Preliminary Population Pharmacokinetics Supports Phase 2 Dose Selection for Masked Anti–PD-L1 Antibody CX-072

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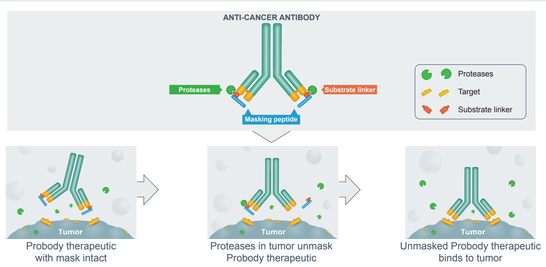
BACKGROUND

- PROBODY therapeutic candidates (Pb-Tx) are antibody prodrugs with cleavable peptide masks designed to reduce off-tumor, on-target toxicities.[1] The mask is designed to inhibit Pb-Tx binding in the periphery yet can be removed by tumor-associated proteases, restricting target engagement to the tumor (**Figure 1**)
- Preliminary clinical pharmacokinetic (PK) analyses are reported here that support the selection of the Phase 2 dose for investigational Pb-Tx CX-072, an anti–programmed death-ligand 1 (PD-L1) Pb-Tx, from the ongoing Phase 1/2 PROCLAIM-CX-072 study (NCT03013491)[2,3]

Figure 1. Structure of a Pb-Tx.

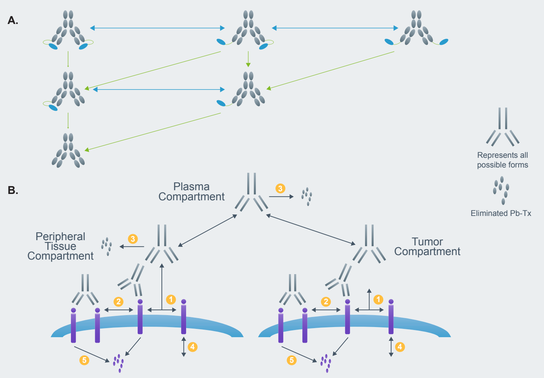


Pb-Tx, Probody therapeutic.

METHODS

- A quantitative systems pharmacology (QSP) model was used to project the CX-072 plasma trough level (C_{min}) corresponding to 95% intratumoral receptor occupancy (RO) (**Figure 2**)[4]
- Human PK and anti-drug antibody (ADA) data were obtained at selected times postdose following IV administration of 0.03 to 30 mg/kg CX-072 in the PROCLAIM-CX-072 study (**Tables 1 and 2**)
  - Population PK (POPPK) modeling was performed with NONMEM v7.3.0 software
  - Exploratory analysis and simulations were done with R v3.3.1 or later
  - Covariates were selected for POPPK using forward addition (P<0.05) followed by backward deletion (P<0.01)

Figure 2. The QSP model.

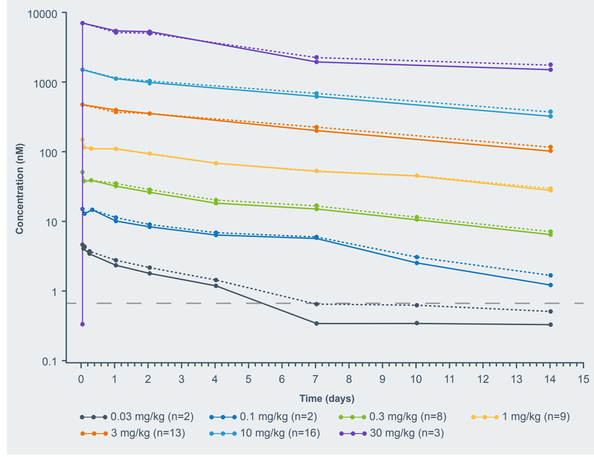


The CX-072 trough concentration corresponding to a targeted 95% intratumoral receptor occupancy was estimated using the QSP model, which accounts for events at the Pb-Tx, target, and compartmental levels. (A) Reversible events (bidirectional arrows) and irreversible cleavage reactions (unidirectional arrows) are captured. (B) These 6 forms of the Pb-Tx distribute to the plasma, peripheral, and tumor compartments. The Pb-Tx may engage in monovalent (step 1) or bivalent (step 2) binding to target. The Pb-Tx may be eliminated by nonspecific (step 3) and specific (target-mediated [step 5]) routes. Provisions for receptor trafficking and concentrations are included in the QSP model (step 4).
Pb-Tx, Probody therapeutic; QSP, quantitative systems pharmacology.

RESULTS

- The preliminary POPPK analyses were informed using available PK data as of August 2019 from patients receiving CX-072 Q2W as monotherapy in the dose-escalation and expansion cohorts of PROCLAIM-CX-072 (**Table 1, Figure 3**)

Figure 3. Preliminary dose 1 median concentration of intact (solid lines) and total (dashed lines) CX-072 (nM) versus time (day) following administration of up to 30 mg/kg CX-072 Q2W in human patients and following intensive collection in the dose-escalation/biomarker and dose-effect cohorts.



The concentration profiles for intact CX-072 and total CX-072 appear similar at a given dose, suggesting that CX-072 circulates predominantly in the protected form. The similar elimination phase kinetics across the 0.1–30 mg/kg dose levels suggest limited importance of target-mediated drug disposition.
[a] Dashed horizontal line represents the limit of quantitation (LOQ) for CX-072 assay. In representations below LOQ, data are assigned a value of LOQ/2.

Table 1. Overview of Data Used to Assess the Preliminary Clinical PK/PD of CX-072 Administered as Monotherapy in PROCLAIM-CX-072[a]

Dose, Route, and Regimen	Sampling Schedule[b]
0.03, 0.1, 0.3, 1, 3, 10, and 30 mg/kg IV infusion Q2W beyond 2 years as long as patients continued to experience clinical benefit	Dose-escalation/biomarker and dose-effect cohorts: Predose: cycle 1, day 1 (C1D1), C1D15, C1D29, C1D43, C2D1, C2D29, C3D1, C4D29, and every 4 cycles thereafter EOI + 30 min on C2D1 and C2D29 C1D1: EOI + 30 min, EOI + 24 h, EOI + 48 h, EOI + 168 h Cohort expansion: Predose: C1D1, C1D29, C2D1, C2D29, C4D29, and every 4 cycles thereafter EOI + 30 min on C1D1 and C2D29 All parts: EOT,[c] follow-up visit

EOI, end of infusion; EOT, end of treatment; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; Q2W, every 2 weeks.
[a] See Thistlethwaite F, et al. ASCO 2020 oral presentation. Abstract 3005.
[b] Prescribed PK collection under Amendment 5 of PROCLAIM-CX-072.
[c] EOT is approximately 30 days following last dose of study drug; follow-up visit is 90 days following last dose of study drug.

Table 2. Analytes Assayed in the PROCLAIM-CX-072 Study

Analyte	Description
Intact CX-072	Prodrug form of CX-072
Total CX-072	Intact and activated forms of CX-072

- The preliminary POPPK model estimates for CX-072 time-invariant CL and volume of distribution at steady state were 0.306 L/day and 4.84 L, respectively (**Table 3**)
  - The threshold for apparent ADA effect on CL in the ADA effect population ($ADA_{doselim}$) was fixed to 400 mg (5 mg/kg equivalent) based on log-likelihood profiling
  - The interindividual variability was estimated to be 35.9% on CL. For patients receiving 10 mg/kg CX-072, the geometric mean (% coefficient of variation [CV]) intact CX-072 terminal half-life was 11.7 (33%) days; the fraction circulating as intact CX-072 was estimated at 87.2 (9.5%)

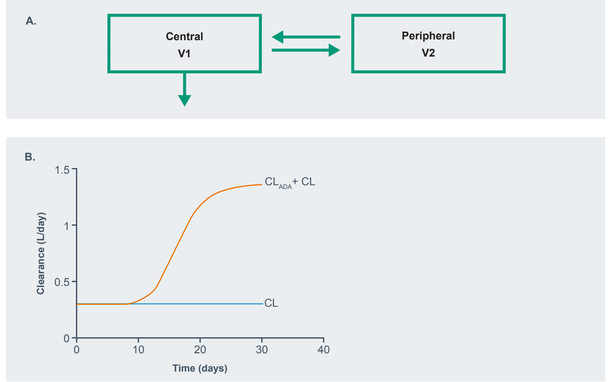
Table 3. Parameter Estimates for the Intact CX-072 Human POPPK Model

Parameter	Estimate	RSE (%)	Residual or IIV (% CV)
CL, L/day	0.306	4.06	
V1, L	3.35	2.99	
V2, L	1.49	12.7	
Q, L/day	0.487	24.6	
$EMAX_{CLADA}$, L/day	1.07	8.25	
Probability of ADA effect, %	64.6	15.6	
Log (CL_{ADA} TM50), days	2.80	2.05	
CL_{ADA} Hill coefficient	7.41	22.3	
$ADA_{doselim}$, mg	400		
Albumin on CL	–1.39	15.0	
Body weight on CL	0.553	24.1	
Body weight on V1	0.602	13.2	
σ^2 Proportional residual error, cycle 1	0.218	12.7	21.8
σ^2 Proportional residual error, > cycle 1	0.292	14.3	29.2
ω^2 CL	0.129	9.99	35.9
ω^2 V1	0.0562	20.9	23.7
ω^2 V2	0.424	17.4	65.1

Notes: $ADA_{doselim}$ was fixed to values corresponding to the minimum objective function value from log-likelihood profiling. The fraction circulating as intact CX-072 was estimated based on the ratio of CL estimates for total to intact CX-072 for patients receiving 10 mg/kg CX-072.
ω2, variance of omega; σ2, variance of sigma; ADA, antidrug antibody; $ADA_{doselim}$, threshold for apparent ADA effect on CL in the ADA effect population; CL, clearance; CL_{ADA}, apparent ADA effect on CL; $EMAX_{CLADA}$, maximum increase in CL in the ADA effect population; IIV, interindividual variability; Q, intercompartmental clearance; RSE, relative standard error; TM50, time to half-maximal increase (in CL in the ADA effect population); V1, central volume, V2, peripheral volume.

- As has been reported for the PD-L1 inhibitor atezolizumab,[5] preliminary multiple-dose data suggested a dose- and time-dependent effect of ADA on intact CX-072 exposures for some patients
- A mixture model was included in the POPPK evaluation to discriminate between patients who showed an apparent ADA effect on clearance (CL) and those who did not (**Figure 4**)

Figure 4. Preliminary human POPPK model diagram and diagnostics.



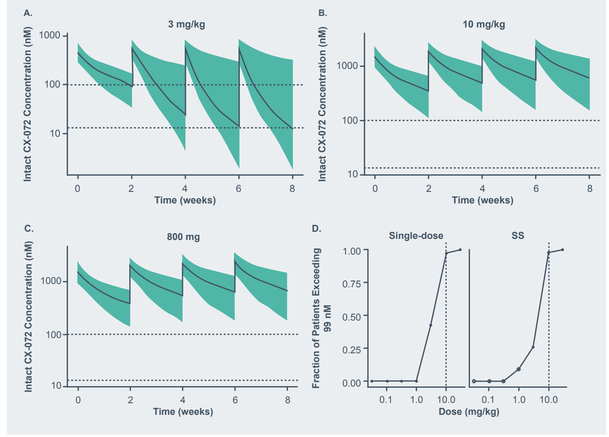
(A) Model diagram for CX-072 intact POPPK model that was parameterized with (B) time-invariant clearance for no ADA effect (CL) and time-dependent clearance for ADA effect ($CL+CL_{ADA}$) populations, respectively.
ADA, anti-drug antibody; POPPK, population pharmacokinetics.

CONCLUSIONS

- Preliminary PK analysis supports selection of 800 mg CX-072 Q2W as the recommended monotherapy dose and 800 mg Q3W × 4 when combined with ipilimumab (supported by available preliminary clinical [Thistlethwaite F, et al. ASCO 2020 oral presentation. Abstract 3005] and translational [Lyman SK, et al. ASCO 2020 poster. Abstract 3108] data obtained in PROCLAIM-CX-072)

- The QSP model that incorporated all cleaved and uncleaved species predicted that an intact CX-072 C_{min} of 13–99 nM would be required for the targeted 95% intratumoral RO assumed to be required for efficacy for the PD-L1 inhibitor atezolizumab.[6] POPPK simulations suggested that >95% of patients receiving CX-072 10 mg/kg Q2W would meet or exceed this targeted C_{min} regardless of ADA (**Figure 5**)
- Additional observed data indicated that the majority of patients receiving 10 mg/kg CX-072 Q3W × 4 with 3 mg/kg ipilimumab (IPI) Q3W × 4 in the CX-072-IPI combination part of PROCLAIM-CX-072-001 maintained the targeted C_{min}. Simulations suggested no clinically meaningful difference in exposure following a fixed dose of CX-072 800 mg relative to the 10 mg/kg weight-based dose (**Figure 5B and 5C**)
  - The median model-estimated intra-individual area under the curve (AUC) ratio for intact CX-072 was 1.08 following CX-072 800 mg relative to CX-072 10 mg/kg

Figure 5. Human POPPK model simulations for intact CX-072.



Simulated intact CX-072 PK profiles (solid line and shaded regions represent median and 90% prediction interval, respectively) following (A) 3 mg/kg, (B) 10 mg/kg, and (C) 800 mg Q2W CX-072. Dashed lines represent the target trough concentration range (13–99 nM) from the QSP model. (D) Simulated fraction of patients exceeding trough targets following the indicated dose of CX-072 Q2W following a single dose (left panel) and at steady state (right panel); dashed vertical line corresponds to 800 mg. The dose- and time-dependent effect of ADA on intact CX-072 exposures is evident in moving from the CX-072 3-mg/kg Q2W dose level, where a decreasing fraction of patients is projected to surpass the targeted C_{min} concentration range with multiple dosing, to the 10 mg/kg dose level, where >95% of patients are projected to meet or exceed the targeted C_{min} regardless of ADAs.
PK, pharmacokinetics; POPPK, population pharmacokinetics; Q2W, every 2 weeks; QSP, quantitative systems pharmacology; SS, steady state.

FUTURE DIRECTIONS FOR RESEARCH

- This study provides the preliminary PK analysis supporting the dose selection for CX-072, a Pb-Tx directed against PD-L1, for further evaluation in Phase 2 studies

References

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Acknowledgments

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