3599

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

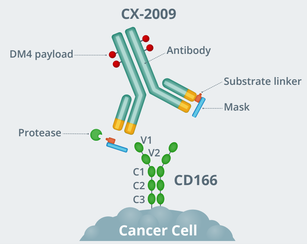
Mark Stroh,[1] Rachel Li,[1] Hong Lu,[1] Russ Wada,[2] Jennifer Richardson,[1] and Amy Peterson[1]

[1]CytomX Therapeutics, Inc., South San Francisco, California; [2]Certara, Princeton, New Jersey

BACKGROUND

- Probody therapeutic candidates are antibody prodrugs with cleavable peptide masks designed to reduce off-tumor, on-target toxicities.[1] The mask is designed to block binding in the periphery and is removed by tumor-associated proteases, resulting in intratumoral binding
- CX-2009 is a Probody drug conjugate (PDC) directed against CD166/ALCAM (**Figure 1**), which is a target overexpressed in carcinomas but not suitable for traditional antibody drug conjugate targeting because it is also expressed in many normal tissues
  - CX-2009 incorporates the maytansinoid DM4, a potent microtubule inhibitor
- Preliminary clinical pharmacokinetics (PK) data, exploratory exposure-response (ER), and dose-response (DR) analyses are presented here for the investigational PDC CX-2009 from the ongoing Phase 1/2 PROCLAIM-CX-2009 study (NCT03149549)

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



METHODS

- Human PK and anti-drug antibody (ADA) data were obtained at selected times post dose following intravenous (IV) CX-2009 administration either every 3 weeks (Q3W) at doses ranging from 0.25–10 mg/kg or CX-2009 every 2 weeks (Q2W) at the 6 mg/kg dose in the ongoing Phase 1/2 study PROCLAIM-CX-2009-001 (NCT03149549; **Table 1, Table 2**)
  - Covariates were selected for population PK (POPPK) modeling based on an earlier data cut and confirmed at $P<0.01$
  - Preliminary exploratory ER and DR analyses were conducted for selected endpoints

Table 1. Overview of PROCLAIM-CX-2009-001 and Data Used to Assess the Preliminary Clinical PK/PD of CX-2009 Administered as Monotherapy

Dose, Route, and Regimen	Sampling Schedule[a]
Q2W IV 6 mg/kg (n=5)	Q2W: C1D1 and C2D1: predose, EOI + 15 min, EOI + 1 hour C1D2, C1D3, C1D4, C1D8, C1D15 C2D8, C2D15 C3, C4, C6, C8, and every 8 cycles thereafter: D1 predose
Q3W IV 0.25 mg/kg (n=1) 0.5 mg/kg (n=3) 1 mg/kg (n=3) 2 mg/kg (n=3) 4 mg/kg (n=10) 5 mg/kg (n=10) 6 mg/kg (n=10) 7 mg/kg (n=10) 8 mg/kg (n=20) 9 mg/kg (n=9) 10 mg/kg (n=8)	Q3W: C1D1 and C3D1: predose, EOI + 15 min, EOI + 1 hour C1D2, C1D3, C1D4, C1D8, C1D15 C3D8, C3D15 C2, C4, C6, C8, and every 8 cycles thereafter: D1 predose
	All schedules: EOT, follow-up visit[b]
Total[c] N=92	

C, cycle; D, day; EOI, end of infusion; EOT, end of treatment; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; POPPK, population pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks.
[a] Cycle length is 21 days and 28 days, respectively, for Q2W and Q3W schedules.
[b] Once any time >90 days after the last dose of CX-2009.
[c] Numbers reflect available preliminary PK data for POPPK modeling as of October 2019.

RESULTS

- Preliminary CX-2009 PK data from 92 subjects were available as of October 2019
  - CX-2009 circulated predominantly as CX-2009 intact with similar terminal elimination phase kinetics across the 0.25–10 mg/kg dose groups (**Figure 2A**)
  - Free DM4 and DM4-Me each circulated at ≤4 mol% of CX-2009 total (**Figure 2B**)

Figure 2A. Preliminary dose 1 CX-2009 intact (solid lines) and CX-2009 total (dashed lines) median plasma concentrations (nM) versus time (day) following administration of up to 10 mg/kg CX-2009 Q3W in human subjects. The concentration profiles for CX-2009 total and CX-2009 intact appear similar at a given dose, suggesting that CX-2009 circulates predominantly in the protected form. The similar elimination phase kinetics especially across the 1–10 mg/kg dose levels suggests limited importance of target-mediated drug disposition (TMDD).

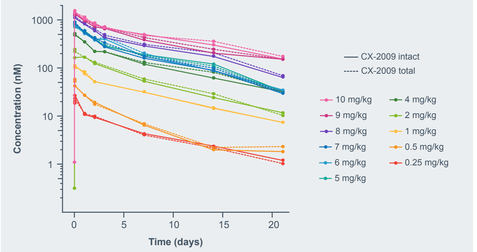


Figure 2B. Preliminary dose 1 conjugated DM4, CX-2009 total, DM4-Me, and free DM4 median plasma concentrations (nM) versus time (days) following administration of 7 mg/kg CX-2009 Q3W in human subjects. Since CX-2009 has a drug to Probody ratio of approximately 3.5, conjugated DM4 has a peak concentration that is correspondingly greater than CX-2009 total in this depiction. DM4-Me and free DM4 both circulate as the minority species.

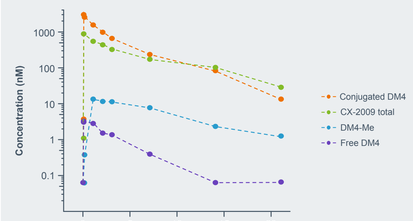


Table 2. Analytes Assayed in the Phase 1/2 PROCLAIM-CX-2009 Study

Analyte	Description
CX-2009 intact	Prodrug form of CX-2009 ± DM4
CX-2009 total	Intact and activated forms of CX-2009 ± DM4
Conjugated DM4	DM4 conjugated to CX-2009 (intact or activated)
Free DM4	DM4 that is not conjugated to CX-2009 (intact or activated)
DM4-Me	S-methyl DM4, a DM4 metabolite with potent cytotoxic activity

DM4, *N*2′-deacetyl-*N*2′-(4-mercapto-4-methyl-1-oxopentyl)-maytansine.

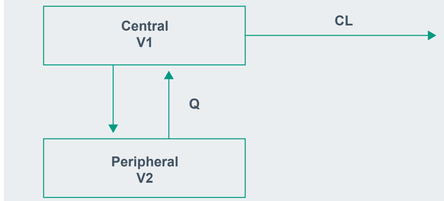
Table 3. Parameter Estimates for the Preliminary CX-2009 Intact POPPK Model in Human Subjects

Parameters	Estimate	Bootstrap Estimate	IIV (% CV)
CL (L/day)	0.473	0.473 (0.433, 0.521)	
V1 (L)	2.96	2.96 (2.84, 3.09)	
Q (L/day)	0.799	0.807 (0.644, 1.015)	
V2 (L)	1.55	1.55 (1.30, 1.83)	
Body weight on CL	0.796	0.799 (0.493, 1.112)	
Body weight on V1	0.714	0.712 (0.539, 0.894)	
Tumor burden on CL	0.173	0.172 (0.074, 0.265)	
σ Proportional residual error	0.250	0.249 (0.218, 0.281)	
ω^2 CL	0.142	0.136 (0.084, 0.212)	38%
ω^2 V1	0.0356	0.0334 (0.0143, 0.0611)	19%
Correlation CL.V1	0.70		

ω^2, variance of omega; σ, standard deviation of sigma; CL, clearance; CV, coefficient of variation; IIV, interindividual variability; Q, intercompartmental clearance; RSE, relative standard error; V1, central volume; V2, peripheral volume.
Bootstrap estimate is median (95% CI).
Covariate effects listed for POPPK model were based on multivariate screening at $P<0.01$; since ADAs were not a statistically significant covariate on CX-2009 intact CL, an estimate for ADAs on CL is not listed in the table.
Model-predicted percentage of CX-2009 circulating as intact was based upon the CL estimate for CX-2009 total to that for CX-2009 intact.

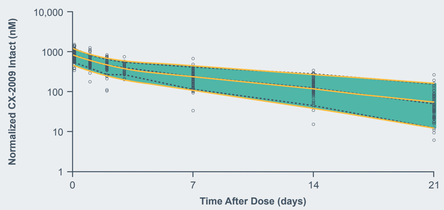
- A 2-compartment POPPK model with linear elimination was fit to the CX-2009 intact concentration data (**Figures 3A and 3B**)
  - The preliminary CX-2009 POPPK model estimates for CX-2009 intact clearance (CL), volume of distribution at steady-state, and half-life were 0.47 L/day, 4.51 L, and 7.14 days, respectively, with 91% of CX-2009 circulating as CX-2009 intact. ADA was not a statistically significant covariate on CX-2009 intact CL (**Table 3**)

Figure 3A. Structure of the preliminary POPPK model for CX-2009 intact.



CL, clearance; Q, intercompartmental clearance; V1, central volume; V2, peripheral volume.

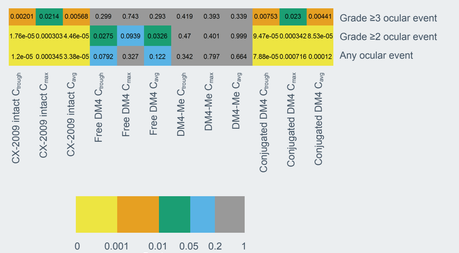
Figure 3B. Observed, normalized CX-2009 intact concentrations (points) superimposed over 90% prediction interval (shaded) from the CX-2009 intact POPPK model in human subjects. Both the central tendency and the variability of CX-2009 intact appear to be well captured by the POPPK model.



Dashed and solid lines represent median and 90% interval for observed and POPPK model-predicted CX-2009 intact data, respectively.

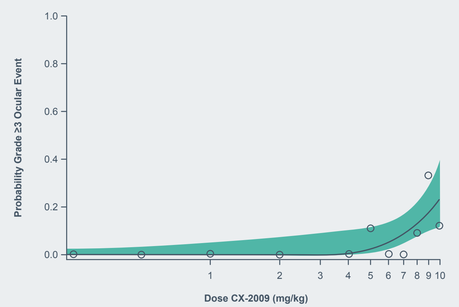
- Preliminary ER analysis suggested possible relationships between selected adverse events and dose 1 trough concentration (C_{trough}), maximum concentration (C_{max}), and average concentration (C_{avg}) for CX-2009 intact, free DM4, DM4-Me, and conjugated DM4 (**Figure 4A**)
- Overall *P* values were lowest for CX-2009 intact exposure metrics
- A preliminary DR analysis suggested that the frequency of grade ≥3 ocular toxicity events increased at dose equivalents of >7 mg/kg Q3W (**Figure 4B**)

Figure 4A. Preliminary relationships between ocular events (indicated on right side of heat map) and dose 1 exposure metrics for CX-2009 intact, free DM4, DM4-Me, and conjugated DM4 (indicated on bottom of heat map) in human subjects. Overall *P* values (values in text) appear to be lowest for CX-2009 intact relative to other analytes, and are significant ($P<0.05$) for all CX-2009 intact exposure metrics.



C_{avg}, average concentration; C_{max}, maximum concentration; C_{trough}, trough concentration.
P values for logistic regression indicated as text in heat map representation.

Figure 4B. Probability for grade ≥3 ocular toxicity (line: prediction; shaded: 90% confidence limit; circles: observed) by dose in human subjects. Both model-predicted (line) and observed (circles) probability for grade ≥3 ocular toxicity rise at dose levels of >7 mg/kg Q3W. Ocular prophylaxis (ophthalmic vasoconstricting agents and corticosteroid) was only implemented as a mandatory procedure at doses of 8 mg/kg Q3W and 6 mg/kg Q2W [Boni V, et al. ASCO 2020 poster: Abstract 526].

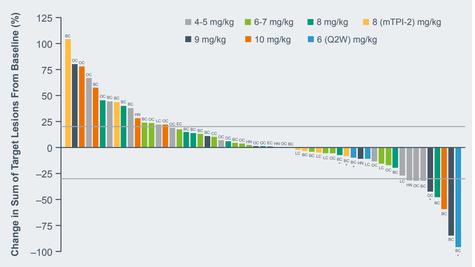


- Evidence of clinical activity has been observed at doses of 4 mg/kg Q3W or higher (**Figure 5A**)
- Possible correlations between disease control (DC) with dose 1 C_{trough}, C_{max}, and C_{avg} for CX-2009 intact, free DM4, DM4-Me, and conjugated DM4 were further examined
- The only statistically significant relationship was between DC and CX-2009 intact C_{trough} ($P=0.023$)
- POPPK simulations suggest that the targeted 90 nM trough concentration (generated from nonclinical data using systems pharmacology[2] would be contained within the 90% prediction interval of CX-2009 intact levels following CX-2009 7 mg/kg (**Figure 5B**)

CONCLUSIONS

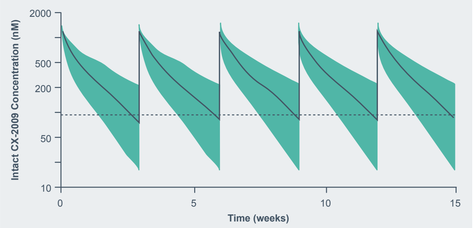
- Preliminary CX-2009 PK data following CX-2009 0.25–10 mg/kg suggest that CX-2009 circulates predominantly as CX-2009 intact, and that CX-2009 intact PK data are not strongly influenced by target-mediated drug disposition or ADAs
- Preliminary DR and POPPK simulations support further evaluation of 7 mg/kg CX-2009 Q3W in selected cohort expansions [Boni V, et al. ASCO 2020 poster. Abstract 526]

Figure 5A. Best percentage change in sum of target lesion dimensions from baseline with CX-2009 treatment in cancer patients.



BC, breast carcinoma; CC, cholangiocarcinoma; EC, endometrial carcinoma; HN, head and neck squamous cell carcinoma; LC, non–small cell lung carcinoma; OC, epithelial ovarian carcinoma.
All doses were administered Q3W unless otherwise indicated.
Asterisk (*) denotes subjects still on treatment.
Note: Subjects treated with ≤2 mg/kg had disease progression and were not included in the plot.

Figure 5B. Simulated CX-2009 intact plasma concentration profile (line: median; shaded: 90% prediction interval) following 7 mg/kg CX-2009 Q3W superimposed over the targeted CX-2009 intact trough concentration (dashed horizontal line) in human subjects. The targeted CX-2009 intact trough concentration appears to be within the 90% prediction interval at trough following CX-2009 7 mg/kg Q3W.



FUTURE DIRECTIONS FOR RESEARCH

- This study provides the dose selection rationale for CX-2009, a PDC directed against the broadly expressed CD166/ALCAM target, for further evaluation in selected cohort expansions
- To lessen the potential for ocular toxicity at 7 mg/kg (the recommended Phase 2 dose when CX-2009 is given Q3W), future studies will incorporate mandatory ocular prophylaxis

References

1. Kavanaugh WM. *Expert Opin Biol Ther*. 2020;20:163-71.
2. Stroh M, et al. *CPT Pharmacometrics Syst Pharmacol*. 2019;8:676-84.

Acknowledgments

This study was sponsored by CytomX Therapeutics, Inc. Editorial assistance was provided by Echelon Brand Communications, an OPEN Health company, Parsippany, NJ, and was funded by CytomX Therapeutics, Inc.

Email address for questions or comments: mstroh@cytomx.com