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 release fully functional antibodies. The masks are designed to inhibit Pb-Tx binding in the periphery yet can be removed by tumor-associated proteases, unlocking target engagement to the tumor (Figure 1). Preliminary pharmacokinetic (PK) analyses are required to support the selection of the Phase 2 dose level. This study provided the preliminary PK analysis supporting the dose selection for CX-072, a Pb-Tx directed against a tumor-associated protein.

RESULTS

The preclinical Pb-Tx PK analyses were performed using available PK data as of August 2019 from patients receiving CX-072 as monotherapy in the dose-escalation and expansion cohorts of PROGRAM CX-072 (Table 1, Figure 5).

Figure 5. Structure of a Pb-Tx.

The median model-estimated intra-individual area under the curve (AUC) ratio for intact CX-072 was 1.08 (Table 3). The QSP model that incorporated all cleaved and uncleaved species predicted that an intact CX-072 concentration of 2.9 mg/L could be achieved in patients following intensive collection in the dose-escalation formulation and dosing cohorts.

Figure 3. Preliminary dose 1 median concentration of intact CX-072 (violet line) and total CX-072 (blue line) following administration of up to 30 mg/kg CX-072 in human patients and following intensive collection in the dose-escalation formulation and dosing cohorts.

The preclinical Pb-Tx PK model estimates for CX-072 free-invariant Cx and volume of distribution at steady state were 0.26 L/kg and 2.04 L/kg, respectively (Table 6).

Figure 4. Preliminary human POPPK model diagram and diagnostics.

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 concentration profiles at the targeted trough concentration for intact CX-072 were estimated at 0.75 mg/L (C2D29).

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

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CONCLUSIONS

The QSP model that incorporated all cleaved and uncleaved species predicted that intact CX-072 Cx of 2.9 mg/L could be achieved in patients following intensive collection in the dose-escalation formulation and dosing cohorts.

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

Mature analyses were performed to support the Phase 2 dose selection for CX-072. Dashed lines represent the target trough concentration range (13–99 nM) from the QSP model. (D) Simulated fraction of patients exceeding the target concentration range. (E) Simulated fraction of patients achieving the target concentration range.

FUTURE DIRECTIONS FOR RESEARCH

• This study provided 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.

Table 3. Analytes Assayed in the PROGRAM CX-072 Study

References