target engagement to tumors that express CD166. Off-tumor/on-target toxicity should be reduced; non-specific payload toxicity should be similar to that of other DM4 antibody drug conjugates

METHODS

- The objectives of this single-arm, dose-escalation, multi-cohort, multicenter study are to determine the safety profile, including the maximum tolerated dose (MTD), preliminary efficacy, PK, and biologic correlates of response to CX-2009

Clinical Study Design

- The design of this Phase 1/2 dose-escalation/expansion study was previously presented at the American Association for Cancer Research, 2019[4] (NCT03149549). Briefly, CX-2009 is administered at escalating doses every 3 weeks (Q3W, 0.25-10 mg/kg) or every 2 weeks (Q2W, 4-6 mg/kg) in patients with advanced cancer
- Once a cohort was cleared, additional patients, amenable to pre and post tumor biopsies for exploratory analyses could be enrolled.
- Phase 2 expansion in select cohorts could initiate once the MTD was identified on either schedule (Q3W or Q2W)
- DLTs are defined as grade 3–5 treatment-related AEs (TRAEs), including febrile neutropenia, any central nervous system event, neurotoxicity, and ocular toxicity

Patients

- Patients were required to submit tumor tissue for CD166 IHC testing.
- Patients were excluded if they had prior treatment with a mytansinoid-conjugated ADC; grade 1 or higher neuropathy; an active or chronic corneal disorder

RESULTS

- As of 20 April 2020, 96 patients (n=86 Q3W dosing, n=10 Q2W dosing) were enrolled and treated at 27 centers (**Table 1**)
- 4 patients enrolled in the 4 mg/kg Q2W dose after 14 Feb 2020, and are not included in the results of safety and activity due to unverified data due to COVID-19 restrictions

Table 1. Patient Demographic, Baseline Characteristics and Exposure

	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)

Patient Treatment and Disposition

- All patients treated in the Q3W cohorts are off treatment for disease progression (n=47), symptomatic deterioration (n=14), adverse events (n=11), voluntary subject withdrawal (n=7), death (n=5) and investigator decision (n=2)

Table 2. Demographic and Cancer Characteristics and Exposure in Patients With Advanced Breast Cancer (n=36)

	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)

SAFETY

Recommended Phase 2 Dose = 7 mg/kg Q3W

Table 3. Overall Summary of AEs

	CX-2009 Dose (mg/kg)							
Category, n	≤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

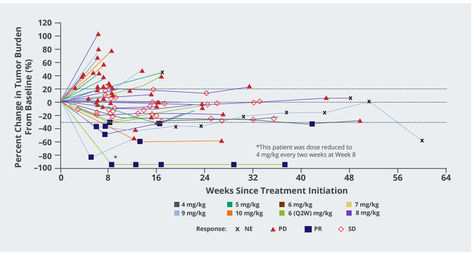
- No DLTs were reported at doses up to 7 mg/kg Q3W
  - DLTs were vomiting (n=1) in the 8-mg/kg Q3W cohort and increased liver transaminases (n=1) and peripheral neuropathy (n=1) in the 6-mg/kg Q2W cohort
  - 4 mg/kg Q2W is currently under investigation
- DM4-related toxicities, including ocular, neuropathic and hepatic[5] were higher in frequency at dose equivalents greater than 7 mg/kg Q3 week compared to 7 mg/kg or lower.
- Dose-dependent related ocular AEs:
  - Any grade and grade 3+ ocular AEs were reported in 28% and 2%, respectively, of patients treated with CX-2009 doses ≤7 mg/kg
  - Any grade and grade 3+ ocular AEs were reported in 64% and 20%, respectively, of patients treated with CX-2009 doses ≥8 mg/kg
- TRAEs leading to discontinuation of CX-2009 occurred in 11 patients: eye disorders: keratitis, punctate keratitis, blurred vision (n=7); neuropathy (n=2); nausea (n=1); sepsis (n=1)
- *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)

Table 4. Grade ≥3 CX-2009-Related AEs in ≥2 Patients by Preferred AE Term and CX-2009 Dose

	CX-2009 Dose (mg/kg)							
Preferred Term, n	≤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)
At least 1 TRAE	1	3	2	2	14	5	3	4
AST increase	0	0	0	0	4	0	1	3
Keratitis	0	1	0	0	2	2	2	1
ALT increase	0	0	0	0	2	0	1	2
Anemia	1	0	0	0	3	0	0	0
Nausea	0	0	0	1	1	1	0	1
Hyponatremia	0	0	2	0	0	1	0	0
Fatigue	0	1	0	0	0	0	0	1
Hypokalemia	0	0	0	0	1	1	0	0
Peripheral neuropathy	0	0	0	1	0	1	1	0
Peripheral sensory neuropathy	0	1	1	0	0	0	0	0
Vomiting	0	0	0	1	1	0	0	0

ACTIVITY

Figure 3. Spider plot in evaluable patients who received ≥4 mg/kg Q3W (n=68)

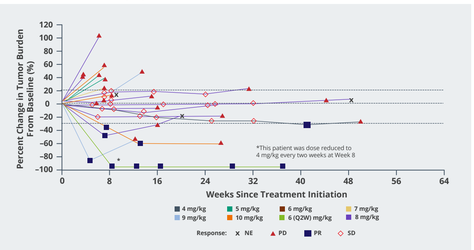


- All 10 patients who received less than 4 mg/kg CX-2009 came off treatment at or before the first post baseline tumor assessment
- Evidence of target lesion reduction was observed across multiple tumor types

Figure 4. Waterfall plots in evaluable patients who received CX-2009 ≥4 mg/kg Q3W

- Evaluable patients must have received ≥1 dose CX-2009 and had a post-baseline tumor assessment

Figure 5. Spider plot in response evaluable patients with HER2- breast cancer who received CX-2009 ≥4 mg/kg Q3W



- Durable clinical benefit was demonstrated in patients with HR+/HER2– breast cancer and TNBC treated with CX-2009 at doses ≥4 mg/kg

Table 5. Response Assessments (RECIST v1.1) in Evaluable Patients With HER2– Breast Cancer Who Received CX-2009 ≥4 mg/kg

	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%)

- Clinical benefit rate (CBR) is defined any CR or PR, or stable disease for at least 16 (CBR16) or 24 weeks (CBR24)

CONCLUSIONS

- The results of this trial validate CD166 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
  - CD166: a previously undruggable ADC target
- Tumor volume regression was observed at doses ≥4 mg/kg Q3W
- Confirmed partial responses and clinically meaningful disease control, as measured by CBR16 (39%) and CBR24 (35%), was observed in patients with breast cancer
- Based on activity and tolerabilty, the recommended Phase 2 dose of CX-2009 is 7 mg/kg Q3W
  - This is supported further by PK modeling and nonclinical data (Stroh M, et al.ASCO 2020 poster. Abstract 3599)
- Optimization of a CD166 IHC assay is ongoing to support a potential selection strategy
- CX-2009 is being further explored as monotherapy in patients with HR+/HER2- breast cancer and will be evaluated in a separate study as monotherapy and in combination with CX-072 (an anti-PD-L1 Probody) in patients with triple-negative breast cancer.

References

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