PROCLAIM-CX-072: A First-in-Human Trial to Assess Tolerability of the Protease-Activatable Anti–PD-L1 Probody™ CX-072 in Solid Tumors and Lymphomas

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BACKGROUND
- Tumors can evade host immunity by expression of programmed cell death ligand 1 (PD-L1), a ligand that negatively regulates programmed cell death 1 (PD-1), an inhibitory receptor expressed on activated T cells.1
- Antibodies targeting PD-L1 have shown activity against a variety of cancers and are being tested in combination with other immunotherapies in an effort to improve response rates. However, significant life-threatening immune-related toxicities (irAES) are known toxicities of antibodies that block the PD-1/PD-L1 axis, especially when used in a wide variety of combinations, including with ipilimumab, vemurafenib, pazopanib, or cisplatin.2,3
- Probody therapeutics are fully recombinant antibody prodrugs that remain relatively inactive because of a protease-resistant masking linker peptide until they are activated by proteases associated with the tumor microenvironment (TME).10
- CX-072 is a Probody therapeutic directed against PD-L1 for the treatment of patients with cancer.

OBJECTIVE
- The PROCLAIM-CX-072 (PBO) Clinical Assessment (Poa) study is evaluating the tolerability and preliminary antitumor activity of multiple doses of CX-072 as monotherapy or as combination therapy with ipilimumab or vemurafenib in patients with advanced, unresectable solid tumors or lymphoma.

STUDY DESIGN
- This is a first-in-human, open-label, multicenter, dose-escalation, phase 1/2 study of CX-072.
- The study will include four dose escalation groups receiving CX-072: one monotherapy group (Part A), one combination therapy with ipilimumab and two distinct schedules (Parts B1 and B2), one combination therapy with vemurafenib (Part C), and one monotherapy group in a dose-expansion phase (Figure 3).
- Within each part, dose escalation will follow a 3+3 design.
- Initiation of cohort enrollment in Parts B1, B2, and C requires successful completion of the subsequent monotherapy dose level tested in Part A for 2 weeks and until disease progression.
- Treatment will continue for up to 2 years or until disease progression is confirmed or toxicity becomes unacceptable.

END POINTS
- Primary End Points
  - Safety and tolerability of CX-072 alone or in combination with ipilimumab or vemurafenib
  - MTD and dose-limiting toxicities of CX-072 alone or in combination with ipilimumab or vemurafenib

- Secondary End Points
  - Objective response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST version 1.1), immune-related RECIST, or modified Chevalier-Lucangeli classification for lymphomas
  - Time to response
  - Duration of response
  - Progression-free survival
  - Incidence of anti-drug antibodies
  - Single- and multiple-dose pharmacokinetic profile of CX-072 alone and of CX-072 in combination with ipilimumab or vemurafenib
  - Overall survival

ASSESSMENTS
- The following assessments will be performed at each study visit: adverse events, including events of special interest, physical examination, vital signs, hematology, serum chemistry, B symptoms (lymphoma patients), Eastern Cooperative Oncology Group performance status, and concomitant medications.
- Imaging for tumor response assessment will be performed every 8 weeks for the first 12 months, then every 12 weeks thereafter.
- Blood samples for pharmacokinetic, pharmacodynamic, and biomarker analyses will be obtained at prespecified time points.
- After the last dose of study medication, patients will be evaluated every 3 months for disease progression and overall survival until study withdrawal or death.
- Archival tissue or fresh biopsy samples must be provided at baseline, and patients in Part B2 must be willing to undergo 1 on-treatment tumor biopsy.
- All patients involved in the study may consent to biopsies to aid in translational analyses.

Translational Analyses
- Several translational strategies will be used to investigate Probody therapeutic activation, PD-L1 inhibition, and immune response pattern in the tumor (Table 2, Figure 4).

Table 2. Translational End Points Included in PROCLAIM-CX-072

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<thead>
<tr>
<th>End Point</th>
<th>Description</th>
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<tbody>
<tr>
<td>Probody therapeutic activation</td>
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REFERENCES