TPS3107

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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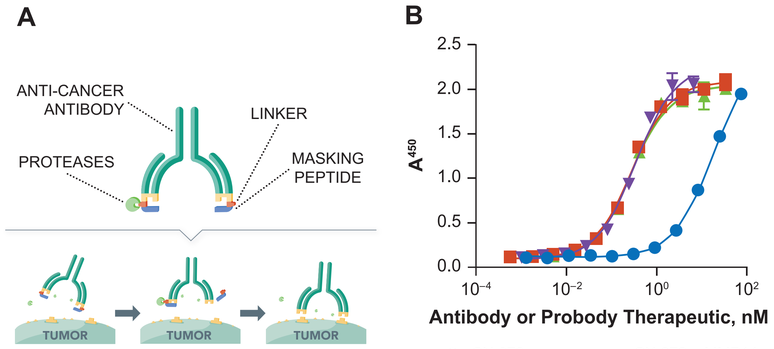
BACKGROUND

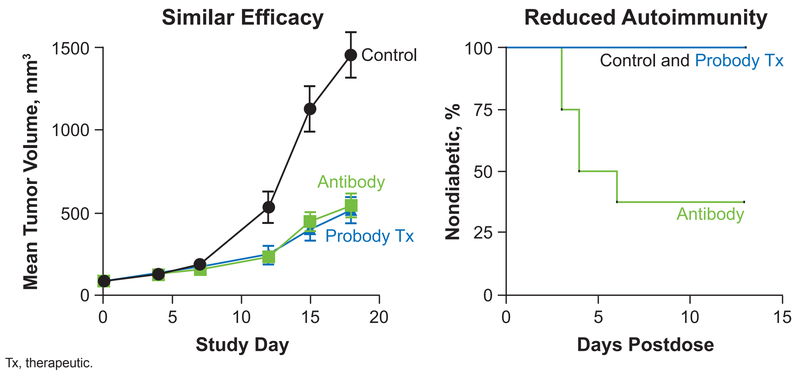
- Tumors can evade host immunity by expression of programmed cell death ligand 1 (PD-L1), a ligand that negatively regulates programmed cell death 1 (PD-1), an inhibitory receptor expressed on activated T cells[1]
- Antibodies targeting PD-L1 have shown activity against a variety of cancers and are being tested in combination with other immunotherapies in an effort to improve response rates[2]
- 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,[3,4] vemurafenib/cobimetinib, pazopanib, or osimertinib[5,6]
- Probody therapeutics are fully recombinant antibody prodrugs that remain relatively inactive because of a protease-cleavable masking linker peptide until they are activated by proteases associated with the tumor microenvironment (**Figure 1**).[7,8] In preclinical studies, Probody therapeutics have demonstrated efficacy similar to that of parental antibodies and safety profiles better than those of parental antibodies (**Figure 2**)
- CX-072 is a Probody therapeutic directed against PD-L1 for the treatment of patients with cancer
  - Given that CX-072 is activated by tumor-associated proteases, it is expected to be relatively inactive in peripheral tissue, thereby potentially reducing systemic irAEs compared with other PD-1/PD-L1 inhibitors
- In preclinical studies, a surrogate for CX-072 displayed potent antitumor activity[9]
  - Protease activation was required for CX-072 to bind to PD-L1 in vitro (**Figure 1B**)
  - In in situ studies of tumor samples from 200 patients with a variety of malignancies, >90% of the samples demonstrated Probody activation. This corroborates the presence of tumor microenvironment proteases in the overwhelming majority of tumors necessary to ensure activation of the Probody therapeutic
  - A surrogate for CX-072 demonstrated efficacy equivalent to that of the parental antibody while minimizing the induction of autoimmune diabetes in nonobese diabetic mice
  - A surrogate for CX-072 exhibited reduced peripheral binding to blood T cells in tumor-bearing mice compared with the parental antibody

Figure 1. Probody therapeutics are protease-activatable antibody prodrugs. (A) Schematic representation of Probody therapeutic activation in the tumor microenvironment. (B) CX-072 exhibits protease-dependent binding to PD-L1 in vitro based on ELISA.



ELISA, enzyme-linked immunosorbent assay; MMP14, matrix metalloproteinase 14; uPA, urokinase-type plasminogen activator. CX-072 (blue) shows reduced binding to recombinant PD-L1 by ELISA, whereas proteolytic activation of CX-072 with uPA or MMP-14 (red, green) restores binding to levels comparable to that of the parental antibody (purple).

Figure 2. In preclinical studies, Probody therapeutics display efficacy similar to that of parental antibodies (comparable reduction in tumor growth) with improved safety (reduced autoimmunity).



Tx, therapeutic.

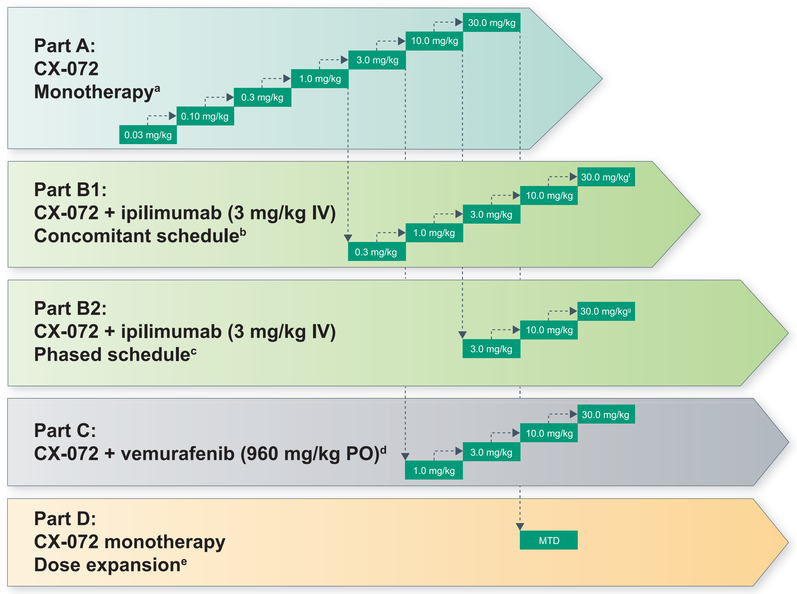
OBJECTIVE

- The PROCLAIM-CX-072 (**PRO**body **CL**inical **A**ssessment **I**n **M**an) 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 group and two distinct schedules (Parts B1 and B2), one combination therapy with vemurafenib group (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
  - Enrollment for Part D, the expansion phase, will be initiated after dose escalation for Part A is complete and the maximum tolerated dose (MTD) has been determined
- Treatment will continue for up to 2 years or until disease progression is confirmed or toxicity becomes unacceptable

Figure 3. PROCLAIM-CX-072 phase 1/2 study design.



IV, intravenously; MTD, maximum tolerated dose; PO, by mouth.
[a]CX-072 monotherapy will be administered IV every 14 days.
[b]CX-072 plus ipilimumab will be administered IV every 21 days × 4 doses, followed by CX-072 monotherapy IV every 14 days.
[c]During dose escalation, CX-072 monotherapy will be administered IV every 14 days × 4 doses. If tolerated, CX-072 plus ipilimumab will be administered IV every 21 days × 4 doses, followed by CX-072 monotherapy IV every 14 days.
[d]CX-072 will be administered IV every 14 days plus vemurafenib twice daily.
[e]CX-072 monotherapy will be administered at the MTD, determined from Part A, IV every 14 days.
[f]If 30 mg/kg CX-072 plus 3 mg/kg ipilimumab is judged to be safe (as per protocol and confirmed by the Safety Review Committee), escalation of CX-072 with 10 mg/kg ipilimumab will be initiated, starting with 10 mg/kg CX-072 and proceeding, as tolerated, to 30 mg/kg CX-072.
[g]If no MTD is established for the combination with 3 mg/kg ipilimumab, the 10 mg/kg and 30 mg/kg dose levels of CX-072 will be evaluated in combination with 10 mg/kg ipilimumab.

Patients

- Up to 150 patients will be enrolled in the study in both the dose escalation and the expansion cohorts
- Key eligibility criteria are shown in **Table 1**

Table 1. Key Eligibility Criteria

All parts	• Age ≥18 years • ECOG performance status 0-1
Part A	• Advanced, unresectable solid tumor or lymphoma with no further standard of care available • PD-1/PD-L1 inhibitor naive • PD-1/PD-L1 inhibitor therapy unavailable for patient's disease
Part B1	• Advanced, unresectable solid tumor or lymphoma with no further standard of care available • PD-1/PD-L1 inhibitor naive • PD-1/PD-L1 inhibitor therapy unavailable for patient's disease • CTLA-4 inhibitor naive
Part B2	• Advanced, unresectable solid tumor or lymphoma with no further standard of care available • Previously treated with a PD-1/PD-L1 inhibitor (discontinued for reasons other than toxicity) • CTLA-4 inhibitor naive
Part C	• Advanced, unresectable melanoma • *BRAF*^{V600E} mutation positive • BRAF inhibitor naive • PD-1/PD-L1 inhibitor naive
Part D	• Advanced, unresectable PD-L1–responsive tumor types[a] • Measurable disease • PD-L1 positive or status unknown (not known to be PD-L1 negative) • PD-1/PD-L1 inhibitor naive

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.
[a]Based on emerging data; future amendments will be updated.

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 Cheson/Lugano 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

Exploratory Objectives

- Protease activity and degree of CX-072 cleavage in tumor and peripheral blood
- Immunomodulatory activity of CX-072 in on-treatment biopsy samples
- Potential predictive markers of CX-072 activity

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

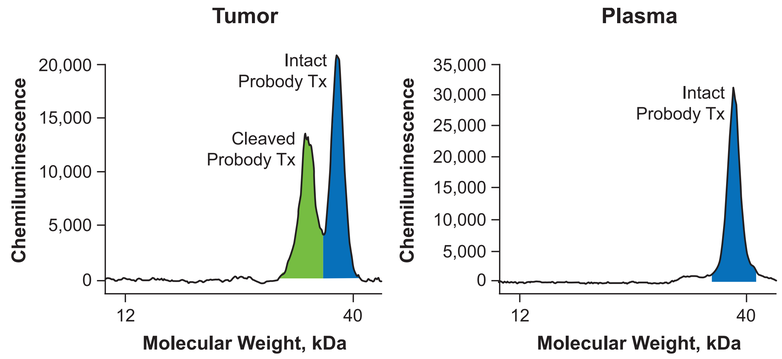
- Several translational strategies will be used to investigate Probody therapeutic activation, PD-L1 inhibition, and immune response pattern in the tumor (**Table 2, Figure 4**)

Table 2. Translational Analyses Included in PROCLAIM-CX-072

Goal	Sample(s)	Assay	Description
Probody therapeutic activation	Biopsy, plasma	WES™	Capillary electrophoresis with immunodetection
	Biopsy	QZ™ assay	Protease activity detection
PD biomarkers	Biopsy	Nanostring™	Gene expression panel
	Biopsy	IHC	Immune cell infiltration
	Plasma	Luminex®	Cytokine panel
PD-L1 expression	Biopsy	IHC	PD-L1 expression

IHC, immunohistochemistry; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1.

Figure 4. Preclinical measurement of cleaved (green) and intact (blue) Probody therapeutic by WES assay in tumor and plasma.



kDa, kilodalton; Tx, therapeutic.

STUDY PROGRESS

- The study started in January 2017, and sites are open for Part A in the United States and the European Union. Enrollment is expected to be opened for Parts B1 and C in the second half of 2017 and for Part D in the first half of 2018
- This study is registered with ClinicalTrials.gov, number NCT03013491
- For more information, please visit https://clinicaltrials.gov/ct2/show/NCT03013491 or contact clinicaltrials@cytomx.com

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