CTMX-M-2009-001

Statistical Analysis Plan

A Phase 1-2, Open-Label, Dose-Finding, Proof of Concept, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CX-2009 in Adults With Metastatic or Locally Advanced Unresectable Solid Tumors (PROCLAIM-CX-2009)

NCT# NCT03149549

07/October/2020

Statistical Analysis Plan

SPONSOR:	CytomX Therapeutics, Inc.
PROTOCOL TITLE:	A Phase 1-2, Open-Label, Dose-Finding, Proof of Concept, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CX-2009 in Adults with Metastatic or Locally Advanced Unresectable Solid Tumors
STUDY CODE:	CTMX-M-2009-001
VERSION:	2.0 (07OCT2020)

The undersigned certify that they have read, reviewed and approved this document.

Authors (IDDI): Michael Hussey, DrPH - Managing Director, IDDI Inc.

DocuSigned by:
Michael Hussey
Signer Name: Michael Hussey
Signing Reason: I approve this document
Signing Time: 09-Oct-2020 | 8:26 PM CEST
080C12B1CE9A4DF1BC5FA7D8449E6400

CytomX Representative: Claire Sherman, Executive Director, Biostatistics

DocuSigned by:
Claire Sherman
Signer Name: Claire Sherman
Signing Reason: I approve this document
Signing Time: 09-Oct-2020 | 12:42 PM PDT
9F7FC361DE48490E84418F0C42670BC8

Table of Contents

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DOR	duration of response
DSMB	data and safety monitoring board
ECG	electrocardiogram
FDA	Food and Drug Administration
ICF	informed consent form
IR	infusion reaction
IV	intravenous
IWRS	interactive web response system
MedDRA	medical dictionary for regulatory activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
q 21 days	every 21 days
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
REP	response evaluable population
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD	stable disease
SOC	system organ class
SP	safety population
SRC	safety review committee
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TMTB	total measured tumor burden
TTR	time to response
WHODrug	World Health Organization Drug Dictionary

1. Purpose

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling for CytomX Therapeutics, Inc. protocol module number CTMX-M-2009-001 (A Phase 1-2, Open-Label, Dose-Finding, Proof of Concept, First-in-Human Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CX-2009 in Adults with Metastatic or Locally Advanced Unresectable Solid Tumors). The analysis specified in this SAP will be used to support safety review committee (SRC) and data and safety monitoring board (DSMB) analyses, publications, and FDA submissions. The proposed analyses may not be carried out if the sample size is not adequate.

The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

This SAP is based on the following study documents:

- Protocol Core Amendment 01, 11 November 2016
- Protocol Module Amendment 06, 09 August 2017,
- Protocol Substudy V1.0, 04 May 2018
- Annotated Case Report Forms

The enrollment in CTMX-M-2009-001 was stopped by sponsor decision as of 07 July 2020, with a final enrollment of XX subjects into Parts A, A2, B, and C1.

2. Study Population

This study of CX-2009 will enroll adult subjects with advanced solid tumors in the following indications: breast carcinoma (BC), castration-resistant prostate carcinoma (CRPC), non-small cell lung carcinoma (NSCLC), epithelial ovarian carcinoma (eOC), endometrial carcinoma (EC), head and neck squamous cell carcinoma (HNSCC), or cholangiocarcinoma (CCC). These 7 tumor types have been selected for their known high levels of CD166 expression and sensitivity to MTIs. Prior to the decision to stop enrolment in the study, approximately 563 subjects were planned to be enrolled into the study. Inclusion and exclusion criteria are detailed in Sections 4.1 and 4.2 of the protocol.

3. Study Objectives

The study objectives as per the protocol are presented below.

3.1 Primary Objectives

Part A – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The primary objective of Part A is to determine the safety profile of CX-2009, the MTD/RP2D, and the DLTs of CX-2009 when administered intravenously (IV) every 21 days as monotherapy to subjects with selected advanced or recurrent solid tumors.

Part A2 – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The primary objectives of Part A2 are to determine the following in subjects treated with CX-2009 every 21 days:

- Characterize the protease activity and measure the cleavage of CX-2009 in tumor biopsies and peripheral blood in subjects with demonstrated high tumor expression of CD166 by IHC; and

- Obtain additional characterization of the safety CX-2009 when administered as monotherapy at dose levels evaluated in Part A.

Part B – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The primary objective of Part B is to evaluate the efficacy of CX-2009 when administered IV every 21 days as monotherapy at the MTD/RP2D (as defined in consideration of available data from Part A and Part A2) in subjects with selected advanced or recurrent solid tumors with demonstrated high tumor expression of CD166 by IHC. Efficacy will be assessed on the basis of the ORR by the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1.

Part C1 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The primary objective of Part C1 is to determine the safety profile of CX-2009, the MTD/RP2D, and the DLTs of CX-2009 when administered IV every 14 days as monotherapy to subjects with selected advanced or recurrent solid tumors with demonstrated high expression of CD166 by IHC.

3.2 Secondary Objectives

Part A – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The secondary objectives of Part A are to determine the following in subjects treated with CX-2009 every 21 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 as monotherapy on the basis of:
  - ORR by the RECIST Version 1.1;
  - Time to tumor response (TTR);
  - Duration of response (DOR);
  - Progression-free survival (PFS); and
  - Overall survival (OS);

- Characterize the pharmacokinetics (PK) of CX-2009 including the following analytes:
  - Intact CX-2009 (referring to the prodrug form of CX-2009 ± DM4);
  - Total CX-2009 (intact and activated forms of CX-2009 ±DM4);
  - Total CX-2009-conjugated DM4 (antibody conjugated-DM4);
  - Free DM4;
  - DM4-Me – a DM4 metabolite with potent cytotoxic activity; and

- Assess the incidence antidrug antibody (ADA) formation to CX-2009.

Part A2 – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The secondary objectives of Part A2 are to determine the following in subjects with demonstrated high tumor expression of CD166 and treated with CX-2009 every 21 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 as monotherapy on the basis of:
  - ORR by the RECIST Version 1.1;
  - TTR;
  - DOR;
  - PFS; and
  - OS;

- Characterize the PK of CX-2009 including the following analytes:
  - Intact CX-2009 (referring to the prodrug form of CX-2009 ± DM4);
  - Total CX-2009 (intact and activated forms of CX-2009 ±DM4);
  - Total CX-2009-conjugated DM4 (antibody conjugated-DM4);
  - Free DM4;
  - DM4-Me; and
- Assess the incidence ADA formation to CX-2009.

Part B – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The secondary objectives of Part B are to determine the following in subjects with demonstrated high tumor expression of CD166 and treated with CX-2009 every 21 days:

- Obtain additional characterization of the safety of CX-2009 at the MTD/RP2D;
- Evaluate efficacy in subjects treated with CX-2009 as monotherapy on the basis of:
  - DOR;
  - TTR;
  - PFS; and
  - OS;

- Characterize the PK of CX-2009 with respect to the following analytes:
  - Intact CX-2009 (referring to the prodrug form of CX-2009 ± DM4);
  - Total CX-2009 (intact and activated forms of CX-2009 ±DM4);
  - Total CX-2009-conjugated DM4 (antibody conjugated-DM4);
  - Free DM4;
  - DM4-Me; and
- Assess the incidence ADA formation to CX-2009.

Part C1 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The secondary objectives of Part C1 are to determine the following in subjects with demonstrated high tumor expression of CD166 and treated with CX-2009 every 14 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 as monotherapy on the basis of:
  - ORR by the RECIST Version 1.1;
  - TTR;
  - DOR;
  - PFS; and
  - OS;

- Characterize the PK of CX-2009 with respect to the following analytes:
  - Intact CX-2009 (referring to the prodrug form of CX-2009 ± DM4);
  - Total CX-2009 (intact and activated forms of CX-2009 ±DM4);
  - Total CX-2009-conjugated DM4 (antibody conjugated-DM4);
  - Free DM4;
  - DM4-Me; and
- Assess the incidence ADA formation to CX-2009.

3.3 Exploratory Objectives

Part A – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The exploratory objectives of Part A are to determine the following in subjects treated with CX-2009 every 21 days:

- Explore potential predictive markers associated with CX-2009 clinical activity such as CD166 expression in tumor specimens prior to and while receiving treatment; and
- Characterize the protease activity in optional pretreatment tumor biopsies and activation of CX-2009 in optional on-treatment tumor biopsies and peripheral blood.

Part A2 – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The exploratory objectives of Part A2 are to determine the following in subjects treated with CX-2009 every 21 days:

- Evaluate the relationship between CX-2009 dose and exposure, exploratory biomarkers, safety, and efficacy of CX-2009 as monotherapy in subjects with selected advanced or recurrent solid tumors with demonstrated high tumor expression of CD166; and
- Explore potential predictive markers associated with CX-2009 clinical activity such as CD166 expression in tumor specimens from subjects with demonstrated high tumor expression of CD166 while receiving treatment.

Part B – CX-2009 Monotherapy: Every 21-Day Dosing Regimen

The exploratory objectives of Part B are to determine the following in subjects treated with CX-2009 every 21 days:

- Explore potential predictive markers associated with CX-2009 clinical activity such as CD166 expression in tumor specimens prior to and while receiving treatment from subjects with demonstrated high tumor expression of CD166;
- Measure the intact and activated CX-2009 in on-treatment tumor biopsies and peripheral blood; and
- Characterize the protease activity in pretreatment tumor biopsies.

Part C1 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The exploratory objectives of Part C1 are to determine the following in subjects treated with CX-2009 every 14 days:

- Explore potential predictive markers associated with CX-2009 clinical activity such as CD166 expression in tumor specimens prior to and while receiving treatment; and
- Characterize the activation of CX-2009 in optional on-treatment tumor biopsies and peripheral blood.

4. Study Methods

4.1 Overview of Study Design

This is a Phase 1-2, open-label, multicenter, dose-finding, and proof of concept study for CX-2009 as monotherapy in subjects with advanced solid tumors in selected indications.

The study (as of Protocol Amendment 06) has 7 parts, as described below (Figure 1). Since the enrollment ended after Parts A, A2, B, and C1, the description is limited to those parts.

Part A: Dose escalation and determination of MTD/RP2D of the CX-2009 monotherapy every 21-day dosing regimen (n≤79: based on actual enrollment of initial cohorts and assumption of remaining cohorts and up to 38 total subjects enrolled into the mTPI-2 design cohort): This part will initiate with accelerated dose titration in 1 single-subject cohort (0.25 mg/kg [mpk], adjusted ideal body weight [AIBW]), followed by a standard 3+3 design to determine the MTD, and end in a mTPI-2 design cohort with up to 38 subjects with demonstrated high CD166 expression to determine the RP2D. The mTPI-2 design is a rule-based design similar to the 3+3 design and allows dose escalation/de-escalation. It is assumed to be of similar accuracy in determining the optimal dose as model-based design (Ji et al, 2007) but allows a more flexible sample size. To understand the statistical rationale for the design, please refer to Section 9 and Appendix C of the CTMX-M-2009-001 Protocol Module.

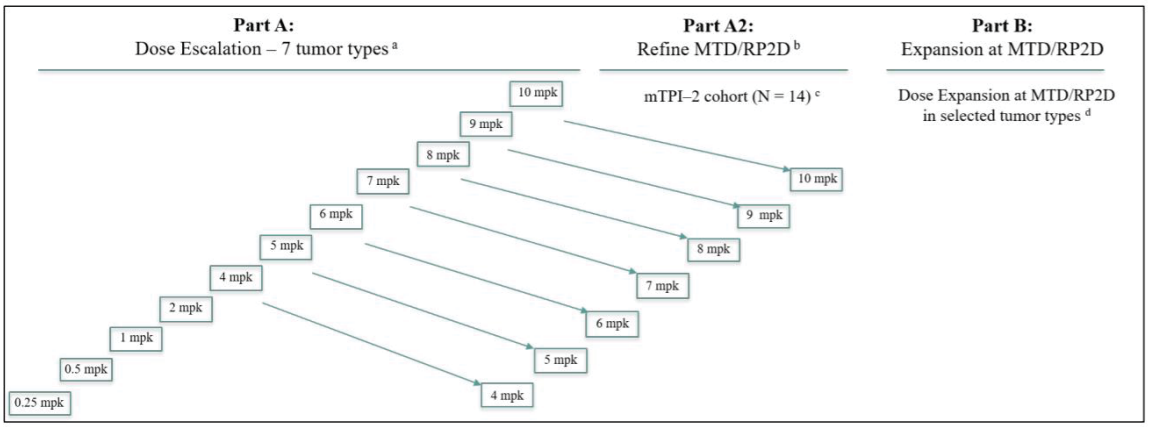
Part A2: Additional enrollment into previously cleared CX-2009 monotherapy dose levels from Part A (n≤42) for every 21-day dosing regimen: This part will help inform selection of the optimal MTD/RP2D by requiring measurable disease, mandating biopsies to assess Probody therapeutic CX-2009 performance, and selecting for confirmed high CD166 expressing tumors by IHC. Additionally, the relationship between dose/exposure and safety as well as antitumor activity will further enhance MTD/RP2D selection by including more subjects for safety evaluation and selecting for confirmed high CD166 expression in tumors by IHC in Part A2. Part A2 will interrogate dose levels beginning at 4 mg/kg and up to the MTD/RP2D determined in Part A. The expression of CD166 will be evaluated on archival samples using a Clinical Laboratory Improvement Amendments of 1998 (CLIA)-validated IHC assay.

Part B: Dose expansion (proof of concept) at the MTD/RP2D of CX-2009 monotherapy every 21-day dosing regimen with proof of concept in selected tumor types (maximum n≤200): This part will explore efficacy of CX-2009 by requiring measurable disease and selecting for confirmed high CD166 expressing tumors. Part B will enroll up to a total of 40 subjects in each of 1 or more of the 5 tumor types listed in Table 4 in the CTMX-M-2009-001 Protocol Module. Part B will only be initiated if, after the review of dose escalation data (Parts A and A2), an every 21-day dosing regimen is considered for further development.

Part C1: Dose escalation and determination of the MTD/RP2D of the CX-2009 monotherapy every 14-day dosing regimen in subjects with high CD166 expression (n≤18): The highest dose level tested in this clinical study for CX-2009 was 10 mg/kg administered every 21 days, which successfully cleared the DLT evaluation period. The every 14-day dosing regimen equivalent of 10 mg/kg administered every 21 days is ≥7 mg/kg. In order to provide an additional margin of safety coverage for Part C1, the starting dose will be 6 mg/kg, AIBW, administered every 14 days. The mTPI-2 design will be used to determine the MTD/RP2D for this schedule. The following cohort's dose will be increased according to the defined dose escalation

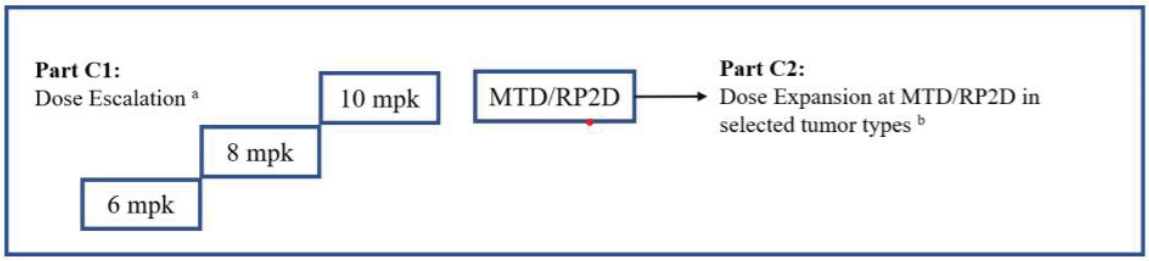
rules to 8 mg/kg and then to 10 mg/kg based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6 from the CTMX-M-2009-001 Protocol Module). The maximum dose level that will be tested in Part C1 will be 10 mg/kg. Part C1 will include up to 18 subjects. Subjects will be selected from the following indications: BC, NSCLC, or HNSCC.

Figure 1: Study Design Schema: Parts A, A2, and B (every 21-day Dosing Regimen)



[a] Part A eligible tumor types: BC, CRPC, NSCLC, OEC, EC, HNSCC, and CCC.
[b] Part A2 restricted to subjects with BC, NSCLC, OEC, EC, and HNSCC.
[c] Part A mTPI-2 cohort eligible tumor types: BC, NSCLC, and HNSCC.
[d] Part B eligible tumor types: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, and HNSCC.
Note: Parts A (mTPI-2 cohort only), A2, and B will enroll subjects with confirmed high CD166 expressing tumors.
BC = breast cancer; CCC = cholangiocellular carcinoma; CRPC = castrate-resistant prostate carcinoma; EC = endometrial carcinoma; HER2 = human epidermal growth factor receptor 2; HNSCC = head and neck squamous cell carcinoma; HR = hormone receptor (ie, estrogen and/or progesterone); mpk = mg/kg; MTD = maximum tolerated dose; mTPI-2 = modified toxicity probability interval 2; NSCLC = non-small cell lung carcinoma; OEC = ovarian epithelial cancer; RP2D = recommended Phase 2 dose; TNBC = triple negative breast cancer.

Figure 2: Study Design Schema: Parts C1 and C2 (every 14-day Dosing Regimen)



a Part C1 eligible tumor types: BC, NSCLC, and HNSCC.
b Part C2 eligible tumor types: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, and HNSCC.
Note: Parts C1 and C2 will enroll subjects with confirmed high CD166 expressing tumors.
BC = breast cancer; OEC = ovarian epithelial cancer; HER2 = human epidermal growth factor receptor 2; HNSCC = head and neck squamous cell carcinoma; HR = hormone receptor (ie, estrogen and/or progesterone); NSCLC = non-small cell lung carcinoma; mpk = milligram per kilogram; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; TNBC = triple negative breast cancer.

4.2 Subject Eligibility and Enrollment

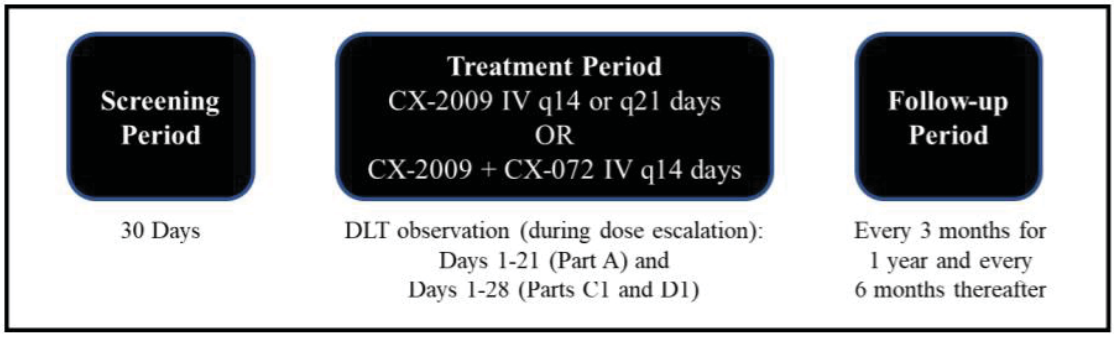
At the time of the sponsor decision to stop enrollment into the study, there were 99 subjects enrolled and treated in the study: 37 in Part A, 39 in Part A2, 10 in the mTPI-2 cohort, 3 in Part B, and 10 in Part C1.

4.3 Study Periods and Follow-Up

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points. The schedule of procedures in Appendix B of the CTMX-M-2009-001 Protocol Module summarizes the frequency and timing of efficacy, safety, and other study measurements. Refer to the Common Core Document for a description of each procedure.

As with any Phase 1 study, an individual subject's participation in the study is difficult to predict. It is estimated that average treatment will last approximately 6 months, followed by Follow-Up contact every 3 to 6 months for another 1 to 2 years, or as long as the subject remains alive (Figure 3).

Figure 3: Study Periods



Notes: An EOT Visit will be conducted 30 days (±7 days) after the last infusion of study treatment. Follow-Up: If subject has not had progression, imaging assessments will continue until progression is documented. If subject had documented progression, the subject will continue in survival Follow-Up Visits every 3 months (±14 days) after the EOT Visit for 1 year and then every 6 months (±14 days) (this may be by telephone), or until death. Subsequent cancer treatment will be collected. Survival Follow-Up will be done every 3 months (±14 days) as described above.
DLT = dose-limiting toxicity; EOT = end of treatment; IV = intravenous; q14 = every 14; q21 = every 21.

Following the completion of study treatment, subjects with progressive disease per RECIST v1.1 as measured by investigator assessment, will return for an end of treatment (EOT) Visit and then enter the Follow-Up Period for monitoring of survival. Subjects who for other reasons stop study drug treatment and subjects with stable disease, confirmed partial response, or confirmed complete response will enter the Follow-Up Period for monitoring of DOR and PFS.

The study will be completed approximately 2 years from the date the last subject is enrolled or when the last subject has completed treatment and the last Follow-Up Visit.

The EOT Visit will be conducted 30 days (±7 days) after the last infusion of CX-2009. Once a subject experiences progressive disease, they will continue to be monitored for survival. All subjects will return for Follow-Up Visits every 3 months after the EOT Visit for 1 year and then every 6 months to ensure resolution of toxicities and as applicable, confirm negative pregnancy status. During the EOT Visit, subjects will be followed for resolution of toxicity. Women of childbearing potential will undergo monthly pregnancy testing while on study drug and through 50 days after the last dose of CX-2009, or 6 months after the last dose of CX-072, as applicable, whichever is later. Thereafter, Follow-Up Visits will be conducted for survival information and may be performed by telephone.

4.4 Administration of the study drug

Treatment will be administered on an outpatient basis, with inpatient admission as needed for any treatment or monitoring outside of clinic hours or for management of significant acute toxicity.

CX-2009 will be administered at a dosage of 0.25, 0.5, 1, 2, 4, 5, 6, 7, 8, 9, 10 mg/kg/dose (Adjusted Ideal Body Weight should be applied [Appendix F of the CTMX-M-2009-001 Protocol Module]).

4.5 Discontinuation of Subjects from Treatment

Subject MUST discontinue the study drug for any of the following reasons:

- The subject experiences clinically significant or confirmed (RECIST v1.1) disease progression (or irRECIST in Parts D1 and D2);
- The subject is unwilling or unable to adhere to the Module;
- The subject withdraws consent or is lost to follow-up;
- The subject experiences an intercurrent illness that prevents further administration of study drug;
- The subject requires new/other anti-cancer treatment;
- The subject experiences a DLT or an adverse event related to study drug which precludes further administration of the study drug;
- The subject experiences a prolonged treatment delay (as defined in Section 5.5.4 of the CTMX-M-2009-001 Protocol Module);
- The subject becomes pregnant, either prior to the first dose of study drug or at any time during treatment;
- In the Investigator's judgment, the subject should discontinue treatment;
- Death of the subject; or
- The Sponsor terminates the study.

Subjects who discontinue study drug administration, for reasons other than TRAEs, may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled. Subjects who have enrolled in the study and have withdrawn prior to receiving the first dose will be designated as screen failures. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

5. Study Endpoints

5.1.1 Primary Safety Domains

Incidence and nature of DLTs, adverse events, serious adverse events, and adverse events of special interest, as well as physical examinations, vital sign measurements, triplicate electrocardiograms, clinical laboratory evaluations, and treatment discontinuation due to toxicity will be evaluated for safety assessment.

5.1.2 Primary Efficacy Endpoint

The primary criteria for defining evidence of anti-cancer activity and also for management of subject care will be a clinical response as defined by RECIST (Version 1.1). ORR is the primary efficacy endpoint and ORR is defined as the proportion of subjects with complete response (CR) or partial response (PR) on two consecutive tumor assessments at least 4 weeks apart according to RECIST (RECIST v1.1).

5.1.3 Secondary Efficacy

Efficacy in this study will be explored in subjects treated with CX-2009 as monotherapy on the basis of:

- TTR;
- DOR;
- PFS; and
- OS.

6. Data Capture and Processing

Electronic data capture will be used for the study. Data will be recorded on source documentation at each study location and entered into the eCRF electronically by the study center personnel for each study subject. Data collected on each subject will be documented on the appropriate eCRF. Completed eCRFs are to be reviewed and electronically signed by the Investigator or his/her designee.

7. Analysis and Reporting

7.1 Interim Analyses

No formal interim analysis is planned.

Administrative interim analyses on safety and efficacy or on PK, immunogenicity, and selected biomarkers may be performed several times prior to completion of the study in order to facilitate program decisions and to support study presentations or publications.

7.1.1 Safety Review Committee (SRC)

A Safety Review Committee (SRC) has been established for the study. The SRC will consist of selected Investigators from the trial and representatives from CytomX who will review on a regular basis, approximately monthly, the cumulative safety data from each cohort in the study in order to:

- Approve dose escalation to the next cohort in Part A, Part A2, or Part C1 of the study;
- Recommend modifications to the dose or schedule as it pertains to subject safety; or
- Recommend modifications to the protocol related to subject oversight (e.g., additional safety monitoring, changes to inclusion/exclusion criteria).

The SRC will review safety data in conjunction with the Statistical and Medical Groups from CytomX.

7.1.2 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) has been established for the study. The DSMB will review table summaries and listings provided by IDDI in conjunction with the Statistical and Medical Groups from CytomX. Tables including, but not limited to, subject disposition, demographics and baseline characteristics, drug exposure, and AEs will be provided. Details on the DSMB are provided in Appendix D of the CTMX-M-2009-001 Protocol Module and in a separate DSMB charter. The DSMB will make recommendations to the Sponsor, who will make ultimate decisions regarding study alteration or discontinuation.

7.1.3 Final Analysis

Data summaries, figures, and listings will be prepared as identified in this SAP following database lock.

8. Sample Size Determination

Enrollment into the study was stopped by the sponsor with 99 subjects enrolled and treated across Parts A, A2, B, and C1. The previously planned sample size was a maximum of 563 subjects enrolled across Parts A, A2, B, C1, C2, D1, and D2. No subjects were enrolled in Parts C2, D1, or D2 for this study.

Refer to the CTMX-M-2009-001 Protocol Module for explanation on the original sample size calculation and statistical assumptions related to the design of the study.

9. Definition of Populations

Analysis populations for tabulations and figures are defined below for the following populations: safety analysis population (SP) and the response evaluable population (REP). Subject disposition will be based on the number of subjects providing signed informed consent.

9.1 Safety Analysis Population (SP)

The safety analysis population includes all enrolled subjects who receive at least one dose of study drug. The safety analysis population is used for evaluating subject characteristics, treatment administration, safety endpoints and efficacy analyses related to PFS and OS.

9.2 Response Evaluable Population (REP)

The response evaluable population includes all subjects in the safety analysis population who have an adequate baseline disease assessment and at least one post-baseline disease assessment. The response-evaluable population is used for efficacy analyses related to objective response, including objective response rate (ORR), TTR, and DOR.

10. General Statistical Considerations

10.1 General Statistical Methodology

Data will be analyzed using SAS (Version 9.4 or higher). All consented subjects are identified by an 8-digit Subject Number where the first four digits represent site and the last four digits are the sequential enrollment within a site (e.g. 1234-0001).

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, median, standard deviation, and median and range values. Where relevant, Q1 and Q3 may be presented.

The tables will be created by dose level and by cancer type, unless otherwise specified. For tables by dose level, all available data from Parts A, A2, and B will be pooled with ≤2 mg/kg presented as a single dose group and 4, 5, 6, 7, 8, 9, 10 mg/kg presented as separate dose groups; Part C1 dosing 4 mg/kg Q2W and 6

mg/kg Q2W will also be presented as separate dose groups. Data from planned, protocol-specified visits and unplanned visits will be included in listings, unless otherwise noted. Baseline tables will contain a total column when appropriate.

10.1.1 Handling of Missing Data

All data will be analyzed as they were collected in the database. Missing data, other than as described in Section 0, will not be imputed.

10.1.2 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for pre-specified and exploratory analyses. Additional computed variables may be required to aid in analysis.

Missing Date Components of AEs, Concomitant Medications (including Prior Cancer Treatments), and Medical History

Every attempt will be made to obtain complete dates for any AEs, CMs, and Medical History; however, in the case of incomplete dates, the missing Day, Month or Year will be represented in listings as "UN", "UNK" or "UNKN", respectively. Missing Hour or Minute in times will be represented as "UN".

Missing date components for AEs, CMs, and Medical History will not be imputed; however, AEs with incomplete start dates (and times, in the case of infusion-related reactions) will be attributed to treatment according to the following algorithm:

- Only the year is reported: If the year is after or the same as the day of the first dose, the event will be considered treatment-emergent.
- Only the month and year are reported: If the month is after or the same as the day of the first dose, event will be considered treatment-emergent.
- Only the time is missing: If the event occurred on or after the day of the first dose in the treatment period, then the event will be considered treatment-emergent.

Dates with missing day values will be imputed to the 15th of the month when calculating time since the last prior cancer regimen or procedure. If a date is missing both day and month values, then the date will not be imputed and the prior cancer regimen or procedure will not be considered for selection as the last.

Study Days Relative to First Infusion of Study Medication

Study Day 1 is the day of the first infusion of CX-2009 (for subjects enrolled only to the main CTMX-M-2009-001 study) or the day of the first treatment with Zr-CX-2009 (for subjects enrolled to the CTMX-M-2009-001 imaging substudy); negative Study Days occur prior to first infusion of study treatment; and positive Study Days are those after the first study treatment – e.g., Study Day -1 is the day immediately preceding the first study treatment, Study Day 2 is the day immediately following the first study treatment.

Time on Study

Time on study (months) is calculated as the study termination date minus the first infusion date (+1) – this value is divided by 30.4375 to obtain the time in months. If the study termination date is missing, the data cutoff date will be used.

Time Since Prior Regimens or Procedures

Time since prior regimens or procedures (weeks) is calculated as the first infusion date minus the end date of the last prior (relative to study) regimen or procedure (+1) – this value is divided by 7 to obtain the time in weeks. Regimen or procedure end dates will be imputed to the 15th of the month when only the month and year are reported. If only the year is reported, then end date will not be imputed and the regimen or procedure will not be eligible for selection as the last prior regimen or procedure.

Time Since Initial Histopathological Diagnosis

Time since initial histopathological diagnosis (years) is calculated as the date of informed consent minus the date of the initial histopathological diagnosis (+1) – this value is divided by 365.25 to obtain the time in years.

Time Since Most Recent Disease Recurrence/Progression

Time since most recent disease recurrence/progression (years) is calculated as the date of informed consent minus the date of the most recent disease recurrence/progression (+1) – this value is divided by 365.25 to obtain the time in years.

AEs with Missing Relationship

Every attempt will be made to obtain complete information for AEs regarding relationship(s); however, in the case of missing data:

- AEs with missing relationship designations will be considered "Related" to study treatment provided the AE onset date/time occurs on or after the initial dose of CX-2009 was initiated.

Duration of Treatment

Duration of treatment for CX-2009 will be derived by subtracting the start date of the first infusion from the stop date of the last infusion (+1) - this value is divided by 30.4375 to obtain the time in months.

Percent of Infusion

The percent of each dose received will be calculated using the following formula rounded to one decimal place:

$$\text{Percent of Dose} = \frac{\text{Total Dose of Study Medication Administered}}{\text{Total Planned Dose of Study Medication}} \times 100$$

Duration of Infusion (min)

Duration of infusion in minutes will be derived by subtracting the Infusion Start Time from the Infusion Stop Time.

Laboratory Values with < or > Inequality Symbols

Some continuous laboratory data include "<" or ">" symbols. Data will be presented in listings with their inequality symbol; however, for tabulation of summary statistics of safety laboratory results, the number associated with the inequality sign will be used for statistical calculations.

Definition of Baseline

Unless otherwise specified, a baseline measurement will be taken as the last non-missing value prior to the start of study treatment.

11. SUBJECT CHARACTERISTICS AND DEMOGRAPHICS

11.1 Enrollment and Disposition of Subjects

A summary table will include all subjects and present the total number of subjects consented, treated (including on treatment, off treatment, in follow-up, and off study), and in each analysis population. In addition, the number and percentage of the study treatment termination reasons and the study discontinuation reasons will be presented. The percentages will be based on the total number of subjects treated.

Subjects who discontinued the study 30 or fewer days from the last dose of study drug are considered to have discontinued the study during the treatment period. Subjects who discontinue the study more than 30 days after the last dose of study drug are considered to have discontinued the study while in follow-up.

11.2 Protocol Deviations

Protocol deviations will be listed for all subjects in the SP for whom deviations were reported. The listing will include the deviation classification (major or minor) as well as the deviation category.

11.3 Demographics and Baseline Characteristics

Descriptive statistics will be generated for all demographic and baseline characteristics by dose level and cancer type in order to descriptively assess the comparability of the cohorts. The variables to be summarized are:

Demographics -

- Age at enrollment,
- Date of Birth (listing only),
- Sex,
- Child-bearing potential,
- Race and
- Ethnicity

Baseline subject characteristics –

- Height (cm),
- Weight (kg),
- ECOG Performance Status, and
- Cigarette smoking history:
  - Current versus former smokers,
  - Years since last use,
  - Number of packs per day, and
  - Years of tobacco use.
- Subject cancer type and characterization:
  - Time since initial histopathological diagnosis (years),
  - Time since the most recent disease recurrent/progression (years),
  - Cancer type,
  - Stage at Study Entry,
  - CD166 Status at Baseline
  - Disease characterization (Locally Advanced unresectable, Metastatic),

    - Whether or not the disease is measureable,
- Subject prior cancer treatment:
    - Number of prior cancer treatment regimens per subject
    - Time since last prior cancer treatment end date (weeks)
    - Prior use of platinum-containing compounds (Yes/No)
    - Prior use of anti-PD-1/anti-PD-L1 treatment (Yes/No)
    - Prior use of any microtubule inhibitor (Yes/No)
    - Prior use of any platinum-containing compounds or microtubule inhibitor (Yes/No)
    - Prior radiotherapy (Yes/No)
    - Time since last prior cancer procedure (weeks)

Categories for platinum-containing compounds, anti-PD-1/anti-PD-L1 treatment, microtubule inhibitors will be based on a search list provided by CytomX prior to the database lock.

Other prior cancer treatment information including the regimen or procedure, treatment duration, best overall response, reason for therapy ended, and time since disease progression will be captured in a listing.

12. Safety and Tolerability Analysis

The primary objectives of the study is to evaluate the safety and tolerability of multiple doses of CX-2009, administered as monotherapy to subjects with advanced solid tumors and to determine the MTD and DLTs of CX-2009.

Safety will be assessed on the basis of AEs, clinical laboratory data, vital signs, ECG parameters, and physical examinations. Dosing and exposure to CX-2009 will be presented.

All safety data will be listed by subject within part and dose cohort in chronological order. Summary tabulations of safety data will be performed as noted in the following sections.

12.1 Adverse Events and Serious Adverse Events

Adverse events will be collected from start of treatment through the follow-up period. Serious adverse events occurring during the screening period will be collected on the Adverse Events form. All other AEs occurring during the screening period will be collected on the Medical History form.

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Adverse events will also be graded by the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Only treatment-emergent adverse events (TEAE) occurring and reported while on-treatment and up to and including 30 days after the last dose of study drug will be included in the adverse event summaries. A treatment-emergent AE is an event that emerges during treatment (including on or after the day of Zr-CX-2009 treatment in subjects enrolled in the CTMX-M-2009-001 imaging substudy) having been absent pre-treatment, or worsens relative to the pre-treatment state. AEs occurring between informed consent and first dose as well as AEs occurring 31 or more days after last dose will be listed.

AE presentation will include incidence, grade (by NCI-CTCAE criteria), and relationship to study drug.

An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an adverse event. The relationship to study drug will be categorized as "Related" or "Not Related." Related AEs/SAEs are those judged by the Investigator to be definitely, probably, or possibly related or Unknown relationship to a study drug.

TEAEs, including serious TEAEs, will be listed by subject within part and dose cohort in chronological order of AE start date/time.

The verbatim term and MedDRA system organ class (SOC) and preferred term (PT) will be included in the listings along with start and end dates, time on study, severity, seriousness, relationship of the event to study drugs, action taken with the study drugs, other action taken, outcome, infusion reaction (IR) (Y/N), DLT (Y/N), and AE of special interest (AESI) (Y/N).

The following listings will be provided:

- TEAEs
- TEAEs with CTCAE Grade 3 or Higher
- TEAEs related to CX-2009
- TEAEs related to CX-2009 with CTCAE Grade 3 or Higher
- Infusion reactions
- TEAEs leading to discontinuation of study drug
- TEAEs leading to death
- All SAEs
- SAEs related to CX-2009
- SAEs related to CX-2009 with CTCAE Grade 3 or higher
- TEAE of Special Interest
- DLT AEs
- Deaths

If there are no subjects who meet the criteria for any of these listings, the listing will be generated and will contain a statement, "No <criteria> were reported." for example, if there are no deaths on study, the statement would be "No deaths were reported."

Overall AE summary tables will each be prepared by dose level, by cancer type, and by Breast Cancer cohort (TNBC, HR+/HER2-, HER2+), and will include the number and percentage of subjects with reports of:

- TEAEs
- TEAEs related to CX-2009
- TEAEs with CTCAE Grade 3 or higher
- TEAEs with CTCAE Grade 3 or higher related to CX-2009
- TEAEs classified as infusion reactions
- TEAEs classified as infusion reactions with CTCAE Grade 3 or higher
- TEAEs leading to study drug discontinuation
- TEAEs leading to study drug discontinuation and related to CX-2009

- Dose-Limiting Toxicities (DLTs)
- Treatment-emergent SAEs (TESAEs)
- TESAE related to CX-2009
- TEAEs leading to death
- TEAEs leading to death and related to CX-2009
- TEAEs of Special Interest
- TEAEs of Special Interest with CTCAE Grade 3 or higher
- TEAEs of Ocular Toxicity related to CX-2009
- TEAEs of Ocular Toxicity related to CX-2009 with CTCAE Grade 3 or higher
- TEAEs of Neuropathy related to CX-2009
- TEAEs of Neuropathy related to CX-2009 with CTCAE Grade 3 or higher
- TEAEs of Hepatic Disorders related to CX-2009
- TEAEs of Hepatic Disorders related to CX-2009 with CTCAE Grade 3 or higher

This overall AE summary table will also be produced for the DSMB meetings. TEAEs categorized as Ocular Toxicity, Neuropathy, or Hepatic Disorders will be defined based on a search list provided by CytomX prior to database lock.

Only TEAEs (excluding unrelated, fatal AEs with PT="Malignant neoplasm progression") will be included in the AE summaries and be tabulated by MedDRA SOC and PT within part and dose cohort. Tables presenting summaries of frequencies and percentages of subjects reporting at least one TEAE within each MedDRA SOC and PT by dose level and by cancer type will be provided for TEAEs and TESAEs as follows:

- All TEAEs
- Grade 3 or higher TEAEs
- TEAEs related to CX-2009
- TEAEs related to CX-2009 by maximum severity grade
- Grade 3 or higher TEAEs related to CX-2009
- Grade 3 or higher TEAEs related to CX-2009 by maximum severity grade
- TEAEs leading to study drug discontinuation
- TEAEs leading to death
- TEAEs leading to death related to CX-2009
- TEAEs of Special Interest by maximum severity grade
- TEAEs of Ocular Toxicity related to CX-2009 by maximum severity grade
- TEAEs of Neuropathy related to CX-2009 by maximum severity grade
- TEAEs of Hepatic Disorders related to CX-2009 by maximum severity grade
- TESAEs
- Grade 3 or higher TESAEs
- Grade 3 or higher TESAEs related to CX-2009

Each subject will be counted only once within each level of the summary (PT or SOC). If a subject experiences more than one TEAE within a PT or SOC, only the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

The above list of summary tables will also be produced by MedDRA PT (based on descending frequency of the total column) by dose level or by cancer type.

The TEAE summary tables by SOC and PT will be provided upon request to the DSMB.

TEAE profile summaries will also be created for infusion reactions. This table will summarize the frequency of events, time from event onset to the start time of the first infusion (hours), time from the event onset to the start time of the most recent infusion (hours), duration of the event (hours), duration category (<1 hour, 1 to 6 hours, >6 hours), severity grade, outcome, action taken, and other action taken with medication.

Profile summaries will also be created for TEAEs of Ocular Toxicity, TEAEs of Neuropathy, and TEAEs of Hepatic Disorders. These tables will summarize the time from event onset to the start time of the first infusion (days), duration of the event (days), duration category (<=7 days, 7 to 14 days, >14 days), severity grade, outcome, action taken, and other action taken with medication.

A tabular summary of deaths by study period (Screening, Treatment, Follow-Up) will be provided by dose level and by cancer type.

No inferential statistical tests will be performed for safety analyses.

12.2 Study Drug Administration and Exposure

Drug exposure will be summarized by CX-2009 Monotherapy dose level and by cancer type. The number of doses administered for CX-2009 will be summarized categorically and continuously. The duration of treatment (in weeks) will be summarized continuously as will the percent of dose of each study drug.

The duration (weeks) will be calculated as (date of last dose of study drug - date of first dose of study drug + 1)/7.

The number and percent of subjects who were administered a dose different from the planned total dose and the reason they received a dose different from the planned total dose will be summarized. Subjects may have more than one reason in this summary.

A listing of exposure to the study drugs will be provided.

12.3 Concomitant Medications

All medications taken within 30 days before the administration of study drug and all concomitant medications and therapies administered during the study will be recorded on the relevant eCRF. Prior medications are defined as medications taken before the date of the first infusion. Concomitant medications are defined as medications taken on or after the baseline visit during the study treatment period. If a medication is taken on the date of the first infusion and is continued after the Baseline visit, it will be considered as both a prior and concomitant medication. Medications will be coded using the World Health Organization Drug Dictionary (WHODrug) version dated March 2020 (B3). Concomitant medications will be tabulated. Medication data will be summarized by Anatomic Therapeutic Classification (ATC) Level 4 within ATC Level 2 by dose level and by cancer type. Each subject will only be counted once within each level of the summary (ATC level 2 or ATC level 4).

12.4 Clinical Laboratory Tests

The clinical laboratory tests collected on study are as follows:

- Hematology: Red Blood Cells, Hemoglobin, Hematocrit, Platelet, White Blood Cells, Absolute Neutrophils, Neutrophils, Absolute Lymphocyte, Lymphocyte, Absolute Monocyte, Monocyte, Absolute Basophils, Basophils, Absolute Eosinophils, Eosinophils, Blast Count, Reticulocyte count, MCV, MCH, MCHC
- Blood chemistry: Albumin, Total Protein, Uric Acid, Sodium, Potassium, Chloride, Calcium, Calculated Creatinine Clearance, Phosphorus, Chloride, Bicarbonate, CO2, Blood Urea Nitrogen (BUN), Hemoglobin A1c, Urea, Creatinine, Lipase, Amylase, Magnesium, Glucose, Lactate Dehydrogenase (LDH), Serum ALT, Serum AST, Total Bilirubin, Alkaline Phosphatase.
- Coagulation: Prothrombin time (PT) (sec), activated Partial Thromboplastin Time (aPTT) (sec), International Normalized Ratio (INR)
- Urinalysis:
  - Blood, Protein, Glucose as negative, trace, positive, 0, +, ++, +++, >+++ (listings only)
  - Specific gravity, pH, Leukocytes, Ketones, Urobilinogen: Low, normal, high

Select laboratory tests will be graded using the NCI-CTCAE version 4.03. The lab tests will be assigned Grades 1, 2, 3, or 4 if they meet the CTCAE criteria, regardless of designation of "Low" or "High" for the value. Grading will only be performed based on quantitative criteria (e.g. no clinical input required for grading). The following toxicities will be graded: aPTT prolonged, ALT increased, Hypoalbuminemia, ALP increased, AST increased, Blood bilirubin increased, Hypocalcemia, Hypercalcemia, Creatinine increased, Hypoglycemia, Hyperglycemia (fasting), Anemia, Hemoglobin increased, INR increased, Lymphocyte count decreased, Lymphocyte count increased, Hypomagnesemia, Hypermagnesemia, Neutrophil count decreased, Hypophosphatemia, Platelet count decreased, Hypokalemia, Hyperkalemia, Hyponatremia, Hypernatremia, White blood cell count decreased, Leukocytosis.

Shift tables will be created separately for Hematology and Blood Chemistry parameters, by dose level and by cancer type. The presentation in the table will be by CTCAE toxicity, and Grade 0 will be assigned for those values which are available and not assigned Grade 1, 2, 3 or 4. If the toxicity is bi-directional (e.g. Lymphocyte Count decreased, Lymphocyte count increased), then for the high direction Grade 0 will be assigned for the "low" direction. Similarly, for the low direction, Grade 0 will be assigned for the "high" direction. The shift tables will present shifts from baseline to worst post-baseline value. The worst post-baseline value could be any non-missing value collected after the first infusion up to and including 30 days after the last infusion.

Listings that include all laboratory results for any subject with any laboratory result outside of the normal range will be provided.

12.5 Other Safety Measures

12.5.1 Vital Signs

The mean change from baseline in vital signs will be presented in a figure for each vital sign parameter for both dose level and cancer type: Temperature (°C), Pulse rate (beats/min), Respiratory rate (breaths/min), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse Oximetry (%) along with Weight (kg).

Separate lines will be presented by either dose level or cancer type as applicable in the figure.

The figures will be presented by nominal time since treatment start (weeks), and only values obtained in protocol-specified windows will be summarized. If more than one value is obtained in a protocol-specified window, the value closest to the target day in the window will be used. If there is more than one value equidistant from the target within the window, the value occurring before the target day will be used.

12.5.2 ECGs

All ECGs will be 12-lead. ECG assessments, including QTcF intervals, will be listed in chronological order by subject for any subject with an abnormal (not clinically significant or clinically significant) overall result.

13. Efficacy Analysis

13.1.1 Primary Efficacy Endpoint

The ORR is the primary efficacy endpoint. For solid tumors, response evaluation will be based on the RECIST criteria (v1.1) and ORR is defined as the proportion of subjects with complete response (CR) or partial response (PR) on two consecutive tumor assessments with scan dates at least 4 weeks apart according to RECIST (RECIST v1.1).

The primary efficacy analysis will be based on the REP. Exact 2-sided 95% Cis (using the Clopper-Pearson method) will be calculated for all proportion estimates.

A listing of tumor data including total tumor burden, RECIST v1.1 response assessments (target lesion evaluation, non-target lesion evaluation, and overall subject response) will be provided.

Response Assessment and Best Overall Response – RECIST v1.1

Efficacy outcomes will be summarized by dose level and by cancer type using RECIST v1.1 among the REP. The overall number of subjects for each dose; and the number, proportion, and 95% exact 2-sided CI (using the Clopper-Pearson method) of confirmed CR and PR, unconfirmed CR and PR, SD, PD, not evaluable (NE), overall response (CR + PR), disease control (CR + PR + SD) will be calculated. A summary table of the above response assessments by part using RECIST v1.1 among the REP will be provided. A swim lane plot of response assessment status over time using RECIST v1.1 will be produced.

The best overall response is the best response recorded from the start of study treatment until the end of treatment taking into account any requirement for confirmation. If the best overall response is determined before the end of treatment (e.g., for an interim data cut), then it is the best response recorded from the start of study treatment until the date of the data cut.

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (as may happen in the case of an assessment of PD).

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (i.e., ~8 weeks later and no

earlier than 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 1.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 7 weeks. If the first post-baseline response assessment is an SD and the assessment was less than 7 weeks from first dose of study drug, then the SD would be changed to NE. For the dose escalation parts of the study (i.e., parts A, A2), the reporting of CR/PR does not require confirmation as the primary objective is safety. Confirmation is required for the expansion cohorts (i.e., Part B).

Table 1: Best Overall Response Algorithm

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Tumor burden assessed using RECIST v1.1 will be calculated as the sum of (the longest diameter of target non-nodal lesions plus the short axis of target nodal lesions). The percent change from baseline will be plotted by time on study as a spider plot. The maximum percent change from baseline will be plotted in a waterfall plot. The spider and waterfall plots will include all visits regardless of whether or not a response assessment has been recorded (as long as all baseline target lesions were measured at the visit).

Additional efficacy figures may be provided by breast cancer subtypes (TNBC, HR+/HER2-, HER2+) as required.

13.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- DOR,
- TTR,
- PFS, and
- OS.

Time-to-Event Endpoints

DOR

DOR is defined as the time from the date of the first documentation of objective tumor response (i.e., ORR = CR or PR) that is subsequently confirmed to the date of the first documentation of objective disease progression or death due to any cause, whichever occurred first. DOR is only calculated for subjects in the REP who have a confirmed objective tumor response. Subjects who neither progress nor die will be censored on the date of their last tumor assessment.

Table 2 Date of Censoring – DOR

Description of Situation	Date of Progression or Censoring	Outcome
No disease progression nor death on-study	Date of last tumor assessment	Censored

TTR

TTR is defined as the time from the date of the first dose of study drug to first documentation of confirmed objective tumor response. TTR is only calculated for subjects in the REP.

PFS

PFS is defined as the time from the date of the first dose of study drug to the date of first documentation of objective tumor progression (i.e., PD) or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on their date of first dose of study treatment. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last tumor assessment prior to the initiation of subsequent anti-cancer therapy. PFS is calculated for using the SP.

Table 3. Date of Progression or Censoring -- PFS

Description of Situation	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of first dose of study drug	Censored

Death before first disease assessment	Date of death	Progressed
No disease progression nor death on-study	Date of last tumor assessment with a response assessment other than not evaluable	Censored
Death without a reported progression	Date of death	Progressed
No on-study tumor assessments and did not die	Date of first dose of study drug	Censored
Subjects who started anti-cancer therapy without a prior reported progression	Date of their last tumor assessment with a response assessment other than not evaluable prior to the initiation of subsequent anti-cancer therapy	Censored
Died or progressed (on treatment*) after a missed assessment	Date of death or disease progression	Progressed
Died or progressed in follow-up	Date of last tumor assessment with a response assessment other than not evaluable	Censored

* Subjects who discontinued the study 30 or fewer days from the last dose of study drug are considered to have discontinued the study during the treatment period. Subjects who discontinue the study more than 30 days after the last dose of study drug are considered to have discontinued the study while in follow-up.

OS

OS is defined as the time from the date of the first dose of study drug to the date of death due to any cause (as captured on the Study Discontinuation, Treatment Termination, Substudy Discontinuation, Survival Status and/or AE CRF pages). Two analyses of OS will be conducted. The first will analyze all on-treatment deaths (deaths occurring within 30 days of last dose of study drug) while the second will analyze all on-study deaths (deaths occurring after first dose of study drug while on study). Subjects who are last known to be alive and/or lost to follow-up are censored at the date of last contact (as captured on the Discontinuation Call, Study Discontinuation, Treatment Termination, Survival Status, and/or Substudy Discontinuation CRF pages). Interim analyses of OS would use the data cut date as the censoring date of last contact if the subject is last known to be alive and/or lost to follow-up. OS is calculated for using the SP.

Table 4. Date of Censoring

Description of Situation	Date of Progression or Censoring	Outcome
Last known to be alive and/or lost to follow-up	Date of last contact	Censored

Please note that the scan date of the tumor assessment associated with the reported response assessment will be used as the tumor response date referenced above (i.e., first documentation of objective tumor response, first documentation of objective disease progression, and first documentation of objective tumor progression).

Estimates of time-to-event endpoints (DOR, TTR, PFS, and OS) will be obtained using the Kaplan-Meier method. Kaplan-Meier curves will be provided for these endpoints. A swim lane plot will be provided for DOR. DOR and TTR will also be summarized using descriptive statistics for confirmed objective responders.

The median, and 95% CIs around the DOR, TTR, PFS, and OS will also be calculated using the Kaplan-Meier method. The range of TTR, PFS and OS will be provided as well. Frequencies and percentages will be summarized for event rates and censored observations of the time-to-event endpoints. Six- and twelve-month and 2-year survival rates will be included as well. The number and percentage of disease progressions and deaths will be included (replacing the event rate) in the PFS summary.

CBR16 and CBR24

Breast cancer patients will also have CBR16 and CBR24 summarized by dose level and also by cancer subtype (TNBC, HR+/HER2-, HER2+). CBR16 is defined as the proportion of subjects with best overall response of CR or PR or with SD for at least 16 weeks. CBR24 is defined as the proportion of subjects with best overall response of CR or PR or with SD for at least 24 weeks. CBR16 and CBR24 will only be calculated for subjects in the REP.

SD Duration is defined as the time interval from the start of the treatment to the date of subsequent PD or on-treatment death. In the absence of PD or on-treatment death before the analysis cut-off date, it is the time from the start of treatment to the date of the last adequate tumor assessment before the cut-off date.

13.1.3 Efficacy Measures during Follow-up

Following the completion of study treatment, subjects with progressive disease will enter the follow-up period for monitoring of survival; subjects with SD, PR, or CR will enter the follow-up period for monitoring of DOR and PFS. Once a subject experiences progressive disease, they will continue to be monitored for survival.

13.1.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2, 3, 4, and 5) will be presented in a listing.

14. Pharmacokinetic, Immunogenicity, and Pharmacodynamic Assessments

14.1 PK Assessments

A third-party PK vendor will conduct all analyses related to PK data. Details of the PK analyses will be provided in a separate PK analysis plan.

14.2 Immunogenicity Assessments

Serum samples will be collected from study participants, as described in the protocol to assess the immunogenicity of CX-2009. Samples will be initially screened for anti-drug antibodies (ADA). If the sample is found to be ADA positive in the screening assay, a confirmatory assay and a titer assay will be performed to further characterize antidrug antibodies.

Samples will be drawn at times indicated in the CTMX-M-2009-001 Protocol Module.

Immunogenicity results will be listed by part and dose cohort. ADA statistical analyses will be detailed and summarized in a separate report.

15. Exploratory Analyses

15.1 Pharmacodynamics and Exploratory Biomarkers

The overall goal of the biomarker portion of CTMX-M-2009-001 is to explore

- A) Probody mechanistic proof of concept, and
- B) Potential predictive markers associated with CX-2009 clinical activity.

This information will help to further build the translational program for the development of Exploratory studies will evaluate:

- Probody activation in tumors compared to a peripheral normal tissue compartment (blood);
- The potential link between markers, such as the target of CX-2009 (i.e., CD166), and mitotic markers (e.g., Ki-67), and the biological activity of CX-2009; and
- The presence of activated proteases in the human TME capable of removing the peptide mask and thereby activating the Probody-Tx.

If the exploratory study results are presented in the CSR, a description of the methodology will be included there.

15.2 Additional Exploratory Analyses

Upon review of the data, additional exploratory analyses may be conducted. If these are presented in the CSR, a description of the methodology will be included there.

16. References

International Conference on Harmonization (ICH) guideline "Statistical principles for Clinical trials": E9, 1998.