CLINICAL STUDY REPORT

1.0 TITLE PAGE

Study Title:	An Open-label, Dose-finding, and Proof of Concept Study of the PD-L1 Probody® Therapeutic, CX-072, as Monotherapy and in Combination with Yervoy® (Ipilimumab) or with Zelboraf® (Vemurafenib) in Subjects with Advanced or Recurrent Solid Tumors or Lymphomas
Name of Investigational Product:	CX-072
Indication Studied:	Metastatic or Advanced Unresectable Solid Tumors or Lymphomas
Study Sponsor:	CytomX Therapeutics, Inc.
Street Address:	151 Oyster Point Boulevard, Suite 400
City, State Postal Code:	South San Francisco, CA 94080-1913
Country:	USA
Protocol Number:	CTMX-C-001 (Core Document) Module CTMX-M-072-001
Development Phase of Study:	Phase 1/2a
Study Initiation Date (first patient registered):	19 Jan 2017
Date of Early Study Termination, if any:	Not applicable
Study Completion Date:	27 Oct 2020
Report Date:	14 Nov 2022
Report Status:	FINAL REPORT
Medical Monitor:	Lawrence Lu, MD
Institution:	CytomX Therapeutics, Inc.
Address:	151 Oyster Point Boulevard, Suite 400 South San Francisco, CA 94080-1913
GCP Compliance Statement:	The Investigators agreed to conduct the study in compliance with the study protocol, with the International Standard of Good Clinical Practice (GCP) procedures, and with the principles of the Declaration of Helsinki (1964) and relevant amendments.

2.0 SYNOPSIS

Name of the Sponsor:
CytomX Therapeutics, Inc.

Name of Finished Product:
Pacmilimab

Name of Active Ingredient:
CX-072

Title of Study: An Open-label, Dose-finding, and Proof of Concept Study of the PD-L1 Probody® Therapeutic, CX-072, as Monotherapy and in Combination with Yervoy® (Ipilimumab) or with Zelboraf® (Vemurafenib) in Subjects with Advanced or Recurrent Solid Tumors or Lymphomas

Lead Investigator and Study Center:
Aung Naing, Principal Investigator of MD Anderson Cancer Center

Publications:

Kist de Ruijter L, Hooiveld-Noeken JS, Giesen D, et al. First-in-human study of the biodistribution and pharmacokinetics of ^{89}Zr-CX-072, a novel immunopet tracer based on an anti–PD-L1 probody. Clin Cancer Res. 2021;27(19):5325-33.

Naing A, Thistlethwaite F, De Vries EGE, et al. CX-072 (pacmilimab), a Probody® PD-L1 inhibitor, in advanced or recurrent solid tumors (PROCLAIM-CX-072): an open-label dose-finding and first-in-human study. J Immunother Cancer. 2021;9(7):e002447.

Sanborn RE, Hamid O, de Vries EGE, et al. CX-072 (pacmilimab), a Probody PD-L1 inhibitor, in combination with ipilimumab in patients with advanced solid tumors (PROCLAIM-CX-072): a first-in-human, dose-finding study. J Immunother Cancer. 2021;9(7):e002446.

Stroh M, Green M, Millard BL, et al. Model-informed drug development of the masked anti–PD-L1 antibody CX-072. Clin Pharmacol Ther. 2021;109(2):383-93.

Study Period:	**Development Phase:**
19 Jan 2017 to 27 Oct 2020	1/2a

Primary Objectives

- Parts A through C:
  1. To evaluate the safety and tolerability of multiple doses of CX-072 administered as monotherapy or in combination with ipilimumab or vemurafenib to patients with metastatic or locally advanced unresectable solid tumors or lymphomas
  2. To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the following:
     - CX-072 as a monotherapy administered to programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) naive patients
     - CX-072 in combination with ipilimumab administered to PD-1/PD-L1 and CTLA-4 inhibitor naive patients
     - CX-072 in combination with ipilimumab administered to patients who had prior treatment with a PD-1/PD-L1 inhibitor
     - CX-072 in combination with vemurafenib administered to PD-1/PD-L1 naive patients
- Parts D and E:
  1. To obtain preliminary and confirmatory evidence of the efficacy of CX-072 monotherapy, respectively, via the objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) (tumor types include undifferentiated pleomorphic sarcoma [UPS], small bowel adenocarcinoma [SBA], cutaneous squamous cell carcinoma [cSCC], Merkel cell carcinoma

[MCC], thymic epithelial tumor [TET], anal SCC, triple-negative breast cancer [TNBC] with skin lesions, and high tumor mutational burden [hTMB] [Part D only]), as assessed by Investigator (Part D) or by independent review facility (IRF) (Part E).

Secondary Objectives

- Parts A through C:
  1. To obtain preliminary evidence of anticancer activity on the basis of the following endpoints in patients treated with CX-072 as monotherapy or when administered in combination with ipilimumab or vemurafenib:
     - ORR by RECIST v1.1
     - ORR by modified immune-related response criteria as defined in the Common Core Document or Modified Cheson/Lugano Classification for Lymphomas
     - Time to response (TTR)
     - Duration of response (DOR)
     - Progression-free survival (PFS)
  2. To characterize the incidence of antidrug antibodies (ADAs) against CX-072 and ipilimumab
  3. To characterize the single and multidose pharmacokinetic (PK) profile of CX-072 when administered alone, and CX-072, ipilimumab, and vemurafenib when administered in combination
  4. To assess overall survival (OS) in patients receiving CX-072
- Parts D and E:
  1. To further characterize the efficacy of CX-072 monotherapy as evidenced by the following:
     - DOR as assessed by Investigator (Part D) or by IRF (Part E)
     - ORR by RECIST v1.1 by PD-L1 expression (Part E)
     - ORR by modified immune-related (ir) RECIST as defined in the Common Core Document
     - PFS
  2. To evaluate safety and tolerability of CX-072 administered as monotherapy
  3. To characterize the incidence of ADAs against CX-072
  4. To characterize the PK profile of CX-072
  5. To assess OS in patients receiving CX-072

Exploratory Objectives

Parts A through D:

1. To obtain preliminary evidence of anticancer activity on the basis of objective responses in patients treated with CX-072 as monotherapy, or when administered in combination with ipilimumab, or vemurafenib as evidenced by the ORR by irRECIST
2. To explore potential predictive markers associated with CX-072 clinical activity based on levels of expression of PD-L1 in tumor specimens (fixed and frozen) prior to and while receiving treatment
3. To characterize the protease activity and degree of CX-072 cleavage in tumor and peripheral blood
4. To investigate the immunomodulatory activity of CX-072 in on-treatment biopsies (fixed and frozen)
5. To perform an analysis of tumor mutation burden in patients that respond to treatment in Part D
6. Other exploratory biomarkers such as circulating markers or cytokines may also be evaluated

Part E:

1. To explore potential predictive markers associated with CX-072 clinical activity, including but not limited to levels of expression of PD-L1 in tumor specimens (fixed and frozen) prior to and while receiving treatment, both overall and in various subgroups, depending on tumor type
2. Other exploratory biomarkers such as circulating markers or cytokines may also be evaluated in tumor biopsies and/or peripheral blood samples.

Methodology:

The study was a first-in-human (FIH), open-label, multicenter, dose-escalation, multidose study of CX-072 (as monotherapy and/or in combination with other anticancer agents) in patients with advanced solid tumors and/or lymphomas. Approximately 60 sites were utilized. The study was divided into 7 parts (Part A, Part A2, Part B1, Part B2, Part C, Part D, and Part E). However, the study closed without opening Part E and it is not discussed further. Enrolled patients continued on study through the follow-up period. Investigators may have elected to allow patients who continued to receive clinical benefit to continue to receive study drug, if permitted by the Sponsor, through the long-term extension (LTE) part of the study.

Parts A through C were designed to evaluate the safety and determine the MTD and/or maximum achieved dose (MAD) of CX-072 as monotherapy and in combination with ipilimumab or vemurafenib. Part D was designed to obtain preliminary and confirmatory evidence of anticancer activity. All patients in Part A2 (CX-072 monotherapy), patients in Part B2 receiving CX-072 + 3 mg/kg ipilimumab (but not patients receiving 6 mg/kg ipilimumab), and the cohort of patients with TNBC with skin lesions in Part D underwent pre- and on-study treatment tumor biopsies to explore potential predictive markers associated with CX-072 clinical activity.

Number of Patients Enrolled:

196

Criteria for Eligibility:

Patients who fulfilled the following criteria at screening were eligible for admission into the study:

Inclusion criteria for patients in Part A:

- Any metastatic or advanced unresectable solid tumor or lymphoma, measurable or nonmeasurable disease allowed, no further standard of care (SOC) therapy available
- Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (in which there was no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they were treated)

Inclusion criteria for patients in Part A2:

- Any metastatic or advanced unresectable solid tumor or lymphoma (at least 2 patients in each cohort with TET), measurable disease allowed, no further SOC therapy available
- Tumor proportion score ≥ 1% membranous staining based on the DAKO PD-L1 immunohistochemistry (IHC) 22C3 pharmDx
- Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (in which there was no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they were treated)
- Agreement to participate in biomarker analysis and a had tumor site that was safe to biopsy

Inclusion criteria for patients in Part B1:

- Any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET), measurable or nonmeasurable disease allowed, no further SOC therapy available
- Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (in which there was no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they were treated)

Inclusion criteria for patients in Part B2:

- Any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) with measurable disease allowed, no further SOC therapy available
- Previous treatment with a PD-1/PD-L1 inhibitor
- Discontinued treatment with a PD-1/PD-L1 inhibitor for reasons other than toxicity
- Naive to treatment with a CTLA-4 inhibitor
- Agreement to participate in biomarker analysis and had a tumor site that was safe to biopsy (only in cohorts receiving CX-072 + 3 mg/kg ipilimumab [but not 6 mg/kg ipilimumab])

Inclusion criteria for patients in Part C:

- Metastatic or advanced unresectable melanoma with B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E mutation–positive, as detected by a diagnostic approved test (in the region where the patient was treated), measurable or nonmeasurable disease allowed
- Naive to treatment with BRAF inhibitors
- Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy is not available to the patient)

Inclusion criteria for patients in Part D:

- Measurable disease was required
- Must have been willing to provide a blood sample at screening for hTMB testing
- Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there was no available life-prolonging immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available to the patient) of the following tumor types:
  - UPS
    - Metastatic or advanced unresectable UPS
    - TPS ≥ 1% membranous staining or unknown PD-L1 status
    - Patients must have had SOC surgery and/or radiation for their UPS; patients with metastatic disease should have received at least 1 prior systemic therapy according to local guidelines
  - SBA
    - Had metastatic or locally advanced unresectable SBA of the duodenum, jejunum, or ileum (excluding neuroendocrine, ampullary, and appendiceal tumors)
    - Had at least 1 and no more than 3 prior lines of systemic chemotherapy for metastatic or advanced unresectable disease; adjuvant therapy did not count as first-line therapy unless cancer recurs < 6 months after last administration of that regimen
  - cSCC
    - Had metastatic or locally advanced unresectable primary cSCC
  - MCC
    - Metastatic or advanced unresectable MCC
    - Prior surgical resection was performed if resectable or potentially of benefit
    - Radiation therapy administered if of potential benefit, with documented progression following completion of radiation therapy
  - TET
    - Histologically confirmed diagnosis of TET (classified in accordance with 2015 World Health Organization criteria) with Stage 2, 3, or 4 disease per Masaoka-Koga 1994; details provided in Appendix 2 of Module CTMX-M-072-001
    - Received at least 1 prior chemotherapy regimen
  - Anal SCC
    - Metastatic or locally advanced unresectable anal SCC
    - Must have had prior radiation therapy and/or chemotherapy treatment
  - TNBC with skin lesions
    - Must have had histologically confirmed estrogen receptor (ER)–, progesterone receptor–, and HER2-negative breast cancer; defined as ER < 1%, progesterone receptor < 1%, and HER2 negative according to American Society of Clinical Oncology (ASCO)/College of American Pathologists guidelines by local testing according to institutional standards. Patients with weakly ER- or progesterone receptor–positive disease, defined as ER and/or

progesterone receptor < 5% by IHC, were eligible, if the treating physician considered the patient not eligible for endocrine therapy

- Have had locally advanced and locally recurrent skin or subcutaneous metastases not suitable for definitive (or curative) surgical resection or radiotherapy
- Received at least 1 and no more than 3 systemic chemotherapy regimens for metastatic breast cancer and had documented disease progression on most recent therapy
- Willing to provide a fresh skin tumor biopsy (fixed and frozen) from a non-target lesion

- hTMB
  - Metastatic or advanced unresectable cancer with hTMB as determined using a Clinical Laboratory Improvement Amendments validated assay (at least 16/megabase [Mb]) from a recent tumor tissue or blood sample
  - Failed or refused available SOC therapy specific for their tumor type

Inclusion criteria for all patients in Parts A through D:

1. Agreement to provide mandatory archival/baseline biopsy. A tumor biopsy was required at baseline if there was no other record of histological diagnosis of tumor.
2. For patients in Part A2 or Part B2 (for Part B2, only those patients receiving 3 mg/kg of ipilimumab), and those who agreed to participate in the biomarker analysis and who had a tumor site that was safe to biopsy, patients must have had a biopsy within 90 days of study entry and were willing to undergo at least 1 on-treatment tumor biopsy.
3. Patients with treated brain metastases were eligible if the brain metastases were stable and the patient did not require radiation therapy or steroids. Active screening for brain metastases (eg, brain computed tomography [CT] or magnetic resonance imaging [MRI]) was not required.
4. At least 18 years of age
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Anticipated life expectancy of at least 3 months
7. Screening laboratory values must have met the following criteria:
   a) White blood cells > 2000/μL or 2.0 × 109/L
   b) Neutrophils ≥ 1500/μL or 1.5 × 109/L
   c) Platelets ≥ 100 × 103/μL or 100 × 109/L
   d) Hemoglobin ≥ 9.0 g/dL (may have been transfused) or 90.0 g/L
   e) Creatinine ≤ 2 mg/dL or 176.8 μmol/L
   f) Aspartate aminotransferase (AST) ≤ 2.5 × upper limit of normal (ULN); ≤ 5 × ULN for patients with liver metastasis; < 3 × ULN for patients in Part C (vemurafenib + CX-072). No upper limit for patients with hepatocellular carcinoma (HCC) or pancreatic cancer.
   g) Alanine aminotransferase (ALT) ≤ 2.5 × ULN; ≤ 5 × ULN for patients with liver metastasis; < 3 × ULN for patients in Part C (vemurafenib + CX-072). No ULN for patients with HCC or pancreatic cancer.
   h) Total bilirubin within ULN (unless diagnosed with Gilbert's syndrome; those patients must have had a total bilirubin < 3.0 mg/dL or 51.3 μmol/L). No upper limit for patients with HCC.
   i) Amylase and lipase ≤ 1.5 × ULN. No upper limit for patients with pancreatic cancer.
8. Women of childbearing potential and males must have agreed to use a highly effective method of contraception (details provided in Appendix 5 of Module CTMX-M-072-001) prior to study entry, while on study drug, and for a period of 105 days following the last treatment and for 180 days if receiving vemurafenib.
   a) Highly effective methods of contraception that result in a low failure rate (ie, < 1% per year) when used consistently and correctly included implants, injectables, combined hormonal contraceptives, some intrauterine devices, sexual abstinence, or a vasectomized partner.
      i) Combined hormonal contraceptives were not a highly effective method of contraception for patients taking vemurafenib in Part C.

ii) True abstinence, when in line with the preferred and usual lifestyle of the patient, was considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal were not acceptable methods of contraception).

9. The ability to understand and the willingness to sign a written informed consent form (ICF) and adhere to study schedule and prohibitions

Inclusion Criteria for the LTE:

1. Previously participated in Study CTMX-M-072-001
2. Actively receiving CX-072 monotherapy; patients must have been assessed by the Investigator as still receiving clinical benefit from CX-072 in Study CTMX-M-072-001 without unacceptable toxicity
3. Demonstrated compliance as assessed by the Investigator during Study CTMX-M-072-001.
4. Women of childbearing potential and males must have agreed to use a highly effective method of contraception (details provided in Appendix 5 of Module CTMX-M-072-001) prior to study entry, while taking study drug, and for a period of 105 days following the last treatment.
5. Written informed consent must have been obtained prior to enrolling in the LTE.

Patients who fulfilled any of the following criteria at screening were not eligible for admission:

Exclusion Criteria for Parts A through D:

1. Prior therapy with a chimeric antigen receptor (CAR) T-cell containing regimen
2. Baseline QTc was > 470 ms or taking any medication known to prolong the QT interval
3. Prior history of myocarditis irrespective of the cause
4. Treatment with strong cytochrome P450 (CYP) 3A4 inhibitors or inducers, as well as use of CYP1A2 substrates with a narrow therapeutic window assigned to the vemurafenib treatment arm. http://medicine.iupui.edu/clinpharm/ddis/main-table/
5. History of severe allergic or anaphylactic reactions to human mAb therapy or known hypersensitivity to any Probody therapeutic
6. Active or history of uveal, mucosal, or ocular melanoma is excluded in Parts B2 and C
7. History of interstitial lung disease for patients with TET
   a) Patients with TET were excluded in Parts B1 and B2.
8. Human immunodeficiency virus (HIV) or AIDS-related illness, acute or chronic hepatitis B or C; patients with HIV that had an undetectable viral load and a CD4 cell count > 400/mL and who remained on antiretroviral regimen were eligible for enrollment into anal SCC cohorts in Parts D and E and hTMB cohort in Part D
9. History of or current active autoimmune diseases, including but not limited to inflammatory bowel diseases, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, systemic sclerosis, systemic lupus erythematosus, autoimmune vasculitis, autoimmune neuropathies, type 1 insulin dependent diabetes mellitus, or myasthenia gravis
10. History of syndrome or medical condition(s) that required systemic steroids (> 10 mg daily prednisone equivalents) or immunosuppressive medications
11. History of allogeneic tissue/solid organ transplant, prior stem cell or bone marrow transplant
12. Chemotherapy, biochemotherapy, or immunotherapy or any investigational treatment within 14 days prior to receiving any study drug; radiation therapy within 3 months prior to receiving study medication (except for radiotherapy for the purposes of palliation confined to a single field that is not the target lesion)
13. Patients in Part C could not have a glomerular filtration rate < 60 mL/min/1.73 m^2.
14. Major surgery (requiring general anesthesia) within 3 months, or minor surgery (excluding biopsies conducted with local/topical anesthesia), or gamma knife treatment within 14 days (with adequate healing)

of administration of any study drug

15. Unresolved acute toxicity of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 Grade > 1 (or baseline, whichever was greater) that may have put the patient at high risk under the current treatment. Alopecia and other nonacute toxicities were acceptable.
16. History of malignancy that was active within the previous 2 years except for localized cancers that were not related to the current cancer being treated and considered to have been cured and, in the opinion of the Investigator, presented a low risk for recurrence. These exceptions included, but are not limited to, basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
17. Received a live vaccine within 30 days prior to first dose of study drug
18. Known pre-existing condition of age-related macular degeneration
19. Intercurrent illness, including but not limited to symptomatic congestive heart failure (ie, New York Heart Association Class III or IV), unstable angina pectoris, clinically significant and uncontrolled cardiac arrhythmia, nonhealing wound or ulcer, or psychiatric illness/social situations that would limit compliance with study requirements
20. Pleural effusion, pericardial effusion, or recurrent ascites drainage
21. Ongoing or active infection (including fever within 48 hours of screening)
22. Participation in an ongoing clinical study involving treatment with medications, radiation, or surgery
23. Women who were pregnant or breastfeeding

Test Product, Dose and Mode of Administration, Batch Number:

CX-072 was supplied as a sterile, preservative-free solution in 100-mg vials at a concentration of 10 mg/mL. CX-072 was administered by slow IV push over 3 to 5 minutes at the dose of 0.03 mg/kg and by IV infusion over 60 minutes for doses of 0.1, 0.3, 1, 3, and 10 mg/kg. The 30 mg/kg infusion of CX-072 was administered at ≥ 90 minutes to comply with regulatory guidelines for endotoxin limit for parenteral drugs. Administration of the 0.03 and 0.1 mg/kg dose levels were limited to sites in the United States.

Batch number(s): See Appendix 16.1.6.

Statistical Methods:

The safety analysis population included all enrolled patients who received at least 1 dose of study drug. The safety analysis population was used for evaluating patient characteristics, treatment administration, and safety endpoints.

The response-evaluable population (REP) included all patients in the safety analysis population who had an adequate (ie, evaluable) baseline disease assessment. The REP was used for efficacy analyses related to objective response, including ORR, TTR, and DOR. The response-evaluable population with postbaseline assessment (REP-PBDA) included all patients in the REP who had an adequate disease assessment at baseline and at least 1 postbaseline assessment. The REP-PBDA was used for efficacy sensitivity analyses related to objective response.

Data were tabulated by dose level. Data were analyzed using SAS (v 9.4 or higher) and presented in tables, figures, or listings. Categorical data were summarized in contingency tables presenting frequencies and percentages. Continuous data were summarized using number of non-missing values (n), mean, median, standard deviation, and median and range values. Where relevant, the first quartile (Q1) and third quartile (Q3) were presented.

The primary efficacy endpoint was ORR, defined as the proportion of patients with complete response (CR) or partial response (PR) based on the RECIST v1.1 on 2 consecutive tumor assessments with scan dates at least 4 weeks apart. For lymphomas, objective response was evaluated by Modified Cheson/Lugano Classification for Lymphomas. The primary efficacy analysis was based upon the REP. A pooled estimate of ORR was computed from patients allocated to Parts A and A2. In addition, ORR estimates were determined for each tumor type represented in Part D. Exact 95% confidence intervals for ORR were derived via the Clopper-Pearson method. A listing of tumor data including total tumor burden, RECIST v1.1 response assessments (target lesion evaluation, non-target lesion evaluation, and overall patient response), overall tumor response per irRECIST response, and overall lymphoma response were provided.

A Safety Review Committee and a Data Safety Monitoring Board were established for the study.

Safety Results:

A total of 196 patients with metastatic or locally advanced unresectable solid tumors or lymphomas received CX-072 monotherapy (151 patients), or CX-072 in combination with ipilimumab (34 patients) or vemurafenib (11 patients).

In general, there were no significant trends in safety observed across the CX-072 monotherapy dose levels. CX072 was tolerated in patients administered doses up to 30 mg/kg, and an MTD was not reached in this study. In patients receiving CX-072 monotherapy, the most common overall treatment-related adverse events (TRAEs) were infusion-related reaction (20.8%) and fatigue (15.1%) in the dose-finding phase (Parts A and A2) and fatigue and AST increased (15.3% each) and ALT increased (12.2%) in the escalation phase (Part D). A total of 21 (39.6%) patients in Parts A and A2 experienced at least 1 serious treatment-emergent adverse event (TEAE), and 6 (11.3%) patients discontinued treatment with CX-072 due to TEAEs. Three patients in Parts A and A2 had Grade ≥ 3 immune-related adverse events (irAEs; febrile neutropenia and thrombocytopenia, ALT increased, AST increased, and pneumonitis). A total of 33 (33.7%) patients in Part D experienced at least 1 serious TEAE, and 2 (1.8%) patients discontinued treatment with CX-072 due to TEAEs. Three patients in Part D had Grade ≥ 3 irAEs (myocarditis, immune-mediated pneumonitis, and rash maculo-papular). There were no TEAEs leading to death in patients who received CX-072 monotherapy. The recommended Phase 2 dose (RP2D) for CX-072 monotherapy was determined to be 10 mg/kg every 14 days.

Prior to a protocol amendment mandating a maximum ipilimumab dose of 6 mg/kg, 1 patient received 10 mg/kg. Of the 34 patients enrolled in the ipilimumab combination therapy dose-escalation phase, the most frequent TRAEs were pruritus (37.0%) and nausea (33.0%) in Part B1 and diarrhea, fatigue, nausea, and vomiting (28.6% each) in Part B2. A total of 13 (48.1%) patients in Part B1 experienced at least 1 serious TEAE, and 3 (11.1%) patients discontinued treatment with CX-072 due to TEAEs. Six patients in Part B1 had 7 Grade ≥ 3 irAEs (colitis [2 events], pneumonitis, transaminases increased, Guillain-Barré syndrome, diarrhea, and neutropenia). A total of 3 (42.9%) patients in Part B2 experienced at least 1 serious TEAE, and 1 (14.3%) patient discontinued treatment with CX-072 due to a TEAE. One patient in Part B2 had a Grade ≥ 3 irAE (colitis). There were no TEAEs leading to death in patients receiving CX-072 plus ipilimumab. The MTD and RP2D for this combination was 10 mg/kg of CX-072 plus 3 mg/kg of ipilimumab every 3 weeks (Q3W).

Of the 11 patients treated with the combination of CX-072 and vemurafenib (Part C), the most common TRAEs were rash (63.3%) and anemia and blood bilirubin increased (45.4% each). A total of 8 (72.7%) patients in Part C experienced at least 1 serious TEAE, and 5 (45.4%) patients discontinued treatment with CX-072 due to a TEAE. There were no Grade ≥ 3 irAEs in Part C, and 2 patients had TEAEs leading to death (metastases to meninges and cardiopulmonary failure).

No clinically meaningful changes in hematology, blood chemistry, coagulation, thyroid, urinalysis, or liver toxicity were observed during the conduct of this trial. The collected ECG data did not raise any cardiovascular safety concerns.

Fifteen patients from the main study chose to enroll in the LTE, in which they continued to receive treatment for up to 1 additional year. In these patients, no significant differences in safety signals were observed when compared to the safety profile of patients in the main study.

Efficacy Results:

Of the 114 patients in the REP who received CX-072 at the RP2D of 10 mg/kg, 3 (2.6%) had CR and 11 (9.6%) had PR, leading to an ORR of 14/114 (12.3%). When differentiated by cancer type, ORR was 35.7% for cSCC, 28.6% for hTMB, 13.3% for anal SCC, 6.7% for TNBC, 5.0% for UPS, and 0% for SBA and TET. One PR was observed in the dose-escalation phase in a patient with anaplastic thyroid cancer who received 10 mg/kg of CX-072. No responses were observed in patients in the other dose-level groups.

The median DOR in the 14 patients with confirmed CR/PR was 16.7 months (range, 9-24 months). Among the 14 patients with objective responses, 10 continued CX-072 treatment via the LTE portion of the study.

The median PFS for patients who received 10 mg/kg of CX-072 in Parts A, A2, and D was 2.0 months. The median OS for patients who received 10 mg/kg of CX-072 in Parts A, A2, and D was 9.9 months.

Conclusions:

CX-072 is designed to restrict the inhibition of PD-L1 to the tumor microenvironment and potentially reduce off-tumor toxicity related to PD-L1 inhibition. This was a Phase 1, FIH, dose-finding, dose-escalation study with the purpose of determining appropriate dosing and evaluating safety, tolerability, and efficacy of CX-072 monotherapy and combination therapy with ipilimumab and vemurafenib in previously treated patients with various advanced, unresectable solid tumors. Overall, CX-072 was well tolerated in this study and demonstrated a manageable safety profile, which is consistent with other PD-L1 or PD-1 inhibitors.

In this study, an MTD for monotherapy CX-072 was not reached in doses up to 30 mg/kg. Overall, there were significant trends in safety observed across the CX-072 monotherapy dose levels. Because of the preliminary antitumor efficacy and similar tolerability across dose levels in Parts A and A2, 10 mg/kg of CX-072, the determined RP2D, was chosen for further investigation as monotherapy in the dose-expansion phase (Part D) and was the dose level of interest in combination therapy. At this dose, CX-072 demonstrated a low rate of immune-mediated toxicity and showed signs of antitumor activity, with an ORR of 12.3% and a disease control rate of 42.1%. Additionally, the PK of CX-072 analytes has been evaluated following IV administration of CX-072 administered as monotherapy 0.03 to 30 mg/kg CX-2009 every 2 weeks (Q2W), the geometric mean (GM) clearance (CL) and volume of distribution at steady state (V_{ss}) for intact CX-072 ranged from 0.278 to 0.690 L/day and 1.87 to 3.95 L, respectively, with no monotonic trending of either CL or V_{ss} over this dose range. The arithmetic mean terminal half-life ($t_{1/2}$) of intact CX-072 ranged from 4.41 to 6.00 days; the GM of intra-individual intact CX-072 to total CX-072 ratios for the area under the plasma concentration-time curve evaluated until end of dosing interval ($AUC_{0\text{-}tau}$) and the maximum plasma concentration (C_{max}) following the first dose, 0.03 mg/kg to 30 mg/kg Q2W, ranged from 0.662 to 1.00 and 0.936 to 1.05, respectively. There appeared to be approximately dose-proportional increases in AUC0-tau and C_{max} following the first dose of CX-072, 0.03 mg/kg to 30 mg/kg Q2W.

When CX-072 was combined with ipilimumab (Parts B1 and B2), there were no treatment-related deaths, and no new safety signals were identified. -The MTD and RP2D for the CX-072 and ipilimumab combination was determined to be 10 mg/kg of CX-072 plus 3 mg/kg of ipilimumab every 3 weeks (Q3W).

Unlike CX-072 monotherapy and combination doses with ipilimumab, for patients treated with CX-072 in combination with vemurafenib, there were no Grade ≥ 3 irAEs, and 2 patients had TEAEs leading to death (metastases to meninges and cardiopulmonary failure). However, it is difficult to draw any substantial conclusions because the patient sample size was very small (N=11).

Probody therapeutics have the potential to improve the safety and tolerability of immune therapies in patients with cancer. The results of this study indicate that monotherapy does of CX-072 were well tolerated with limited off-tumor toxicity in comparison to other anti–PD-1/PD-L1 inhibiters. Moreover, CX-072 in combination with ipilimumab could provide a more favorable safety profile than traditional CTLA-4 and PD-1/PD-L1 combination therapies. The data support further clinical investigation of CX-072 in combination with other immune checkpoint inhibitors or targeted therapies.

Date of Report: 14 Nov 2022