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 (PROCLAIM-CX-2009)

NCT# NCT03149549

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PROCLAIM CLINICAL STUDY
MODULE CX-2009

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)

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SIGNATURE PAGE

STUDY 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 (PROCLAIM-CX-2009)

I, the undersigned, have read this Module and agree that it contains all necessary information required to conduct the study.

24 Feb 2020

Alison L. Hannah, MD
Senior Vice President and Chief Medical Officer, Clinical Development
CytomX Therapeutics, Inc.

Date

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read the contents of the Common Core Document CTMX-C-001, Module CTMX-M-2009-001, and any subsequent amendments. I will provide copies of these documents, and access to all information furnished by CytomX Therapeutics, Inc. to all study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to CytomX Therapeutics, Inc., and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment may be suspended at any time by CytomX Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the health and well-being of the study subjects.

I agree to conduct this study in full accordance with: (i) the Common Core Document CTMX-C-001, Module CTMX-M-2009-001, and any subsequent amendments; (ii) applicable regulatory requirements; (iii) Institutional Review Board/Independent Ethics Committee regulations; and (iv) the International Council for Harmonisation Guidelines for Good Clinical Practices.

Investigator's Signature Date

Investigator's Printed Name

SYNOPSIS

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 (PROCLAIM-CX-2009)

MODULE NUMBER

CTMX-M-2009-001

INVESTIGATIONAL PRODUCT

CX-2009

PHASE

Phase 1-2

INDICATION(S)

Metastatic or locally advanced unresectable solid tumors

INTRODUCTION AND STUDY RATIONALE

CX-2009 is an antibody-based prodrug, referred to as a Probody™ therapeutic derived from a proprietary, humanized anti–cluster of differentiation 166 (CD166) monoclonal antibody (mAb), and conjugated to N-succinimidyl 4-(2-pyridyldithio) butanoate-$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4). CX-2009 has a drug to antibody ratio (DAR) of 3.5, similar to the DARs observed in other DM4 antibody-drug conjugates (ADCs) in clinical use. Expression, purification, DM4 conjugation, formulation, characterization, stability, and administration of CX-2009 are similar to those for other mAbs.

Probody therapeutics differ from unmodified mAbs by the recombinant addition of a prodomain at the amino-terminus of the light chain, which blocks the antibody binding to its target antigen and can be removed by tumor-associated protease activity. In this way, CX-2009 is expected to be activated in tumors and bind to its target CD166 but to be relatively inactive outside of the tumor microenvironment (TME). The substrate of CX-2009 is designed to be cleaved by a number of proteases associated with TMEs, including serine protease and matrix metalloproteinase classes. These proteases were chosen to activate CX-2009 because of their association with the human TME. In numerous cell line xenograft and patient-derived xenograft tumor models, treatment with CX-2009 has led to significant tumor growth inhibition or regression. It was also observed that, at the anticipated therapeutic dose levels, CX-2009 shows extended exposure in cynomolgus monkeys compared with the corresponding CD166-targeting ADC, consistent with CX-2009 avoidance of the antigen sink in normal tissues. Together, these results indicate that CX-2009 can be efficiently activated in the tumor, while maintaining low binding to normal tissues.

Parts A, B, and C of the study will test CX-2009 administered as monotherapy. Parts D and E will test the combination of CX-2009 plus CX-072, a Probody therapeutic directed against programmed death ligand 1 (PD-L1), with the rationale that the combination of a maytansinoid ADC and an anti–PD-L1 antibody has the potential to produce durable clinical benefit. The rationale for the combination of an ADC with immune checkpoint inhibitor (ICI) is presented in Section 1.6, including non-clinical data combining CX-2009 with CX-072. Briefly, ADCs have been demonstrated to kill cancer cells, resulting in

immunogenic cell death. In addition, the cytotoxic payload may provide phenotypic and functional dendritic cell maturation and activation in a manner that may potentiate the activity of ICIs. Clinical trials investigating an ADC (such as ado-trastuzumab emtansine) in combination with an ICI (such as atezolizumab) are on-going. CX-2009 administered every 14 days and every 21 days as monotherapy and in combination with CX-072 will be evaluated in order to optimize the dosing regimen and facilitate other potential combination evaluations.

This study is composed of 2 distinct documents:

- A common core ("Core"; see separate synopsis [Appendix A]), and
- A CX-2009-specific module ("Module"; this document).

Briefly, the Core is a stable document that contains all the design features typically included in a standard Phase 1-2 protocol, but without reference to a specific experimental agent. The exact same core document is used for all Probody therapeutic first in human (FIH) studies, serving as a centerpiece for all Probody therapeutics in development. It includes, for example, guidelines for drug accountability, efficacy and safety parameters, and study administrative procedures. The CX-2009 Module (this current document), on the other hand, is customized for this specific Probody therapeutic, and all protocol guidelines necessary to safely manage subject care are included within the Module. Familiarity with both the Core and the CX-2009 Module is required for proper conduct of the study.

The Core plus Module system is a mechanism for bundling the clinical evaluation of Probody therapeutics within 1 unified program, with a common study design and common Investigator oversight. See the Core synopsis for a more detailed discussion of the Core design and rationale.

OBJECTIVES

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 maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D), and the dose-limiting toxicities (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; and
- Obtain additional characterization of the safety of 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. Efficacy will be assessed on the basis of the objective response rate (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.

Part C2 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The primary objective of Part C2 is to evaluate the efficacy of CX-2009 when administered IV every 14 days as monotherapy at the MTD/RP2D to subjects with selected advanced or recurrent solid tumors. Efficacy will be assessed on the basis of the ORR by the RECIST Version 1.1.

Part D1 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The primary objective of Part D1 is to determine the safety profile, the MTD/RP2D, and the DLTs of CX-2009 in combination with CX-072, both administered IV every 14 days to subjects with selected advanced or recurrent solid tumors.

Part D2 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The primary objective of Part D2 is to evaluate the efficacy of CX-2009 in combination with CX-072, both administered IV every 14 days at the MTD/RP2D to subjects with selected advanced or recurrent solid tumors. Efficacy will be assessed on the basis of ORR per RECIST Version 1.1.

Part E1 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The primary objective of Part E1 is to determine the safety profile, the MTD/RP2D, and the DLTs of CX-2009 in combination with CX-072, both administered IV every 21 days to subjects with selected advanced or recurrent solid tumors.

Part E2 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The primary objective of Part E2 is to evaluate the efficacy of CX-2009 in combination with CX-072, both administered IV every 21 days at the MTD/RP2D to subjects with selected advanced or recurrent solid tumors. Efficacy will be assessed on the basis of ORR per RECIST Version 1.1.

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 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; and
  - *S*-methyl DM4 (DM4-Me) - a DM4 metabolite with potent cytotoxic activity; and
- Assess the incidence of 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 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 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; and
  - DM4-Me; and
- Assess the incidence of 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 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; and
  - DM4-Me; and
- Assess the incidence of 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 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; and
  - DM4-Me; and
- Assess the incidence of ADA formation to CX-2009.

Part C2 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The secondary objectives of Part C2 are to determine the following in subjects treated with CX-2009 every 14 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; and
  - DM4-Me; and
- Assess the incidence of ADA formation to CX-2009.

Part D1 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The secondary objectives of Part D1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - ORR by the RECIST Version 1.1;
  - ORR by immune-related RECIST (irRECIST) as defined in the Core;
  - TTR;

  - DOR;
  - PFS; and
  - OS;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

Part D2 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The secondary objectives of Part D2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Obtain additional characterization of the safety of CX-2009 administered with CX-072 at the MTD/RP2D;
- Evaluate efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - DOR;
  - TTR;
  - PFS;
  - OS; and
  - ORR by irRECIST as defined in the Core;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

Part E1 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The secondary objectives of Part E1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - ORR by the RECIST Version 1.1;
  - ORR by irRECIST as defined in the Core;
  - TTR;
  - DOR;
  - PFS; and
  - OS;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

Part E2 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The secondary objectives of Part E2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Obtain additional characterization of the safety of CX-2009 administered with CX-072 at the MTD/RP2D;
- Evaluate efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - DOR;
  - TTR;
  - PFS;
  - OS; and
  - ORR by irRECIST as defined in the Core;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;

- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

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

Part C2 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The exploratory objectives of Part C2 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 on-treatment tumor biopsies and peripheral blood.

Part D1 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The exploratory objectives of Part D1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

Part D2 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The exploratory objectives of Part D2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

Part E1 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The exploratory objectives of Part E1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

Part E2 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The exploratory objectives of Part E2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

STUDY DESIGN

This is a Phase 1-2, open-label, multicenter, dose-finding, and proof of concept study for CX-2009 as monotherapy and (where permitted by local Health Authority) in combination with CX-072 in subjects with advanced solid tumors in the following indications: breast cancer (BC), castrate-resistant prostate carcinoma (CRPC), non-small cell lung carcinoma (NSCLC), ovarian epithelial cancer (OEC), endometrial carcinoma (EC), head and neck squamous cell carcinoma (HNSCC), or cholangiocellular carcinoma (CCC). See Table 4 for an overview of the eligible tumor types and enrollment numbers for each part. These tumor types have been selected for their known high levels of CD166 expression and sensitivity to microtubule inhibitors (MTIs).

The study is divided into 9 parts: Parts A, A2, B, C1, C2, D1, D2, E1, and E2 (see Figure 4), each designed to inform dose selection for the next phase of development. Part A is designed to define the MTD in 2 separate stages: a standard 3+3 escalation followed by a modified toxicity probability interval 2 (mTPI-2) cohort, in subjects receiving CX-2009 every 21 days. Part A2 is designed for biomarker evaluation (particularly Probody therapeutic activation) in order to further inform dose optimization. Part B is focused on expanding clinical experience in order to further define the safety profile at the MTD/RP2D as well as to obtain a preliminary assessment of efficacy in a select number of cancers. Part B may be initiated as soon as the MTD/RP2D is defined in Part A and available data from Part A2 are reviewed in consultation with the Safety Review Committee (SRC; see Appendix E). Part C1 is designed to define the MTD/RP2D in subjects receiving CX-2009 every 14 days. Part C2 is focused on expanding clinical experience in order to further define the safety profile of CX-2009 and to obtain a preliminary assessment of efficacy when administered every 14 days at the MTD/RP2D. Dose expansion for CX-2009 monotherapy may occur under the every 21-day dosing regimen (Part B) and/or the every 14-day dosing regimen (Part C2), depending on available data from Parts A, A2, and C1.

Parts D and E involve co-administration of CX-2009 and CX-072. As such, these cohorts are only open to those countries in which the Health Authority permits these cohorts to activate. Part D1 is designed to define the MTD/RP2D in subjects receiving CX-2009 in combination with CX-072 every 14 days. Part D2 is focused on expanding clinical experience to further define the safety profile of CX-2009 administered in combination with CX-072 and to obtain a preliminary assessment of efficacy of the combination when administered every 14 days at the MTD/RP2D. Part E1 is designed to define the MTD/RP2D in subjects receiving CX-2009 in combination with CX-072 every 21 days. Part E2 is focused on expanding clinical experience to further define the safety profile of CX-2009 administered in combination with CX-072 and to obtain a preliminary assessment of efficacy of the combination when administered every 21 days at the MTD/RP2D.

Part A:
Dose escalation and determination of the 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 initiates with accelerated dose titration in 1 single-subject cohort (0.25 mg/kg, adjusted ideal body weight [AIBW]), followed by a standard 3+3 design to determine the MTD, and ends in an 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 2007) but allows a more flexible sample size. To understand the statistical rationale for the design, please refer to Section 9 and Appendix C.

One subject will be enrolled into the first cohort until the first dose level is enrolled and treated successfully. Should a subject in cohort 1 experience a ≥Grade 2 adverse event (AE) that is at least possibly related to the study drug, 2 more subjects will be enrolled at that dose level and evaluated based on 3+3 design rules. Should the first subject in cohort 1 experience a DLT, the dose level will be expanded to 3 subjects and if there is no additional DLT, the dose level will be expanded to 6 subjects. All subsequent cohorts will utilize a 3+3 design and will enroll sufficient evaluable subjects to allow for DLT evaluation. Dosing increments will be less than 100.0% if a subject in the single-subject cohort experiences a ≥Grade 2 toxicity. The first subject in each new dose cohort will be dosed at least 24 hours prior to any other subjects in that cohort being dosed, to allow for observation of possible severe and/or serious acute (eg, infusion-related) toxicities that might affect subsequent subject enrollment or dosing decisions.

Enrollment will continue in each cohort until the MTD or the RP2D is defined, or the highest dose (ie, 10 mg/kg, AIBW) has been tested and deemed safe, whichever is lower. AIBW should be applied using the formula provided in Appendix F.

Once the MTD is defined or the highest dose is tested (ie, 10 mg/kg, AIBW), up to 38 subjects can be enrolled at the MTD to refine dose selection using mTPI-2, a rule-based design similar to the 3+3 design that allows dose escalation/de-escalation. Up to 6 subjects can be treated at each dose level and up to 14 subjects can be treated at the identified MTD/RP2D dose level. Assuming that up to 5 dose levels (6 mg/kg to 10 mg/kg, AIBW) may be explored in the mTPI-2 cohort, a maximum sample size of 38 subjects may be enrolled. AEs that meet DLT criteria (within the 21-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D will be based predominantly on safety and may take other factors into account such as PK/pharmacodynamics (PD) and clinical activity.

Subjects may be permitted individual dose escalations to previously cleared dose levels following consultation with the Medical Monitor.

The DLT assessment period for dose escalation is 21 days.

Part A2:
Additional enrollment into previously cleared CX-2009 monotherapy dose levels from Part A (n ≤ 42) for every 21-day dosing regimen

Part A2 will help to inform selection of the optimal MTD/RP2D by requiring measurable disease, mandating tumor biopsies to assess Probody therapeutic CX-2009 performance, and selecting for confirmed high CD166 expressing tumors by immunohistochemistry.

Part A2 will initiate enrollment after the 4 mg/kg cohort in Part A has completed the DLT period and with the recommendation of the SRC. Six subjects must be enrolled into each cohort before the next sequential cohort can be enrolled. Doses administered in Part A2 can never exceed the most recently cleared dose in Part A. All toxicities observed in Part A2, regardless of whether they are observed early or late in the dosing course, will be reviewed by the SRC and used to make recommendations for further enrollment in all parts of the study.

Up to a total of 42 subjects will be enrolled at up to 7 dose levels with 6 subjects per cohort per dose.

Available data from Part A2 will be considered by the SRC when making dosing recommendations and performing cohort review in Part A. As of November 2019, the RP2D for further study of CX-2009 monotherapy when given every 21 days in Part B was determined to be 7 mg/kg; this dose will continue to be assessed for safety and may be modified if supported by the data.

Part A2 will be restricted to subjects with BC, NSCLC, OEC, EC, and HNSCC. These tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied.

Tumor biopsies are required 3 to 5 days after the first dose of CX-2009. To enroll a subject in Part A2, the Investigator must consider the subject safe to biopsy and the subject must consent to biopsy collection.

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)

Part B will explore efficacy of CX-2009 by requiring measurable disease. Part B will enroll up to a total of 40 subjects each in 1 or more of the following indications: triple-negative breast cancer (TNBC), hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative BC, NSCLC, OEC, or HNSCC. As of November 2019, Part B will be initiated in subjects with HR-positive/HER2-negative BC at a dose of 7 mg/kg.

Part C1:
Dose escalation/de-escalation and determination of the MTD/RP2D of the CX-2009 monotherapy every 14-day dosing regimen (n ≤ 24)

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 was 6 mg/kg, AIBW, administered every 14 days. The initial starting dose for Part C1 was not determined to be tolerated (see Section 1.3.4.1); a lower dose (4 mg/kg) will therefore be explored on the every 14-day schedule. Subsequent dose escalation/de-escalation (if any) will be based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed (Figure 6). Part C1 will include up to 24 subjects. Subjects will be selected from the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC.

AEs that meet DLT criteria (within the 28-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D at an every 14-day dosing regimen will be based predominantly on safety and may take other factors into account such as PK/PD and clinical activity.

Subjects who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

Part C2:
Dose expansion at the MTD/RP2D of CX-2009 monotherapy every 14-day dosing regimen in selected tumor types (maximum n ≤ 200)

Part C2 will explore efficacy of CX-2009. Part C2 will enroll up to a total of 40 subjects each in 1 or more of the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC. These tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied.

Part C2 may be initiated as soon as the MTD/RP2D for the 14-day regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part C1), an every 14-day dosing regimen is considered for further development.

Part D1:
Dose escalation/de-escalation and determination of the MTD/RP2D for the CX-2009 + CX-072 combination in an every 14-day dosing regimen in selected tumor types (n ≤ 24)

Part D1 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. The dose of CX-072 will be fixed at the RP2D (800 mg every 14 days). The starting dose for CX-2009 will be set at the every 14-day monotherapy RP2D as determined in Part C1. Lower starting doses may be used based on emerging safety data and in consultation with the SRC. The mTPI-2 design will be used to determine the MTD/RP2D for the combination dosed every 14 days. The following cohort's dose will be increased or decreased according to the defined dose escalation rules based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6). Part D1 will enroll subjects in 1 or more of the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC.

Part D1 will evaluate dose levels based on DLT events and treatment-related AEs leading to treatment delay or discontinuation, including events of special interest (eg, ocular toxicity and peripheral neuropathy).

AEs that meet DLT criteria (within the 28-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D will be based predominantly on safety and may take other factors into account such as PK/PD and clinical activity.

Subjects who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

Part D2:
Dose expansion at the MTD/RP2D of the CX-2009 + CX-072 combination in an every 14-day dosing regimen in selected tumor types (maximum n ≤ 200)

Part D2 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. Part D2 will explore efficacy of CX-2009 plus CX-072 for the every 14-day dosing regimen at the dose selected in Part D1. Part D2 will enroll up to a total of 40 subjects each in 1 or more of the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC. Part D2 may be initiated as soon as the MTD/RP2D for the 14-day combination regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part D1), an every 14-day combination dosing regimen is considered for further development.

Part E1:
Dose escalation and determination of the MTD/RP2D for the CX-2009 + CX-072 combination in an every 21-day dosing regimen in selected tumor types (n ≤ 24)

Part E1 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. The dose of CX-072 will be fixed at the RP2D (1200 mg every 21 days). The starting dose of CX-2009 will be 7 mg/kg (the every 21-day monotherapy RP2D as determined in Parts A/A2). Lower starting doses may be used based on emerging data and in consultation with the SRC. The mTPI-2 design will be used to determine the MTD/RP2D for the combination dosed every 21 days. The following cohort's dose will be increased or decreased according to the defined dose escalation rules based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6). Part E1 will enroll subjects in 1 or more of the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC. Part E1 will evaluate dose levels based on DLT events and treatment-related AEs leading to treatment delay or discontinuation, including events of special interest (eg, ocular toxicity and peripheral neuropathy).

AEs that meet DLT criteria (within the 21-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D will be based predominantly on safety and may take other factors into account such as PK/PD and clinical activity.

Subjects who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

Part E2:
Dose expansion at the MTD/RP2D of the CX-2009 + CX-072 combination in an every 21-day dosing regimen in selected tumor types (maximum n ≤ 200)

Part E2 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. Part E2 will explore efficacy of CX-2009 plus CX-072 for the every 21-day dosing regimen at the dose selected in Part E1. Part E2 will enroll up to a total of 40 subjects each in 1 or more of the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC. Part E2 may be initiated as soon as the MTD/RP2D for the 21-day combination regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part E1), an every 21-day combination dosing regimen is considered for further development.

Allocation of subjects between Parts C, D, and E: In case Parts C, D, and E are open for enrollment concurrently and subjects meet the eligibility criteria for all parts, the Sponsor in conjunction with the Principal Investigator will determine to which part the subjects are allocated. The Sponsor will determine which tumor types will be selected for additional evaluation for Parts B, C2, D2, and E2.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION

CX-2009 will be supplied as a lyophilized powder (cake) in 25 mg vials to be reconstituted with 5 mL of sterile water for injection (WFI) to a final concentration of 5.0 mg/mL. CX-2009 will be administered as an IV infusion over 90 (±10) minutes with careful monitoring of infusion-related reactions (IRRs). The SRC can modify the infusion rate for any dose if a ≤Grade 2 IRR occurs or if it is deemed to improve safe administration of CX-2009. If a ≥Grade 3 IRR occurs, this Module may be amended.

CX-072 drug product is currently being supplied as a sterile solution for IV administration. CX-072 is supplied in a 10 mL volume, and each vial contains 100 mg of CX-072 formulated with suitable compendial excipients. Upon regulatory approval, the CX-072 drug product is planned to be supplied as a lyophilized powder (cake) in single-use vials for reconstitution with sterile WFI before IV administration. CX-072 is administered at a fixed dose of 800 mg over 60 (±10) minutes for Parts D1 and D2 and 1200 mg over 60 (±10) minutes for Parts E1 and E2.

When CX-2009 and CX-072 are administered on the same day, CX-072 is to be administered first, followed by a saline flush, followed by the CX-2009 infusion. CX-2009 is to be infused no sooner than 30 minutes after completion of the CX-072 infusion.

EFFICACY VARIABLES

The primary criteria for defining evidence of anticancer activity and also for management of subject care will be a clinical response as defined by RECIST (Version 1.1). Efficacy in subjects treated with the combination CX-2009 plus CX-072 (Parts D1, D2, E1, and E2) will be explored additionally on the basis of ORR by irRECIST as defined in the Core (Appendix A). Management of subjects in Parts D1, D2, E1, and E2 may also take into consideration tumor response assessed by irRECIST.

PHARMACOKINETIC, IMMUNOGENICITY, AND EXPLORATORY BIOMARKER VARIABLES

Pharmacokinetics

Concentration versus time data will be tabulated and plotted for the individual and mean CX-2009 (total and intact), CX-2009-conjugated DM4 and free DM4, and DM4-Me analytes and for total and intact CX-072 moieties. PK parameters, including area under the plasma concentration-time curve (AUC), maximal plasma concentration (C_{max}), minimal plasma concentration (C_{min}), clearance, and volume of distribution at steady state, will be calculated for CX-2009 (total and intact), DM4 (conjugated and free), and DM4-Me analytes as appropriate and as data allow. Additional parameters such as terminal elimination half-life and accumulation may be calculated, and dose proportionality will be assessed for subjects with sufficient data. Estimates for these parameters will be tabulated and summarized (eg, mean, standard deviation, and coefficient of variation). CX-072 (total and intact moieties) C_{max} and C_{min} will be tabulated individually and summarized using descriptive statistics (eg, mean, standard deviation, and coefficient of variation).

Additional exploratory model-based PK analyses may be conducted and the results of these analyses may be reported in a document separate from the clinical study report.

Exploratory Biomarkers

Probody therapeutics differ from unmodified mAbs by the recombinant addition of a prodomain at the amino-terminus of the light chain, which blocks the antibody binding to its target antigen and can be removed by tumor-associated protease activity. In this way, CX-2009 and CX-072 are expected to be activated in tumors and bind to their targets, CD166 and PD-L1 respectively, but to be relatively inactive outside of the TME.

The overall goal of the biomarker portion of CTMX-M-2009-001 is to explore A) Probody therapeutic mechanistic proof of concept, and B) potential predictive markers associated with the clinical activity of CX-2009 alone or in combination with CX-072.

Exploratory studies will include the evaluation of:

- Probody therapeutic activation in tumors and in blood;
- The potential link between tumor markers, such as the target of CX-2009 (ie, CD166), the target of CX-072 (ie, PD-L1) and the biological activity of CX-2009 alone or in combination with CX-072;
- The potential link between exploratory biomarkers in blood and the biological activity of CX-2009 alone or in combination with CX-072; and
- The presence of activated proteases in the human TME capable of removing the peptide mask and thereby activating the Probody therapeutic.

In order to address the above objectives, tissue samples will be collected throughout the course of the study.

For Parts A and C1, pretreatment and on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

For Part A2, tumor biopsies (fixed and frozen) are required 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

For Parts B and C2, consent to pretreatment and on-treatment tumor biopsies will be mandatory in at least 7 subjects for each tumor type. For these subjects, tumor biopsies (fixed and frozen) will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

For Parts D1, D2, E1, and E2, on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected 3 to 5 days after the third dose, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

SAFETY VARIABLES

Safety variables include the incidence and nature of DLTs, AEs, and serious adverse events (SAEs), as well as physical examinations, vital sign measurements, triplicate electrocardiograms, clinical laboratory evaluations, and treatment discontinuation due to toxicity.

SAMPLE SIZE DETERMINATION

A maximum of 993 subjects will be enrolled into the study: Part A ≤79 subjects, Part A2 ≤42 subjects, Part B ≤200 subjects, Part C1 ≤24 subjects, Part C2 ≤200 subjects, Part D1 ≤24 subjects, Part D2 ≤200 subjects, Part E1≤24 subjects, and Part E2≤200 subjects. No more than 40 subjects will be enrolled with a given tumor type in each part. Dose expansion for CX-2009 monotherapy may occur under the every 21-day dosing regimen (Part B) and/or the every 14-day dosing regimen (Part C2), depending on available data from Parts A, A2, and C1. Dose expansion for CX-2009 in combination with CX-072 may occur under the every 14-day dosing regimen (Part D2) and/or the every 21-day dosing regimen (Part E2), depending on available data from Parts D1 and E1. Selection of the regimen and tumor type for dose expansion will be made in consultation with the SRC.

Part A, dose escalation with an every 21-day dosing regimen, of the study consists of an accelerated titration design, followed by a 3+3 design, and ending in a cohort using the mTPI-2 design. During dose escalation (3+3 design), the exact sample size will be determined by the observed safety profile, which will determine the number of subjects per cohort and the number of cohorts.

Once the MTD is defined or the highest dose is tested (ie, 10 mg/kg, AIBW), up to 38 subjects can be enrolled at the MTD to refine dose selection using mTPI-2, a rule-based design similar to the 3+3 design

that allows dose escalation/de-escalation. In November 2019, the selection of 7 mg/kg as the MTD/RP2D was made based on factors including safety, efficacy, and PK/PD, by the Sponsor with input from the SRC.

Part B, with an every 21-day dosing regimen, is designed to provide a preliminary assessment of efficacy at the MTD/RP2D. Given the confirmed ORR seen to date in subjects with HR-positive/HER2-negative BC receiving monotherapy CX-2009 on the every 21-day schedule, a 2-stage enrollment design will no longer be incorporated. The SRC will continue to review on-going safety and efficacy data throughout the course of the clinical study. The sample size was selected to estimate the ORR. With 40 subjects treated, if 8 subjects have confirmed objective responses, the observed ORR will be 20% (90% CI: 10% - 33%); the lower bound of the 90% CI would therefore exclude an ORR of 10%.

Part C1, dose escalation/de-escalation using the mTPI-2 design with an every 14-day dosing regimen, will enroll up to 24 subjects (3 to 6 subjects at each dose level) for the purposes of MTD/RP2D decisions.

Part C2, with an every 14-day dosing regimen, is designed to provide a preliminary assessment of clinical activity at the MTD/RP2D. Once the MTD/RP2D is defined in Part C1, expansion cohorts of up to 40 subjects in selected tumor types will be enrolled as described in Part B to evaluate the antitumor activity using the MTD/RP2D in Part C2. A 2-stage design may be incorporated into this cohort.

Part D1, dose escalation/de-escalation using the mTPI-2 design for CX-2009 with an every 14-day dosing regimen in combination with CX-072, will enroll up to 24 subjects (3 to 6 subjects at each dose level) for the purposes of MTD/RP2D decisions.

Part D2, dose expansion of CX-2009 plus CX-072 with an every 14-day dosing regimen, is designed to provide a preliminary assessment of clinical activity at the MTD/RP2D. Once the MTD/RP2D is defined in Part D1, expansion cohorts of 40 subjects in selected tumor types will be enrolled as described in Part B to evaluate the antitumor activity of CX-2009 plus CX-072. A 2-stage design may be incorporated into this cohort.

Part E1, dose escalation using the mTPI-2 design for CX-2009 with an every 21-day dosing regimen in combination with CX-072, will enroll up to 24 subjects (3 to 6 subjects at each dose level) for the purposes of MTD/RP2D decisions.

Part E2, dose expansion of CX-2009 plus CX-072 with an every 21-day dosing regimen, is designed to provide a preliminary assessment of clinical activity at the MTD/RP2D. Once the MTD/RP2D is defined in Part E1, expansion cohorts of 40 subjects in selected tumor types will be enrolled as described in Part B to evaluate the antitumor activity of CX-2009 plus CX-072. A 2-stage design may be incorporated into this cohort.

Enrollment within the expansions will be suspended if either of the following Safety Stopping Rules are met in the first 6 subjects enrolled in Parts B, C2, D2, and E2:

- DLT rate is >30% within 21 days (Parts B and E2) or within 28 days (Parts C2 and D2) of the first dose of study drug
- >20% of subjects have a treatment interruption or discontinuation within the first 6 weeks of the first dose of study drug or within 6 weeks of a single dose reduction step for subjects who experience events with their first dose of study drug

One of the major exploratory objectives aims at evaluating the relative Probody therapeutic activation in the tumor versus blood across various indications. The relative degree of Probody therapeutic activation in the tumor versus blood is expected to be influenced by Probody therapeutic dose, protease activity, and tumor target (CD166) expression. The variable nature of the protease activity and target expression in the

tumor between subjects is expected to lead to variation in relative Probody therapeutic activation. For Part A2, tumor biopsies are required 3 to 5 days after the first dose of CX-2009. For the dose expansion (Part B), consent to pretreatment and on-treatment tumor biopsies will be mandatory for at least 7 subjects for each tumor type.

Based on nonclinical data, the differential activation between tumor and blood has a mean of about 20.0% and a standard deviation of about 5.0%. For Part A2 with 6 subjects enrolled in a dose cohort, the 90.0% CI (based on t-distribution with 5 degrees of freedom) for the differential activation is (16.0%, 24.0%). For each of the expansion cohorts in Parts B and C2, the 90.0% CI (based on t-distribution with 6 degrees of freedom) for the differential activation based on the best case scenario of 7 subjects is (16.3%, 23.7%), and based on the more likely scenario of 4 subjects is (14.1%, 25.9%). In addition, the variability in protease activity between subjects might further reduce our ability to measure Probody therapeutic activation in the tumor. It is anticipated that the requested tumor biopsies will provide reasonable estimates for this FIH study. If tumor biopsies are not mandatory, fewer subjects would be available for analysis, and the estimates would be less precise.

SITES

This is a multicenter study that will be conducted globally. Germany will participate only in Part B or C2 of the study. UK will not participate in Parts D1, D2, E1, and E2 of the study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

a.m.	*ante meridian,* before noon
ACTH	adrenocorticotropic hormone
AD	acceptable dose
ADA	antidrug antibody
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AIBW	adjusted ideal body weight
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BC	breast cancer
BRCA	BReast CAncer gene
BSA	body surface area
BUN	blood urea nitrogen
CA125	cancer antigen 125
CBC	complete blood count
CCC	cholangiocellular carcinoma
CD*x*	cluster of differentiation *x*
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximal plasma concentration
C_{min}	minimal plasma concentration
CMV	cytomegalovirus
CR	complete response
CRPC	castrate-resistant prostate carcinoma
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CYP	cytochrome P450
d	day
DAR	drug to antibody ratio
dL	deciliter
DLT	dose-limiting toxicity

List of Abbreviations and Definitions of Terms

DM1	$N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl) maytansine
DM4	$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine
DM4-Me	*S*-methyl DM4
DOR	duration of response
DOV	day of visit
DSMB	Data and Safety Monitoring Board
EC	endometrial carcinoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOI	end of infusion
EOT	end of treatment
FDA	Food and Drug Administration
FIH	first in human
FRα	folate receptor alpha
FSH	follicle-stimulating hormone
FT4	free thyroxine
g	gram
GI	gastrointestinal
GLP	Good Laboratory Practices
HCG	human chorionic gonadotropin
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest nonseverely toxic dose
HR	hormone receptor
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
IEC	independent ethics committee
IgG_1	immunoglobulin G subclass 1
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRR	infusion-related reaction

List of Abbreviations and Definitions of Terms

irRECIST	Immune-related Response Criteria in Solid Tumours
IV	intravenous(ly)
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LH	luteinizing hormone
m^2	square meter
mAb	monoclonal antibody
mg	milligram
mIU	milli-International Unit
mL	milliliter
mpk	milligram per kilogram
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval 2
MUC1	mucin 1
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluated
nM	nanomolar
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung carcinoma
OEC	ovarian epithelial cancer
ORR	objective response rate
OS	overall survival
PAB	partial additive bag
PARP	polyadenosine diphosphate ribose
PD	pharmacodynamic(s)
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PLT	platelet count
PO	*per os,* oral
POPPK	population pharmacokinetics
PR	partial response

List of Abbreviations and Definitions of Terms

PSA	prostate-specific antigen
PT	prothrombin time
QSP	quantitative systems pharmacology
q*x*w	once every *x* weeks
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumours
RO	receptor occupancy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SPDB-DM4	N-succinimidyl 4-(2-pyridyldithio) butanoate-DM4
SRC	safety review committee
SUSAR	suspected unexpected serious adverse reaction
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TNFα	tumor necrosis factor alpha
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
TTR	time to tumor response
ULN	upper limit of normal
WFI	water for injection
µg	microgram
µL	microliter
µm	micrometer
µM	micromolar

1 INTRODUCTION AND BACKGROUND INFORMATION

This study is composed of 2 distinct documents:

- A common core ("Core"; see separate synopsis [Appendix A]), and
- A CX-2009-specific module ("Module"; this document).

Briefly, the Core is a stable document that contains all the design features typically included in a standard Phase 1-2 protocol, but without reference to a specific experimental agent. The exact same core document is used for all Probody therapeutic first in human (FIH) studies, serving as a centerpiece for all Probody therapeutics in development. It includes, for example, guidelines for drug accountability, efficacy and safety parameters, and study administrative procedures. The CX-2009 Module (this current document), on the other hand, is customized for this specific Probody therapeutic, and all protocol guidelines necessary to safely manage subject care are included within the Module. Familiarity with both the Core and the CX-2009 Module is required for proper conduct of the study.

The Core plus Module system is a mechanism for bundling the clinical evaluation of Probody therapeutics within 1 unified program, with a common study design and common Investigator oversight. See the Core synopsis for a more detailed discussion of the Core design and rationale.

1.1 CD166 (Activated Leukocyte Adhesion Molecule) in Human Cancer

Antibody-drug conjugates (ADCs) are monoclonal antibodies (mAbs) that have been conjugated to cytotoxic small molecules through a linker. ADCs have shown their greatest clinical utility when targeting antigens expressed at very high levels on cancer cells. This is exemplified by the approvals of ado-trastuzumab emtansine (Kadcyla®) for human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) and brentuximab vedotin (Adcetris®) for cluster of differentiation 30 (CD30)-positive Hodgkin disease and anaplastic large cell lymphoma. There are cell surface antigens that are highly expressed on cancer cells and therefore attractive for ADC targets, but may not have been progressed as ADC therapeutics because of concerns around their expression in normal tissues. One such target is CD166, also known as activated leukocyte cell adhesion molecule. CD166 is reported to be a cell adhesion molecule and to be expressed on many cell types, including activated leukocytes, neurons, as well as epithelial and endothelial cells. CD166 has been reported to be a ligand for the CD6 receptor, which is expressed on T lymphocytes and implicated in T cell proliferation and activation (Weidle 2010). However, the biological functions of CD166 are not well established.

CD166 shows homogenous high (3+) expression by immunohistochemistry (IHC) in most samples of multiple cancer types, but also is expressed in multiple normal tissues, including lung, gastrointestinal (GI) tract, and liver. Thus, CD166 has not previously been developed as a target for traditional ADCs.

1.2 Probody Therapeutics

Trademark of CytomX Therapeutics, Inc. (Probody™) therapeutics are fully recombinant antibody prodrugs, activated preferentially by proteases present in tumor microenvironments (TMEs). Because Probody therapeutics are designed to minimize interaction with targets outside of the TME, they potentially enable an ADC approach to effectively and safely target antigens such as CD166, which are expressed both in tumors and normal tissues. Nonclinical in vivo studies show that Probody therapeutics remain substantially unable to bind its target in normal tissues and in circulation.

1.3 CX-2009 Overview

CytomX has developed an anti-human CD166 Probody therapeutic, termed CX-2009, selected for specific binding, internalization, and ability to elicit cytotoxicity. In addition, CX-2009 exhibits cross reactivity to cynomolgus monkeys, thus facilitating safety assessments in this species. CX-2009 is a humanized immunoglobulin G subclass 1 (IgG_1) isotype N-succinimidyl 4-(2-pyridyldithio) butanoate-$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (SPDB-DM4) drug conjugate and has been tested in nonclinical models for efficacy and safety. Treatment with CX-2009 at therapeutically relevant doses has led to significant tumor growth inhibition or regression in models of multiple tumor types including: lung, breast cancer (BC), ovarian epithelial cancer (OEC), head and neck squamous cell carcinoma (HNSCC), and cholangiocellular carcinoma (CCC). These same doses were demonstrated to be well tolerated in cynomolgus monkeys.

CD166 expression is particularly high in a number of cancers that are also sensitive to maytansinoid payloads or other microtubule inhibitors (MTIs) (National Comprehensive Cancer Network Guidelines). Maytansine, or its derivatives such as $N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4), is a benzoansamacrolide and is considered to have a high affinity for tubulin located at the ends of microtubules. The suppression of microtubule dynamics causes cells to undergo cell cycle arrest, ultimately resulting in cell death via apoptosis. Two maytansine derivatives: emtansine, also referred to as $N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine (DM1); and ravtansine, also referred to as SPDB-DM4, have been widely used in combination with irreversible and reversible linkers to generate ADCs (Bouchard 2014).

Frequently occurring cancer types also have high CD166 expression. These include breast, prostate, lung, ovarian, endometrial, head and neck, and biliary cancers, where prevalence of high CD166 expression (≥2+ IHC) ranges from approximately 60.0% to greater than 90.0% (Table 1). Thus, CX-2009 potentially represents a novel therapeutic approach, addressing a significant unmet medical need for a significant proportion of subjects across multiple cancer types.

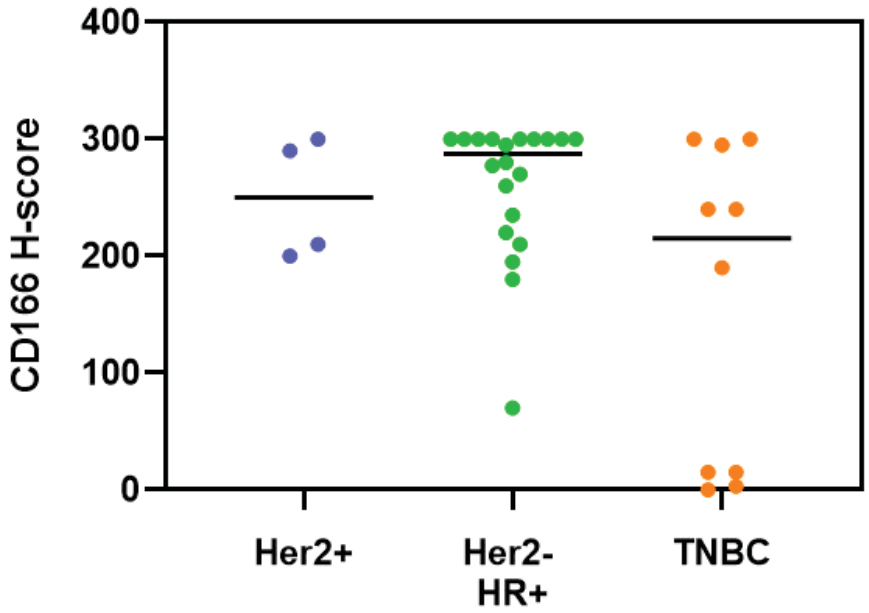
Table 1. Prevalence of CD166 Expression in Human Cancers

Cancer Type	Prevalence of ≥2+IHC CD166 Expression (IHC ≥2+) (%)	Prevalence of CD166-Negativity (IHC <1+) (%)	Number of Cases Examined (n)
Biliary	56.5	11.9	177
Breast	87.1	1.7	533
Endometrial	75.2	6.0	315
HNSCC	81.1	0.8	122
Lung	71.0	8.2	465
Ovarian	70.5	3.9	129
Prostate	98.3	0.8	119

CD166 = cluster of differentiation 166; HNSCC = head and neck squamous cell carcinoma; IHC = immunohistochemistry.
Source: CytomX Report RPT-NC-N-0025-00-01.

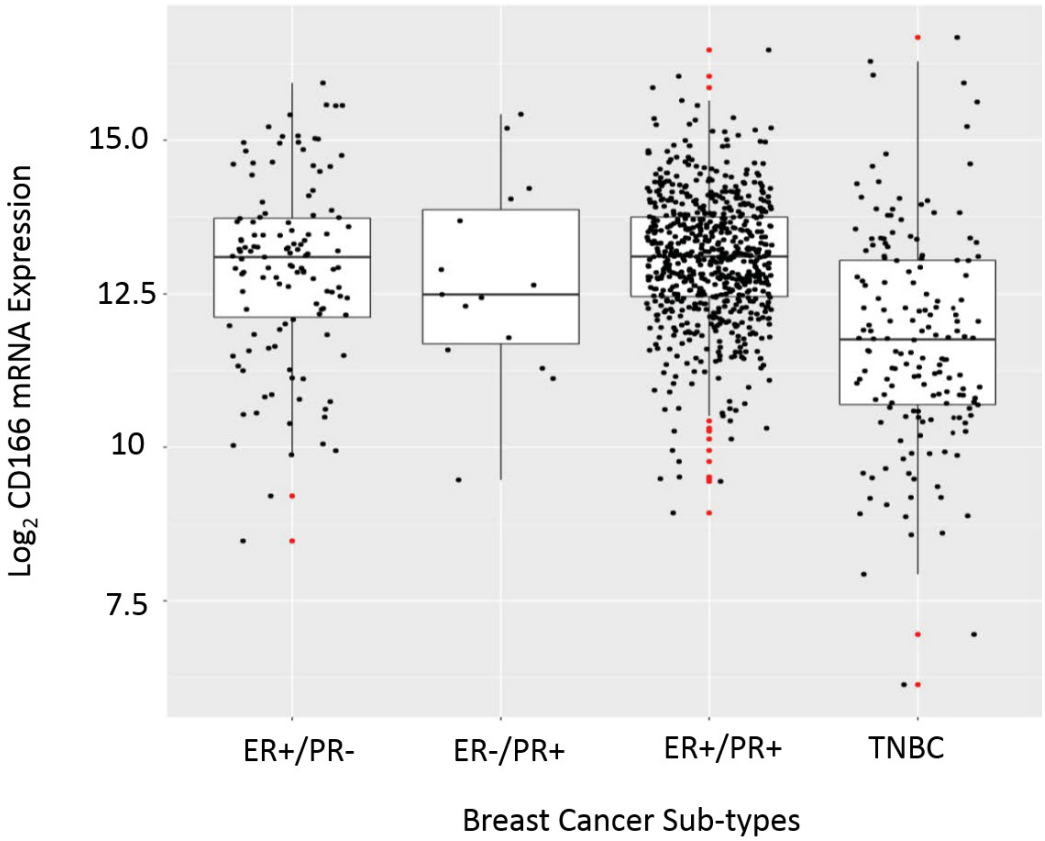
In the Sponsor's analysis using the selected antibody for the IHC assay and tumor specimen data from the initial 39 BC subjects enrolled in this study in the central laboratory, it is estimated that greater than 90% of hormone receptor (HR)-positive/HER2-negative BC subjects will express CD166 and that approximately 50% of triple-negative breast cancer (TNBC) subjects will express CD166 (Figure 1). These data are replicated by using transcriptomic [messenger ribonucleic acid] assays based on 2 separate publicly available databases (METABRIC and The Cancer Genome Atlas [Figure 2]).

Figure 1. CD166 Expression in CX-2009 Breast Cancer Sub-types



CD166 = cluster of differentiation 166; Her2 = human epidermal growth factor receptor 2; HR = hormone receptor; TNBC = triple-negative breast cancer.

Figure 2. CD166 Expression in Breast Cancer Sub-types (TCGA)



CD166 = cluster of differentiation 166; ER = estrogen receptor; mRNA = messenger ribonucleic acid; PR = progesterone receptor; TCGA = The Cancer Genome Atlas; TNBC = triple negative breast cancer.

Subject selection in TNBC will help to eliminate subjects who have zero or low levels of CD166 expression and are unlikely to respond to CX-2009.

CX-2009 is a Probody therapeutic derived from a proprietary, humanized anti-CD166 mAb, and conjugated to SPDB-DM4. CX-2009 has a drug to antibody ratio (DAR) of 3.5, similar to the DARs observed in other DM4 ADCs in clinical use. Expression, purification, DM4 conjugation, formulation, characterization, stability, and administration of CX-2009 are similar to those for other mAbs.

The substrate of CX-2009 is designed to be cleaved by a number of proteases associated with TMEs, including serine protease and matrix metalloproteinase classes (Overall 2006, LeBeau 2013). These proteases were chosen to activate CX-2009 because of their association with the human TME. In numerous cell line xenograft and patient-derived xenograft tumor models, treatment with CX-2009 has led to significant tumor growth inhibition or regression. It was also observed that, at the anticipated therapeutic dose levels, CX-2009 shows extended exposure in cynomolgus monkeys compared with the corresponding CD166-targeting ADC, consistent with CX-2009 avoidance of the antigen sink in normal tissues. Together, these results

indicate that CX-2009 can be efficiently activated in the tumor, while maintaining low binding to normal tissues.

1.3.1 DM4 and DM4-Me Metabolism and Potential for Drug-Drug Interactions

In vitro studies evaluated the potential for involvement of human cytochrome P450 (CYP) isoforms in the metabolism of DM4 and *S*-methyl DM4 (DM4-Me). These studies identified CYP3A4 as the predominant CYP enzyme responsible for the oxidative metabolism of DM4 and DM4-Me in human hepatic microsomes. The biological significance of DM4 metabolism by CYP3A4 remains to be determined as the primary metabolite of DM4, DM4-Me, is not a product of oxidative metabolism but involves the methylation of DM4 by thiol *S*-methyltransferase (Sun 2011). Cytochrome P450 3A4 may however play a primary role in the biotransformation of DM4-Me.

The potential for induction of specific CYP enzymes (CYP1A2, CYP2B6, and CYP3A4) by DM4 and DM4-Me was evaluated in cultured primary human hepatocytes. The results show no evidence for induction of CYP1A2, CYP2B6, and CYP3A4 in cultured human hepatocytes exposed to DM4 or DM4-Me. These data suggest that DM4-containing ADCs including CX-2009 will have a low likelihood of causing a drug-drug interaction mediated by induction of CYP isoforms.

1.3.2 Nonclinical Toxicity Studies for CX-2009

The toxicity of CX-2009 was evaluated in a Good Laboratory Practices (GLP)-compliant 21-day repeat-dose study in cynomolgus monkeys, where findings included injury to nerves (spinal cord and sciatic), hematologic tissues (bone marrow and lymphoid), and epithelial tissues (skin, tongue, and corneal).

Hematologic findings consisted primarily of decreased cellularity in the bone marrow and lymph nodes; these findings were accompanied by hematology changes including moderate to marked decreases in neutrophils and were largely reversed following a 21-day recovery period. Myeloid toxicity is frequently observed with microtubule-targeted agents and was the primary toxicity noted in monkeys following administration of free DM4.

Epithelial findings noted in the skin, tongue, and cornea consisted of single-cell necrosis and increased mitoses, sometimes accompanied by inflammation or infiltrates, epidermal hyperplasia, and hyperkeratosis. In skin, these microscopic findings correlated with clinical observations of black, red, dry, swollen, or flaking skin. In the cornea, the findings correlated with ophthalmic observations of diffuse, very slight to moderate pigmentation of the epithelium, and 1 case of blepharitis and ulcerative keratitis. The epithelial findings were reversed or in the process of reversing following a 21-day recovery period. Ocular toxicity has been a common dose-limiting toxicity (DLT) for several DM4-ADCs (Younes 2012, Moore 2017).

The CX-2009-related finding of axonal degeneration was present at all dose levels; while it was not reversed following a 21-day recovery period, the finding was of minimal or slight severity, did not result in measurable neurological impairment, and the lesion did not progress in severity over the duration of the study. Peripheral neuropathy is a well-described side effect of MTIs (Dumontet 2010). While generally not dose limiting, peripheral neuropathy has been reported in clinical trials of Kadcyla (ado-trastuzumab emtansine or T-DM1) as well as most DM4-ADCs and is an expected toxicity for CX-2009 (Younes 2012, Diéras 2014, Moore 2017).

1.3.3 CX-2009 Starting Dose for Escalation in Part A

To avoid exposing subjects to unsafe levels of anticancer ADCs, but also minimize the number of subjects exposed to sub-efficacious dose levels, it has been suggested that the FIH starting dose for ADCs be at least 1 and fewer than 4 dose doublings below the expected maximum tolerated dose (MTD) (Saber 2015). The MTD for DM4-ADCs containing a cleavable disulfide linker (SPDB or sulfo-SPDB) and administered once every 3 weeks have been in a 4 mg/kg to 6 mg/kg range (Table 2). CX-2009 is anticipated to have a MTD in the same range as other DM4-ADCs based on GLP toxicity study findings, which were similar to those reported for other maytansinoid ADCs and consistent with the activity of DM4.

Based on the projected MTD of 4 mg/kg to 6 mg/kg, a CX-2009 starting dose of 0.25 mg/kg, which is 4 doublings below the lower end of the projected MTD range, is expected to be safe.

Table 2. Human MTD for Disulfide Bond-DM4-containing ADCs

ADC	Target	Human MTD/RP2D/AD
Anetumab ravtansine (BAY 949343)	Mesothelin	6.5 mg/kg q3w Note: half of subjects at MTD require dose reduction (Hassan 2015)
Coltuximab ravtansine (SAR3419)	CD19	160 mg/m^2 (4.32 mg/kg) q3w (Younes 2012)
SAR566658, huDS6-SPDB-DM4	CA6	190 mg/m^2 (5.14 mg/kg) q3w (Boni 2013)
IMGN242 (huC242-DM4)	MUC1	168 mg/m^2 (4.54 mg/kg) q3w (Goff 2009)
Indatuximab ravtansine (BT062)	CD138	160 mg/m^2 (4.32 mg/kg) q3w 100 mg/m^2 (2.7 mg/kg) weekly x3 then 1 week off when combined with lenalidomide and low-dose dexamethasone (Zuber 2012, Kelly 2016)
Mirvetuximab soravtansine (IMGN853)	Folate receptor	6 mg/kg AIBW q3w (Borghaei 2015, Moore 2017)
AVE9633	CD33	150 mg/m^2 (4.1 mg/kg) Days 1 and 8 every month (Lapusan 2012)

AD = acceptable dose; ADC = antibody-drug conjugate; AIBW = adjusted ideal body weight; CD*x* = cluster of differentiation *x*; DM4 = N$^{2'}$-deacetyl-N$^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine; MTD = maximum tolerated dose; MUC1 = mucin 1; q3w = every 3 weeks; RP2D = recommended Phase 2 dose; SPDB = N-succinimidyl 4-(2-pyridyldithio) butanoate.

Selection of the FIH starting dose based on the minimum anticipated biological effect level is not proposed as this would likely result in a starting dose that is approximately 10 dose doublings

below the anticipated MTD of CX-2009 and therefore inconsistent with the recommendations of Saber 2015. Additionally, the GLP toxicity study findings for CX-2009 are similar to those reported for other maytansinoid ADCs and are consistent with the effects of DM4.

Another approach to FIH starting dose selection for anticancer ADCs is to use 1/6 of the highest nonseverely toxic dose (HNSTD) in cynomolgus monkeys, scaled for body surface area (BSA). This formula has generally been found to result in an acceptable balance of safety and efficient dose escalation in Phase 1 trials of ADCs (Saber 2015). An HNSTD was not defined in the GLP toxicity study of CX-2009 due to histopathological findings of axonal degeneration, which did not reverse over a 3-week dose-free interval. There were no clinical observations consistent with functional neuropathy.

Peripheral neuropathy is a well-described side effect of MTIs (Dumontet 2010). While generally not dose limiting, peripheral neuropathy has been reported in clinical trials of Kadcyla as well as most DM4-ADCs and is an expected toxicity for CX-2009 (Diéras 2014, Moore 2017). Resolution rates of ADC-related peripheral neuropathy have ranged from ~19.0% to 54.0% upon treatment discontinuation (Stagg 2016).

In Table 3, CX-2009 is compared to 2 other maytansinoid ADCs, IMGN242 and Kadcyla, which also produced axonal degeneration in monkeys. The dose-dependent incidence and low severity of axonal injury associated with CX-2009 in monkeys appears generally similar to that of Kadcyla and IMGN242, which have been safely administered to cancer patients at starting doses of 0.3 mg/kg and 0.5 mg/kg, respectively.

Table 3. Neurotoxicity of CX-2009 and Other Maytansinoid ADCs in Monkeys

Article (Schedule)	GLP Toxicity Study (Cynomolgus) Dose Levels (mg/kg)	Axonal Degeneration, Sciatic Nerve: Incidence, Severity [a]	Axonal Degeneration, Spinal Cord: Incidence, Severity	Clinical Starting Dose (mg/kg) MTD (mg/kg) DLT
CX-2009 (q3w×2) C16-026	5 10 15	4/12, minimal to mild 8/12, minimal to mild 10/10, minimal to mild	5/12, minimal 11/12, minimal 10/10, minimal	
IMGN242 (huC242-DM4) (single dose) CRT18-001	5 (NOAEL) 15 (HNSTD) 25	0/2 2/2, Grade 2 NE [b]	0/2 2/2, Grade 1 NE	5 4.54 Blurred vision (Goff 2009)
Kadcyla (T-DM1) (q3w×4) (Poon 2013)	3 10 (HNSTD) 30	0/14 6/14, minimal 14/14, slight to severe	0/14 8/14, minimal 14/14, slight to severe	0.3 3.6 Thrombocytopenia (Krop 2010)

a Male and female combined; terminal and recovery animals combined.

b Not evaluated; animals did not survive to scheduled sacrifice on Day 29.

ADC = antibody-drug conjugate; DLT = dose-limiting toxicity; DM1 = $N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl) maytansine; DM4 = $N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine; GLP = Good Laboratory Practices; HNSTD = highest nonseverely toxic dose; MTD = maximum tolerated dose; NE = not evaluated; NOAEL = no observed adverse effect level; q3w×2 = once every 3 weeks with a maximum of 2 doses; q3w×4 = once every 3 weeks with a maximum of 4 doses.

Axonal degeneration in CX-2009-treated animals was of minimal or mild severity, did not progress over the course of the study, and was not associated with clinical signs of neuropathy. Considering these factors, as well as the predictable and dose-dependent nature of this finding, and the monitorability of peripheral neuropathy in the clinic, an FIH starting dose of 0.25 mg/kg is considered to provide a reasonable safety factor while still allowing for efficient dose escalation in patients with advanced cancer. This dose is slightly below the human dose equivalent to 1/6 of the lowest dose tested in the GLP toxicity study (5 mg/kg) after scaling for BSA ([5 mg/kg ÷ 6] ÷ 3.1 = 0.27 mg/kg). No ocular toxicity was observed at the 5 mg/kg dose level in monkeys. A starting dose of 0.25 mg/kg is also 4 doublings below the lower end of the projected MTD range of 4 mg/kg to 6 mg/kg and is therefore consistent with published guidance as described above. An FIH starting dose of 0.25 mg/kg is therefore proposed for CX-2009.

1.3.4 Summary of CX-2009 Clinical Experience

Clinical data from Module CTMX-M-2009-001 as of a 30 November 2019 data lock point are summarized below.

Median duration of exposure to CX-2009 as of the data lock point was 7.3 weeks (maximum 60 weeks).

1.3.4.1 Summary of CX-2009 Clinical Safety

A total of 92 subjects treated with CX-2009 had available safety data. All but 6 subjects received CX-2009 once every 21 days at doses ranging from 0.25 mg/kg to 10 mg/kg. Six subjects received CX-2009 once every 14 days at a dose of 6 mg/kg. Please refer to the Investigator's Brochure (IB) for the most up-to-date information.

Overview of Treatment-emergent Adverse Events

Approximately 91.3% (84 of 92) of subjects had adverse events (AEs) that were judged by the Investigator to be related to study treatment. Forty-two (45.7%) had ocular toxicity that was related to CX-2009, with symptoms similar to other DM4 ADCs.

Twenty-six (28.3%) subjects experienced peripheral neuropathy related to CX-2009. The majority (13/26) had events that were Grade 1. Five subjects had Grade 3 peripheral neuropathy related to CX-2009.

Twenty (21.7%) subjects experienced infusion-related reactions (IRRs), the majority of which were Grade 1 or 2 (1 subject had a Grade 3 IRR). A previous analysis noted that the majority of subjects who had an IRR at the first infusion cycle, did not experience recurrence at subsequent infusions when premedication was administered.

Treatment-related SAEs and Treatment-related AEs Grade 3 or Higher

Eleven (12.0%) subjects experienced treatment-related serious adverse events (SAEs). Thirty-four (37.0%) subjects experienced Grade 3/4 treatment-related adverse events (TRAEs), including 10 with ocular toxicity (n = 8 Grade 3, n = 2 Grade 4) and 5 with peripheral neuropathy (all Grade 3).

There was 1 death related to study treatment according to Investigator's assessment.

Refer to the most recent version of the CX-2009 IB for the most updated and complete safety data.

Dose-Limiting Toxicities

One DLT was observed in Part A (8 mg/kg every 21 days); a Grade 3 event of vomiting that resolved (22 subjects were treated at this dose and schedule). No DLTs were observed at 9 and 10 mg/kg in 9 and 8 subjects, respectively.

Three DLTs were reported in 2 out of 5 evaluable subjects who received CX-2009 at a dose of 6 mg/kg every 14 days (Part C1) including a Grade 3 increased aspartate aminotransferase (AST) and a Grade 3 increased alanine aminotransferase (ALT) in 1 subject, and a Grade 3 peripheral neuropathy in another subject.

Treatment-emergent Adverse Events Related to CX-2009 at the Every 21-day Monotherapy RP2D of 7 mg/kg

As of 30 November 2019, treatment-emergent adverse events (TEAEs) related to CX-2009 reported in 2 or more subjects who received a dose of 7 mg/kg (n=9) administered every 21 days included nausea (44%), fatigue and infusion-related reactions (33% each), vomiting and arthralgia (22% each). Grade 3 TEAEs related to CX-2009 occurred in 2 subjects (1 subject with a Grade 3 peripheral neuropathy and a second subject reporting both Grade 3 nausea and Grade 3 vomiting). No Grade 4 TEAEs related to CX-2009 or DLTs were reported at this dose level. Following a review of the safety and PK data, 7 mg/kg was determined as the monotherapy every 21-day RP2D (see Section 5.2).

1.3.4.2 Summary of CX-2009 Clinical Efficacy

As of 30 November 2019, 2 out of 92 (2.2%) response-evaluable subjects had a confirmed partial response (PR), 6 out of 92 (6.5%) had unconfirmed PRs, and 21 out of 92 (22.8%) achieved stable disease ([SD]; at least 1 on-study scan with SD).

1.4 PD-1 and PD-L1 Inhibitors

The immune system has recently emerged as a highly promising target for the treatment of cancer. T cells are capable of recognizing many cancers as foreign, and, when optimally mobilized, can induce potent and durable responses in patients against many cancer types. However, tumors can evade immunity by exploiting the same mechanisms that in healthy tissue serve to regulate immune function. One such mechanism is through expression of programmed death ligand 1 (PD-L1), a ligand that negatively regulates T cell activity through its interaction with programmed death 1 (PD-1), an inhibitory receptor expressed on activated T cells. The normal role of PD-L1 is to minimize immune-mediated damage to tissues under conditions of chronic T cell stimulation or from attack by autoreactive T cells. Expression of PD-L1 is dynamic and induced most potently by interferon gamma produced by activated T cells, and it functions in a negative feedback loop to suppress the activity of T cells involved in a local tissue attack. PD-L1 is now understood to be a dominant means by which tumors can evade the immune system. Clinical trials have confirmed the capacity of PD-1/PD-L1 blockade to restore tumor specific immunity and improve outcomes for patients with cancer, leading to regulatory approvals to treat a number of tumor types (Balar 2017).

1.5 CX-072 Overview

CX-072 is a Probody therapeutic directed against PD-L1 for the treatment of cancer and is the first under the CytomX Probody platform to be studied in humans. CX-072 is designed to widen the therapeutic window by reducing interaction with PD-L1 in normal tissue environments while maintaining interaction with tumor tissue.

CX-072 is a Probody therapeutic derived from a proprietary human anti–PD-L1 mAb. In patients with various cancers, anti–PD-L1 mAb (atezolizumab, avelumab, and durvalumab) and anti-PD-1 mAb (nivolumab, pembrolizumab, and cemiplimab) have demonstrated clinical safety and effectiveness as monotherapy and/or in combination with other immunotherapies (LaFleur 2018). However, significant life-threatening toxicities have been observed with these agents, particularly in combination regimens. The most common SAEs that lead to premature discontinuation of therapy or death are immune-related and are most likely attributable to drug-induced inflammation outside of the tumor (Larkin 2015). CX-072 is intended to provide antitumor efficacy similar to that of other PD-L1 and PD-1 inhibitors, but with an improved safety profile, especially when given in combination with other therapeutics.

Expression, purification, formulation, characterization, quality attributes, stability, and administration of CX-072 are similar to that of other mAbs.

CX-072 is designed to be activated by a number of proteases associated with the TME, including serine proteases and matrix metalloproteinases classes. These proteases were chosen because there is published evidence that they are activated in human tumors (Overall 2006, LeBeau 2013), and generally, they have low activity in blood or in select normal tissues.

1.5.1 Summary of CX-072 Nonclinical Safety Data

GLP-compliant 4-week repeat-dose general toxicity studies of CX-072 were conducted in rats and cynomolgus monkeys. These studies evaluated dose levels of 20, 60, and 200 mg/kg administered once weekly over 28 days (5 doses) by IV infusion, followed by a 4-week postdose recovery.

CX-072 was well tolerated by rats and monkeys in the GLP toxicity studies, with no significant effect on clinical signs, body weights, clinical pathology, ophthalmology, or safety pharmacology endpoints. No toxicologically significant effects on immune function were noted with CX-072 treatment as assessed by peripheral blood immunophenotyping and plasma cytokine analyses. A single mortality in one 200 mg/kg/dose female monkey that occurred soon after the third dose was considered possibly procedure-related.

In the rat GLP-compliant study, CX-072–related microscopic findings included liver Kupffer cell hypertrophy, pancreatic acinar cell atrophy, and pancreatic mononuclear cell inflammation. Changes in the pancreas persisted in recovery animals. An additional finding in recovery animals was mononuclear cell inflammation of the thyroid. The inflammatory changes in the pancreas and thyroid are suggestive of immune checkpoint inhibition and, as such, are consistent with the anticipated pharmacological effects of CX-072. The marked severity and persistent nature of the thyroid and pancreas findings in some mid-dose and high-dose animals was considered potentially adverse, therefore the no observed adverse effect level (NOAEL) was 20 mg/kg.

In the monkey GLP study, CX-072 was associated with microscopic findings of perivascular inflammation, primarily in the gallbladder, heart, aorta, pancreas, and multiple levels of the GI

tract. This pattern of inflammation is characteristic of biotherapeutic induced vasculitis in animal species, a finding that is often attributed to immunogenicity but may also be a direct pharmacological effect of ICIs such as CX-072 (Frazier 2015). While adverse, these changes were not observed in recovery animals and were therefore reversible. Based on these findings, the NOAEL was 60 mg/kg/dose for females and could not be determined for males. The HNSTD in male and female monkeys was 200 mg/kg.

Additional information may be found in the CX-072 IB.

1.5.2 Summary of CX-072 Clinical Experience

Study CTMX-M-072-001, an FIH, Phase 1-2a study is currently ongoing and is composed of 7 parts: Part A – monotherapy dose escalation; Part A2 – biomarker assessment and dose effect; Parts B1 and B2 – combination with ipilimumab; Part C – combination with vemurafenib; and Parts D and E – monotherapy treatment expansion in select tumor types.

Enrollment in the dose escalation phase of Part A (the Phase 1 monotherapy portion of the study; CX-072 doses up to 30 mg/kg) has been completed without reaching the MTD. The recommended Phase 2 dose (RP2D) was determined to be 10 mg/kg CX-072 once every 14 days, which is equivalent to the 800 mg every 14 days fixed dose.

Clinical data from Parts A, A2, and D (monotherapy) are summarized below.

1.5.2.1 Summary of CX-072 Clinical Safety

Overview of Treatment-emergent Adverse Events

As of 30 November 2019, 111 out of 114 (approximately 97%) subjects who received CX-072 monotherapy at the 10 mg/kg dose level experienced a TEAE, 61 (53.5%) subjects experienced a TEAE ≥Grade 3, and 3 (2.6%) subjects experienced an immune-related adverse event (irAE) ≥Grade 3.

Twelve out of 114 (approximately 11%) subjects who received CX-072 monotherapy at the 10 mg/kg dose level experienced IRRs, all of which were ≤Grade 2.

Treatment-related SAEs and Treatment-related AEs Grade 3 or Higher

Of 114 subjects who received CX-072 monotherapy at the 10 mg/kg dose level, 6 (5.3%) subjects had treatment-related SAEs, and 12 (10.5%) subjects had TRAEs ≥Grade 3.

There were no treatment-related deaths reported according to Investigator's assessment.

Refer to the most recent version of the CX-072 IB for the most recent and complete safety data.

1.5.2.2 Summary of CX-072 Clinical Efficacy

As of 30 November 2019, in the 114 efficacy-evaluable subjects who received 10 mg/kg CX-072 as monotherapy in Parts A, A2, and D, 12 (10.5%) subjects achieved a PR (10 confirmed, 2 unconfirmed) and 37 (32.5%) subjects achieved SD. The disease control rate was 43.0%.

1.6 Rationale for the Combination of CX-2009 and CX-072

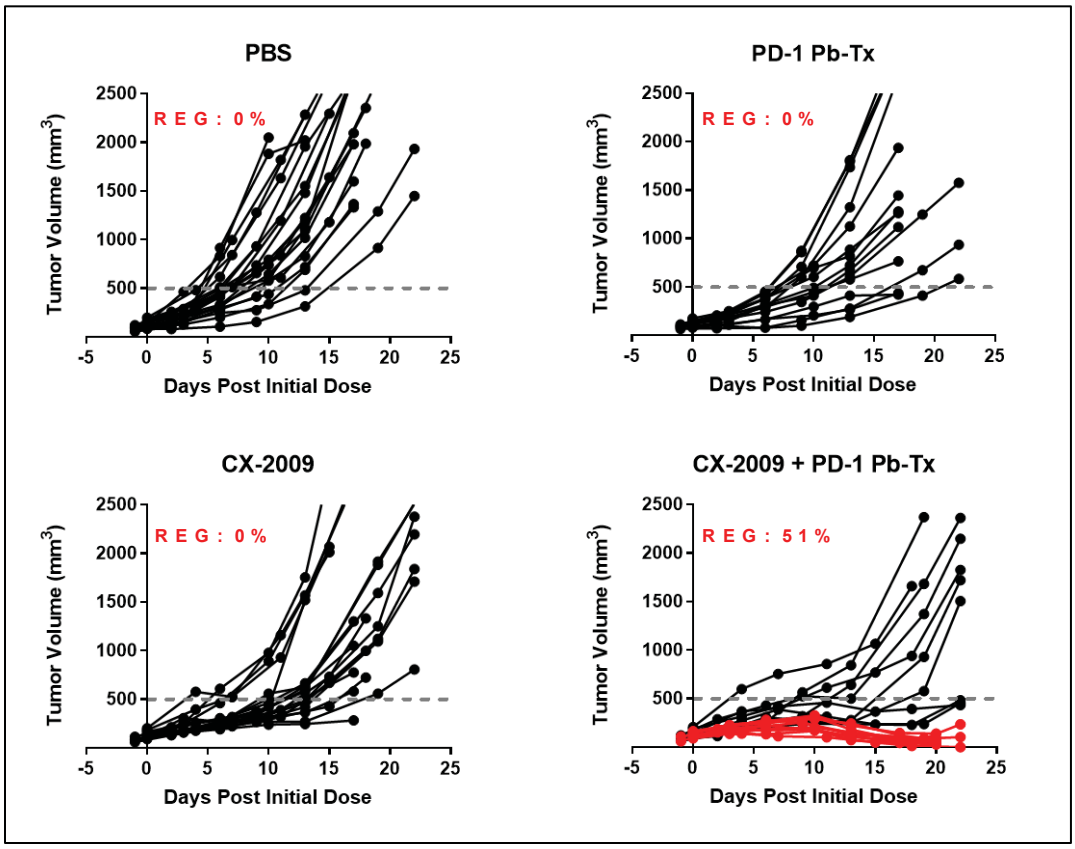
Immune checkpoint inhibitors (ICIs) have been shown to induce potent and durable antitumor immunity in many cancer types. Nevertheless, a minority of patients benefit from single-agent immunotherapy (Du 2017; Jacquelot 2017). Combination of ICIs with conventional chemotherapy has been evaluated for that reason in various indications and led to several approvals (KEYNOTE 189 Gandhi 2018; Impower 133 Horn 2018; Impassion 130 Schmid 2018; and Impower 150 Socinski 2018). Combinations with conventional chemotherapy come with the liability of chemotherapy-related toxicities. A more targeted approach with an ADC may offer means to mitigate part of this toxicity. Data summarized below suggest that combining ICIs with ADC or Probody drug conjugate therapeutics may provide enhanced antitumor activity compared to monotherapy. It has been demonstrated that ADCs are not only capable of killing cancer cells but also can modulate the immune response. Cytotoxic payload/ADCs have been shown to induce immunogenic cell death in vitro and in vivo (Rios-Doria 2017). Immunologic cell death is described as the release of danger signals or damage-associated molecular patterns that elevate the immunogenic potential of dying cells (Garg 2015). In addition to elevating the immunogenic potential of cancer cells, cytotoxic payloads can also provoke phenotypic and functional dendritic cell maturation and activation (Müller 2014). Thus, it appears that cytotoxic payloads not only have cytotoxic effects, but may also potentiate an immune response through multiples modalities. These observations provide a mechanistic rationale for the combination of ADCs and ICIs.

These concepts have been translated in published nonclinical studies where the combination of ADCs bearing various payloads synergized with immunotherapies (Müller 2015, Rios-Doria 2017). Müller et al also reported that T cells are recruited in the TME upon T-DM1 therapy in human and murine BCs (Müller 2015).

The activity of CX-2009 in combination with an effector-null surrogate Probody therapeutic to mouse PD-1 was investigated in a subcutaneous mouse cell line cancer model (Liu 2019 and data on file). As both anti–PD-1 and anti–PD-L1 block signaling in this pathway which results in inhibition of T cell responses, the use of anti–PD-1 Probody therapeutic was considered sufficient to address the impact of pathway blockade in these combination studies. The syngeneic CT26 mouse colon cancer cell line was transfected with human CD166 (CT26-hCD166), the target for CX-2009, to render the cell line sensitive to CX-2009 activity. BALB/c mice were implanted subcutaneously with CT26-hCD166, and tumors allowed to establish prior to the initiation of CX-2009 and anti–PD-1 Probody therapeutic dosing. Neither CX-2009 nor

anti-PD-1 Probody therapeutic monotherapy result in regressions in mice with established CT26-hCD166 tumors (Figure 3); however, the combination produced tumor regressions in 51% of mice (highlighted in red). These results suggest that a Probody therapeutic to the PD-1 pathway combined with CX-2009 can synergize to improve antitumor activity in this nonclinical model.

Figure 3. CX-2009 Enhances the Antitumor Activity of a Mouse Anti-PD-1 Probody Therapeutic in the CT26 HuCD166 Syngeneic Model



Notes: Red graph lines indicate the combination of CX-2009 + PD-1 Pb-Tx produced tumor regressions in 51% of mice.
huCD166 = human cluster of differentiation 166; Pb-Tx = Probody therapeutic; PBS = phosphate-buffered saline; PD-1 = programmed death 1.
Source: data on file.

Data are available from 2 clinical studies of maytansinoid-based ADCs in combination with ICIs which support the benefit of these combinations in patients. In the Phase 1b FORWARD II study, mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting ADC, was combined with pembrolizumab in platinum-resistant ovarian cancer patients. The confirmed objective response rate (ORR) suggests a trend toward clinical benefit (Matulonis 2018).

The KATE2 trial was a randomized Phase 2 study of atezolizumab combined with trastuzumab emtansine (T-DM1) versus placebo combined with T-DM1 in previously treated HER2-positive advanced BC patients. In the PD-L1+ subgroups, the combination of T-DM1 + atezolizumab

resulted in a 54% ORR while the T-DM1 + placebo arm had a 33% ORR (Emens 2018). In the PD-L1+ subgroups, progression-free survival (PFS) was extended from 4.1 months in the T-DM1 + placebo group to 8.5 months in the T-DM1 + atezolizumab group (stratified hazard ratio, 0.60). These data indicate a potential durable clinical benefit for combination of an anti-PD-L1 antibody and a maytansinoid ADC in a PD-L1+ patient population.

In this module, CX-2009 will be combined with CX-072 investigating 2 schedules (every 14 days and every 21 days). Given the safety profile of CX-072, the starting dose for CX-072 will be fixed at 800 and 1200 mg for these 2 schedules, respectively. The starting dose for CX-2009 for these 2 schedules (every 14 days and every 21 days) will be set at the every 14-day monotherapy RP2D as determined in Part C1 and at 7 mg/kg every 21 days (the every 21-day RP2D as previously determined in Part A/A2), respectively. Lower starting doses may be used based on emerging safety data and in consultation with the SRC.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 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.

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

2.1.3 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. Efficacy will be assessed on the basis of the ORR by the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1.

2.1.4 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.

2.1.5 Part C2 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The primary objective of Part C2 is to evaluate the efficacy of CX-2009 when administered IV every 14 days as monotherapy at the MTD/RP2D to subjects with selected advanced or recurrent solid tumors. Efficacy will be assessed on the basis of the ORR by the RECIST Version 1.1.

2.1.6 Part D1 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The primary objective of Part D1 is to determine the safety profile, the MTD/RP2D, and the DLTs of CX-2009 in combination with CX-072, both administered IV every 14 days to subjects with selected advanced or recurrent solid tumors.

2.1.7 Part D2 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The primary objective of Part D2 is to evaluate the efficacy of CX-2009 in combination with CX-072, both administered IV every 14 days at the MTD/RP2D to subjects with selected advanced or recurrent solid tumors. Efficacy will be assessed on the basis of ORR per RECIST Version 1.1.

2.1.8 Part E1 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The primary objective of Part E1 is to determine the safety profile, the MTD/RP2D, and the DLTs of CX-2009 in combination with CX-072, both administered IV every 21 days to subjects with selected advanced or recurrent solid tumors.

2.1.9 Part E2 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The primary objective of Part E2 is to evaluate the efficacy of CX-2009 in combination with CX-072, both administered IV every 21 days at the MTD/RP2D to subjects with selected advanced or recurrent solid tumors. Efficacy will be assessed on the basis of ORR per RECIST Version 1.1.

2.2 Secondary Objectives

2.2.1 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);
  - PFS; and
  - Overall survival (OS);
- Characterize the pharmacokinetics (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; and
  - DM4-Me - a DM4 metabolite with potent cytotoxic activity; and
- Assess the incidence of antidrug antibody (ADA) formation to CX-2009.

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

The secondary objectives of Part A2 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;
  - 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; and
  - DM4-Me; and
- Assess the incidence of ADA formation to CX-2009.

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

The secondary objectives of Part B are to determine the following in subjects 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; and
  - DM4-Me; and
- Assess the incidence of ADA formation to CX-2009.

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

The secondary objectives of Part C1 are to determine the following in subjects 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; and
  - DM4-Me; and
- Assess the incidence of ADA formation to CX-2009.

2.2.5 Part C2 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The secondary objectives of Part C2 are to determine the following in subjects treated with CX-2009 every 14 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; and
  - DM4-Me; and
- Assess the incidence of ADA formation to CX-2009.

2.2.6 Part D1 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The secondary objectives of Part D1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - ORR by the RECIST Version 1.1;
  - ORR by immune-related RECIST (irRECIST) as defined in the Core;
  - TTR;
  - DOR;
  - PFS; and
  - OS;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

2.2.7 Part D2 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The secondary objectives of Part D2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Obtain additional characterization of the safety of CX-2009 administered with CX-072 at the MTD/RP2D;
- Evaluate efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - DOR;
  - TTR;
  - PFS;
  - OS; and
  - ORR by irRECIST as defined in the Core;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

2.2.8 Part E1 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The secondary objectives of Part E1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Evaluate preliminary efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - ORR by the RECIST Version 1.1;
  - ORR by irRECIST as defined in the Core;
  - TTR;
  - DOR;
  - PFS; and
  - OS;
- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

2.2.9 Part E2 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The secondary objectives of Part E2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Obtain additional characterization of the safety of CX-2009 administered with CX-072 at the MTD/RP2D;
- Evaluate efficacy in subjects treated with CX-2009 plus CX-072 on the basis of:
  - DOR;
  - TTR;
  - PFS;
  - OS; and
  - ORR by irRECIST as defined in the Core;

- Characterize the PK of CX-2009 when it is administered in combination with CX-072 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; and
  - DM4-Me;
- Assess the incidence of ADA formation to CX-2009 when it is administered in combination with CX-072;
- Characterize the PK profile of CX-072 when it is administered in combination with CX-2009; and
- Assess the incidence of ADA formation to CX-072 when it is administered in combination with CX-2009.

2.3 Exploratory Objectives

2.3.1 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.

2.3.2 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; and
- Explore potential predictive markers associated with CX-2009 clinical activity such as CD166 expression in tumor specimens while receiving treatment.

2.3.3 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;
- Measure the intact and activated CX-2009 in on-treatment tumor biopsies and peripheral blood; and
- Characterize the protease activity in pretreatment tumor biopsies.

2.3.4 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 protease activity in optional pretreatment tumor biopsies and activation of CX-2009 in optional on-treatment tumor biopsies and peripheral blood.

2.3.5 Part C2 – CX-2009 Monotherapy: Every 14-Day Dosing Regimen

The exploratory objectives of Part C2 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 on-treatment tumor biopsies and peripheral blood.

2.3.6 Part D1 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The exploratory objectives of Part D1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

2.3.7 Part D2 – CX-2009 + CX-072 Combination: Every 14-Day Dosing Regimen

The exploratory objectives of Part D2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 14 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

2.3.8 Part E1 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The exploratory objectives of Part E1 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

2.3.9 Part E2 – CX-2009 + CX-072 Combination: Every 21-Day Dosing Regimen

The exploratory objectives of Part E2 are to determine the following in subjects treated with CX-2009 plus CX-072 every 21 days:

- Explore potential predictive markers associated with clinical activity of the treatment combination such as CD166 expression and PD-L1 status in tumor specimens prior to and while receiving treatment;
- Characterize the protease activity and the activation of CX-2009 and CX-072 in optional on-treatment tumor biopsies and peripheral blood; and
- Investigate the immunomodulatory activity of the treatment combination in optional on-treatment tumor biopsies (fixed and frozen).

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 1-2, open-label, multicenter, dose-finding, and proof of concept study for CX-2009 as monotherapy and (where permitted by local Health Authority) in combination with CX-072 in subjects with advanced solid tumors in the following indications: breast cancer (BC), castrate-resistant prostate carcinoma (CRPC), non-small cell lung carcinoma (NSCLC), OEC, endometrial carcinoma (EC), HNSCC, or CCC. Table 4 provides an overview of the eligible tumor types and enrollment numbers for each part. These tumor types have been selected for their known high levels of CD166 expression and sensitivity to MTIs. A maximum of 993 subjects will be enrolled into the study. No more than 40 subjects will be enrolled with a given tumor type in each part.

The study is divided into 9 parts: Parts A, A2, B, C1, C2, D1, D2, E1, and E2 (see Figure 4), each designed to inform dose selection for the next phase of development. Part A is designed to define the MTD in 2 separate stages: a standard 3+3 escalation followed by a modified toxicity probability interval 2 (mTPI-2) cohort, in subjects receiving CX-2009 every 21 days. Part A2 is designed for biomarker evaluation (particularly Probody therapeutic activation) in order to further inform dose optimization. Part B is focused on expanding clinical experience in order to further define the safety profile at the MTD/RP2D as well as to obtain a preliminary assessment of efficacy in a select number of cancers. Part B may be initiated as soon as the MTD/RP2D is defined in Part A and available data from Part A2 are reviewed in consultation with the Safety Review Committee (SRC; see Appendix E). Part C1 is designed to define the MTD/RP2D in subjects receiving CX-2009 every 14 days. Part C2 is focused on expanding clinical experience in order to further define the safety profile of CX-2009 and to obtain a preliminary assessment of efficacy when administered every 14 days at the MTD/RP2D. Dose expansion for CX-2009 monotherapy may occur under the every 21-day dosing regimen (Part B) and/or the every 14-day dosing regimen (Part C2), depending on available data from Parts A, A2, and C1.

Parts D and E involve co-administration of CX-2009 and CX-072. As such, these cohorts are only open to those countries in which the Health Authority permits these cohorts to activate. Part D1 is designed to define the MTD/RP2D in subjects receiving CX-2009 in combination with CX-072 every 14 days. Part D2 is focused on expanding clinical experience to further define the safety profile of CX-2009 administered in combination with CX-072 and to obtain a preliminary assessment of efficacy of the combination when administered every 14 days at the MTD/RP2D. Part E1 is designed to define the MTD/RP2D in subjects receiving CX-2009 in combination with CX-072 every 21 days. Part E2 is focused on expanding clinical experience to further define the safety profile of CX-2009 administered in combination with CX-072 and to obtain a preliminary assessment of efficacy of the combination when administered every 21 days at the MTD/RP2D.

Table 4. Tumor Types and Enrollment by Part in Study CTMX-M-2009-001

Tumor Type	Study Part								
	A	A2	B	C1	C2	D1	D2	E1	E2
BC	X	X							
TNBC			X	X	X	X	X	X	X
HR-positive/ HER2-negative BC			X	X	X	X	X	X	X
CRPC	X [a]								
NSCLC, including adenocarcinoma and squamous cell subtypes	X	X	X	X	X	X	X	X	X
OEC	X [a]	X	X	X	X	X	X	X	X
EC	X [a]	X							
HNSCC	X	X	X	X	X	X	X	X	X
CCC	X [a]								
Total Enrollment (N ≤ 993):	≤79	≤42	≤200 [b,c]	≤24	≤200 [b,c]	≤24	≤200 [c]	≤24	≤200 [c]

[a] Not an eligible tumor type for the mTPI-2 cohort.

[b] Dose expansion for CX-2009 monotherapy may occur under the every 21-day dosing regimen (Part B) and/or the every 14-day dosing regimen (Part C2), depending on available data from Parts A, A2, and C1.

[c] No more than 40 subjects will be enrolled with a given tumor type in each part.

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; NSCLC = non-small cell lung carcinoma; OEC = ovarian epithelial cancer; TNBC = triple-negative breast cancer.

The study will be conducted in US, UK, Spain, Netherlands, and Germany. Germany will participate only in Part B or C2 of the study. UK will not participate in Parts D1, D2, E1, and E2 of the study.

For all Parts, subjects who have enrolled in the study and have withdrawn prior to receiving the first dose will be designated as screen failures.

A definition of high CD166 expression is provided in Appendix I.

A DLT-evaluable subject is defined as one having received at least 1 dose of CX-2009 (or CX-2009 and CX-072) and then having completed the full DLT observation period (either 21 or 28 days depending on the schedule), or one who subsequently withdrew due to a drug-related toxicity.

Part A:

Dose escalation and determination of the 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 initiates with accelerated dose titration in 1 single-subject cohort (0.25 mg/kg, adjusted ideal body weight [AIBW]), followed by a standard 3+3 design to determine the MTD, and ends in an 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 2007) but allows a more flexible sample size. To understand the statistical rationale for the design, please refer to Section 9 and Appendix C.

Part A2:

Additional enrollment into previously cleared CX-2009 monotherapy dose levels from Part A (n ≤ 42) for every 21-day dosing regimen

Part A2 will help to inform selection of the optimal MTD/RP2D by requiring measurable disease, mandating tumor biopsies to assess Probody therapeutic CX-2009 performance, and selecting for confirmed high CD166 expressing tumors by IHC.

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)

Part B will explore efficacy of CX-2009 by requiring measurable disease. Part B will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. As of November 2019, Part B will be initiated in subjects with HR-positive/HER2-negative BC at a dose of 7 mg/kg.

Part C1:

Dose escalation/de-escalation and determination of the MTD/RP2D of the CX-2009 monotherapy every 14-day dosing regimen (n ≤ 24)

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 was 6 mg/kg, AIBW, administered every 14 days. The initial starting dose for Part C1 was not determined to be tolerated (see Section 1.3.4.1); a lower dose (4 mg/kg) will therefore be explored on the every 14-day schedule. Subsequent dose escalation/de-escalation (if any) will be based upon the

observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed (Figure 6). Part C1 will include up to 24 subjects. Subjects will be selected from the following indications: TNBC, HR-positive/HER2-negative BC, NSCLC, OEC, or HNSCC.

Part C2:

Dose expansion at the MTD/RP2D of CX-2009 monotherapy every 14-day dosing regimen in selected tumor types (maximum n ≤ 200)

Part C2 will explore efficacy of CX-2009. Part C2 will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. Part C2 may be initiated as soon as the MTD/RP2D for the 14-day regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part C1), an every 14-day dosing regimen is considered for further development.

Part D1:

Dose escalation/de-escalation and determination of the MTD/RP2D for the CX-2009 + CX-072 combination in an every 14-day dosing regimen in selected tumor types (n ≤ 24)

Part D1 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. The dose of CX-072 will be fixed at the RP2D (800 mg every 14 days). The starting dose for CX-2009 will be set at the every 14-day monotherapy RP2D as determined in Part C1. Lower starting doses may be used based on emerging safety data and in consultation with the SRC. The mTPI-2 design will be used to determine the MTD/RP2D for the combination dosed every 14 days. The following cohort's dose will be increased or decreased according to the defined dose escalation rules based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6). Part D1 will enroll subjects in 1 or more of the tumor types listed in Table 4.

Part D2:

Dose expansion at the MTD/RP2D of the CX-2009 + CX-072 combination in an every 14-day dosing regimen in selected tumor types (maximum n ≤ 200)

Part D2 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. Part D2 will explore efficacy of CX-2009 plus CX-072 for the every 14-day dosing regimen at the dose selected in Part D1. Part D2 will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. Part D2 may be initiated as soon as the MTD/RP2D for the 14-day combination regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part D1), an every 14-day combination dosing regimen is considered for further development.

Part E1:

Dose escalation and determination of the MTD/RP2D for the CX-2009 + CX-072 combination in an every 21-day dosing regimen in selected tumor types (n ≤ 24)

Part E1 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. The dose of CX-072 will be fixed at the RP2D (1200 mg every 21 days). The starting dose of CX-2009 will be 7 mg/kg (the every 21-day monotherapy RP2D as determined in Parts A/A2). Lower starting doses may be used based on emerging data and in consultation with the SRC. The mTPI-2 design will be used to determine the MTD/RP2D for the combination dosed every 21 days. The following cohort's dose will be increased or decreased according to the defined dose escalation rules based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6). Part E1 will enroll subjects in 1 or more of the tumor types listed in Table 4.

Part E2:

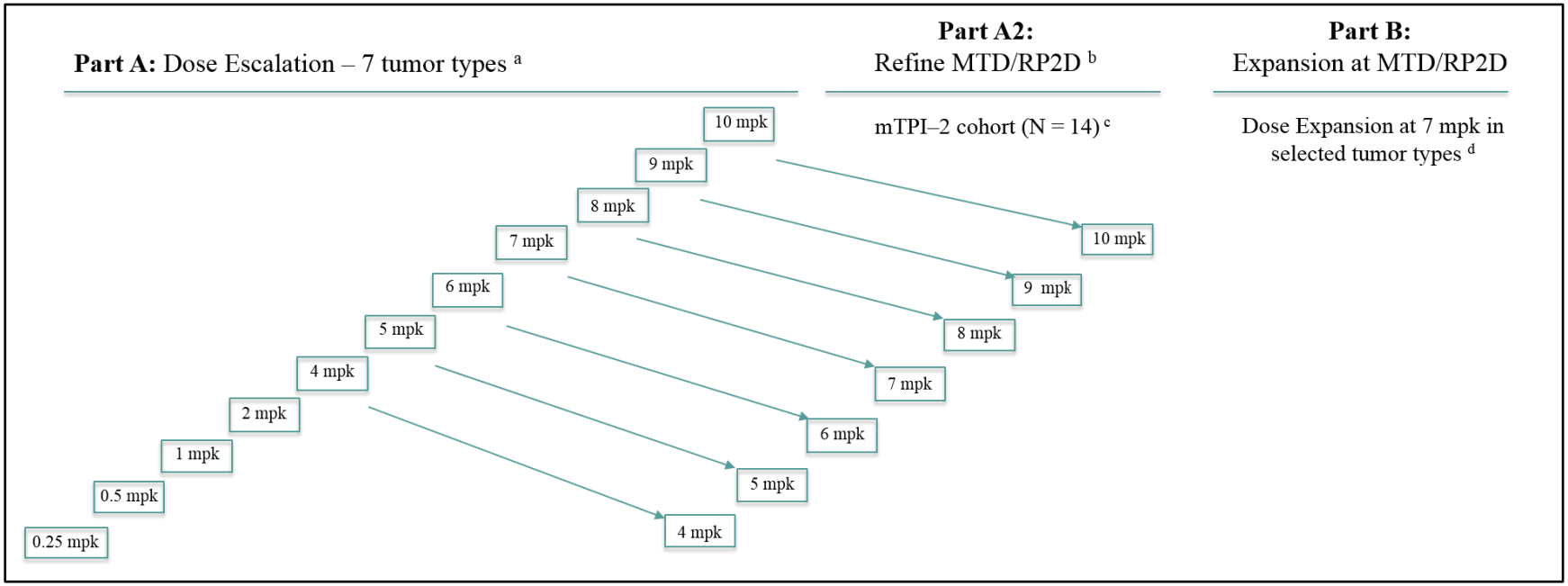
Dose expansion at the MTD/RP2D of the CX-2009 + CX-072 combination in an every 21-day dosing regimen in selected tumor types (maximum n ≤ 200).

Part E2 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. Part E2 will explore efficacy of CX-2009 plus CX-072 for the every 21-day dosing regimen at the dose selected in Part E1. Part E2 will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. Part E2 may be initiated as soon as the MTD/RP2D for the 21-day combination regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part E1), an every 21-day combination dosing regimen is considered for further development.

Allocation of Subjects Between Parts C, D, and E

In case Parts C, D, and E are open for enrollment concurrently and subjects meet the eligibility criteria for all parts, the Sponsor in conjunction with the Principal Investigator will determine to which part the subjects are allocated. The Sponsor will determine which tumor types will be selected for additional evaluation for Parts B, C2, D2, and E2.

Figure 4. 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) and A2 will enroll subjects with confirmed high CD166 expressing tumors.

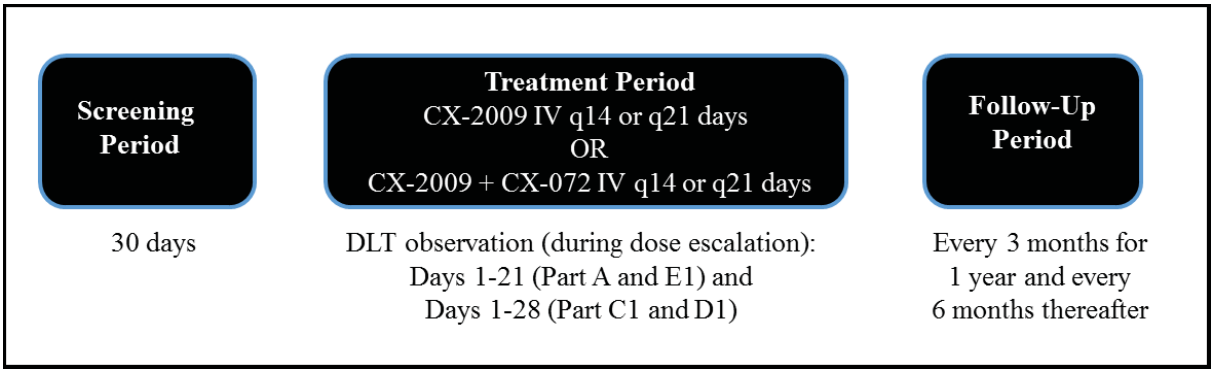
BC = breast cancer; CCC = cholangiocellular carcinoma; CRPC = castrate-resistant prostate carcinoma; EC = endometrial carcinoma; HER2 = human epidermal growth factor receptor 2; HNSCC = head and neck squamous cell carcinoma; HR = hormone receptor; mpk = mg/kg; MTD = maximum tolerated dose; mTPI-2 = modified toxicity probability interval 2; NSCLC = non-small cell lung carcinoma; OEC = ovarian epithelial cancer; RP2D = recommended Phase 2 dose; TNBC = triple negative breast cancer.

3.1.1 Duration of Treatment, Follow-Up, and Study Completion

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points. The schedules of procedures in Appendix B summarize the frequency and timing of efficacy, safety, and other study measurements. Refer to the Core (Appendix A) 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 5).

Figure 5. 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 may continue in the study if experiencing clinical benefit (as assessed by the Investigator) following consultation with the Medial Monitor; otherwise, 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 (or irRECIST, for subjects in Parts D1, D2, E1, and E2) 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 have SD, PR, or 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 study treatment. Once a subject experiences progressive disease, the subject may continue in the study if experiencing clinical benefit (as assessed by the Investigator) following consultation with the Medial Monitor; otherwise, the subject 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.

3.2 Part A (CX-2009 Monotherapy): Dose Escalation and Determination of MTD/RP2D for 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 Modified Toxicity Probability Interval-2 Design Cohort)

The primary objectives of Part A are to assess safety, tolerability, and to determine the MTD/RP2D and DLTs of CX-2009 when administered as monotherapy. Up to 79 subjects with measurable advanced or recurrent solid tumors will be enrolled in the dose escalation portion of the study to determine the MTD/RP2D. As of November 2019, this cohort was closed with 47 subjects enrolled.

One subject will be enrolled into the first cohort until the first dose level is enrolled and treated successfully. Should a subject in cohort 1 experience a ≥Grade 2 AE that is at least possibly related to the study drug, 2 more subjects will be enrolled at that dose level and evaluated based on 3+3 design rules. Should the first subject in cohort 1 experience a DLT, the dose level will be expanded to 3 subjects and if there is no additional DLT, the dose level will be expanded to 6 subjects. All subsequent cohorts will utilize a 3+3 design and will enroll sufficient evaluable subjects to allow for DLT evaluation. Dosing increments will be less than 100.0% if a subject in the single-subject cohort experiences a ≥Grade 2 toxicity. The first subject in each new dose cohort will be dosed at least 24 hours prior to any other subjects in that cohort being dosed, to allow for observation of possible severe and/or serious acute (eg, infusion-related) toxicities that might affect subsequent subject enrollment or dosing decisions.

Enrollment will continue in each cohort until the MTD or the RP2D is defined, or the highest dose (ie, 10 mg/kg, AIBW) has been tested and deemed safe, whichever is lower. AIBW should be applied using the formula provided in Appendix F.

Once the MTD is defined or the highest dose is tested (ie, 10 mg/kg, AIBW), up to 38 subjects can be enrolled at the MTD to refine dose selection using mTPI-2, a rule-based design similar to the 3+3 design that allows dose escalation/de-escalation. Up to 6 subjects can be treated at each dose level and up to 14 subjects can be treated at the identified MTD/RP2D dose level. Assuming that up to 5 dose levels (6 mg/kg to 10 mg/kg, AIBW) may be explored in the mTPI-2 cohort, a maximum sample size of 38 subjects may be enrolled. AEs that meet DLT criteria (within the 21-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose

escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D will be based predominantly on safety and may take other factors into account such as PK/pharmacodynamics (PD) and clinical activity.

The mTPI-2 cohort will evaluate up to 5 dose levels based on DLT events and TRAEs leading to treatment delay or discontinuation, including events of special interest (eg, ocular toxicity and peripheral neuropathy). As events of special interest have been observed at later time points, TRAEs leading to treatment interruption (ie, missed dose) or treatment discontinuation will be evaluated over an extended interval that encompasses the first 3 infusions (42 days). An event for the mTPI-2 cohort is defined as either a DLT or a TRAE leading to treatment interruption (ie, missed dose) or treatment discontinuation. The decision-making tables for the mTPI-2 cohort are provided in Appendix C.

For dosing, AIBW should be applied (Appendix F).

Subjects may be permitted individual dose escalations to previously cleared dose levels following consultation with the Medical Monitor.

The DLT assessment period for dose escalation is 21 days.

Subjects in Part A who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

As of November 2019, the RP2D for CX-2009 administered every 21 days was determined to be 7 mg/kg. For justification of this dose, refer to Sections 1.3.4.1 and 5.2.

3.3 Dose-Limiting Toxicity

All AEs will be captured according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 (and considered for assessment of DLTs as outlined by the criteria in Table 5).

Table 5. Dose-Limiting Toxicity

Suspected DLT Criteria	DLT	
	Yes	No
Grade 5 AEs judged by the Investigator to be treatment-related or judged by the Sponsor as treatment-related, regardless of Investigator attribution.	X	
Grade 4 AEs* judged by the Investigator to be treatment-related or judged by the Sponsor as a DLT, regardless of Investigator attribution.	X	
***Grade 4 Exceptions** • The following Grade 4 hematologic AEs: – Grade 4 lymphopenia; and – Grade 4 neutropenia lasting <7 days that is not associated with fever, or other clinically significant symptoms, or is corrected with supportive measures (eg, growth factors)/appropriate management. • Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.		X
Grade 3 AEs** judged by the Investigator to be treatment-related or by the Sponsor, regardless of Investigator attribution, including: • Any Grade 3 AE that does not resolve to Grade ≤1 or to baseline with appropriate therapies within 7 days of onset; • Any Grade 3 febrile neutropenia; • Any clinically significant Grade 3 CNS event; • Any Grade 3 neurotoxicity; and • Any Grade 3 ocular toxicity (limiting self-care ADL) that does not resolve within 7 days and which did occur despite proper application of preventive measures.	X	
****Grade 3 Exceptions** • Isolated Grade 3 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset; • Grade 3 asthenia which persists for up to 7 days; • "Tumor flare" – defined as local pain, irritation, or rash localized at sites of known or suspected tumor; and • Grade 3 infusion reaction which resolves to ≤Grade 1 within 6 hours.		X
Grade 2 pneumonitis, Guillain-Barré syndrome, transverse myelitis, myocarditis, pericarditis, and arrhythmias necessitating discontinuation of CX-072.	X	
Any clinically significant immune-mediated AE judged by the Investigator to be related to CX-072 that necessitates discontinuation of CX-072.	X	

ADL = activities of daily living; AE = adverse event; CNS = central nervous system; DLT = dose-limiting toxicity.

Enrollment will continue in each cohort until the MTD or the RP2D is defined, or the highest dose (ie, 10 mg/kg, AIBW) has been tested and deemed safe, whichever is lower. Interim dose level(s) may be explored in consultation with the SRC.

The first subject in each new dose cohort will be dosed at least 24 hours prior to any other subjects in that cohort to allow for observation of possible severe and/or serious acute (eg, infusion-related) toxicities that might affect subsequent subject enrollment or dosing decisions. The first dose level will be enrolled as a single-subject cohort. Dose escalation rules are outlined in Table 6.

Table 6. Monotherapy Dose Escalation Rules for 3+3 Design

Number of Subjects in Cohort	Number of DLTs/Subjects	Action
1	0/1	Monotherapy dose completed
1	1/1	Add 2 additional subjects to the cohort (add 3 additional subjects if no further DLTs are observed); all subsequent cohorts 3+3 design
3	0/3	Monotherapy dose completed
3	1/3	Add 3 additional subjects to the cohort
3	≥2/3	Dose level is above the MTD, escalation ceases
6	1/6	Monotherapy dose completed
6	≥2/6	Dose level is above the MTD, escalation ceases

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

3.4 Part A2 (CX-2009 Monotherapy): Additional Enrollment Into Previously Cleared Dose Levels From Part A (n ≤ 42) for Every 21-Day Dosing Regimen

Part A2 will help to inform selection of the optimal MTD/RP2D by investigating Probody therapeutic concentration and activation within the tumor. For that purpose, subjects will be asked to consent to on-treatment tumor biopsies.

Part A2 will initiate enrollment after the 4 mg/kg cohort in Part A has completed the DLT period and with the recommendation of the SRC. Six subjects must be enrolled into each cohort before the next sequential cohort can be enrolled. Doses administered in Part A2 can never exceed the most recently cleared dose in Part A. All toxicities observed in Part A2, regardless of whether they are observed early or late in the dosing course, will be reviewed by the SRC and used to make recommendations for further enrollment in all parts of the study.

Up to a total of 42 subjects will be enrolled at up to 7 dose levels with 6 subjects per cohort per dose. As of November 2019, this cohort was closed with 39 subjects enrolled.

Available data from Part A2 will be considered by the SRC when making dosing recommendations and performing cohort review in Part A. As of November 2019, the RP2D for further study of CX-2009 monotherapy when given every 21 days in Part B was determined to be 7 mg/kg; this dose will continue to be assessed for safety and may be modified if supported by the data.

Part A2 will be restricted to subjects with BC, NSCLC, OEC, EC, and HNSCC. These tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied.

Tumor biopsies are required 3 to 5 days after the first dose of CX-2009. To enroll a subject in Part A2, the Investigator must consider the subject safe to biopsy and the subject must consent to biopsy collection.

3.5 Part B (CX-2009 Monotherapy): Dose Expansion/Proof of Concept at MTD/RP2D for Every 21-Day Dosing Regimen With Proof of Concept in Selected Tumor Types (Maximum n ≤ 200)

To explore efficacy of CX-2009, indication-specific expansion cohorts will be opened to obtain preliminary evidence of clinical activity. Part B will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. As of November 2019, the RP2D of CX-2009 was determined to be 7 mg/kg on the 21-day schedule. Part B will begin enrollment; the initial tumor type selected will be HR-positive/HER2-negative breast cancer. Additional tumor types may also be selected.

If subjects with a specific tumor type are previously treated at the MTD/RP2D in Part A2, they may count towards the first 14 subjects targeted for that tumor type for Part B.

Note: Dose expansion for CX-2009 monotherapy may occur under the every 21-day dosing regimen (Part B) and/or the every 14-day dosing regimen (Part C2), depending on available data from Parts A, A2, and C1. Selection of the regimen for dose expansion will be made in consultation with the SRC.

3.6 Part C1 (CX-2009 Monotherapy): Dose Escalation/De-escalation and Determination of MTD/RP2D for Every 14-Day Dosing Regimen (n ≤ 24)

Part C1 initiated at a dose level of 6 mg/kg every 14 days, AIBW (selected from among the following indications: BC, NSCLC, or HNSCC). Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed (Figure 6). Subsequent dose escalation/de-escalation (if any) will be based upon the observed safety tolerability profile as determined in consultation with the SRC.

Part C1 will evaluate dose levels based on DLT events and TRAEs leading to treatment delay or discontinuation, including events of special interest (eg, ocular toxicity and peripheral neuropathy).

AEs that meet DLT criteria (within the 28-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D with an every 14-day dosing regimen will be based predominantly on safety and may take other factors into account such as PK/PD and clinical activity.

Subjects who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

3.7 Part C2 (CX-2009 Monotherapy): Dose Expansion at the MTD/RP2D for Every 14-Day Dosing Regimen in Selected Tumor Types (Maximum n ≤ 200)

To explore efficacy of CX-2009 for every 14-day dosing regimen, indication-specific expansion cohorts will be opened to obtain preliminary evidence of clinical activity. Part C2 will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. These tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied. Part C2 may be initiated as soon as the MTD/RP2D for the 14-day regimen is defined in consultation with the SRC and will only be initiated if, after the review of dose escalation data (Part C1), an every 14-day dosing regimen is considered for further development.

Allocation of Subjects Between Parts C, D, and E. In case Parts C, D, and E are open for enrollment concurrently and subjects meet the eligibility criteria for all parts, the Sponsor in conjunction with the Principal Investigator will determine to which part the subjects are allocated. The Sponsor will determine which tumor types will be selected for additional evaluation for Parts B, C2, D2, and E2.

Note: Dose expansion for CX-2009 monotherapy may occur under the every 21-day dosing regimen (Part B) and/or the every 14-day dosing regimen (Part C2), depending on available data from Parts A, A2, and C1. Selection of the regimen for dose expansion will be made in consultation with the SRC.

3.8 Part D1 (CX-2009 + CX-072): Dose Escalation/De-escalation and Determination of MTD/RP2D for Every 14-Day Dosing Regimen in Selected Tumor Types (n ≤ 24)

Part D1 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. The dose of CX-072 will be fixed at the RP2D (800 mg every 14 days). The starting dose for CX-2009 will be set at the every 14-day monotherapy RP2D as determined in Part C1. Lower starting doses may be used based on emerging safety data and in consultation with the SRC. The mTPI-2 design will be used to determine the MTD/RP2D for this schedule. The following cohort's dose will be increased or decreased according to the defined dose escalation rules based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6). Part D1 will enroll subjects in 1 or more of the tumor types listed in Table 4. The tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied.

Part D1 will evaluate dose levels based on DLT events and TRAEs leading to treatment delay or discontinuation, including events of special interest (eg, ocular toxicity and peripheral neuropathy).

AEs that meet DLT criteria (within the 28-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D will be based predominantly on safety and may take other factors into account such as PK/PD and clinical activity.

Subjects who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

3.9 Part D2 (CX-2009 + CX-072): Dose Expansion for Every 14-Day Dosing Regimen in Selected Tumor Types (Maximum n ≤ 200)

Part D2 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. To explore efficacy of CX-2009 plus CX-072 for the every 14-day dosing regimen, indication-specific expansion cohorts will be opened to obtain preliminary evidence of clinical activity. Part D2 will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. The tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied. The expansion may be initiated as soon as the MTD/RP2D for the 14-day regimen is defined in consultation with the SRC and will only be initiated if after the review of dose escalation data (Part D1), an every 14-day dosing regimen is considered for further development.

3.10 Part E1 (CX-2009 + CX-072): Dose Escalation and Determination of MTD/RP2D for Every 21-Day Dosing Regimen in Selected Tumor Types (n ≤ 24)

Part E1 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. The dose of CX-072 will be fixed at the RP2D (1200 mg every 21 days). The starting dose of CX-2009 will be 7 mg/kg (the every 21-day monotherapy RP2D as determined in Parts A/A2). Lower starting doses may be used based on emerging data and in consultation with the SRC. The mTPI-2 design will be used to determine the MTD/RP2D for this schedule. The following cohort's dose will be increased or decreased according to the defined dose escalation rules based upon the observed safety tolerability profile as determined in consultation with the SRC. Prior to a dose escalation/de-escalation, a minimum of 3 evaluable subjects must be assessed per the mTPI-2 algorithm (Figure 6). Part E1 will enroll subjects in 1 or more of the tumor types listed in Table 4. The tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied.

Part E1 will evaluate dose levels based on DLT events and TRAEs leading to treatment delay or discontinuation, including events of special interest (eg, ocular toxicity and peripheral neuropathy).

AEs that meet DLT criteria (within the 21-day DLT period) and delayed AEs that lead to treatment interruption/discontinuation within the first 6 weeks, thus encompassing the first 3 doses (DLT rate ≤30.0%; delayed AE rate ≤20.0%), will be monitored. Decision for dose escalation/de-escalation will be made by the Sponsor in consultation with the SRC guided by the decision-making table (Appendix C). The selection of MTD/RP2D will be based predominantly on safety and may take other factors into account such as PK/PD and clinical activity.

Subjects who discontinue study drug administration for reasons other than DLTs may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled.

3.11 Part E2 (CX-2009 + CX-072): Dose Expansion for Every 21-Day Dosing Regimen in Selected Tumor Types (Maximum n ≤ 200)

Part E2 is only open to those countries in which the Health Authority permits the combination of CX-2009 and CX-072 to be investigated. To explore efficacy of CX-2009 plus CX-072 for the every 21-day dosing regimen, indication-specific expansion cohorts will be opened to obtain preliminary evidence of clinical activity. Part E2 will enroll up to a total of 40 subjects each in 1 or more of the tumor types listed in Table 4. The tumor types have been selected for their responsiveness to MTIs and general availability of lesion safe to be biopsied. The expansion may be initiated as soon as the MTD/RP2D for the 21-day regimen is defined in consultation with the SRC and will only be initiated, if after the review of dose escalation data (Part E1), an every 21-day dosing regimen is considered for further development.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

A subject may be approached for informed consent so that archival tumor tissue may be tested for CD166 expression (prior to the subject being otherwise eligible for entry into this study). An abbreviated informed consent form would be used for this purpose.

After signing the informed consent form (ICF), subjects will be evaluated for CTMX-M-2009-001 study eligibility during the Screening Period (no more than 30 days before study drug administration) according to the following inclusion/exclusion criteria.

4.1 Inclusion Criteria

Subjects who fulfill the following criteria at Screening will be eligible for admission into the study:

1. Histologically confirmed diagnosis of active metastatic or locally advanced unresectable solid tumor in subjects who have disease progression after treatment with available therapies that are known to confer clinical benefit, or who are intolerant to treatment, in the following indications (with guidance for standard treatment below).

   Subjects participating in Parts A and A2 and all subjects except those with HR-positive/HER2-negative must submit an archival tumor tissue sample to the central laboratory for evaluation of CD166 expression and demonstrate confirmed high CD166 expression by IHC. For subjects without available archival tumor tissue, only those subjects who consent and for whom the Principal Investigator determines that tumor biopsy can be safely performed can undergo biopsy collection for the purpose of determining eligibility.

   Eligible Indications, by Part: see Table 4

   Criterion Specific to Parts B, C, D, and E:

   - Subjects must have received the standard prior treatments for metastatic or advanced unresectable measurable disease as outlined below:

   Standard Prior Treatments, by Tumor Type:

   TNBC (Parts B, C1, C2, D1, D2, E1, and E2):

   - Histologically or cytologically confirmed TNBC based on the most recent analyzed biopsy or other pathology specimen. Pathologic results should show HR-positive <10% by IHC and HER2-negative disease by American Society for Clinical Oncology (ASCO) guidelines (Allison 2020); the Principal Investigator should use his/her best medical judgment to decide whether the subject's BC should be best managed as HR-positive or triple-negative disease;
   - Refractory to or relapsed after 1 but no more than 3 prior standard therapeutic regimens for advanced/metastatic TNBC (for regimen counting rules, see Appendix J); rapid progression following adjuvant therapy (<12 months from last dose) will count as a

regimen for advanced/metastatic disease. If locally approved, this must include an ICI in combination with cytotoxic chemotherapy (such as atezolizumab with nab-paclitaxel). Standard therapeutic regimens may include cytotoxic therapy, an ADC, a polyadenosine diphosphate ribose (PARP) inhibitor, or an investigational therapy;

- Subjects must have received a taxane (paclitaxel or docetaxel)-based regimen in any setting (neoadjuvant, adjuvant, localized or advanced/metastatic disease); and
- Parts D and E: PD-L1 expression data are not required; subjects with known PD-L1 negative disease (using any commercially available antibody) are not eligible;

<u>HR-positive/HER2-negative BC (Parts B, C1, C2, D1, D2, E1, and E2):</u>

- Tumor tissue must be obtained and forwarded to the central laboratory for determination of CD166 expression by IHC but this result is not required during the screening period;
- Refractory to or relapsed after at least 2 and no more than 4 prior systemic chemotherapy regimens for metastatic BC (not including single-agent hormonal therapy);
- An eligible subject must have received:
  - At least 1 prior anticancer hormonal treatment in any setting (neoadjuvant, adjuvant, locally advanced or metastatic disease);
  - At least 1 cyclin-dependent kinase inhibitor 4/6 in any setting (eg, palbociclib, abemaciclib, ribociclib, or a member of this class);
  - At least 1 prior cytotoxic chemotherapy in the metastatic setting (eg, microtubulin-targeted agents including taxanes, antimetabolites, anthracyclines, alkylating agents, topoisomerase 1 or 2 inhibitor, etc), or mammalian target of rapamycin inhibitor;
  - Investigational drugs and drugs that are commercially available but not approved for BC count as a regimen (for regimen counting rules, see Appendix J); and
- Parts D and E: PD-L1 expression data are not required; subjects with known PD-L1 negative disease (using any commercially available antibody) are not eligible;

<u>CRPC (Part A):</u>

- Received at least 1 prior therapy (eg, abiraterone + prednisone, or docetaxel + prednisone, or enzalutamide);

<u>NSCLC, Including Adenocarcinoma and Squamous Cell Subtypes (All Parts):</u>

- No more than 3 prior regimens for locally advanced/metastatic disease (including chemoradiation);
- Should have received at least 1 platinum-containing regimen, at least 1 taxane-containing regimen, and 1 anti–PD-1 or anti–PD-L1 therapy (if anti-PD-1 or anti-PD-1 therapy is approved and available for the subject's indication in their locality); and
- Subjects harboring known genomic aberrations for which an approved targeted therapy is locally available (eg, non-resistant epidermal growth factor receptor [EGFR] mutations,

EGFR T790M mutation, anaplastic lymphoma kinase (ALK) rearrangement, ROS rearrangement, BRAF V600E mutation) must have received at least 1 prior treatment with an approved targeted therapy;

OEC (All Parts):

- Subjects must have platinum-resistant or platinum-refractory ovarian carcinoma (progression within 180 or 90 days from last dose of platinum); no more than 2 prior platinum-containing regimens are permitted;
- Subjects with platinum-resistant disease must have also progressed on chemotherapy plus bevacizumab;
- Subjects with BRCA mutations must be refractory to or ineligible per local prescribing guidelines for PARP inhibitors (eg, olaparib or rucaparib) if approved and available; and
- Subjects may have received up to 3 regimens for advanced/metastatic disease;

EC (Parts A, A2):

- Should have received at least 1 platinum-containing regimen for extra-uterine or advanced disease;

HNSCC (All Parts):

- Must have received a platinum-containing regimen and anti–PD-1 if approved and available for subject's indication in their locality;
- Must have progressed on at least 1 additional regimen for advanced/metastatic disease including either a taxane, cetuximab, or methotrexate; and
- Subjects may have received up to 3 regimens for advanced/metastatic disease;

CCC (Part A):

- Failed at least 1 prior line of a gemcitabine-containing regimen;

2. Agrees to provide tumor tissue; archival, new, or recent acquisition confirmed to be available prior to initiation of study drug for performance of correlative tissue and cellular studies from a tumor site not previously irradiated:
   - Part A2: subjects must consent to an on-treatment tumor biopsy at 3 to 5 days after the first dose of CX-2009; and
   - Parts B and C2 (monotherapy dose expansions): at least 7 subjects of each tumor type must consent to provide a pretreatment and on-treatment tumor biopsy and peripheral blood samples 3 to 5 days after the first dose of CX-2009;
3. Evaluable or measurable disease required for dose escalation (Part A) and measurable disease per RECIST v1.1 required for all other parts;
4. Subjects with treated brain metastases (surgery, stereotactic radiation, whole brain radiation, or a combination of these modalities) are eligible if the subject's brain metastases have been documented to be stable by head imaging (2 scans at least 28 days apart, including the scan

obtained during the screening period) and the screening clinical examination and the subject does not require radiation therapy, or high-dose steroids (defined as prednisone 10 mg/day or its equivalent). Active screening for subjects not known to have brain metastases (eg, brain computed tomography or magnetic resonance imaging) is not required;

5. At least 18 years of age;
6. Eastern Cooperative Oncology Group performance status of 0 or 1;
7. Anticipated life expectancy of at least 3 months;
8. Screening laboratory values must meet the following criteria:
   - Absolute neutrophil count ≥1500/μL;
   - Platelet count ≥75 × 10^3/μL (must not have been transfused within previous 10 days);
   - Hemoglobin ≥9.0 g/dL (may have been transfused);
   - Serum creatinine ≤1.5 × institution's upper limit of normal (ULN);
   - AST ≤2.5 × institution's ULN; ALT ≤2.5 × institution's ULN (AST, ALT <5 × ULN for subjects with CCC with liver metastases);
   - Serum total bilirubin ≤1.5 × institutional ULN (total bilirubin must be ≤3.0 × institution's ULN in subjects with Gilbert's syndrome). Serum total bilirubin ≤3.0 × institutional ULN for subjects with CCC with liver metastases;
   - For Parts B, C, D, and E only:
     – Hemoglobin ≥ 9.0 g/dL (without transfusion within 30 days of Cycle 1 Day 1);
     – AST, ALT, and alkaline phosphatase (ALP) ≤2.5 × institution's ULN (without exemption for liver or bone metastases);
     – International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤1.5 × ULN (unless subject is on therapeutic anticoagulation, at which time the INR and aPTT must be in the target therapeutic anticoagulation range); and
     – Serum albumin ≥2.5 g/dL.
9. Women of childbearing potential (defined as women who have experienced menarche and who are not permanently sterile or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause) and males must agree to use a highly effective method of contraception prior to study entry, while on study drug, and for a period of 50 days after the last dose of CX-2009 or 6 months after the last dose of CX-072, whichever is later;
   - Highly effective methods of contraception which result in a low failure rate (ie, <1.0% per year) when used consistently and correctly include implants, injectables, combined hormonal contraceptives, some intrauterine devices, sexual abstinence, or a vasectomized partner;
     – True abstinence, when in line with the preferred and usual lifestyle of the subject, is 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, post-ovulation method] and withdrawal are not acceptable methods of contraception.); and

10. The ability to understand and the willingness to sign a written informed consent document and adhere to study schedule and prohibitions.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria at Screening will not be eligible for admission:

1. Neuropathy >Grade 1;
2. Active or chronic corneal disorder, including but not limited to the following: Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, and also active ocular conditions requiring ongoing treatment/monitoring such as wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, presence of papilledema, and acquired monocular vision. In addition, the following exclusions apply:
   - Subjects with cataract surgery until 30 days after last dose of steroid eye drops calculated from Cycle 1 Day 1 (subjects with untreated cataracts are not excluded);
   - Subjects with prior refractive surgery of any type (eg, Lasik surgery) within 1 year prior to Cycle 1 Day 1;
   - Subjects with any other type of recent ocular surgery excluded until 30 days after last dose of eye drops calculated from Cycle 1 Day 1 (not including artificial tears); or
   - Subjects whose severe or refractory dry eye or other ocular surface disease requires 2 or more ophthalmic medications (not including artificial tears);
3. Serious concurrent illness, including, but not limited to the following:
   - Clinically relevant active infection including known active hepatitis B or C, human immunodeficiency virus infection, or cytomegalovirus infection or any other known concurrent infectious disease, requiring IV antibiotic, antiviral, or antifungal therapy within 2 weeks of study enrollment;
   - History of or current active autoimmune diseases, including but not limited to myasthenia gravis, inflammatory bowel diseases, rheumatoid arthritis, autoimmune thyroiditis which is not a sequela of prior immune checkpoint therapy, autoimmune hepatitis, systemic sclerosis, systemic lupus erythematosus, autoimmune vasculitis, autoimmune neuropathies, or type 1 insulin dependent diabetes mellitus;
   - Significant cardiac disease such as recent myocardial infarction (≤6 months prior to Day 1), unstable angina pectoris, uncontrolled congestive heart failure (New York Heart Association >class II), uncontrolled hypertension (NCI CTCAE v4.03 Grade 3 or higher), uncontrolled cardiac arrhythmias, severe aortic stenosis, or ≥Grade 3 cardiac toxicity following prior chemotherapy;

- History of multiple sclerosis or other demyelinating disease, Eaton-Lambert syndrome (para-neoplastic syndrome), history of hemorrhagic or ischemic stroke within the last 6 months, or alcoholic liver disease;
- Non-healing wound(s) or ulcer(s) except for ulcerative lesions caused by the underlying neoplasm;
- Psychiatric illness/social situations that would limit compliance with study requirements; or
- Interstitial lung disease irrespective of etiology;

4. Advanced or metastatic Stage IV NSCLC subjects with known EGFR or ALK genomic alterations unless they have progressed on treatment with appropriate targeted therapy;
5. Any other anticancer treatment such as chemotherapy, immunotherapy, biochemotherapy, radiotherapy, investigative therapy, or (Parts D and E only) high-dose steroids (defined as prednisone 10 mg/day or its equivalent) within 30 days of receiving study drug (14 days for oral medications). Subjects on stable doses of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK-L) agents are permitted to enroll. Low-dose steroids, luteinizing hormone-releasing hormone, aromatase inhibitors (eg, anastrozole), at doses that have been stable for ≥30 days are permitted for subjects with CRPC;
6. History of severe allergic or anaphylactic reactions to previous mAb therapy;
7. Prior treatment with maytansinoid-containing drug conjugates (eg, Kadcyla [T-DM1]);
8. Subjects with a previously documented absence of thiol-*S*-purine methyltransferase activity;
9. Unresolved acute toxicity NCI CTCAE v4.03 Grade >1 (or baseline, whichever is greater) from prior anticancer therapy. Alopecia and other nonacute toxicities are acceptable;
10. History of malignancy that is active within the previous 2 years except for localized cancers that are not related to the current cancer being treated, are considered to have been cured and in the opinion of the Investigator, present a low risk for recurrence, including basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the prostate, cervix or breast;
11. Currently receiving anticoagulation therapy with warfarin;
12. The subject has undergone major surgery (requiring general anesthesia) within 3 months prior to dosing. Subjects who have undergone major surgery within this time period may be enrolled, after consultation with the Medical Monitor;
13. Subjects who have received a live vaccine within 28 days prior to the planned first dose of CX-2009 (examples include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine);
14. Participating in an ongoing clinical study involving treatment with medications, radiation, or surgery;

15. Women who are pregnant or breast feeding; or
16. Subjects who are >20.0% below their ideal body weight, as determined using the formula in Appendix F.

4.3 Additional Exclusion Criteria for Parts D1, D2, E1, and E2

17. History of myocarditis regardless of the cause;
18. History of intolerance to prior ICI therapy defined as the need to discontinue treatment due to an irAE;
19. History of any syndrome or medical condition that requires treatment with systemic steroids (≥10 mg daily prednisone equivalents) or immunosuppressive medications. However, subjects who require brief courses of steroids (eg, as prophylaxis for IV contrast or for treatment of an allergic reaction) may be eligible with Sponsor approval. Inhaled or topical steroids are permitted;
20. History of allogeneic tissue/solid organ transplant, stem cell transplant, or bone marrow transplant.
21. For HR-positive/HER2-negative BC, subjects must have not received prior PD-1 or PD-L1 inhibitors.

4.4 Withdrawal Criteria

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

- The subject experiences clinically significant or confirmed (RECIST) disease progression (or irRECIST in Parts D1, D2, E1, and E2), unless the subject experiences clinical benefit (as assessed by the Investigator); treatment beyond progression is permitted following consultation with the Medical Monitor or designee; however, the subject should be monitored and if continued progression occurs as defined by irRECIST, the subject must be withdrawn from the study drug;
- 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 anticancer treatment;
- The subject experiences an AE 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);
- 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 TREATMENTS

5.1 Treatment Groups

Subjects will be treated with CX-2009 as monotherapy or with CX-2009 in combination with CX-072. Table 4 provides an overview of the eligible tumor types and enrollment numbers for each part.

5.2 Rationale for Dosing

5.2.1 CX-2009 as Monotherapy

5.2.1.1 Every 14-day Dosing Regimen

The rationale for the every 14-day dosing regimen is based on both modeling results and observed preliminary clinical data as described below. A targeted concentration range of 90 to 190 nM for CX-2009 was derived upon both (1) observed tumor growth inhibition data in a mouse xenograft model, and (2) a quantitative systems pharmacology (QSP) model that was used to scale these results from mouse to human. The QSP model captures known mechanisms of Probody therapeutic receptor binding, cleavage, elimination, tissue and tumor biodistribution, and receptor and receptor-drug complex endocytosis (Desnoyers 2013). The targeted concentration range reflects a range of assumed tumor interstitial to plasma ratios from the literature (Baxter 1995). Preliminary population PK (POPPK) and exposure-response analyses have been conducted using available data from study CTMX-M-2009-001. Preliminary exploratory exposure-safety analyses as of October 2019 were examined for possible correlations between selected TEAEs, including ocular toxicity, and maximal plasma concentration (C_{max}), minimal plasma concentration (C_{min}), and area under the concentration-time curve (AUC) for intact CX-2009, free DM4 and DM4 Me, and total CX-2009-conjugated DM4. Overall, p-values were the lowest for the intact CX-2009 exposure metrics. For ocular toxicity of Grade 3 and higher, there were statistically significant relationships ($p<0.05$) for intact AUC, intact C_{max}, and intact C_{min}. These results suggest that relative to the every 21-day dosing regimen, an every 14-day dosing regimen may permit a greater fraction of subjects to remain above the 90 nM targeted C_{min} with a lower dose of CX-2009, possibly reducing the fraction of subjects who experience C_{max}-related TEAEs.

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 (which will be further tested in Parts C1 and C2) equivalent of 10 mg/kg administered every 21 days is approximately 7 mg/kg. In order to provide an additional margin of safety coverage for Part C1, the starting dose was 6 mg/kg, AIBW administered every 14 days. Six subjects were enrolled in this cohort. There were 3 DLTs in 2 of 5 evaluable subjects (a Grade 3 neuropathy in one and Grade 3 AST/ALT elevations in another). The SRC reviewed the data and recommended that subjects currently on 6mg/kg every 14-day dosing regimen be dose

reduced to 4 mg/kg every 14-day dosing regimen, this is the next planned dose for evaluation in Part C1.

5.2.1.2 Every 21-day Dosing Regimen

Selection of the starting dose of 0.25 mg/kg CX-2009 every 21 days is based on nonclinical safety data on CX-2009 as well as nonclinical and clinical experience with other DM4-conjugated antibodies. Initially selected dose levels for Part A in the original Module were based on publicly available data for antibodies conjugated to DM4. Dose levels being implemented a subsequent amendment were based on a subsequently conducted analysis using available toxicology, pharmacology, and the QSP analysis outlined in Section 5.2.1.1.

The monotherapy every 21-day RP2D of 7 mg/kg administered every 21 days has been selected for Part B based upon observed clinical data and POPPK simulations. In the every 21-day dosing regimen, doses up to 10mg/kg were given without a protocol-defined DLT. However, there was a difference noted in the incidence of Grade 3 or higher keratitis at doses above 7 mg/kg administered every 21 days versus lower doses. As of the 28 October 2019 data cut date, observed clinical safety data suggest Grade 3 or greater ocular toxicity was reported more frequently at dose levels of 8 mg/kg administered every 21 days and above. There was 1 report of Grade 3 ocular toxicity at a doses of 5 mg/kg administered every 21 days (there were no Grade 4 ocular toxicities at any dose of 7 mg/kg administered every 21 days or lower) and 9 reports of Grade 3/4 ocular toxicity at doses of 8 mg/kg administered every 21 days and above (6mg/kg administered every 14 days from Part C1 was included in this group). Evidence of clinical activity was also observed at doses of 4 mg/kg administered every 21 days or higher. At doses of ≤ 7mg/kg, of 38 subjects treated, the ORR was approximately 8% (all uPR) in a heavily pretreated population. The POPPK simulations suggested that relative to the 8 mg/kg every 21-day dose level, the next greatest fraction of subjects was expected to surpass the targeted 90 nM C_{min} at the 7 mg/kg every 21-day dose level.

5.2.2 CX-2009 + CX-072 as Combination Therapy Every 14 Days, Dose Escalation/De-escalation (Part D1) and Expansion (Part D2)

5.2.2.1 CX-072 Dose – Parts D1 and D2

A fixed dose of 800 mg CX-072 every 14 days (equivalent to the 10 mg/kg every 14 days weight-based dose) is proposed for combination with CX-2009 in Part D of study CTMX-M-2009-001. The 800 mg CX-072 every 14-day dose is the RP2D for CX-072 monotherapy in study CTMX-M-072-001, and subjects currently being enrolled in Parts A2 and D of that study are receiving 10 mg/kg CX-072 every 14 days (equivalent to the 800 mg CX-072 every 14 days fixed dose) as monotherapy. Published exposure-response information for the PD-L1 inhibitor atezolizumab (Stroh 2017) as well as the totality of available nonclinical and preliminary clinical data from study CTMX-M-072-001 were leveraged to support the 800 mg every 14-day fixed dose monotherapy regimen. A targeted C_{min} for CX-072 was established

based upon an assumed required PD-L1 receptor occupancy (RO) for efficacy for atezolizumab (Deng 2016) as well as on results from a QSP model that was used to incorporate the effect of Probody properties on the C_{min} required for this RO in the tumor for CX-072. Preliminary data from study CTMX-M-072-001 suggest that ADAs have been observed in subjects receiving CX-072, and that a fraction of those receiving <10 mg/kg CX-072 every 14 days have not maintained the targeted C_{min} despite repeat dosing. Subjects receiving 10 mg/kg CX-072 every 14 days have maintained the targeted C_{min} regardless of ADA status. Because at high concentrations CX-072 can bind to its target even when the mask is intact, 10 mg/kg CX-072, the minimum dose at which the targeted C_{min} was maintained, was selected as the every 14-day dose. A subsequent model-based evaluation did not suggest there would be a clinically meaningful change in exposure following the fixed dose of 800 mg CX-072 every 14 days (equivalent to the 10 mg/kg every 14-day weight-based dose) for investigation as the monotherapy RP2D in study CTMX-M-072-001. Clinical safety data for CX-072 and CX-2009 further suggest that 10 mg/kg CX-072 every 14 days is well tolerated as monotherapy with a manageable toxicity profile, and that there would be non-overlapping toxicities for CX-072 and CX-2009. Accordingly, the CX-072 800 mg every 14-day monotherapy RP2D is proposed as the single dose level and schedule for combination with CX-2009 in Part D of study CTMX-M-2009-001.

5.2.2.2 CX-2009 Dosing – Parts D1 and D2

CX-2009 is planned to be administered in combination with CX-072 800 mg every 14 days in Parts D1 and D2 of study CTMX-M-2009-001. To match the every 14-day dosing schedule of CX-072, CX-2009 is likewise planned to be dosed every 14 days. The starting dose for CX-2009 will be set at the every 14-day monotherapy RP2D as determined in Part C1. Lower starting doses may be used based on emerging safety data and in consultation with the SRC.

5.2.3 CX-2009 + CX-072 as Combination Therapy Every 21 Days, Dose Escalation (Part E1) and Expansion (Part E2)

5.2.3.1 CX-072 Dose – Parts E1 and E2

A fixed dose of 1200 mg CX-072 administered every 21 days, which is equivalent to the 800 mg every 14-day dose, is planned for combination with CX-2009 in Parts E1 and E2 of study CTMX-M-2009-001.

5.2.3.2 CX-2009 Dosing – Parts E1 and E2

CX-2009 is planned to be administered in combination with CX-072 1200 mg every 21 days in Parts E1 and E2 of study CTMX-M-2009-001. To match the every 21-day dosing schedule of CX-072, CX-2009 is likewise planned to be dosed every 21 days. The starting dose of CX-2009 when administered with 1200 mg CX-072 every 21 days in Part E1 of study CTMX-M-2009-001 is to be the CX-2009 every 21-day monotherapy RP2D of 7 mg/kg.

5.3 Randomization and Blinding

This is an open-label study. No blinding is needed.

5.4 Breaking the Blind

This is an open-label study. No blinding is needed.

5.5 Drug Supplies and Administration

5.5.1 Formulation and Packaging

CX-2009

CX-2009 will be supplied as a lyophilized powder (cake) in 25 mg vials to be reconstituted with 5 mL of sterile water for injection (WFI) to a final concentration of 5.0 mg/mL. The label for CX-2009 will include standard product information. It will also include: CAUTION: New Drug – Limited by Federal (or United States) Law to Investigational Use. For Clinical Trial Use Only. Return all unused study medication.

CX-072

CX-072 drug product is currently being supplied as a sterile solution for IV administration. CX-072 is supplied in a 10 mL volume, and each vial contains 100 mg of CX-072 formulated with suitable compendial excipients. Upon regulatory approval, the CX-072 drug product is planned to be supplied as a lyophilized powder (cake) in single-use vials for reconstitution with sterile WFI before IV administration. The stability of the drug product is monitored according to the International Council for Harmonisation (ICH) Guidelines. The period of use of CX-072 drug product will be managed based on the evaluation of real time stability data.

5.5.2 Study Drug Preparation and Dispensing

Complete study-specific preparation and dispensing instructions for CX-2009 and CX-072 are described in their respective Pharmacy Manuals.

5.5.3 Study Drug Administration

Study drugs include CX-2009 and CX-072.

Study drugs 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. See Section 5.5.3.1 for management of IRRs.

All doses will be administered through an IV line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 μm) and administered as an IV infusion controlled by a volumetric pump.

Do not co-administer other drugs through the same IV line during the study drug infusion. Study drugs should be administered under the supervision of a physician or other study personnel experienced in the use of IV agents.

When CX-2009 and CX-072 are administered on the same day, CX-072 is to be administered first, followed by a saline flush, followed by the CX-2009 infusion. CX-2009 is to be infused no sooner than 30 minutes after completion of the CX-072 infusion.

Additional information on study drug administration can be found in the Pharmacy Manual.

CX-2009

CX-2009 will be administered as an IV infusion over 90 (±10) minutes with careful monitoring of IRRs. Following completion of the infusion, flush with an adequate amount of normal saline for infusion.

The SRC can modify the infusion rate for any dose if a ≤Grade 2 IRR occurs or if it is deemed to improve safe administration of CX-2009. If a ≥Grade 3 IRR occurs, this Module may be amended.

Do not administer CX-2009 as IV push or bolus injection.

CX-072

800 mg and 1200 mg CX-072 are to be infused over 60 (±10) minutes. Following completion of the infusion, flush with an adequate amount of normal saline for infusion.

5.5.3.1 Management of IRRs

Subjects should not receive any premedication prior to infusions, unless it is determined during the course of the study (by the SRC/Sponsor) that the occurrence of IRRs warrants routine prophylactic treatment (which might include paracetamol/acetaminophen, histamine antagonists, and/or corticosteroids).

Individual subjects who do experience a ≥Grade 2 IRR may receive premedication prior to subsequent treatment cycles after review with the Medical Monitor.

For allergic (hypersensitivity) reactions occurring during or after study drug (CX-2009 or CX-072) administration, follow the guidelines in Table 7.

Table 7. Management of Allergic Reactions

Grade of Allergic Reaction	Treatment
Grade 1: Transient flushing or rash, drug fever <38°C (<100.4°F)	Remain at bedside and monitor subject until recovery from symptoms.
Grade 2: Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours	Stop the study drug infusion, begin an IV infusion of normal saline and treat the subject as follows: • Administer diphenhydramine 50 mg IV (or equivalent) and/or paracetamol/acetaminophen 325-1000 mg PO; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. • If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. • Monitor subject closely. If symptoms recur then the infusion should be discontinued and no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. Premedication (diphenhydramine and paracetamol/acetaminophen) may be given prior to subsequent treatment cycles after review with the Medical Monitor.
Grade 3: Prolonged (eg, >6 hours, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows: • Recommend bronchodilators, epinephrine 0.2-1 mg of a 1:1000 solution for subcutaneous administration or 0.1-0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. • Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. • Study drug will be permanently discontinued unless continuation of therapy is believed to provide potential clinical benefit and no other reasonable alternatives exist, then re-challenge may be pursued at the discretion of the Investigator after consultation with the Medical Monitor. • Investigators should follow their institutional guidelines for the treatment of anaphylaxis.
Grade 4: Life-threatening consequences; urgent intervention indicated.	Follow treatment for Grade 3 allergic reaction and monitor subject until recovery from symptoms. Study treatment will be permanently discontinued.

IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = *per os,* oral.

During an IRR, vital signs will be obtained every 2 to 5 minutes until stable. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

5.5.3.2 Ocular Toxicity

All subjects enrolled in this study must adhere to the following impactful safety measures for the duration of CX-2009 exposure and 21 days after the last dose of CX-2009:

- Avoiding use of corrective contact lenses and switch to corrective glasses throughout the subject's time of participation in the study. Bandage contact lenses may be considered if prescribed by the treating ophthalmologist;
- Wearing ultraviolet A/ultraviolet B sunglasses whenever outdoors, even for short periods of time;
- Using preservative-free artificial tear eye drops for lubrication 3 times daily, starting at least 1 hour after the use of medicated eye drops; and
- All prophylactic measures for the eye during and post-infusion of CX-2009 listed below.

The following protective measures are required for all subjects to potentially reduce the exposure of the corneal limbal stem cells/transient amplifying cells to CX-2009 during and post-infusion:

1. Topical vasoconstrictor eye drops will be administered to both eyes, starting on the day of the infusion, 1 hour prior to each infusion of CX-2009. Brimonidine tartrate ophthalmic solution 0.025% (in the United States) should be administered to both eyes every 6 to 8 hours for 3 days, and brimonidine tartrate ophthalmic solution 0.2% (in Europe) should be administered to both eyes every 12 hours for 3 days, starting 1 hour prior to each infusion of CX-2009. If brimonidine tartrate ophthalmic solution is not available, tetrahydrozoline eye drops 0.05%, or naphazoline eye drops 0.025% may be used. If none of these agents are available or are not medically appropriate, suitable alternatives may be considered by the treating ophthalmologist, provided approval is granted by the Medical Monitor. Vasoconstrictor eye drops may be continued for longer if instructed by the treating ophthalmologist;
2. A cool compress will be applied to the eyes at the time of the infusion and continued for at least 2 hours and as much as tolerated on the day of the infusion; and
3. Topical steroid drops (such as prednisolone acetate eye drops, 1.0% or its equivalent), will be instilled in both eyes at least 30 minutes prior to CX-2009 infusion, and continued 4 times a day for 7 days. In addition, subjects may elect to use a topical ophthalmic steroid ointment at bedtime for 7 nights, starting the day of each CX-2009 infusion. In place of steroid ointment, a subject may consider artificial tears ointment or simply use artificial tears before bedtime. Treatment with topical steroid eye drops and the optional ointment may be continued longer if instructed by the treating ophthalmologist.

Subjects should contact the oncology team as soon as any ocular symptoms are experienced (eg, blurred vision), which will prompt an ophthalmology evaluation. The oncology team may consider initiating treatment with prolonged therapy with steroid eye drops, unless there is

suspicion of infectious conjunctivitis. The Medical Monitor should be informed if ocular symptoms necessitating ophthalmology evaluation are observed.

If ocular toxicity occurs, see Section 5.5.4.1.

5.5.4 Treatment Delays, Dose Modification, and Missed Doses

Treatment or visit delays for public holidays, weather conditions, or other unforeseeable circumstances (including toxicity considered unrelated to study treatment) do not constitute a protocol violation. However, delayed visits should be completed at the first available opportunity.

There must be a minimum of 21 days (Parts A, A2, B, E1, and E2) or 14 days (Parts C1, C2, D1, and D2) between study drug infusions (a window of ±2 days may occur). In exceptional circumstances, an infusion may be delayed for up to 7 days. Infusions that cannot be administered in that timeframe will be considered a missed dose, and the subject's next planned dose should be 42 days (every 21-day dosing regimen; Parts A, A2, B, E1, and E2) or 28 days (every 14-day dosing regimen; Parts C1, C2, D1, and D2) after the last administered dose. A subject will be considered to have experienced a prolonged treatment delay and study drug will be discontinued if the subject misses 2 consecutive infusions, except as provided for in Section 5.5.4.1 and Section 5.5.4.2.

Subjects benefitting from treatment may be allowed longer treatment delays after discussion with the Medical Monitor. Subjects should be assessed for resolution of toxicity (eg, by scheduled physical examination, laboratory testing, etc.) at a frequency deemed by the Investigator to be appropriate for the specific clinical situation.

5.5.4.1 Dose Management for CX-2009

Dose delay or permanent discontinuation of CX-2009 may be required as dictated in Table 8 and Table 9.

Note: Where CX-2009 and CX-072 are administered in combination (Parts D1, D2, E1, and E2), if, in the opinion of the Investigator, a toxicity is considered to be due solely to one component of the study treatment (ie, CX-2009 or CX-072) and the dose of that component is delayed, modified, or permanently discontinued in accordance with the guidelines in the Module, the other component may be administered if there is no contraindication.

Table 8. CX-2009 Dose Modifications for Select Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	No action	No action	Hold until recovery to ≤Grade 2 with transfusion; re-challenge at same dose. [a]	Hold until recovery to ≤Grade 2 with transfusion; re-challenge at same dose [a] if Grade 4 recurs, permanently discontinue CX-2009.
Neutropenia	No action	No action	Hold until recovery to ≤Grade 2; re-challenge at same dose. [a]	Hold and consider supportive measures until recovery to ≤Grade 2; re-challenge at same dose. [a]
Thrombocytopenia	No action	No action	PLT 25,000/mm^3– <50,000 mm^3 Hold until platelet count recovers to ≤Grade 1 and then treat at same dose level.	PLT <25,000/mm^3 Hold until platelet count recovers to ≤Grade 1 and then treat at same dose level.
Increased serum transaminases (AST/ALT) **Note:** Corticosteroids may be considered for the management of liver enzyme elevations	No action	No action	Hold until AST/ALT recovers to ≤Grade 2 and then treat at same dose level.	Permanently discontinue CX-2009.
Hyperbilirubinemia	No action	Hold until total bilirubin recovers to ≤Grade 1 and then treat at same dose level.	Hold until total bilirubin recovers to ≤Grade 1 and then treat at same dose level.	Permanently discontinue CX-2009.
Peripheral neuropathy (sensory motor)	No action	For new or worsening Grade 2 neuropathy, hold CX-2009 until neuropathy improves to Grade 1 or baseline.	For new or worsening Grade 3 neuropathy, hold CX-2009 until neuropathy improves to Grade 1 or baseline. Restart at same dose level. [a] Please note that a dose reduction may be considered in consultation with the Medical Monitor. Discontinue treatment permanently if no improvement within 2 weeks.	For new or worsening Grade 4 neuropathy, hold CX-2009 until neuropathy improves to Grade 1 or baseline. Please note that a dose reduction may be considered; consultation with the Medical Monitor is required. Discontinue treatment permanently if no improvement within 2 weeks.
Life-threatening or Grade 4 reaction	NA	NA	NA	Permanently discontinue CX-2009.

[a] Please note that dose reduction may be considered following consultation with the Medical Monitor.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable; PLT = platelet count.

Neutropenia. Neutropenia should be managed by dosing delays. The dose of CX-2009 should be held for Grade 3 or Grade 4 neutropenia until resolution to baseline or ≤Grade 2. Growth factor support should be considered for subsequent cycles in subjects who experience Grade 3 or Grade 4 neutropenia. In subjects with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation of CX-2009 should be considered.

The dose of CX-2009 should be held for Grade 3 AEs judged by the Investigator to be treatment-related that are not listed in Table 8 until resolution to baseline or Grade 0.

In the event of a major surgery (any intervention requiring more than local anesthesia), stop dosing; resume dosing after consultation with the Medical Monitor.

Ocular Toxicity. In addition to the scheduled examinations, subjects who report new ocular symptoms will undergo repeat examinations as clinically indicated as well as prior to infusion every other cycle (every 42 days for Parts A, A2, B, E1, and E2; every 56 days for Parts C1, C2, D1, and D2). Management of treatment-emergent ocular disorders should include corticosteroid eye drops and/or other measures as indicated by the treating ophthalmologist. For steroid-refractory symptoms, the treating ophthalmologist may recommend other modalities, including higher dose topical corticosteroids, topical cyclosporine, or lifitegrast. These agents are not mandatory but may be used based on the treating ophthalmologist's recommendation. Management of treatment-emergent ocular disorders is described in detail in Table 9.

Table 9. Management of Treatment-emergent Ocular Disorders

Category	Management	Guidelines for CX-2009 Dose Modifications
Category A: Symptomatic but no impact on ADL	•Complete eye examination as outlined in Appendix B; •Ensure protective measures for the eye are being utilized as described in Section 5.5.3.2; •Monitor for worsening symptoms; and •Subjects should have weekly ocular assessments until the symptoms resolve to baseline or are deemed to be irreversible by the Investigator.	Continue CX-2009 dosing.
Category B: Symptomatic impact on ADL including preparing meals, shopping for groceries or clothes, using the telephone, or managing money	•Complete eye examination as outlined in Appendix B. Repeat complete examination as clinically indicated; •Ensure protective measures for the eye are being utilized as described in Section 5.5.3.2; •Monitor for worsening symptoms; •Treatment with corticosteroid eye drops and/or topical ophthalmic steroid ointment at bedtime and/or other measures as indicated by the treating ophthalmologist; and •Subjects should have weekly ocular assessments until the symptoms resolve to baseline or are deemed to be irreversible by the Investigator.	Hold CX-2009 dosing until there is no longer a symptomatic impact on ADL. If a dose is needed to be held due to symptomatic impact on ADL for <2 weeks, resume dosing at the same dose level. If a dose is needed to be held due to symptomatic impact on ADL for > 2 weeks, dose reduction is required.
Category C: Symptomatic impact on self-care ADL (including bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)	•Complete eye examination as outlined in Appendix B. Repeat complete examination as clinically indicated; •Ensure protective measures for the eye are being utilized as described in Section 5.5.3.2; •Treatment with corticosteroid eye drops and/or topical ophthalmic steroid ointment at bedtime and/or other measures as indicated by the treating ophthalmologist; and •Subjects should have weekly ocular assessments until the symptoms resolve to baseline or are deemed to be irreversible by the Investigator.	Hold CX-2009 dosing until there is no longer a symptomatic impact on ADL. Dose reduction is required. A permanent discontinuation consideration should be made with the Investigator, ophthalmologist, and after discussion with the Medical Monitor.

ADL = activities of daily living.

Dose Reduction. Dose reduction steps are outlined in Table 8 and Table 9. In cases where Tables 8 or 9 do not indicate a dose reduction, a dose reduction may be approved with consultation of the Medical Monitor. There cannot be more than 42 days (every 21-day dosing regimen; Parts A, A2, B, E1, and E2) or 28 days (every 14-day dosing regimen; Parts C1, C2, D1, and D2) between dosing unless approved by the Medical Monitor (see Section 5.5.4).

In Parts A, A2, B, D1, D2, E1, and E2, as a first step, CX-2009 dose may be reduced to a dose level 1 mg/kg below the assigned starting dose. Should the AE reoccur after the first dose reduction, a further dose reduction (by another 1 mg/kg reduction) can be attempted if clinically beneficial and following consultation with the Medical Monitor. No subsequent dose escalation of CX-2009 will be authorized for subjects who have had a dose reduction for safety reasons.

In Parts C1 and C2, as a first step, CX-2009 dose may be reduced to a dose level below the assigned starting dose. Should the AE reoccur after the first dose reduction, a further dose reduction (by another 1 mg/kg reduction) can be attempted if clinically beneficial and following consultation with the Medical Monitor. No subsequent dose escalation of CX-2009 will be authorized for subjects who have had a dose reduction for safety reasons.

5.5.4.2 Dose Management for CX-072

The following guidance is for dose modification of CX-072. Delays or permanent discontinuation of CX-072 may be required as outlined in Table 10 and Section 5.5.10. Dose reduction of CX-072 is not permitted. Guidance is adapted from American Society of Clinical Oncology Clinical Practice Guidelines (Brahmer 2018), which should be referenced for additional detail and information when assessing and managing AEs that are considered to be potentially immune related.

If, in the opinion of the Investigator, a toxicity is considered to be due solely to one component of the study treatment (ie, CX-2009 or CX-072) and the dose of that component is delayed, modified, or permanently discontinued in accordance with the guidelines in the Module, the other component may be administered if there is no contraindication.

Additional recommendations for interventions of irAEs depending on severity of the event are provided in Section 5.5.5.

Table 10. CX-072 Dose Modifications for Select Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Skin toxicities including dermatitis, Stevens-Johnson syndrome, or toxic epidermal necrolysis See also Section 5.5.5.11	No action; G1 does not apply to severe cutaneous toxicities (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.).	Hold until recovery to ≤G1 or baseline.	Hold until recovery to ≤G1 or baseline. Consult with a dermatologist.	Permanently discontinue CX-072.
Colitis [a] See also Section 5.5.5.1	No action; may consider holding study treatment and resuming if toxicity does not exceed G1.	Hold until recovery to ≤G1.	Hold until recovery to ≤G1.	Permanently discontinue CX-072.
Increased serum transaminases (AST/ALT) or total bilirubin See also Section 5.5.5.2	No action; monitor laboratory values 1 to 2 times per week.	Hold until recovery to ≤G1 or baseline on prednisone ≤10 mg per day.	Permanently discontinue CX-072.	Permanently discontinue CX-072.
Pneumonitis See also Section 5.5.5.3	No action.	Hold until recovery to ≤G1.	Permanently discontinue CX-072.	Permanently discontinue CX-072.
Hypothyroidism or hyperthyroidism See also Section 5.5.5.4	No action.	Hold until recovery to ≤G1 or baseline (with hormone replacement for hypothyroidism).	Hold until recovery to ≤G1 or baseline (with hormone replacement for hypothyroidism).	Permanently discontinue study treatment.
Adrenal insufficiency See also Section 5.5.5.6	Consider holding until subject is stabilized.	Hold until recovery to ≤G1 or baseline with hormone replacement.	Hold until recovery to ≤G1 or baseline with hormone replacement.	Refer to endocrinologist. Hold CX 072 and contact Sponsor Medical Monitor to discuss discontinuation of study.
Hypophysitis See also Section 5.5.5.8	Consider holding CX-072 until stabilized on replacement therapy.	Hold until recovery to ≤G1 or baseline with hormone replacement.	Hold until recovery to ≤G1 or baseline with hormone replacement.	Refer to endocrinologist. Hold CX 072 and contact Sponsor Medical Monitor to discuss discontinuation of study.
Type 1 diabetes See also Section 5.5.5.7	NA; G1 does not apply to subjects with evidence of Type 1 diabetes or ketosis.	Hold until recovery to ≤G1 or baseline. Urgent endocrine consultation for all subjects. Initiate insulin therapy for all subjects.	Hold until recovery to ≤G1 or baseline. Urgent endocrine consultation for all subjects. Initiate insulin therapy for all subjects.	Refer to endocrinologist. Hold CX 072 and contact Sponsor Medical Monitor to discuss discontinuation of study.
Creatinine	No action; consider holding treatment pending workup.	Hold until recovery to ≤G1 or baseline. Consult nephrology.	Hold until recovery to ≤G1 or baseline. Permanently discontinue for Grade 3 nephritis.	Permanently discontinue CX-072.

Table 10. CX-072 Dose Modifications for Select Adverse Events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Pancreatitis (as diagnosed by biopsy, clinical examination, or symptoms); clinically asymptomatic elevation in amylase and lipase are not sufficient	Monitor for symptoms and laboratory abnormalities.	Hold until recovery to ≤G1 or baseline.	Hold until recovery to ≤G1 or baseline.	Permanently discontinue CX-072.
Myocarditis See also Section 5.5.5.5	NA		For any clinical suspicion, refer to cardiologist for workup, diagnosis, and treatment. Obtain cardiac MRI. Hold CX-072 and contact Sponsor Medical Monitor to discuss discontinuation of study.	
Encephalitis or meningoencephalitis See also Section 5.5.5.10	For any clinical suspicion, refer to neurologist for workup, diagnosis, and treatment. Hold CX-072 and contact Sponsor Medical Monitor to discuss discontinuation of CX-072.			
Ocular inflammatory toxicity (eg, uveitis, conjunctivitis, orbital inflammation, episcleritis) See also Section 5.5.5.9	Refer to ophthalmology.	Hold until recovery to ≤G1 or baseline. Refer to ophthalmology.	Permanently discontinue CX-072. Refer to ophthalmology.	Permanently discontinue CX-072. Refer to ophthalmology.
Guillain-Barre syndrome or myasthenia gravis	For any clinical suspicion, refer to neurologist for workup, diagnosis, and treatment. Hold study treatment and contact Sponsor Medical Monitor to discuss discontinuation of study treatment. For any confirmed diagnosis of any grade, treatment must be discontinued.			
Other immune-related adverse reactions (except those listed above) See also Section 5.5.5.12	No action.	No action; consider holding treatment depending on organs involved.	Hold and contact Sponsor Medical Monitor to discuss treatment, which may include administration of systemic steroids.	Hold and contact Sponsor Medical Monitor to discuss treatment, which may include administration of systemic steroids.
Grade 3 adverse reactions (except those listed above)	NA	NA	Hold until recovery to ≤G1 or baseline.	NA
Life-threatening or Grade 4 adverse reactions (except those listed above)	NA	NA	NA	Permanently discontinue CX-072.

[a] Based on CTCAE for diarrhea as most often used clinically.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event; G1 = Grade 1; MRI = magnetic resonance tomography; NA = not applicable; PD-L1 = programmed death ligand 1.

Resume CX-072 in patients whose adverse reactions recover to Grade ≤1 or baseline, at the discretion of the Investigator unless otherwise stated in Table 10 and/or Section 5.5.5.12.

5.5.5 CX-072 Management of Immune-related Toxicity

All AEs should be monitored and managed according to standard of care. Refer to "Management of irAEs in patients treated with ICI therapy: American Society of Clinical Oncology clinical practice guideline" (Brahmer 2018) for specific guidance. For any suspected immune-related toxicities, other causes should be excluded and treated appropriately per standard of care.

5.5.5.1 Immune-related Colitis

Counsel subject to inform the Investigator of any abdominal pain, nausea, cramping, blood or mucus in stool or changes in bowel habits, fever, abdominal distention, obstipation, or constipation.

For Grade 1 events, consider temporary withholding CX-072 to confirm toxicity does not exceed Grade 1. Withhold CX-072 for Grade 2 or 3 immune-related colitis. For moderate (Grade 2) colitis administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg per day prednisone or equivalent. Gastroenterology should be consulted. For severe (Grade 3) or life-threatening (Grade 4) colitis, administer corticosteroids at a dose of 1 to 2 mg/kg per day prednisone equivalents (for Grade 3) or 1 to 2 mg/kg per day methylprednisolone equivalents (for Grade 4) followed by corticosteroid taper. If Grade 3 symptoms persist for ≥3 to 5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab). Consider colonoscopy/GI endoscopy in cases where subjects have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, cytomegalovirus [CMV] colitis) and for those who are anti-TNF or corticosteroid refractory. When symptoms improve to ≤Grade 1, taper corticosteroids over at least 4 to 6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits. Permanently discontinue CX-072 for Grade 4 or recurrent colitis upon restarting CX-072.

5.5.5.2 Immune-related Hepatitis

Monitor subjects for abnormal liver tests prior to and periodically during treatment with CX-072. (This management guideline may be altered for subjects with evidence of liver metastases who had screening elevation of transaminases; optimal subject management in these subjects should be discussed with the Medical Monitor).

For Grade 1 elevations of AST, ALT, and/or total bilirubin, monitor laboratory values 1 to 2 times per week. For Grade 2 elevations of AST, ALT, and/or total bilirubin (AST or ALT >3.0 to ≤5 × ULN and/or total bilirubin >1.5 to ≤3 × ULN), hold CX-072, recheck laboratory values and increase frequency of monitoring to every 3 days; administer corticosteroid 0.5 to 1 mg/kg per day (prednisone or equivalent) if the abnormal elevation persists with significant clinical symptoms in 3 to 5 days. CX-072 may be resumed only when symptoms improve to ≤Grade 1 and corticosteroid dose is ≤10 mg per day. Taper over at least 1 month. Subjects should be advised to stop unnecessary medications and any known hepatotoxic drugs. For Grade 3 hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN), immediately start corticosteroid 1 to 2 mg/kg per day methylprednisolone or equivalent. Increase frequency of monitoring to every 1 to 2 days. If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine, test for thiopurine

methyltransferase deficiency). Measure laboratory parameters at least daily or every other day; consider inpatient monitoring for subjects with AST/ALT >8 × ULN and/or elevated total bilirubin 3 × ULN. Corticosteroid taper can be attempted around 4 to 6 weeks; re-escalate if needed; optimal duration unclear. For Grade 4 hepatitis, administer 2 mg/kg per day methylprednisolone equivalents and follow guidance for Grade 3.

Permanently discontinue CX-072 for Grade 3 or Grade 4 immune-related hepatitis (for subjects with elevation of liver transaminases at screening, discontinuation of CX-072 should be discussed with the Medical Monitor).

Infliximab might not be the most appropriate treatment option in the situation of immune-related hepatitis given the potential risk of idiosyncratic liver failure, mycophenolate mofetil may be considered.

5.5.5.3 Immune-related Pneumonitis

Monitor subjects for signs and symptoms of pneumonitis. Subjects with Grade 1 pneumonitis should be monitored weekly and CX-072 should be held if there is radiographic evidence of pneumonitis progression. CX-072 may be resumed with radiographic evidence of improvement or resolution. If no improvement, should treat as Grade 2. Subjects should be monitored weekly. For Grade 2 pneumonitis, recommend treatment with corticosteroids at a dose of 1 to 2 mg/kg per day prednisone equivalents, followed by a corticosteroid taper by 5 to 10 mg per week over 4 to 6 weeks. Consider bronchoscopy with bronchoalveolar lavage and empirical antibiotics. Monitor every 3 days. If no improvement after 48 to 72 hours of prednisone, treat as Grade 3. For Grade 3 pneumonitis, empirical antibiotics and corticosteroids (prednisolone IV 1 to 2 mg/kg per day) should be administered. If no improvement after 48 hours, may add 5 mg/kg infliximab or mycophenolate mofetil IV 1 g twice a day or IV immunoglobulin for 5 days or cyclophosphamide; taper corticosteroids over 4 to 6 weeks. Pulmonary and infectious disease consults should be sought if necessary. Subjects should be hospitalized for further management.

Withhold CX-072 for Grade 2 immune-related pneumonitis and permanently discontinue CX-072 for Grade 3 or 4 or recurrent pneumonitis upon restarting CX-072.

5.5.5.4 Immune-related Hypothyroidism and Hyperthyroidism

Monitor thyroid function prior to and periodically (test for thyroid-stimulating hormone [TSH] and free thyroxine (FT4) every 4 to 6 weeks and as clinically indicated) during treatment with CX-072.

For Grade 1 hypothyroidism, CX-072 may be continued with close follow-up and monitoring of TSH and FT4. For Grade 2 hypothyroidism, CX-072 should be withheld, thyroid hormone supplementation prescribed for symptomatic subjects with any degree of TSH elevation or in asymptomatic subjects with TSH levels that persist >10 mIU/L (measured 4 weeks apart). Endocrinology consult should be considered. For Grade 3 hypothyroidism, CX-072 should be

held, supplementation prescribed, and endocrinology consult obtained. For Grade 4 hypothyroidism, treatment should be permanently discontinued, supplementation prescribed, and endocrinology consult obtained. May admit for IV therapy if signs of myxedema (bradycardia, hypothermia).

For Grade 1 hyperthyroidism, may continue CX-072 with close follow-up and monitoring of TSH and FT4 every 2 to 3 weeks until it is clear whether there will be persistent hyperthyroidism. For Grade 2 hyperthyroidism, CX-072 should be held, medical management initiated, and endocrinology consultation considered. For persistent hyperthyroidism (>6 weeks) or clinical suspicion, a workup for Graves' Disease should be initiated. For Grade 3 hyperthyroidism, CX-072 should be held, medical management initiated, and endocrinology consulted. For Grade 4 hyperthyroidism, treatment should be permanently discontinued, supplementation prescribed, and endocrinology consult obtained. For severe symptoms or concern for thyroid storm, should hospitalize subject and initiate prednisone 1 to 2 mg/kg per day or equivalent tapered over 1 to 2 weeks. May also use saturated solution of potassium iodide or thionamide (methimazole or propylthiouracil).

Consider that thyroiditis is transient and within weeks resolves to primary hypothyroidism or normal. Graves' disease is generally persistent and due to increased thyroid hormone production that can be treated with antithyroid medical therapy.

5.5.5.5 Immune-related Myocarditis

Monitor subjects for myocarditis prior to and periodically during treatment with CX-072. For all grades of myocarditis, permanent CX-072 discontinuation should be discussed. Cardiology should be consulted, cardiac magnetic resonance imaging obtained, and high-dose corticosteroids should be administered (1 to 2 mg/kg of prednisone initiated rapidly (oral or IV depending on symptoms). In subjects without an immediate response to high-dose corticosteroids, consider cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or anti-thymocyte globulin. Permanently discontinue CX-072 for any >Grade 2 myocarditis.

5.5.5.6 Immune-related Adrenal Insufficiency

Monitor for signs and symptoms of adrenal insufficiency. Evaluate adrenocorticotropic hormone (ACTH) (a.m.), cortisol level (a.m.), and metabolic panel (sodium, potassium, carbon dioxide, and glucose). Consider ACTH stimulation test for indeterminate results. For evidence of primary adrenal insufficiency (high ACTH, low cortisol), evaluate for a precipitating cause of crisis, such as infection, and perform an adrenal computed tomography scan for metastasis/hemorrhage. For Grade 1 adrenal insufficiency, CX-072 may be held until subject is stabilized on replacement hormone. Withhold CX-072 for Grade 2, Grade 3, or Grade 4 events until the subject is stabilized on replacement hormones. Endocrinology should be consulted for all grades of adrenal insufficiency including for recommendations on replacement and stress dose steroid therapy.

5.5.5.7 Immune-related Type 1 Diabetes

Monitor subjects for hyperglycemia or other signs and symptoms of new or worsening diabetes mellitus, including measuring glucose at baseline. Laboratory evaluation in suspected Type 1 diabetes should include testing for ketosis in urine and an assessment of the anion gap on a metabolic panel. Withhold CX-072 for Grade 2, Grade 3, or Grade 4 events, perform urgent endocrine consultation for all subjects, and initiate insulin therapy for all subjects. Hold CX-072 until glucose control is obtained on therapy with reduction of toxicity to ≤Grade 1.

5.5.5.8 Immune-related Hypophysitis

Monitor for signs and symptoms of hypophysitis. Evaluate ACTH (a.m.), cortisol (a.m.), TSH, FT4, and electrolytes at baseline and determine whether hypophysitis or adrenal insufficiency is to be ruled out. Evaluate additional hormones (eg, follicle-stimulating hormone [FSH], luteinizing hormone [LH], testosterone, estrogen) as clinically indicated. Consider brain imaging (pituitary/sellar cuts) if clinically indicated. Consider holding CX-072 for Grade 1 events until subject is stabilized on replacement therapy. Withhold CX-072 for Grade 2, Grade 3, or Grade 4 events until the subject is stabilized on replacement hormones. Endocrinology should be consulted. Be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies.

5.5.5.9 Immune-related Uveitis and Other Ocular Inflammatory Toxicities

Counsel subject to inform the Investigator of any vision changes, eyelid swelling, proptosis, or pain. Refer to ophthalmology for all subjects (within 1 week for all subjects for Grade 1 events; urgent referral for Grade >1 events). Withhold CX-072 for Grade 2 events until after ophthalmology consult. Treatment for Grade 1 uveitis includes artificial tears. Treatment for >Grade 1 events includes topical and systemic corticosteroids. Resume CX-072 after return to ≤Grade 1. Permanently discontinue CX-072 for Grade 3 and Grade 4 uveitis or episcleritis. Blepharitis does not have a formal grading system. Treatment includes warm compresses and lubrication drops. CX-072 may continue unless the event is persistent and/or serious.

5.5.5.10 Immune-related Encephalitis or Meningoencephalitis

Monitor for changes in neurologic function. Withhold CX-072 for new onset or moderate to severe neurologic symptoms and evaluate to rule out infectious or other causes of neurologic deterioration. Withhold CX-072 for Grade 1, Grade 2, or Grade 3 events and consult with neurology. Consider concurrent IV acyclovir until polymerase chain reaction results are obtained and negative, and treatment with methylprednisolone and additional treatment (eg, IV immunoglobulin, rituximab as recommended by neurology consultation). Permanently discontinue CX-072 for confirmed diagnosis of autoimmune encephalopathy.

5.5.5.11 Immune-related Skin Toxicity

For rash and inflammatory dermatitis, Grade 1 toxicities should be treated with emollients and/or mild-moderate potency topical corticosteroids. Counsel subjects to avoid skin irritants and sun exposure. For Grade 2 toxicities, consider initiating prednisone (or equivalent) at 1 mg/kg, tapering over at least 4 weeks. In addition, treat with topical emollients, oral antihistamines, and topical medium to high potency corticosteroids. For Grade 3 toxicities, initiate 1 to 2 mg/kg (methyl)prednisolone (or equivalent), tapering over at least 4 weeks and treat also with topical emollients, oral antihistamines, and topical medium-high potency corticosteroids. Consult with dermatologist. For Grade 4 toxicities, treat with systemic corticosteroids IV (methyl)prednisolone (or equivalent) 1 to 2 mg/kg with slow tapering when the toxicity resolves. Admit subject immediately with urgent consult by dermatology.

For bullous dermatoses and severe cutaneous adverse reactions refer to Brahmer et al for additional guidance (Brahmer 2018). Refer to dermatology for blisters that are not explained by infectious/transient other causes (eg, herpes simplex, herpes zoster infections, pressure/friction bullae). When symptomatic bullae or erosions are observed on the skin or mucosal surfaces, the cutaneous irAE is, by definition, considered at least Grade 2.

5.5.5.12 Other Immune-related Adverse Reactions

For any suspected irAEs, exclude other causes. Based on the severity of the adverse reaction, withhold CX-072, administer high-dose corticosteroids, and/or if appropriate, initiate hormone replacement therapy. Upon improvement to Grade ≤1, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting CX-072 after completion of corticosteroid taper based on the severity of the event.

Refinement of the recommended treatment of TRAEs will be made as the study progresses.

If any of the immune-related symptoms worsen or do not improve with the guidelines above, tumor necrosis factor alpha (TNFα) inhibitors may be administered at the discretion of the Investigator.

5.5.6 Adverse Event Recovery Monitoring

If recovery of an AE is not seen within 4 weeks, the Investigator must review the subject with the Medical Monitor to determine if the subject should be permanently withdrawn from the study drug or a further period of waiting for resolution is warranted.

5.5.7 Treatment Compliance

CX-2009 and CX-072 will be administered only by study personnel by IV infusion at the study site. The infusion date and start and stop times will be recorded in the source documents and eCRF.

5.5.8 Storage and Accountability

It is the responsibility of the Investigator to ensure that the study drug is stored as specified by the Sponsor and in accordance with applicable regulatory requirements. Drug accountability details are provided in the Core (Appendix A).

CX-2009

CX-2009 vials must be stored at a temperature of 2°C to 8°C. Vials should be stored in the carton. Once CX-2009 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. Stability data for CX-2009 supports 8 hours at room temperature/under room light and 24 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the IV bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between CX-2009 and polyolefin bags have been observed. Do not freeze.

CX-072

CX-072 vials must be stored upright at a temperature of 2°C to 8°C (36°F to 46°F). Vials should be stored in the carton. Once CX-072 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. Stability data for CX-072 supports 8 hours at room temperature/under room light and 24 hours at 2°C to 8°C in the refrigerator following dilution and transfer to the IV bag. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between CX-072 and polyolefin bags have been observed. Vials should be stored in the original carton until time of use. Do not freeze.

5.5.8.1 Product Complaints

A product complaint is any perceived deficiency related to physical, chemical or biological properties, or the labeling, or packaging of a product.

If the solution is cloudy, discolored, or contains extraneous particular matter, quarantine the product and report the deficiency on a Product Complaint Form as described in the Pharmacy Manual. A Complaint Investigator will follow-up to obtain additional information and provide instructions on how to return the product.

Record the product return on the Drug Accountability Log to ensure complete tracking of drug supply.

5.5.9 Discontinuation of CX-2009 for Adverse Events

Subjects with Grade 4 AEs requiring permanent discontinuation of CX-2009 as described in Table 8 and Table 9 must be discontinued. Subjects who fail to resolve AEs as described in

Section 5.5.6 must be discontinued unless a discussion between the Investigator and Medical Monitor documents that a further period of waiting for resolution is warranted.

Where CX-2009 and CX-072 are administered in combination (Parts D1, D2, E1, and E2), if, in the opinion of the Investigator, a toxicity is considered to be due solely to one component of the study treatment (ie, CX-2009 or CX-072) and the dose of that component is delayed, modified, or permanently discontinued in accordance with the guidelines in the Module, the other component may be administered if there is no contraindication.

5.5.10 Discontinuation of CX-072 for Adverse Events

Permanent discontinuation of CX-072 may be required as outlined in Table 10.

Where CX-2009 and CX-072 are administered in combination (Parts D1, D2, E1, and E2), if in the opinion of the Investigator a toxicity is considered to be due solely to one component of the study treatment (ie, CX-2009 or CX-072), and the dose of that component is delayed, modified, or permanently discontinued in accordance with the guidelines in the Module, the other component may be administered if there is no contraindication.

CX-072 should be permanently discontinued for either of the following:

- Inability to reduce corticosteroid dose to ≤10 mg of prednisone or equivalent per day within 12 weeks of initiation of corticosteroid
- Persistent Grade 2 or 3 TRAEs that do not recover to Grade ≤1 or baseline or resolve within 12 weeks after the last dose of CX-072

For adverse reactions that do not recover within 4 weeks, the Investigator must contact the Sponsor Medical Monitor to determine if the subject should be permanently withdrawn from CX-072 or if a longer period of waiting for resolution is warranted.

5.5.11 Additional Guidelines

Refinement of the recommended management of TRAEs will be made as the study progresses.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Medications taken within 30 days before the administration of study drug and concomitant medications and therapies administered during the study will be recorded on the relevant eCRF.

1. The use of herbal remedies, other marketed anticancer chemo/immunotherapy/hormonal drugs, or investigational drugs is not permitted.
2. New chemotherapy, hormonal, radiation, or immunotherapy are not permitted during the screening or treatment periods.

3. Palliative therapies (eg, focal radiotherapy for pain, thoracentesis or paracentesis for comfort) is permitted after consultation with the Medical Monitor. A subject whose brain metastases are progressing on head imaging and who requires radiotherapy will be withdrawn from the study drug.
4. The use of live vaccines is prohibited 28 days prior to the planned first dose of CX-2009, while on study drug, and for 90 days after the last dose of CX-2009. The use of any killed or attenuated vaccines for the prevention of influenza is permitted. The use of other killed or attenuated vaccines for the prevention of infectious diseases may be permitted on a case-by-case basis after discussion with the Medical Monitor. Any vaccinations administered during the study must be documented in the subject's medical records and in the eCRF.

Concomitant medications taken by the subject while in the treatment period should be recorded in the eCRF. After EOT, only concomitant medications administered for irAEs occurring within 90 days after last dose will be recorded. Once a subject enters the Follow-Up Period, only new therapies for the treatment of their cancer should be recorded in the eCRF.

5.6.2 Restricted Medications and/or Procedures

Any other anticancer treatment such as chemotherapy, immunotherapy, biochemotherapy, radiotherapy, investigative therapy, or high-dose steroids (except to treat TEAEs) are prohibited during and within 30 days prior to receiving study drug. Luteinizing hormone-releasing hormone agonists are permitted for pre-menopausal women. For subjects with CRPC, overlapping anti-androgen therapy with CX-2009 is allowed. Anticoagulation therapy with warfarin is also prohibited.

Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. These may include hematopoietic growth factors to treat neutropenia or thrombocytopenia in accordance with ASCO guidelines, transfusions, bone-targeted agents (bisphosphonates and/or RANK-L agents), antiemetics, antidiarrheals, and glucocorticoids, including treatment of an immune-related toxicity or short courses to treat asthma, chronic obstructive pulmonary disease, etc.

Continuation of standard of care medications (particularly hormonal related therapies for prostate carcinoma) that the subject has been on for the previous 30 days at stable doses are allowed.

See Section 5.7 for guidance on the avoidance of concomitant medications that are sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index.

For Subjects Receiving CX-072 (Parts D1, D2, E1, and E2). Inhaled or intranasal corticosteroids (with minimal systemic absorption) may be continued if the subject is on a stable dose. Nonabsorbed intra-articular steroid injections will be permitted. Systemic corticosteroids required for the control of IRRs or irAEs must be tapered and must be at nonimmunosuppressive doses (<10 mg/day of prednisone or equivalent) prior to the next study drug administration. The

use of steroids as prophylactic treatment for subjects with allergies to diagnostic imaging contrast dyes will be permitted.

5.7 Advice to Investigators Related to Potential Drug Interactions

In vitro metabolism studies and studies in mice suggest that DM4 is predominantly metabolized by thiol *S*-methyltransferase to form another highly active metabolite DM4-Me, which is further metabolized into the less active sulfoxide-methyl-DM4 and eliminated in the bile. Because DM4-Me has been shown to be primarily metabolized by CYP3A4 in human hepatic microsomes, its exposure could potentially be increased in the presence of strong CYP3A inhibitors. If concomitant medication with a CYP3A inhibitor cannot be avoided, monitor for risk of increased toxicity. Drinking greater than 1 serving (250 mL) of grapefruit juice per day should be avoided. Appendix G provides examples of CYP3A inhibitors. An in vitro study evaluating the potential for CYP inhibition demonstrated that DM4 and DM4 Me are not direct inhibitors of the 7 CYP isoforms evaluated, however DM4 showed time-dependent inhibition of CYP3A4 and DM4-Me showed weak time-dependent inhibition of CYP2C8 and CYP2C9. Treatment of subjects with concomitant medications that are sensitive substrates of CYP3A or are CYP3A substrates with a narrow therapeutic index should be avoided (see Appendix H for examples).

6 EFFICACY ASSESSMENTS

The primary criteria for defining evidence of anticancer activity and also for management of subject care will be a clinical response as defined by RECIST (Version 1.1). Management of subjects in Parts D1, D2, E1, and E2 may also take into consideration tumor response assessed by irRECIST. Efficacy in this study will be explored in subjects on the basis of:

- ORR by the RECIST (Version 1.1);
- TTR;
- DOR;
- PFS; and
- OS.

Efficacy in subjects treated with the combination CX-2009 plus CX-072 (Parts D1, D2, E1, and E2) will be explored additionally on the basis of:

- ORR by irRECIST as defined in the Core (Appendix A)

Please refer to the Core for a description of the efficacy assessments.

7 PHARMACOKINETIC, IMMUNOGENICITY, AND EXPLORATORY BIOMARKER ASSESSMENTS

7.1 Pharmacokinetic Assessments

Concentration versus time data will be tabulated and plotted for the individual and mean CX-2009 (total and intact), CX-2009-conjugated DM4 and free DM4, and DM4-Me analytes and for total and intact CX-072 moieties. PK parameters, including AUC, C_{max}, C_{min}, clearance, and volume of distribution at steady state, will be calculated for CX-2009 (total and intact), DM4 (conjugated and free), and DM4-Me analytes as appropriate and as data allow. Additional parameters such as terminal elimination half-life and accumulation may be calculated, and dose proportionality will be assessed for subjects with sufficient data. Estimates for these parameters will be tabulated and summarized (eg, mean, standard deviation, and coefficient of variation). CX-072 (total and intact moieties) C_{max} and C_{min} will be tabulated individually and summarized using descriptive statistics (eg, mean, standard deviation, and coefficient of variation).

Additional exploratory model-based PK analyses may be conducted and the results of these analyses may be reported in a document separate from the clinical study report.

Plasma samples will be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion at the times indicated in Appendix B.

If the infusion was interrupted, the reason for interruption will also be documented in the eCRF and a sample will be collected at the end of the infusion and at the times specified after the end of infusion.

7.2 Exploratory Biomarkers

Probody therapeutics differ from unmodified mAbs by the recombinant addition of a prodomain at the amino-terminus of the light chain, which blocks the antibody binding to its target antigen and can be removed by tumor-associated protease activity. In this way, CX-2009 and CX-072 are expected to be activated in tumors and bind to their targets, CD166 and PD-L1 respectively, but to be relatively inactive outside of the TME.

The overall goal of the biomarker portion of CTMX-M-2009-001 is to explore A) Probody therapeutic mechanistic proof of concept, and B) potential predictive markers associated with the clinical activity of CX-2009 alone or in combination with CX-072.

This information will help to further build the translational program for the development of CX-2009 and CX-072.

The presence of activated proteases capable of activating the Probody therapeutics in the human TME will be assessed using a semi-quantitative zymographic assay that combines ex vivo incubation of the Probody therapeutic probe in sections of biopsy and capillary electrophoresis analysis to measure the intact and cleaved Probody therapeutics. A similar capillary

electrophoretic method will be used to measure the Probody therapeutic activation in plasma and on-treatment tumor biopsies following administration of CX-2009 alone or in combination with CX-072. The expression of the target, CD166, will be evaluated using a Clinical Laboratory Improvement Amendments of 1998-validated IHC assay.

Exploratory studies will include the evaluation of:

- Probody therapeutic activation in tumors and in blood;
- The potential link between tumor markers, such as the target of CX-2009 (ie, CD166), the target of CX-072 (ie, PD-L1) and the biological activity of CX-2009 alone or in combination with CX-072;
- The potential link between exploratory biomarkers in blood and the biological activity of CX-2009 alone or in combination with CX-072; and
- The presence of activated proteases in the human TME capable of removing the peptide mask and thereby activating the Probody therapeutic.

7.3 Exploratory Biomarkers Collection

In order to address the above objectives, tissue samples will be collected throughout the course of the study.

For Parts A and C1, pretreatment and on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

For Part A2, tumor biopsies (fixed and frozen) are required 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

For Parts B and C2, consent to pretreatment and on-treatment tumor biopsies will be mandatory in at least 7 subjects for each tumor type. For these subjects, tumor biopsies (fixed and frozen) will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

For Parts D1, D2, E1, and E2, on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected 3 to 5 days after the third dose, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Progressive disease in and of itself is not considered an AE or SAE. Progressive disease is an efficacy finding and should not be reported unless the progressive disease results in death during the reporting period (from date of signed informed consent to 30 days post last study treatment administration). On-study deaths, reported as SAEs due to progressive disease and considered unrelated to study drug will be excluded from treatment-emergent AE analysis.

8.1.1 Suspected Adverse Reaction

A suspected adverse reaction is an AE for which there is a reasonable possibility that the study drug(s) caused the AE. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug(s) and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by the study drug(s).

8.1.2 Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "life threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

8.1.3 Serious Adverse Event or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (see definition above)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect
- Important medical events: Based on medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (eg, anaphylaxis, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization).

8.1.4 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered "unexpected:"

- If it is not listed in the IB or is not listed at the specificity or severity that has been observed; or
- If an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.2 Adverse Event Classification

8.2.1 Relationship to Investigational Drug

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. The relationship to study drug will be categorized as "Yes" or "No."

8.2.2 Severity

The severity of an event describes the degree of impact upon the subject and/or the need for, and extent of, medical care necessary to treat the event.

AE grading will be defined by the NCI CTCAE v4.03. In the event that the NCI CTCAE v4.03 does not apply, the severity descriptions in Table 11 will be used to describe the maximum intensity of the AE.

Table 11. Adverse Event Severity

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention required
Grade 5	Death related to an adverse event

Source: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 19 November 2019.

8.3 Exposure in Utero

The subject will be instructed to notify the Investigator if the subject or subject's partner becomes pregnant during the study. The Investigator must notify the Sponsor or designee within 24 hours via the Pregnancy Notification Form to meet the 24-hour reporting requirement. If it is not possible to report the pregnancy via the Pregnancy Notification Form, telephone or e-mail will be acceptable. The Investigator should obtain informed consent/assent from the subject or subject's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the subject or subject's partner provides informed consent/assent, the Investigator should follow the pregnancy until outcome. A final Pregnancy Notification Form should be completed when the outcome of the pregnancy is known.

Although not an AE per se, pregnancy in either a patient or the partner of a patient taking trial medication should be reported as an SAE to facilitate outcome monitoring by the Sponsor.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these to be medically significant), recorded on the eCRF, and expeditiously reported to the Sponsor as an SAE.

8.4 Monitoring of Adverse Event Data

Safety information in the study will be monitored on an ongoing basis by the Medical Monitor and Investigators and discussed at regular teleconferences.

AEs occurring during the reporting period (up to and including 30 days after administration of the last dose of study drug for all AEs and up to and including 90 days after administration of the last dose of study drug for all irAEs related to CX-072) should be followed until resolution to baseline status, initiation of a new therapy, or stabilization.

Proper instruction will be provided to each site to ensure prompt reporting and communication between the Sponsor, Investigators, Food and Drug Administration (FDA) and other regulatory agencies regarding any DLTs or other AEs of interest.

For SAEs, the Investigator has to complete the SAE Form electronically in the electronic data capture (EDC) system for the study with as much information as possible and submit it in the time frame described in Section 8.6. When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information in the EDC system. If the subject was hospitalized, a copy of the discharge summary and any other relevant hospital records (eg, admission report, laboratory test results, etc.) should be included as part of the subject's medical file.

All AEs in which the relationship is considered "yes" to study drug and all SAEs will be followed until resolved or until a stable status has been achieved. The type of follow-up (eg, phone, site visit, etc.) will be left to the discretion of the Investigator.

8.5 Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally to identify AEs during the course of the study. Any events occurring prior to administration of the first dose, will be recorded on the Medical History eCRF. SAEs will be recorded on the Adverse Event eCRF from informed consent through 30 days following the last dose of CX-2009 and (for irAEs) through 90 days after administration of the last dose of CX-072. Events occurring after administration of the first dose of study drug will be recorded on the Adverse Event eCRF. AEs that occur up to and including 30 days after administration of the last dose of study drug must be reported in the EDC system.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the Adverse Event eCRF for that visit. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the Adverse Event eCRF. In addition, an abnormal test finding will be classified as an AE if 1 or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms;
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention, including significant additional concomitant drug treatment or other therapy. Note: Simply repeating a test finding, in the absence of any of the other listed criteria does not constitute an AE;
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study; and
- The test finding is considered clinically significant by the Investigator based on his/her medical judgment. If an abnormal laboratory result is recorded as an AE, then the corresponding laboratory value must be marked clinically significant in the database. Similarly, if an abnormal laboratory value is marked clinically significant in the database, there should be a corresponding AE entered.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this Module. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus rather than hyperglycemia).

8.6 Notification About Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) for CX-2009 and CX-072 will be distributed to the relevant regulatory authorities, independent ethics committees (IECs), institutional review boards (IRBs), and sites participating in CX-2009 clinical studies. SUSARs for CX-072 will be distributed to the relevant regulatory authorities, ethics committees, IRBs, and sites participating in the CX-072 clinical studies.

8.6.1 Investigator Reporting to Sponsor

All SAEs that occur during the course of the study must be reported to the Sponsor and Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). In addition, all SAEs that occur up to and including 30 days following the last dose of CX-2009 and (for irAEs) through 90 days after administration of the last dose of CX-072 must be reported to the Sponsor within 1 working day from when the Investigator becomes aware of the SAE.

To report the SAE, the Investigator must record the SAE on the AE eCRF in the EDC system as well as any relevant eCRF forms (eg, drug dispensation eCRF, applicable laboratory eCRF). When the AE eCRF is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an e-mail to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE Form to Medpace (fax number listed below) within 24 hours of awareness (see Table 12 for contact information). When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Table 12. Safety Contact Information: Medpace Clinical Safety

	Medpace SAE Reporting Line – USA	Medpace SAE Reporting Line – Europe
Telephone	+1-800-730-5779, dial 3 or +1-513-579-9911, dial 3	+49 89 89 55 718 44
Fax	+1-866-336-5320 or +1-513-579-0444	+49 89 89 55 718 104
e-mail	medpace-safetynotification@medpace.com	medpace-safetynotification@medpace.com

Investigators must report to the Sponsor any SAE, whether or not considered drug related, including those listed in the Module or IB. The report must include an assessment of causality.

For all SAEs, the Investigator is obligated to obtain and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the SAE Form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designee.

8.6.2 Serious Adverse Events Follow-Up

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the AE eCRF and any other relevant eCRFs for the study. If requested, the Investigator must submit any supporting documentation (eg, subject discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.6.3 Reporting to Regulatory Agencies and Central Institutional Review Board/Independent Ethics Committees

The Sponsor will report all relevant information about SUSARs that are fatal or life threatening as soon as possible to the FDA as applicable, applicable competent authorities in all the Member States concerned, and the Central IRB/IEC and in any case no later than 7 days after initial knowledge by the Sponsor of such a case. After the initial 7-day SUSAR report, a final 15-day SUSAR report will be submitted (ie, 8 days after the initial 7-day notification). Subsequently, follow-up for fatal or life-threatening SUSARs will be communications within 15 days.

All other SUSARs will be reported to the FDA as applicable, applicable competent authorities, and the Central IRB/IEC as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will inform all Investigators as required with instructions to submit to local IRBs/IECs per local requirements.

8.7 Rapid Notification of Adverse Events of Special Interest

In addition to SAEs, the following AEs will be reported to the Sponsor or its designee within 24 hours even if the nature of the AE is not deemed serious:

- AEs that potentially meet DLT criteria,
- ≥Grade 3 eye disorders (including blurred vision),
- ≥Grade 2 infusion reactions whether or not the event is a DLT,
- Any Grade 2 neurotoxicity,
- Any potential Hy's Law case (ie, ALT or AST >3 × ULN with concurrent total bilirubin >2 × ULN and ALP <2 × ULN, with lack of alternate etiology); and

For Parts D1, D2, E1, and E2: Any of the following irAEs defined as: AEs requiring the use of systemic corticosteroids within 30 days after the AE onset date with no clear alternate etiology, or requiring the use of systemic hormonal supplementation:

- Pneumonitis,
- Colitis,
- Hepatitis (including AST or ALT elevations >3 × ULN or bilirubin >1.5 × ULN),
- Nephritis (including serum creatinine >1.5 × ULN),
- Pancreatitis,
- Motor and sensory neuropathy (including Guillain-Barré syndrome and myasthenia gravis),
- Myocarditis,
- Encephalitis or meningoencephalitis,
- Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, hypophysitis, diabetes mellitus, and adrenal insufficiency),
- Autoimmune ocular toxicities (eg, uveitis),
- Skin reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis, and
- Diarrhea.

Please refer to Section 8.6 and the Core (Appendix A) for reporting SAEs, DLTs, and events of special interest.

8.8 Module-Specified Events

Subjects with advanced cancer enrolling in this study who have received prior treatment may have some degree of bone marrow suppression from prior therapy and/or laboratory abnormalities due to underlying disease status. Only changes in the grade of baseline laboratory values that require intervention (eg, transfusions, delay in study drug administration) should be reported as AEs.

Common AEs observed with other maytansinoid or MTI (eg, auristatin) ADCs may be expected for CX-2009. These include:

- Blood and lymphatic system disorders: neutropenia, thrombocytopenia, and lymphopenia;
- Nervous system disorders: peripheral neuropathy (sensory and motor) and paresthesia;
- Eye disorders: blurred vision, dry eyes, and keratopathy (including corneal cyst, corneal disorder, corneal epithelial microcysts, keratitis, limbal stem cell deficiency, and punctate keratitis);
- General disorders and administration site conditions: fatigue, pyrexia, pain, confusion, and headache;
- Hepatotoxicity (including increases in AST or ALT);
- Hypokalemia;
- Hypomagnesemia;
- Pulmonary disorders: interstitial lung disease;
- Infections and infestations: upper respiratory tract infection;
- Gastrointestinal disorders: nausea, diarrhea, abdominal pain, vomiting, decreased appetite, and constipation;
- Skin and subcutaneous tissue disorders: rash and pruritus; and
- Respiratory, thoracic, and mediastinal disorders: cough and dyspnea.

Common AEs (>15%) observed with the use of CX-072 (10 mg/kg administered every 21 days; n=114) include:

- Fatigue (34%)
- Anemia (25%)
- Decreased appetite (23%)
- Diarrhea (22%)
- Nausea (22%)
- Increased AST (19%)
- Vomiting (18%)
- Cough (16%)
- Dyspnea (16%)

9 STATISTICAL CONSIDERATIONS

Part A, dose escalation with an every 21-day dosing regimen, of the study consists of an accelerated titration design, followed by a 3+3 design, and ending in a cohort using the mTPI-2 design. During dose escalation (3+3 design), the exact sample size will be determined by the observed safety profile, which will determine the number of subjects per cohort and the number of cohorts.

Once the MTD is defined or the highest dose is tested (ie, 10 mg/kg, AIBW), up to 38 subjects can be enrolled at the MTD to refine dose selection using mTPI-2, a rule-based design similar to the 3+3 design that allows dose escalation/de-escalation. In November 2019, the selection of 7 mg/kg as the MTD/RP2D was made based on factors including safety, efficacy, and PK/PD, by the Sponsor with input from the SRC.

Part B, with an every 21-day dosing regimen, is designed to provide a preliminary assessment of efficacy at the MTD/RP2D. Given the confirmed ORR seen to date in subjects with HR-positive/HER2-negative BC receiving monotherapy CX-2009 on the every 21-day schedule, a 2-stage enrollment design will no longer be incorporated. The SRC will continue to review on-going safety and efficacy data throughout the course of the clinical study. The sample size was selected to estimate the ORR. With 40 subjects treated, if 8 subjects have confirmed objective responses, the observed ORR will be 20% (90% CI: 10% - 33%); the lower bound of the 90% CI would therefore exclude an ORR of 10%.

Part C1, dose escalation/de-escalation using the mTPI-2 design with an every 14-day dosing regimen, will enroll up to 24 subjects (3 to 6 subjects at each dose level) for the purposes of MTD/RP2D decisions.

Part C2, with an every 14-day dosing regimen, is designed to provide a preliminary assessment of clinical activity at the MTD/RP2D. Once the MTD/RP2D is defined in Part C1, expansion cohorts of up to 40 subjects in selected tumor types will be enrolled as described in Part B to evaluate the antitumor activity using the MTD/RP2D in Part C2. A 2-stage design may be incorporated into this cohort.

Part D1, dose escalation/de-escalation using the mTPI-2 design for CX-2009 with an every 14-day dosing regimen in combination with CX-072, will enroll up to 24 subjects (3 to 6 subjects at each dose level) for the purposes of MTD/RP2D decisions.

Part D2, dose expansion of CX-2009 plus CX-072 with an every 14-day dosing regimen, is designed to provide a preliminary assessment of clinical activity at the MTD/RP2D. Once the MTD/RP2D is defined in Part D1, expansion cohorts of 40 subjects in selected tumor types will be enrolled as described in Part B to evaluate the antitumor activity of CX-2009 plus CX-072. A 2-stage design may be incorporated into this cohort.

Part E1, dose escalation using the mTPI-2 design for CX-2009 with an every 21-day dosing regimen in combination with CX-072, will enroll up to 24 subjects (3 to 6 subjects at each dose level) for the purposes of MTD/RP2D decisions.

Part E2, dose expansion of CX-2009 plus CX-072 with an every 21-day dosing regimen, is designed to provide a preliminary assessment of clinical activity at the MTD/RP2D. Once the MTD/RP2D is defined in Part E1, expansion cohorts of 40 subjects in selected tumor types will be enrolled as described in Part B to evaluate the antitumor activity of CX-2009 plus CX-072. A 2-stage design may be incorporated into this cohort.

Enrollment within the expansions will be suspended if either of the following Safety Stopping Rules are met in the first 6 subjects enrolled in Parts B, C2, D2, and E2:

- DLT rate is >30% within 21 days (Parts B and E2) or within 28 days (Parts C2 and D2) of the first dose of study drug
- >20% of subjects have a treatment interruption or discontinuation within the first 6 weeks of the first dose of study drug or within 6 weeks of a single dose reduction step for subjects who experience events with their first dose of study drug

One of the major exploratory objectives aims at evaluating the relative Probody therapeutic activation in the tumor versus blood across various indications. The relative degree of Probody therapeutic activation in the tumor versus blood is expected to be influenced by Probody therapeutic dose, protease activity, and tumor target (CD166) expression. The variable nature of the protease activity and target expression in the tumor between subjects is expected to lead to variation in relative Probody therapeutic activation. For Part A2, tumor biopsies are required 3 to 5 days after the first dose of CX-2009. For the dose expansion (Part B), consent to pretreatment and on-treatment tumor biopsies will be mandatory for at least 7 subjects for each tumor type.

Based on nonclinical data, the differential activation between tumor and blood has a mean of about 20.0% and a standard deviation of about 5.0%. For Part A2 with 6 subjects enrolled in a dose cohort, the 90.0% CI (based on t-distribution with 5 degrees of freedom) for the differential activation is (16.0%, 24.0%). For each of the expansion cohorts in Parts B and C2, the 90.0% CI (based on t-distribution with 6 degrees of freedom) for the differential activation based on the best case scenario of 7 subjects is (16.3%, 23.7%), and based on the more likely scenario of 4 subjects is (14.1%, 25.9%). In addition, the variability in protease activity between subjects might further reduce our ability to measure Probody therapeutic activation in the tumor. It is anticipated that the requested tumor biopsies will provide reasonable estimates for this FIH study. If tumor biopsies are not mandatory, fewer subjects would be available for analysis, and the estimates would be less precise.

9.1 Populations

For assessment of MTD/RP2D, the population will be based on subjects who are evaluable for DLT determination (a "DLT-evaluable" subject is defined as having received at least 1 dose of CX-2009 (or CX-2009 and CX-072) and completed the full DLT observation period (either 21 or 28 days depending on the schedule) or a subject who has withdrawn from the study drug due to a drug-related toxicity. Subjects who are not DLT evaluable may be replaced in the cohort.

For assessment of efficacy (Parts B, C2, D2 and E2), subjects must have undergone at least 1 on-study imaging assessment. Subjects who die prior to his/her first on-study scan will not be counted as evaluable for this assessment.

The efficacy evaluable group for Parts D2 and E2 will include only those subjects who are determined to be PD-L1 positive.

9.2 Other Statistical Analyses

Statistical assessments/methods for safety, efficacy, PK/PD, and immunogenicity are found in Section 11 of the Core. In instances where the statistical analysis plan (SAP) might contradict the analyses specified in the Core, the SAP supersedes the Core.

Available data from Part A2 will be pooled with data from Part A by dose. In addition, efficacy data from Part A2 may be analyzed separately. The relationship between dose and safety/efficacy may be explored. Analyses by dose may be conducted for, but not limited to, the following endpoints: frequency of AEs of special interest, ORR, and percent reduction in tumor burden by dose. A generalized linear model may be used to adjust for covariates or to model the relationship. Because of the limited number of subjects, the above analyses will be conducted if data warrant.

10 DATA SAFETY MONITORING BOARD

The Data and Safety Monitoring Board (DSMB) will monitor the safety of the study. The DSMB will consist of individuals in relevant fields of expertise. It will convene on a regular basis (at least 2 times per year or at a different frequency as otherwise agreed) and will review all safety information to determine whether the study should continue unchanged or whether Module modifications are required to ensure subject safety. Details on the DSMB are provided in Appendix D and in a separate DSMB charter. The DSMB will make recommendations to the Sponsor, who will make ultimate decisions regarding study alteration or discontinuation.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

This study will be conducted in accordance with the current IRB/IEC approved clinical Module, Core, ICH Good Clinical Practice Guidelines, and relevant policies and requirements of the national regulations and laws, including the Health Insurance Portability and Accountability Act of 1996.

11.2 Institutional Review Board or Independent Ethics Committee

The IRB/IEC will meet all FDA requirements governing IRBs (21 Code of Federal Regulations [CFR] Part 56).

The Investigator will provide the Sponsor (or designee) with documentation of IRB/IEC approval of the following documents before the study begins at the study site(s): Module, Core, ICF, and any other relevant materials intended for or directed to subjects (eg, subject diaries, advertisements). The Investigator will supply documentation to the Sponsor of IRB/IEC requirements regarding continuing review and approval of revisions to any of these documents.

11.3 Subject Information and Informed Consent

Written informed consent/assent is required from each subject prior to any testing under this Module, including Screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in 21 CFR Part 50.

The ICF will be used to explain the risks and benefits of study participation in simple terms before the subject will be entered into the study. The ICF will contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written informed consent must be given by the subject after the receipt of detailed information on the study. It is the responsibility of the Investigator to obtain consent/assent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this Module, including Screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by the Sponsor or its designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor.

11.4 Retention of Records

The Investigator must maintain essential study documents (Core, Module, Module amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject ID codes (subject names and corresponding study numbers) will be retained by the site for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor prior to disposing of any study records.

11.5 Publication Policy

All information concerning Probody therapeutics is considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from the Sponsor. No publication or disclosure of study results will be permitted except as specified in a separate, written agreement between Sponsor and the Investigator.

11.6 Financial and Insurance

Financing and insurance are addressed in a separate document.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Changes to the conduct of the study will be prepared by the Sponsor as an amendment to the Module and/or the Common Core Document and implemented only upon joint approval of the Sponsor, or a representative of the Sponsor, and the Investigator(s). Amendments should also receive written IRB/IEC approval prior to implementation, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the Module change and subsequently notify the regulatory authorities and/or the IRB, as appropriate.

12.2 Address List

12.2.1 Sponsor

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Appendix A: Common Core Document CTMX-C-001

AN OPEN-LABEL, DOSE-FINDING AND PROOF OF CONCEPT STUDY FOR PROBODY™ THERAPEUTICS (PROBODY TX) IN SUBJECTS WITH METASTATIC OR LOCALLY ADVANCED UNRESECTABLE SOLID TUMORS AND/OR LYMPHOMAS

COMMON CORE DOCUMENT: CTMX-C-001

Product:	Probody technology platform
Sponsor:	CytomX Therapeutics, Inc. 151 Oyster Point Boulevard, Suite 400 South San Francisco, CA 94080-1913 Tel: (650) 515-3185 Fax: (650) 351-0353
Chief Medical Officer:	Rachel W. Humphrey, MD Senior Vice President CytomX Therapeutics, Inc. Tel: (203) 435-2152
Date of Common Core Document:	24 June 2016
Date of Common Core Document 01:	11 November 2016
Date of Common Core Document 02:	11 May 2018

1. SIGNATURE PAGE

Common Core Document:	CTMX-C-001: An Open-Label, Dose-Finding and Proof of Concept Study for Probody™ Therapeutic (Probody Tx) in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors and/or Lymphomas
Version / Date:	Amendment 02 / 11 May 2018

1.1. Sponsor Approval

05/18/2018

Matthias Will, MD
VP, Clinical Development
CytomX Therapeutics, Inc.

Date

1.2. Investigator Agreement

By signing this page I attest that I have read and understand the contents of the Common Core Document CTMX-C-001 and any subsequent amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the Common Core Document and the Probody™ therapeutic-specific Protocol Module and to my obligations to the Sponsor as described in the Common Core Document and executed contracts between myself, my Institution, and the Sponsor.

Investigator's Signature: _____

Investigator's Name: _____

Institution: _____

Date: _____

2. SYNOPSIS

Name of Sponsor:
CytomX Therapeutics, Inc.

Title of study:
An Open-Label, Dose-Finding and Proof of Concept Study for Probody™ (Probody Tx) Therapeutics in Subjects with Metastatic or Locally Advanced Unresectable Solid Tumors and/or Lymphomas

Investigators / Study center(s): Multicenter program to be conducted globally

Phase of development:
Dose-finding and proof of concept

Introduction and Study Rationale:
Probody™ therapeutics (Probody Txs) are fully recombinant antibody prodrugs, activated preferentially by proteases associated with tumor microenvironments. They are designed to be administered in a form that can be switched on in the tumor microenvironment, with minimal interaction with its target in normal circulating cells or with healthy tissues. In this way, Probody Txs are expected to minimize injury outside of the tumor while maintaining anti-tumor activity. This antibody-masking technology can be potentially applied to any antibody-based treatment and be particularly useful in settings where clinical utility is limited by significant toxicities due to target binding outside of the tumor.

To simplify evaluation of the Probody platform, the program includes a central Common Core Document (Core) and drug-specific protocol modules. The Common Core Document describes all design features related to a standard Phase 1-2 protocol (dose escalation and expansion) that would be applicable to all Probody Txs and combinations. All protocol elements related to subject selection and patient care are in the drug-specific protocol modules.

Common Core Document Overall Objectives (relevant to all Probody Modules)

Primary:

- To evaluate the safety and tolerability of multiple doses of the Probody Tx, administered intravenously, as monotherapy and/or as part of selected combination regimens, to subjects with metastatic or locally advanced unresectable solid tumors and/or lymphomas
- To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of the Probody Tx (as monotherapy and/or in select combinations)

Secondary:

- To obtain preliminary evidence of anti-cancer activity for the Probody Tx (as monotherapy and/or in combination) in subjects with advanced or unresectable solid tumors (during dose-finding) as well as in specific select tumor types (during additional efficacy evaluation)
    - Objective Response Rate (ORR) by the Response Evaluation Criteria in Solid Tumors (RECIST) or tumor-specific criteria, as applicable (eg, The Lugano Classification for lymphoma)
    - ORR by the modified immune-related RECIST criteria will also be determined for Probody Txs likely to be immunostimulating
    - Time to tumor response (TTR)
    - Duration of response (DOR)

- Progression-free survival (PFS)
- Overall survival (OS)

- To characterize the PK of the Probody Tx administered as directed
- To assess the incidence of anti-drug antibody (ADA) formation to the Probody Tx

Exploratory:

- To assess mechanistic features that are common to all Probody Txs (eg, release of the mask in tumor vs non-tumor tissue)
- To assess additional PD markers as per individual Probody Tx-specific Protocol Modules

Overview of Study Design and Schema:

This is an open-label, multiple-dose, dose-finding program of Probody Txs (as monotherapy and/or in combination with other anti-cancer agents) in subjects with advanced solid tumors and/or lymphomas. Additional evaluation of safety and efficacy in select cancer types will be pursued for each Probody Tx monotherapy and/or combination regimens, respectively, as defined in each Probody Tx-specific Protocol Module.

Dose-Finding: Escalation cohorts will be planned for a given Probody Tx, as monotherapy and/or in combination. This period of the program is designed to evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and gauge preliminary anti-tumor activity in subjects with advanced solid tumors and/or lymphomas.

The doses to be evaluated for each regimen (monotherapy and/or combination), as well as the number of cohorts, will be defined in the Probody Tx-specific Module. The general schema, however, is common to all Modules and presented here as follows.

Initially, 1-3 subjects will be enrolled into each dosing cohort, as defined by the Probody Tx-specific Module. Cohort expansion and dose escalation will be based on the number of DLTs experienced (see below) and after consultation by the Sponsor with a panel of active program investigators who will serve as the Safety Review Committee (SRC) and advise the Sponsor for all modules of this core/module program as long as the program is open.

To further explore the relationship between dose and emerging safety or efficacy signals, additional subjects may be accrued at any dose level as specified in the module.

Escalation of the Probody Tx in combination and/or monotherapy will be initiated and continue until the pre-specified top dose is administered safely, the MTD is defined or another interim dose is chosen as dictated by the data.

Efficacy Expansions for Proof of Concept: Further characterization of safety and efficacy will be conducted at the chosen dose and regimen, in a restricted number of pre-selected cancer types, in additional subjects as specified in the module. Additional subjects may be enrolled in an expansion cohort to further characterize efficacy. More than one dose level of each regimen may be tested, depending on the outcome of the dose escalation portion of the study.

Generally, all subjects will be followed until death, either in the Probody-specific module or a rollover follow-up trial. A separate unified rollover module may be used for continued follow-up for all subjects experiencing clinical benefit on any Probody Tx who remain on study drug and/or are still in follow-up.

Eligibility Criteria / Treatment:

Eligibility criteria and investigational product (IP) and reference therapy dosage and mode of administration will be specified in the Probody Tx-specific Module.

Duration of Treatment:

The maximum duration of study treatment for an individual subject enrolled in the study will be defined in each module. In general, subjects will continue on treatment unless they:

- experience clinically significant disease progression
- are unwilling or unable to adhere to the protocol
- withdraws consent or is lost to follow-up
- experience an intercurrent illness that prevents further administration of IP and/or reference therapy
- experience a DLT or an adverse event (AE) related to study drug(s), which precludes further administration of the study drug(s)
- experience a prolonged treatment delay (as per the Probody Tx-specific module)
- become pregnant, either prior to the first dose of study drug or at any time during treatment

Additionally

- The investigator may determine that the subject should discontinue treatment
- The Sponsor may terminate the study.

Criteria for evaluation

Efficacy:

For all Probody Txs, the primary criteria for defining efficacy and also for management of patient care will be RECIST (version 1.1) or tumor-specific response criteria (eg, Lugano Classification for lymphomas). However, response by the modified irRECIST criteria may also be captured for analysis in subjects receiving Probody Txs that are likely to be immunostimulating.

Safety:

Incidence and nature of DLTs, AEs and serious AEs (SAEs), as well as physical examinations, vital sign measurements, triplicate electrocardiograms (ECGs), clinical laboratory evaluations, and treatment discontinuation due to toxicity will be evaluated for safety assessment.

Pharmacokinetics:

The following PK parameters will be generated for the Probody Tx (as monotherapy and/or as a part of a combination regimen): maximum concentration (C_{max}), time at maximum concentration (t_{max}), minimum concentration (C_{min}), volume of distribution (V_d), elimination half-life ($T_{½}$), elimination rate constant (λz), area under the curve (AUC_{0-t} and AUC_{0-inf}) following single-dose, $AUC_{0-\tau}$ for multiple dose, total apparent clearance (CL), and fluctuation (%PTF). Metabolic activation of the Probody may also be explored.

Pharmacodynamics:

Assays of tumor tissue, blood cells, and plasma or serum meant specifically to measure Probody Tx target binding or effect on cellular activity, may be conducted.

Immunogenicity:

Blood samples will be collected to assess the extent of ADA response to Probody Txs. Incidence and titer of anti-Probody Tx antibodies will be defined.

Statistical Analyses:

ORR is the primary efficacy endpoint. For solid tumors, response evaluation will be based on RECIST criteria (v1.1). In addition, immune-related RECIST (irRECIST) criteria will also be used for Probody Txs that are likely to be immunostimulating. Objective response in lymphoma will be based on tumor-specific criteria.

Descriptive summaries will be provided. For continuous measures, these include mean, median, standard deviation and range. For categorical measures, these include counts and percentages.

Time to tumor response and duration of response will be summarized for those subjects with confirmed responses. PFS and OS will be summarized by Kaplan-Meier methodology.

The safety parameters include: AEs, clinical laboratory tests, physical examinations, vital signs, ECOG performance status, ECGs, and immunogenicity tests. Safety parameters may be summarized using descriptive statistics.

Plasma concentrations and PK parameters will be summarized using descriptive statistics. The relationship between biomarker and efficacy endpoints may be explored.

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

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
%PTF	fluctuation
ACLS	Advanced Cardiac Life Support
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the concentration time-curves from time zero to infinity
BMB	bone marrow biopsy
BUN	blood urea nitrogen
CBC	complete blood count
CL	total apparent clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CMR	complete metabolic response
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	clinical study report
CT	computerized (or computed) tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CV	cardiovascular
CXR	chest x-ray
DLBCL	diffuse large B-cell lymphoma

Abbreviation or Specialist Term	Explanation
DLT	dose-limiting toxicities
DOR	duration of response
ECG	electrocardiogram/electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GI	gastrointestinal
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HL	Hodgkin Lymphoma
ICF	informed consent form
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
irPD	immune-related Progressive Disease
IRR	infusion-related reaction
irRC	immune-related Response Criteria
irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
IV	intravenous
LD	longest diameter
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities

Abbreviation or Specialist Term	Explanation
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
Probody Tx	Probody therapeutic
Probody™	Probody is a trademark of CytomX Therapeutics, Inc.
PT	prothrombin time
PTT	partial thromboplastin time
QA	quality assurance
QC	quality control
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumors
RF	rheumatoid factor
SAE	serious AE
SAP	statistical analysis plan
SAR	suspected adverse reaction
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOP	standard operating procedure
SPD	sum of the perpendicular diameters
SRC	Safety Review Committee

Abbreviation or Specialist Term	Explanation
SUSAR	serious and unexpected suspected adverse reaction
$T_{½}$	terminal elimination half-life
TCB	T-cell redirecting bispecifics
T_{max}	time to maximum observed plasma concentration
TMF	trial master file
TMTB	total measured tumor burden
TSH	thyroid-stimulating hormone
TTR	time to tumor response
V_d	volume of distribution
V_{ss}	steady state volume of distribution
WBC	white blood cell
WHO DDE	World Health Organization Drug Dictionary Enhanced
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Probody™ Therapeutics

The use of antibody-based therapies for the treatment of cancer has greatly improved the precision by which tumor proteins and oncogenic pathways are targeted. Nevertheless, tumor targets are rarely, if ever, completely tumor-specific, and despite antibody precision, significant toxicities can result from antibody binding to normal tissue. A small number of tumor targets are expressed highly in the tumor and at low levels in normal tissue, but these have limited clinical utility because they are expressed only in a small number of tumor types and/or are present in a small number of subjects within a given tumor type. There is a need to identify new methods for optimizing the delivery of anti-cancer antibody-based therapeutics to widen the therapeutic index in the majority of patients.

Many examples of the need for antibody-based therapies with improved safety can be cited. For example, antibody-based immunotherapies are particularly impacted by serious on-target toxicities. Despite the importance of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) as inhibitors of anti-tumor immunity, these proteins also serve as important protection against unwanted inflammation outside of the cancer. Severe, often life-threatening, inflammation can be observed in subjects receiving CTLA-4 inhibitors (eg, ipilimumab and tremelimumab), PD-1 inhibitors (eg, nivolumab and pembrolizumab) as well as PD-L1 inhibitors (eg, durvalumab and alemtuzumab). The on-target toxicities of these agents are particularly problematic when they are combined with each other, because synergy of efficacy in the tumor is associated with synergy of toxicity in normal tissues.

Another example is the T-cell redirecting bispecific antibodies (TCBs). The extreme potency of TCBs is responsible for both the promise of these therapies and the difficulty in using them safely, particularly in solid tumors. An EGFR/CD3 bispecific (Micromet), for example, was highly and potently effective in mouse tumor models, but demonstrated diffuse organ inflammation in cynomolgus monkeys, and those animals that achieved the projected therapeutic exposure needed to be terminated early (Lutterbuese et al, 2010). Development of the agent was discontinued. Finally, antibody-drug conjugate (ADC) therapy can also be negatively affected by on-target toxicities. For example, a promising ADC directed against EphA2 (based on nonclinical data) was poorly tolerated in the first Phase 1 cohort in subjects and clinical development was discontinued (Annunziata et al, 2013).

Thus the need for safer, more effective anti-cancer drugs remains a key medical need and enhancing tumor specific targeting may be critical in order to safely deliver to subjects very potent therapies.

Probody therapeutics are fully recombinant antibody prodrugs, activated preferentially by proteases present in tumor microenvironments. They are designed to be administered in a form that has reduced interaction with their target in healthy tissues, but are activated to fully engage their target in the tumor microenvironment. In this way, Probody therapeutics are expected to minimize toxicity while maintaining anti-tumor activity. This approach may be particularly

useful for antibody-based therapies where clinical utility is limited by significant toxicities due to target binding outside of the tumor. Probody therapeutics differ from unmodified monoclonal antibodies by the recombinant inclusion of a prodomain at the amino-terminus of the light chain, which blocks (or "masks") the antibody binding to its target antigen and can be removed by tumor-associated protease activity. The physicochemical and pharmacological behaviors of Probody therapeutics are similar to unmodified monoclonal antibodies in most respects, although normal tissue binding and, therefore, target-mediated clearance are diminished. This antibody-masking technology can be potentially applied to monoclonal antibodies, antibody drug conjugates, bispecific antibodies, and broadly to any antibody-based, anti-cancer therapy.

In summary, by using refined applications of tumor protease biology, antibody-prodrugs can be engineered to be preferentially activated in tumors and spare normal tissue. The technology offers the potential to improve the therapeutic window of antibody-based agents with validated targets and create a therapeutic window with potent agents that can't otherwise be safely administered.

5.2. Study Rationale

Features of the Probody technology warrant a single expanding protocol for evaluation of multiple Probodies.

First, mechanisms of Probody activation are likely common to all Probody therapeutics (Probody Txs) and this is best assessed and analyzed in the same study. For example, assays that define the rate and location of Probody activation will be employed for all Probody Txs in development. Also, while the preclinical data show a characteristic level of activated Probody in the circulation of healthy animals, the extent of activation in subjects with concomitant morbidities will not be known until the clinical studies are initiated. A refined understanding of the subject population that is best served by the administration of antibody-based prodrugs that rely on active proteases for full function likely warrants the evaluation of a large sample size under the supervision of an experienced set of clinicians.

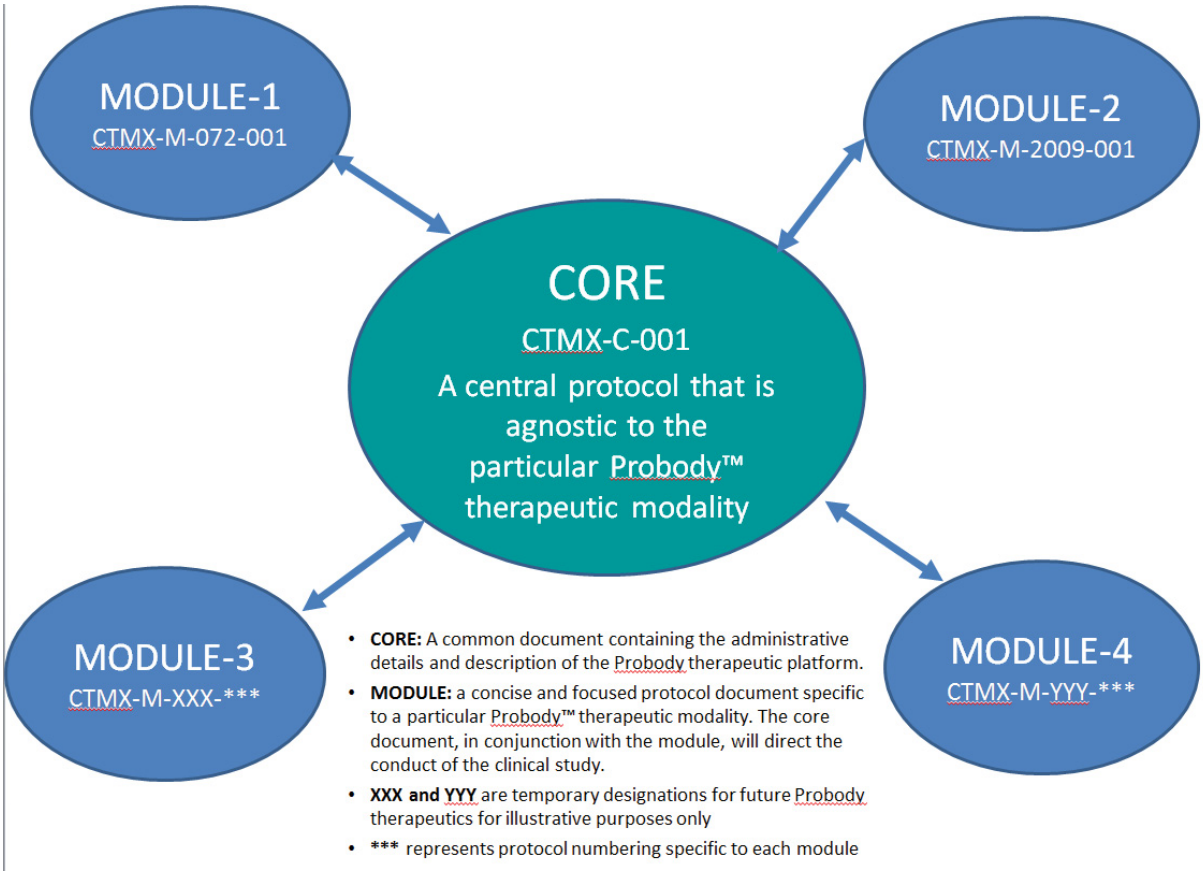
Finally, while the preclinical data show a characteristic level of activated Probody in the circulation of healthy animals, the extent of activation in subjects with concomitant morbidities will not be known until the clinical studies are initiated. A refined understanding of the subject population that is best served by the administration of antibody-based prodrugs that rely on active proteases for full function likely warrants the evaluation of a large sample size under the supervision of an experienced set of clinicians.

As such, the current program is constructed to permit unified clinical oversight of the entire Probody Tx program and is designed (for the sake of simplicity) as two broad parts: a Common Core Document that represents a standard Phase 1-2 design with all of the common elements that are relevant to any Probody in early development. This large and stable document will serve as the centerpiece of the study. Concise, Probody Tx-specific Modules will guide the investigator to study features unique to the investigational Probody Tx under evaluation. All protocol elements that directly guide patient care are in the module.

To maintain clarity and simplicity in the review and conduct of the program, institutional review board/independent ethics committee (IRB/IEC) submissions for each new Probody Tx will include the Common Core Document and relevant protocol module as a single package.

Amendments to the Common Core Document or to the modules, respectively, will be handled independently and a clinical study report (CSR) will be written for each module. The core/module system is a mechanism for bundling the clinical evaluation of Probody Txs under one program with a common study design, sites, investigators, database, and oversight. The figure below represents the relationship of the Probody Tx-specific protocol modules to the Common Core Document.

Figure 1: Relationship of Common Core Document and Protocol Modules



6. STUDY OBJECTIVES

The objectives below apply to the Phase 1-2 studies conducted under the Core.

6.1. Primary Objectives

- To evaluate the safety and tolerability of multiple doses of the Probody Tx, administered intravenously, as monotherapy and/or as part of a select combination regimen, to subjects with metastatic or locally advanced unresectable solid tumors and/or lymphomas; and
- To determine the MTD and DLTs of the Probody Tx (as monotherapy and/or in select combinations).

6.2. Secondary Objectives

- To obtain preliminary evidence of anti-cancer activity for the Probody Tx (as monotherapy and/or in combination) in subjects with advanced or unresectable solid tumors (during dose-finding) as well as in specific select tumor types (during additional efficacy evaluation)
  - ORR by RECIST or tumor-specific criteria, as applicable (eg, The Lugano Classification for lymphoma)
  - ORR by the modified immune-related RECIST criteria will also be determined for Probody Txs likely to be immunostimulating
  - Time to tumor response (TTR)
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
- To characterize the PK of the Probody Tx administered as directed
- To assess the incidence of anti-drug antibody (ADA) formation to the Probody Tx

6.3. Exploratory Objectives

Exploratory objectives that may be included:

- To assess mechanistic features that are common to all Probodies (eg, release of the mask in tumor vs non-tumor tissue); and
- To assess additional PD markers as defined in Probody Tx-specific protocol modules.

7. INVESTIGATIONAL PLAN

7.1. Study Characteristics

In order to simplify evaluation of the Probody platform, the current study is written in two parts, the Common Core Document, which focuses on definitions and analysis plan, and the Probody Tx-specific Protocol Module, which contains all elements related to patient care. Table 2 outlines the components contained with the Common Core vs the Protocol Module.

Table 2: Common Core Document vs Module Components

Element	Common Core Document	Protocol Module
Synopsis	X	
Introduction	Platform-specific	Probody-specific
Objectives	X	X
Number of Subjects	General	Module-specific
Investigational Plan	X	
Selection of Subjects		X
Investigational Product	Drug Accountability	Module-specific drug prep, storage, dosage form, administration
Treatment of Subjects	General dose escalation	Specific dose escalation, AE management, dose modification, withdrawal criteria and other Probody Tx-specific features
DLTs	General Definitions	DLT definition and drug-specific management guidelines
Efficacy, Safety, PK, PD, ADA	Efficacy assessment, safety parameters, etc.	PK, PD, and ADA assessments
Study Procedures	List/description	Schedule of Events
Statistics	X	
Adverse Events		X
Ethics		X
Study Administration	Administrative procedures	

7.2. Program Design

This is an open-label, dose-finding program of Probody Txs (as monotherapy and/or in combination with other anti-cancer agents) in subjects with advanced solid tumors and/or lymphomas. Additional evaluation of safety and efficacy in select cancer types will be pursued during the expansion phase of each module. The Probody Tx-specific module will specify the doses and cancers to be studied in expansion for the monotherapy and/or combination regimens, as applicable.

For the purposes of the Probody Tx program, “investigational product” refers to the Probody Tx. “Reference therapy” refers to any chemotherapeutic, biologic, or other anti-cancer therapy administered as part of the study. “Study drug” is used when referring to both IP and reference therapy.

7.3. Enrollment

The number of subjects enrolled will depend on the number of dose cohorts and treatment arms during dose escalation, as well as the cancers targeted in the expansion phase. This will be defined in the module.

During the efficacy expansion period of the study, a cohort is defined by the regimen (monotherapy and/or specific combination) and individual cancer type. Based on statistical calculations, additional subjects may be enrolled to each cohort as specified in the module. Additional subjects may be enrolled in an expansion cohort to further characterize efficacy.

Investigators will have the option of selecting among the treatment regimens outlined in the module for a particular subject; however, the doses to be administered will be assigned as determined by the dose escalation schema for the module.

7.4. Blinding and Randomization

Unless otherwise stated in the Probody Tx-specific module, all modules will be open-label and non-randomized.

7.5. Pregnancy

Pregnant women are not eligible for inclusion in the study. Measures to be taken to avoid pregnancy and to monitor subjects for potential pregnancy are outlined below.

Prior to Start of Treatment

Before enrolling women of childbearing potential (WOCBP) into a Probody Tx clinical trial, Investigators must advise WOCBP of the importance of avoiding pregnancy during trial participation and the potential risk factors of an unintentional pregnancy.

WOCBP must agree to use an adequate method of contraception to avoid pregnancy throughout their participation in the study and for a period of at least 90 days after the last infusion of study drug, whichever is longer in duration. If male, the subject must agree to use an accepted method of contraception during the same period of time. In addition, because harmful effects may occur to a child who is breast feeding from a woman receiving a Probody Tx, female subjects must not breastfeed during their participation in the study and for 6 months after the last infusion of study drug, whichever is longer in duration. This should be covered during the informed consent process.

All WOCBP must have a negative pregnancy test within 7 days prior to receiving the first infusion of study drug. If the pregnancy test is positive, the subject must not receive study drug and must not be enrolled in the study.

During the Study

After the first Probody Tx infusion, pregnancy tests will be performed routinely while on treatment (at a frequency defined in the module), and at the End of Treatment visit. WOCBP must continue to have negative pregnancy tests throughout the study. The results of all pregnancy tests (positive or negative) must be recorded on the eCRF.

In addition, all WOCBP or fertile men with partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant (eg, missed or late menstrual period) at any time during study participation.

If, following initiation of study treatment, it is subsequently discovered that a subject is pregnant or may have been pregnant at the time of IP and/or reference therapy exposure, the IP and/or reference therapy will be discontinued. Exceptions to IP/reference therapy discontinuation may be considered for life-threatening conditions only after consultation with the Sponsor and Medical Monitor. The Investigator must immediately notify the Sponsor and Medical Monitor of this event and record the pregnancy on the eCRF.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

8. INVESTIGATIONAL PRODUCT

8.1. IP Accountability

8.1.1. Drug Inventory

The Investigator will be responsible for ensuring that the IP is used only in accordance with the approved Protocol Module, for maintaining IP accountability at the clinical trial site, and ensuring that a current record of IP disposition is maintained at the study site. Records or logs must comply with applicable regulations and guidelines, and should include:

- The number of vials received and placed in the storage area, and date of receipt;
- The number of vials currently in the storage area;
- The lot number or batch number of each vial;
- The dates and initials of the person responsible for inventory entry/movement of each vial;
- The number of vials dispensed to each subject, with each subject identified by unique subject identifiers, and each vial used identified by lot/batch number;
- The number of vials transferred to another area for dispensing or storage, and date of transfer; any transfer of study drug to another location (eg, satellite site) will require documentation of chain of custody and cold chain maintenance in accordance with product stability standards;
- Non-study disposition (eg, vials that are lost or wasted);
- The number of vials returned to the Sponsor or Sponsor's designee, if applicable, and date of return;
- The number of vials destroyed at the study site, if applicable, and date of destruction; and
- Retained samples sent to a third party for bioavailability/bioequivalence, if applicable, and the date samples were sent.

The Sponsor or the Sponsor's designee will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

8.1.2. Return of IP

Upon completion or termination of the study, all unopened vials of IP must be returned to the Sponsor or Sponsor's designee, according to Sponsor's shipping instructions, unless authorized by the Sponsor or Sponsor's designee to be destroyed at the site.

- All vials of IP returned to the Sponsor or Sponsor's designee must be accompanied by the appropriate documentation and clearly identified by the Probody Tx-specific

Module number and study site number on the outermost shipping container. Returned supplies should be in the original containers.

- Empty or partially used containers should not be returned to the Sponsor or Sponsor's designee. It is the Investigator's responsibility to arrange for disposal of all partially used or empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept, including written authorization for disposal/destruction granted by the Sponsor or Sponsor's designee, arrangement for disposal, and appropriate documentation and records of the disposal will be maintained.

The return of unopened vials of IP should be arranged by the responsible study monitor.

8.2. Subject Compliance

IP and/or reference therapy administered as an intravenous (IV) infusion at the clinical site by the study staff will be documented in the subject's medical record. In the case of oral medications, subject compliance may be monitored by the use of subject diaries, pill counts, or other methods to be specified on the study portal. Subjects will be encouraged to comply with all study procedures.

9. TREATMENT OF SUBJECTS

9.1. Dosage and Administration

9.1.1. Study Drug Preparation and Administration

Refer to the Probody Tx-specific module for details pertaining to the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each trial treatment group of the specific study.

9.1.2. Cohort Initiation

Detailed information for Probody Tx-specific cohort initiation will be detailed in the modules; however, the first subject in each new dose cohort will be dosed a minimum of 1 day prior to any other subjects in that cohort, to allow for observation of possible severe and/or serious acute (eg, infusion-related) toxicities that might affect subsequent subject enrollment or dosing decisions.

9.1.3. Dose-Finding

Initially, 1-3 subjects will be enrolled into each cohort, as defined in the Probody Tx-specific module. Cohort expansion and dose escalation will be based on the number of DLTs experienced, as monotherapy and/or in combination with reference therapy. After establishing the DLT rate, additional subjects (monotherapy and/or combination therapy, respectively) may be enrolled to further evaluate the relationship between dose and safety or efficacy as specified in the module.

Unless otherwise specified in the Probody Tx-specific module, the DLT evaluation interval is defined as up to 28 days after administration of the first dose of IP.

9.2. Dose Escalation Guidelines

Until a DLT or treatment related ≥ Grade 2 related toxicity is observed requiring cohort expansion, single-subject cohorts may be explored at the beginning dose levels. In this way, the number of subjects exposed to subtherapeutic doses will be minimized.

In this setting, as soon as a DLT is observed in a single-subject cohort, or a subject experiences a ≥ Grade 2 study drug-related adverse event (AE), or cohort escalation reaches a starting dose level as defined in the module, cohorts will be enrolled using the standard 3 + 3 design. Cohort escalation may only take place after all individuals in a given cohort have reached the end of the DLT window and the Sponsor has approved further dose escalation.

Subjects who withdraw from the study for any reason during the DLT evaluation interval for reasons other than a DLT will be replaced. Dose escalation will proceed between cohorts according to the schema outlined in the module (or with smaller increments if significant AEs are observed).

After the rate of DLTs has been defined for a specific dose in 3 or 6 subject cohorts, additional subjects may be accrued at any dose level to better define the relationship between dose and emerging safety of efficacy signals, as specified in the module.

Escalation of the Probody Tx as monotherapy will be initiated first, and continue until the pre-specified top dose is administered safely or the maximum tolerated dose (MTD) is defined, whichever comes first.

Separate tracks of dose escalation of each combination regimen within a module, may also be conducted. The timing of initiation of the combination evaluation will differ, depending on the Probody Tx under evaluation (and as characterized in the relevant module). Initiation of combination evaluation could be as early as the time of successful clearing of monotherapy Cohort 2 and after consultation with the SRC. The dose of the combination agent(s) will be defined in each Probody Tx-specific module.

Once combination dose escalation has been initiated, it will proceed independently of the monotherapy escalation and continue until the pre-specified top doses for each agent are administered safely or the MTD is defined, whichever comes first. However, at the time of any dose escalation decision, the Sponsor and SRC will review available safety data from the monotherapy and/or combination cohort before a decision to escalate is made.

If one of the planned dose cohorts is determined to exceed the MTD and/or a review of ongoing safety/tolerability supports testing an intermediate dose, an alternative dose escalation schema may be explored. Escalation steps will not exceed those stipulated in the module without a formal amendment.

Subjects may be permitted individual dose escalations if indicated in a specific module.

9.3. Dose-Limiting Toxicity (DLT) and Maximally Tolerated Dose (MTD)

All AEs will be captured according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 and considered DLTs. Refer to the Probody Tx-specific module for detailed information.

Grade 1 or 2 AEs will not be considered DLTs unless specified in Probody Tx-specific Modules.

9.4. Dose Modifications and Dosing Delays Due to Toxicity

Drug-specific dose modifications and management of AEs are discussed in the module.

9.5. Additional Safety Cohorts (Expansion)

To further characterize safety and efficacy of each regimen at the chosen dose in a restricted number of pre-selected cancer types, additional subjects in each cancer type may be enrolled. Additional subjects may be enrolled in an expansion cohort to further characterize efficacy. More than one dose level of each regimen may be tested, depending on the outcome of dose escalation.

All subjects will be followed until death, as long as the Module is still open.

Archived samples or fresh baseline biopsies may be mandatory for subjects enrolled to the study. Requirements for on-treatment biopsies will be outlined in the Probody Tx-specific module.

9.6. Safety Monitoring

Study drug administration should always be conducted in a facility equipped to manage severe adverse events such as anaphylaxis or cardiac arrest (eg, monitor/defibrillator, epinephrine and other Advanced Cardiac Life Support [ACLS] medications, intubation equipment, etc).

Each subject receiving a Probody Tx will be evaluable for safety. The safety parameters include laboratory values, vital signs, physical findings, and spontaneous reports of adverse events reported to the Investigator by subjects.

Each subject will be assessed periodically for the development of any toxicity and assessed according to the NCI CTCAE v4.03.

Refer to the Probody Tx Investigator Brochure for a summary of the possible risks and side effects. Refer to the module for the management of acute (allergic reactions) and non-acute toxicity. Further management will depend upon the judgment of the Investigator in consultation with the Medical Monitor, as necessary.

A Safety Review Committee (SRC) comprised of at least 3 members, including participating Investigators and CytomX Medical Monitor(s) will monitor AE data. This committee will review available dosing and safety study data from the current and previous cohorts before providing recommendations related to dose escalation for the subsequent cohort. Recommendations to proceed with dose escalation, to modify the dose escalation schema, or modify the protocol related to subject oversight will be made by the SRC.

9.7. Prior and Concomitant Medications

Because toxicities and adverse events experienced by subjects on study can be related not only to IP, but also to medications and/or therapies administered immediately prior to or while on study, Investigators (or their designee) must record medications and therapies being taken by the subject in the 30 days prior to the first administration of IP in the eCRF, and should include the concurrent use of all other prescription or over-the-counter medications, or alternative therapies taken while the subject is in the study.

Probody Tx-specific modules will address prohibited medications; however, the following guidelines should be used regarding prior and concomitant medications:

- Systemic (or intrathecal) therapies and/or radiotherapy intended to treat the subject's cancer other than those specified in the Probody Tx-specific Module are not permitted while on the study. Subjects who receive anti-cancer therapy (approved or experimental) outside of the treatment described in the Module will need to be withdrawn from study treatment.
- Supportive care measures considered standard of care for subjects with the cancers specified within the Probody Tx-specific Module, such as growth factors and transfusion support, may be permitted while on study.
- Systemic corticosteroid use at prednisone-equivalent doses > 50 mg/day are not permitted while on study, except for the acute treatment of reversible adverse events (eg, infusion-related reactions [IRR]) or prophylaxis against IRR.

- In the event that a subject develops tumor lysis syndrome, follow institutional practices for management and report the event as an SAE.

Refer to the Probody Tx-specific module for specific recommendations and/or exclusions pertaining to concomitant medications.

9.8. Continuation of Study Treatment

Dosing of the Probody Tx as monotherapy and/or as combination therapy will be permitted for subjects meeting the following criteria:

- Evidence of ongoing clinical benefit: Subject has evidence of objective response, improvement in symptoms, or no clinically significant documented progression of disease
- Acceptable safety: subject does not experience DLT or treatment-related adverse event that precludes continued treatment with the treatment regimen
- It is felt to be in the subject's best interests to continue study treatment, as determined by the Investigator and the Medical Monitor

9.9. Withdrawal of Subjects

9.9.1. Withdrawal Criteria

Probody Tx-specific withdrawal criteria will be defined in the module. In general, subjects may choose to withdraw from treatment and/or the study at any time for any reason. The reason should be documented in the subject's medical record and recorded on the appropriate eCRF.

Subjects may be withdrawn from the study for any of the following reasons:

- The subject experiences clinically significant disease progression
- The subject is unwilling or unable to adhere to the protocol
- The subject withdraws consent or is lost to follow-up
- The subject experiences an intercurrent illness that prevents further administration of IP and/or reference therapy
- The subject experiences a DLT or an adverse event related to study drug(s) which precludes further administration of the study drug(s)
- The subject experiences a prolonged treatment delay
- The subject becomes pregnant, either prior to the first dose of study drug or at any time during treatment
- In the investigator's judgement, the subject should discontinue treatment
- The Sponsor terminates the study

9.9.2. Withdrawal from Treatment

Subjects may discontinue study treatment, but remain in follow-up. Subjects discontinued from study treatment due to an AE (whether serious or non-serious), including clinically significant abnormal laboratory test values, will be followed for resolution of the event or return to baseline.

Subjects who discontinue study treatment for reasons other than objective evidence of disease progression should be followed to document objective progression after study treatment discontinuation, if possible.

All End of Treatment (EOT) procedures should be completed within 30 (+7) days of the last dose of study drug.

9.9.3. Withdrawal from Study

If it is necessary to withdraw a subject from the study earlier than planned, all End of Study (EOS) procedures should be completed.

9.9.4. Replacement of Subjects

Subjects who withdraw from the study during the DLT evaluation interval for reasons other than a DLT will be replaced.

10. SAFETY, EFFICACY, PK, PD, AND OTHER ASSESSMENTS

10.1. Safety

Refer to the Schedule of Events within the Module for the timing of tests and procedures. Safety will be evaluated by measures that may include those listed below. Additional measures, specific to the Probody Tx and/or cancer type, will be specified in the module.

10.1.1. Adverse Events

AEs will be collected from start of treatment until 30 days after the last dose of study treatment (IP or reference therapy), unless otherwise stipulated in the module.

AEs will be evaluated by classifying and grading all events for severity according to NCI CTCAE, v4.03 (see Study Reference Manual) and for relationship to IP. Refer to Section 12 .

10.1.2. Clinical Laboratory Tests

The Clinical laboratory tests evaluated in the CTMX-C-001 program are listed in the sections below. Blood samples may be drawn from an IV access line used for study drug administration only if the line has been well flushed of study drug per standard local practice. The schedule for laboratory testing will be outlined in the Schedule of Events in each Probody Tx-specific Module.

Safety labs (eg, hematology, serum chemistry, urinalysis) will be performed by local laboratories unless otherwise stipulated in the module. Samples for PK, PD and exploratory tests will be performed by a central laboratory; collection and processing instructions will be detailed in a separate Laboratory Manual.

10.1.2.1. Hematology

Hematology samples collected will be evaluated for complete blood count (CBC) with differential, including blast count, platelet count, and reticulocyte count. CBC includes red blood cells (RBCs), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), and white blood cells (WBCs) with differential count to include neutrophils, eosinophils, basophils, lymphocytes, monocytes, and blasts.

10.1.2.2. Serum Chemistry

Chemistry samples collected will be evaluated for alkaline phosphatase, aspartate aminotransferase (AST) / serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT) / serum glutamic-pyruvic transaminase (SGPT), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), and hemoglobin A1c.

Blood glucose should be fasting to evaluate possible hyperglycemia (pre-existing, or acquired while on study).

Calculated creatinine clearance may be performed using the Cockcroft-Gault equation.

10.1.2.3. Thyroid Function

Blood for thyroid-stimulating hormone (TSH), Free T4 and T3 will be drawn in studies of Probody Tx that may induce an immune response.

10.1.2.4. Immune Safety Assays

In studies of Probody Tx that may induce an immune response, testing may include: free T4 and T3, rheumatoid factor (RF), adrenocorticotropic hormone (ACTH), C-reactive protein (CRP), antinuclear antibody (ANA) titer and pattern.

The following tests, may also be performed on selected stored samples at a later date: anti-DNA antibody, anti-phospholipid antibody, anti-SSA antibody (Ro), anti-islet cell antibody; anti-SSB antibody (La), anti-neutrophil cytoplasm antibody, anti-thyroglobulin antibody, C3 and C4, anti-LKM antibody, and CH50.

Abnormal endocrine results should be followed up with prolactin and a.m. cortisol tests, and may require an endocrine consult and additional testing.

10.1.2.5. Coagulation

Coagulation samples will be evaluated for prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).

10.1.2.6. Urinalysis

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity, plus microscopic exam.

10.1.2.7. Pregnancy

Pregnant women are not eligible for inclusion in the study. A serum pregnancy (human chorionic gonadotropin [HCG]) should be evaluated in all WOCBP. Urine pregnancy tests may be performed in lieu of serum pregnancy tests while the subject is on treatment.

10.1.3. Other Safety Measures

10.1.3.1. Vital Signs

Vital signs will include heart rate and blood pressure (supine), temperature, respiratory rate, and pulse oximetry.

Weight and height will be measured.

10.1.3.2. Electrocardiogram (ECG)

12-lead ECGs should be obtained, in triplicate (approximately 2-5 minutes apart), in digital format (when possible), and archived, while supine at screening, at time points to be specified in the Probody Tx-specific Module.

10.1.3.3. Physical Exam

A complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. A limited, targeted physical exam should be performed as needed by subject symptoms or clinical observations, focused on key organ systems of interest (eg, cardiovascular [CV], pulmonary, gastrointestinal [GI], skin, ophthalmic, or any systems with previously noted abnormal findings).

10.1.3.4. Ophthalmology Exam

Where applicable, a complete ophthalmology exam will be performed by a board-certified ophthalmologist at baseline, post-treatment and as specified in the Probody Tx-specific module and will include visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement and corneal photography (not required at baseline). Baseline testing will also include Schirmer's test. Subjects will be asked about ocular symptoms such as a history of dry eye and contact lens use and an ocular symptom assessment (blurred vision, ocular discomfort, etc) will be performed.

10.1.3.5. Concomitant Medications/Therapies

Concomitant medications/therapies will be recorded.

10.1.3.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance status (Appendix 16.1) will be evaluated during the study.

10.2. Efficacy

Although response is not the primary endpoint of the Phase 1-2 trials conducted under the Common Core Document, tumor response will be assessed by standard criteria to obtain a preliminary estimate of anti-cancer efficacy for the Probody Tx (as monotherapy and/or as combination therapy) in subjects with advanced or unresectable solid tumors. Additional criteria specific to a cancer (eg, the Lugano Classification for lymphomas) will be outlined in the Probody Tx-specific Module, as applicable.

Efficacy parameters may include:

- ORR (RECIST version 1.1 and, as applicable, modified immune-related RECIST [irRECIST] criteria)
- TTR
- DOR
- PFS
- OS

Efficacy will be assessed by RECIST v1.1 (and modified irRECIST for agents thought be immune-active as guided by the drug-specific module), if applicable.

10.2.1. Imaging

Computerized (or computed) tomography (CT) with and/or without contrast or magnetic resonance imaging (MRI) will be performed as appropriate. Bone scans and positron emission tomography (PET) scans may be performed if clinically indicated, but may not be used to measure target lesions. Imaging methods will be employed consistently during the course of each subject's evaluation during the study.

10.2.2. Tumor Markers

Blood draws for tumor makers will be outlined in the module, as applicable.

10.2.3. Response Criteria

RECIST v1.1 guidelines (Eisenhauer et al, 2009) will be used to evaluate response to therapy. Other tumor-specific response criteria will be utilized, as applicable, as well as modified irRECIST criteria (Bohnsack et al, 2014) for agents thought to be immuno-active.

Imaging of the chest, abdomen, and pelvis (as applicable) is required within 30 days prior to the first administration of Probody Tx. CT and magnetic resonance imaging (MRI) are acceptable. Subjects with skin, subcutaneous or lymph node metastases may also have tumor evaluations (including measurements with a ruler) by means of physical examination. During Screening, subjects must have disease that is measurable by standard imaging techniques or evaluable, per RECIST v1.1. For subjects who have received prior radiation therapy, measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented at that disease site subsequent to radiation.

In subjects for whom a baseline scan indicates no evidence of pelvic malignancy, chest/abdomen imaging may be performed (without pelvic imaging) at subsequent evaluations. In selected situations, a combination of CT/MRI is acceptable (ie, CT of chest, MRI of abdomen). The same imaging modalities used to characterize each site of disease at baseline should be used throughout the duration of the study. Imaging of extremities is also permitted and is required if significant metastases are present and are optimally evaluated via CT/MRI of an extremity.

Unless otherwise specified in the Probody Tx-specific Protocol Module Schedule of Events, tumor measurements and disease response assessments are to be performed every 8 weeks after the first dose of study drug through 12 months of treatment and then every 12 weeks from Month 13 until development of progressive disease (PD). Additional assessments may be performed during follow-up and will be specified in the Probody Tx-specific Protocol Module. Tumor measurements and disease response assessment are to be performed at the EOT visit as well.

Anatomical measurements (summed across target lesions) will be documented. When possible, the same qualified physician should interpret results to reduce variability. Radiographic images will be maintained at the study center, and Investigator findings will be filed in the subject's source documents.

10.2.3.1. RECIST v1.1

Assessment of Measurable, Non-measurable, Target and Non-Target Lesions

During Screening, tumor lesions are to be categorized as measurable versus non-measurable and target versus non-target, as follows.

Measurable versus non-measurable

- Measurable lesions can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) with a *minimum* size of: 10 mm by CT or MRI scan for non-nodal lesions and ≥ 15 mm in short axis for nodal lesions, 10 mm caliper measurement by clinical exam, or 20 mm by chest X-ray (CXR).
- Non-measurable: all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) and truly non-measurable lesions (eg, pleural or pericardial effusion, lymphangitic involvement of skin or lung).

Target versus non-target

- Target: all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at Screening. Target lesions are to be selected on the basis of their size (ie, those with the longest diameter) and suitability for accurate repeated measurement. The sum of the longest diameter for all target lesions is to be calculated and recorded in the eCRF as the baseline sum longest diameter. Target lesions cannot be biopsied at any time during the study.
- Non-target: all other lesions not classified as target lesions (or sites of disease) are to be identified as non-target lesions and are to be recorded in the eCRF. Measurement of non-target lesions is not required.

Disease response in target and non-target lesions will be assessed by the Investigator using RECIST v1.1 (Eisenhauer et al, 2009), according to the categories and criteria described in the table below. The best overall response for each subject will be reported as the best response documented over the sequence of objective statuses recorded using the categories and criteria in Table 3.

10.2.4. Definitions of Treatment Outcomes: RECIST v1.1

Table 3: Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines for Tumor Response

Disease Response Criteria for Target and Non-Target Lesions	
Evaluation of Target lesions	
Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Evaluation of Non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Source: Eisenhauer et al, 2009
Key: LD = longest diameter

Table 4: Overall Response Criteria (RECIST v1.1)

Subjects with Target and Non-Target Lesions			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR / Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
Subjects with Non-Target Lesions Only			
Non-Target Lesions		**New Lesions**	**Overall Response**
CR		No	CR
Non-CR / Non-PD		No	Non-CR / Non-PD
Not all evaluated		No	NE
Unequivocal PD		Yes or No	PD
Any		Yes	PD

Source: Eisenhauer et al, 2009
Key: CR = complete response; NE = not evaluable; PD = progressive disease

Any subject with a CR or PR is to have repeat assessments performed no earlier than 4 weeks later to confirm the response.

10.2.4.1. Modified immune-related RECIST (irRECIST)

As noted by Bohnsack et al (2014), RECIST v1.1 has some limitations when applied to immunotherapy in oncology. Tumors that appear to have progressed by RECIST criteria may later regress, possibly reflective of the impact of immune agents on host antitumor response (Chiou & Burotto, 2015).

Modified irRECIST criteria (Appendix 16.2) will be used to evaluate tumor response. Definitions for measurable, non-measurable, target and non-target lesions are outlined in Section 10.2.3.1.

The Bohnsack et al (2014) modifications of the iRECIST criteria differ from the immune-related Response Criteria (irRC) as noted by Wolchock et al (2009) as follows:

1. At the time of unconfirmed progression, the baseline is reset and the immune-related Progressive Disease (irPD) is only achieved if an increase in tumor burden of 20% relative to the new baseline is observed.
2. Target lesions cannot be biopsied at any time during the study.

Table 5: Derivation of modified irRECIST Overall Responses

TMTB of all measurable and new measurable lesions,[α]%	Non-target lesions	New, non-measurable lesions	Overall Response
Reduction of 100	Absent	Absent	irCR[β]
Reduction of 100	irNon-CR/Non-PD	Absent/Stable	irPR
Reduction of 100	Absent/Stable	irNon-CR/Non-PD	irPR
Reduction of ≥ 30	irNN	No unequivocal worsening	irPR
Reduction of < 30 to < 20 increase	Absence of unequivocal worsening		irSD
≥ 20 increase[γ]	Any	Any	irPD[δ]
Any	Unequivocal worsening	Any	irPD[δ]
Any	Any	Unequivocal worsening	irPD[δ]

Source: Bohnsack et al (2014)
TMTB = Total Measured Tumor Burden; irCR = immune-related Complete Response; irPR = immune-related Partial Response; irSD = immune-related Stable Disease; irPD = immune-related Progressive Disease. irNN = no target disease identified at baseline and at follow-up, the subject fails to meet the criteria for irCR or irPD.
[α] Decreases assessed relative to baseline
[β] Lymph nodes must also decrease to < 10 mm in short axis.
[δ] At the time of unconfirmed progression, the baseline is reset and irPD is only achieved if an increase in tumor burden of 20% relative to the new baseline is observed.
[γ] Minimum 5 mm absolute increase in TMTB compared to nadir

10.2.4.2. Tumor-Specific Response Criteria

Tumor-specific response criteria will be assessed, as applicable.

10.2.4.2.1. Lymphoma Specific Response Criteria

The Lugano classification as noted by Cheson et al (2014) and Cheson (2015) will be used to assess response in lymphomas.

Measurable versus non-measurable

- Measurable lesions: Maximum of 6 of the largest dominant nodes, nodal masses, and extranodal lesions that can be accurately measured in 2 diameters. Nodes should preferably be from disparate regions and include mediastinal and retroperitoneal areas, when applicable. Non-nodal lesions include those in solid organs
- Non-measurable: all other lesions, including nodes, nodal masses, and extranodal sites that are abnormal but not selected as dominant as well as truly non-measurable lesions (eg, pleural effusions, ascites, bone lesions).

Table 6: Response Criteria for Lymphoma

Response Criteria	PET-CT-based response	CT-based response[3]
Complete Response (CR):		
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on a PET five point scale (5-PS)[1,2]	Decrease of target nodes/nodal masses to ≤ 1.5 cm in LD and no extralymphatic sites of disease
Non-measured lesion	N/A	Absent
Organ enlargement	N/A	Decrease in size to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Morphology normal; if indeterminate, IHC negative
Partial Response (PR)		
Lymph nodes and extralymphatic sites	Score 4 or 5[1] with reduced uptake compared with baseline and residual mass(es) of any size. These findings at interim suggest responding disease and at End of Treatment indicate residual disease.	SPD decrease of ≥ 50% for ≤ 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm x 5 mm as default value.
Non-measured lesion	N/A	No increase; either absent/normal or regressed
Organ enlargement	N/A	Spleen regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but decreased relative to baseline. If there are persistent focal changes in the marrow in the setting of a nodal response then consider further evaluation by MRI or biopsy or interval scan.	N/A

Response Criteria	PET-CT-based response	CT-based response[3]
No Response or Stable Disease (SD)		
Target nodes/nodal masses, extranodal lesions	No response with score 4 or 5[1] with no significant change in FDG uptake from baseline at interim or End of Treatment.	SPD decrease of < 50% from baseline for ≤ 6 dominant, measureable nodes and extranodal sites
Non-measured lesion	N/A	No increase consistent with progression
Organ enlargement	N/A	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	N/A
Progressive Disease (PD)		
Individual target nodes/nodal masses, extranodal lesions	Score 4 or 5[1] with increase in uptake intensity from baseline and/or new FDG-avid foci consistent with lymphoma at interim or End of Treatment.	Individual node that is abnormal with LD > 1.5cm and increase of ≥ 50 from PPD nadir. Increase in LDi or SD by 0.5cm from nadir for lesions ≤ 2cm or 1.0 cm for lesions > 2cm. New or recurrent splenomegaly. In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (ie, 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, then must increase by ≥ 2 cm from baseline.
Non-measured lesion	None	New or clear progression of pre-existing non-measured lesions.
New lesions	New FDG-avid foci consistent with lymphoma and not another etiology. If uncertain regarding etiology, can consider biopsy or interval scan.	Regrowth of previously resolved lesions or new node > 1.5 cm or new extranodal site > 1.0 cm if any axis if < 1.0 cm in any axis that is unequivocally attributable to lymphoma.
Bone marrow	New or recurrent FDG avid foci	New or recurrent involvement

Source: Cheson 2015

Key: SPD = sum of the product of the perpendicular diameters for multiple lesions; LDi = longest transverse diameter of a lesion; SDi = shortest axis perpendicular to the LDi; PPD = cross product of the LDi and perpendicular diameter.

[1] PET 5 Point Scale (5PS): 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum, but ≤ liver; 4= uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma

[2] "Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, eg, with chemotherapy or myeloid colony stimulating factors, uptake could be greater than normal mediastinum and/or liver. In this context, complete metabolic response (CMR) may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake."

10.3. Pharmacokinetics

Detailed instructions for pharmacokinetic, immunogenicity, pharmacodynamics and exploratory immune function evaluations will be provided in the Laboratory Manual.

Serial blood samples to characterize the PK of the Probody Tx will be collected only in subjects enrolled to the dose-finding cohorts. The entire PK sampling scheme, including time points for collection, will be provided in each Probody Tx-specific Module.

PK parameters that will be measured, calculated, and reported may include the following: maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), half-life ($T_{½}$), clearance (CL), steady state volume of distribution (V_{ss}), time to reach C_{max} (t_{max}), and area under the curve zero to infinity ($AUC_{0\text{-}inf}$).

10.4. Immunogenicity

Serum samples will be collected to assess the extent of ADA response to Probody Txs. Incidence and titer of anti-Probody Tx antibodies will be defined based on samples obtained prior to the first dose and as specified in the Probody Tx-specific module.

10.5. Pharmacodynamics

Exploratory assays measuring target expression and PD parameters that potentially could be used either to select subjects suitable for treatment, or to predict response to treatment with a Probody Tx, will be performed on blood and/or tissue samples. The specific assays will be specified in the Probody Tx-specific Module.

10.6. Exploratory Immune Function Evaluations

Exploratory immune function evaluations may be conducted in subjects treated with a Probody Tx. Exploratory immune function evaluations will be defined in the Probody Tx-specific module.

The Probody Tx-specific Modules will specify the sample collection time points for blood and/or tissue samples, including optional research samples collected and stored for future research which may include disease-related biomarkers (or antibody responses to selected antigens), exploratory humoral and cellular immune responses to tumor antigens and a panel of recall non-tumor antigens. Available slides and tissue samples from tumor biopsies collected before enrollment may also be examined for tumor makers and inflammatory infiltrates.

Optional research-related tumor or other biopsies (eg, inflamed tissue) that do not require general anesthesia may be obtained with the subject's explicit consent to assess morphology and the presence or absence of inflammatory infiltrates, and their cellular characterization.

11. STATISTICAL PLAN AND ANALYSIS

Analyses common to the modules are described in the Common Core Document. Analyses specific to a Protocol Module will be described in a module-specific statistical analysis plan (SAP).

Descriptive summaries will be provided. For continuous measures, these include mean, median, standard deviation, and range. For categorical measures, these include counts and percentages.

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.

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

Analyses may be presented by cancer type, treatment regimen, and dose, when applicable.

11.1. Demographic and Baseline Characteristics

Descriptive statistics will be generated for all demographic and baseline characteristics.

11.2. Safety Analysis

Adverse events will be coded in accordance with the medical dictionary for regulatory activities (MedDRA) Version 16.1. Only treatment-emergent adverse events occurring and reported during the study period will be included in the adverse event summaries. A treatment-emergent AE is an event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state. AE presentation will include incidence, severity (categorized by NCI CTCAE criteria), and relationship to study drug.

Dose-limiting toxicities, study-drug related AEs, and AEs leading to discontinuation will be listed. In addition, changes from baseline in clinical laboratory results and vital signs will be assessed. ECGs and immunogenicity tests may be summarized using descriptive statistics, when applicable.

11.3. Efficacy Analysis

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 at least 4 weeks apart according to RECIST (RECIST v1.1). In addition, immune-related RECIST (irRECIST) criteria will also be used for Probody therapeutics that are likely to be immunostimulating. For lymphoma, objective response will be based on tumor-specific criteria.

The secondary efficacy endpoints include duration of response (DOR), TTR, progression-free survival (PFS), and overall survival (OS).

TTR is defined as the time from the date of the first dose of study drug to first documentation of objective tumor response. TTR is only calculated for subjects in the response-evaluable population who have a confirmed objective tumor response.

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

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 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 enrollment/randomization (as applicable). 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.

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. All deaths will be included in the analysis.

11.3.1. Efficacy Analysis Methods

The primary efficacy endpoint is the ORR and the primary efficacy analysis is based on the response-evaluable population. Exact 2-sided 95% confidence intervals will be calculated for all proportion estimates. Estimates of time-to-event endpoints (DOR, PFS, and OS) will be obtained using the Kaplan-Meier method. DOR and TTR will also be summarized using descriptive statistics for confirmed objective responders

11.4. Pharmacokinetic Analysis

A compartmental analysis will be performed to characterize the PK. A model with a number of compartments consistent with the data will be fit to each subject's data using nonlinear least squares regression. The model will be parameterized in terms of the primary parameters, the clearance(s) (CL) and V_{ss}. Secondary parameters—C_{max}, C_{min}, V_{ss}, distribution and elimination rate constants and $T_{½}$ (if a multi-compartmental model), and AUC $_{(inf)}$—will be calculated from the primary parameters.

Individual subject plasma concentrations, actual blood sampling times, and PK parameters will be listed by dose cohort. Plasma concentrations and PK parameters will be summarized using descriptive statistics. Individual subject observed and model-predicted plasma concentrations and mean observed plasma concentrations will be displayed graphically on linear and semi-logarithmic axes. These data may also be used in a future population PK analysis.

11.5. Immunogenicity

Blood samples for immunogenicity analysis will be collected from all subjects enrolled and evaluated for the development of ADA response.

11.6. Exploratory Analysis

Data may be pooled across modules to study properties common to Probody platform.

11.7. Determination of Sample Size

The sample size of each module is determined by the module objectives. The justification for the sample size will be provided in the Probody Tx-specific module.

11.8. Interim Analysis

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.

11.9. Deviation from Original Analysis Plan

All deviations from the original SAP will be provided in the final CSR.

12. ADVERSE EVENTS

All AE definition and reporting information will be provided in the Probody Tx-specific module.

13. ETHICS

All ethical review and conduct including subject information and informed consent will be provided in the Probody Tx-specific module.

14. STUDY ADMINISTRATION

14.1. Administrative Structure

A list of individuals who will have key positions in this study will be saved in the Module-specific Trial Master File (TMF). This list will include names, titles, and roles of selected individuals from the Sponsor and the Contract Research Organization(s) (CRO[s]) that will contribute to the study.

14.2. Quality Control and Quality Assurance

14.2.1. Overview

Quality assurance (QA) and quality control (QC) systems with written standard operating procedures (SOPs) will be implemented and maintained to ensure that the study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

QC will be applied to each stage of data handling. To ensure the accuracy, consistency, completeness, and reliability of the data, the study will include a combination of the following:

- Investigator meeting(s),
- Site initiation visit,
- Routine site monitoring,
- Ongoing site communication and training,
- Data management quality control checks,
- Continuous data acquisition and cleaning,
- Internal review of data, and
- QC checks of the final CSR.

During and/or after completion of the study, quality assurance personnel named by CytomX or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

In addition, the CytomX (or designee) Clinical QA Department may conduct periodic audits of the study processes, including, but not limited to vendors, clinical database, and final CSR.

14.2.2. Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions for this clinical study. Monitors will work in accordance with Sponsor and CRO SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator or designee and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment or study personnel. During the study, monitors will check that written informed consent/assent has been obtained from all subjects correctly and that data are recorded correctly and completely in the eCRFs. Monitors are also required to compare entries in eCRFs with corresponding source data and to inform the Investigator or designee of any errors or omissions. Monitors will also review adherence to the protocol and to regulatory requirements at the study site and will discuss deviations noted with the Investigator or designee. They will arrange for the study site to receive adequate supply of IP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to the US CFR Title 21 parts 50, 56, and 312 and ICH Guideline for GCP. The monitor will make written reports to the Sponsor following each contact with the Investigator or designee, regardless of whether it is by phone or in person.

14.2.3. Data Management/Coding

Study data will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor or CRO.

AEs will be coded using MedDRA and medications will be coded using WHO Drug Dictionary Enhanced (WHO DDE) drug dictionary.

14.2.4. Quality Assurance Audit

Study sites, the study database and study documentation may be subject to a QA audit during the course of the study, conducted by the Sponsor or designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

14.3. Data Handling and Recordkeeping

14.3.1. Electronic Data

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor will:

a. Ensure and document that the electronic data processing system(s) conforms to the Sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (ie, validation).
b. Maintain SOPs for using these systems.
c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (ie, maintain an audit trail, data trail, edit trail).
d. Maintain a security system that prevents unauthorized access to the data.
e. Maintain a list of the individuals who are authorized to make data changes.
f. Maintain adequate backup of the data.
g. Safeguard the blinding, if any (eg, maintain the blinding during data entry and processing).

Documentation regarding electronic systems used in this protocol is located in the Data Management Plan.

14.3.2. Case Report Form Completion

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.

It is the Investigator's responsibility to ensure the accuracy, completeness and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate eCRF.

A copy of the completed eCRFs and associated queries and audit trail for subjects enrolled at the site will be provided at the completion of the study for retention.

14.3.3. Data Handling

If data are transformed during processing, records will be maintained so that it will be possible to compare the original data and observations with the processed data.

An unambiguous subject identification (ID) code will be used that allows ID of all the data reported for each subject.

14.3.4. Retention of Study Records

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject ID codes (subject names and corresponding study numbers) will be retained by the site for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor prior to disposing of any study records.

14.4. Financing and Insurance

Financing and insurance are addressed in a separate document.

14.5. Confidentiality

To maintain subject privacy, all eCRFs, study drug accountability records, study reports and communications will identify the subject by the assigned subject number. The Investigator will

grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the IP supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of the IP and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

14.6. Publication Policy

All information concerning Probody Txs is considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from the Sponsor. No publication or disclosure of study results will be permitted except as specified in a separate, written agreement between Sponsor and the Investigator.

14.7. Direct Access to Source Data

The Investigators and their respective institutions will allow the Sponsor (or designee), and authorized regulatory authorities to have direct access to all documents pertaining to the study for study-related monitoring, audits, IRB/IEC review, and regulatory inspections as requested by FDA (or other regulatory authorities), the Sponsor, or the Sponsor designee. Direct access to records such as source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc) in addition to case report forms (CRFs) will be permitted.

The Investigator or designee will prepare and maintain adequate and accurate source documents to support all observations and other pertinent data recorded in the eCRF for each subject enrolled into the study.

14.8. Protocol Amendments

Changes to the conduct of the study will be provided in the Probody Tx-specific module.

15. REFERENCES

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16. APPENDICES

16.1. ECOG Performance Status

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

16.2. Modified Immune Related Response Evaluation Criteria in Solid Tumors Guidelines for Tumor Response

Definitions	Modified irRECIST Criteria
1.0 Baseline: Measurable Lesion Definitions and Target Lesion Selection[1]	Follow the definitions from RECIST v1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of: 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions 10 mm caliper measurement by clinical exam 20 mm by chest X-ray
1.1. Baseline: Non-measurable Lesion Definitions[2]	Follow the definitions from RECIST v1.1. Non-target lesions will include: Measurable lesions not selected as target lesions All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie, the longest perpendicular diameter is ≥ 10 and < 15 mm. Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.
1.2 Baseline: Target and Non-Target Lymph Node Lesion Definitions	Follow the definitions from RECIST v1.1.
1.3 Baseline: Non-Target Lesion Selection	All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.
1.4 Baseline: Bone Lesions	Follow the definitions from RECIST v1.1. Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.
1.5 Baseline: Brain Lesions	Brain lesions detected on brain scans can be considered as both target or non-target lesions.
1.6 Baseline: Cystic and Necrotic Lesions as Target Lesions	Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.
1.7 Baseline: Lesions With Prior Local Treatment	During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (eg, previous irradiation, RF-ablation, TACE, surgery, etc). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

Definitions	Modified irRECIST Criteria
1.8 Baseline: No Disease at Baseline	If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign "No Disease" (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the TMTB.
2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements[3]	The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the TMTB at follow-up.
2.1 Follow-up: Definition of Measurable New Lesions[4]	In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.
2.2 Follow-up: Non-Target Lesion Assessment[5]	The RECIST v1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.
2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment[6]	All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.
2.4 irRC Overall Tumor Assessments[7,8]	**irCR**, complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. **irPR**, decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. **irSD**, failure to meet criteria for irCR or irPR in the absence of irPD. **irNN**, no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD. **irPD[9]**, minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. **irNE**, used in exceptional cases where insufficient data exists. **irND**, in adjuvant setting when no disease is detected.

Source: Bohnsack et al, 2014

Key: TMTB = Total Measured Tumor Burden; irCR = immune-related Complete Response; irPR = immune-related Partial Response; irSD = immune-related Stable Disease; irNN = irNon-CR/Non-PD. irPD = immune-related Progressive Disease; irNE = immune-related not evaluable; irND = immune- related no measurable/non-measurable disease.

[1]Up to 5 target lesions may be selected at baseline. Lesions will be measured unidimensionally. The minimum target lesion size at baseline in irRECIST is aligned with RECIST v1.1.

[2]Although irRC does not specifically define non-target lesions, irRC is derived from WHO criteria and indicates accordance with the same for the purposes of definitions of non-target lesions. Further clarifications in alignment with RECIST v1.1 are provided.
[3]Unidimensional measurements are used. Measurements of all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into TMTB at follow-up.
[4]Larger lesions must be preferred as new measurable over smaller lesions, because there will be a greater impact of the TMTB %-increase by these larger lesions for irPD, to support a most conservative approach.
[5]Non-target lesions have a subordinate function. In the event that non-target lesions massively progress one cannot ignore such worsening and in these rare cases irPD based only on non-target lesions will be a valid assessment option.
[6]When new non-measurable lesions substantially worsen in these rare cases irPD based only on new non-measurable lesions will be an assessment option.
[7]The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.
[8]The thresholds for irPR and irPD assessment are aligned with RECIST v1.1, and confirmation of response is not required.
[9]An irPD confirmation scan may be recommended for patients with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.

16.3. Lugano Classification for Lymphomas

Refer to the Cheson et al (2014) publication on the Lugano Classification for detailed recommendations regarding response assessment in lymphoma. Table 3 provides detailed information on the revised criteria for response assessment. Highlights of the reference are provided below (http://jco.ascopubs.org/content/32/27/3059.long).

16.3.1. Recommendations for Revisions to Staging Criteria

The recommendations below are intended for lymphomas with primarily nodal involvement.

Imaging

Based on consensus criteria, PET-CT is recommended for routine stating of fluorodeoxyglucose (FDG)-avid, nodal lymphomas. CT scan is preferred in the other lymphomas.

Tumor Bulk

A single nodal mass, in contrast to multiple smaller nodes, of 10 cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT is retained as the definition of bulky disease for Hodgkin Lymphoma (HL). A CXR is not required to determine bulk. The Lugano Classification recommendation for HL and Non-Hodgkin Lymphoma is to record the longest measurement by CT scan, with the term X no longer necessary.

Spleen Involvement

A single measurement that correlates well with volume is preferable to a volumetric measurement or estimation by equations. The Lugano Classification recommends a cutoff for splenomegaly of > 13 cm.

Liver Involvement

Liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. Diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver involvement.

Bone Marrow Involvement

For histologies other than diffuse large B-cell lymphoma (DLBCL), follow standard practice and perform a 2.5-cm unilateral bone marrow biopsy (BMB), along with immunohistochemistry and flow cytometry.

In DLBCL, a PET-CT scan indicating bone or marrow involvement is usually sufficient to designate advanced-stage disease and a BMB is not required.

16.3.2. Assessment of Response

- PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale; CT is preferred for low or variable FDG avidity.
- A complete metabolic response (CMR) even with a persistent mass is considered a complete remission.

- A PR requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative nodes or extranodal lesions.
- Progressive disease by CT criteria only requires an increase in the PPDs of a single node by ≥ 50%.
- Surveillance scans after remission are discouraged, especially for DLBCL and HL, although a repeat study may be considered after an equivocal finding after treatment. Judicious use of follow-up scans may be considered in indolent lymphomas with residual intra-abdominal or retro-peritoneal disease.

Appendix B: Schedule of Procedures

Table 13. Schedule of Procedures: Parts A, A2, and B

Period/ Procedure	Screening	Treatment Period											FU/EOS [25]
		Cycle 1 DLT Assessment Day 1 to Day 21				Cycle 2			Cycle 3 & On [22]			EOT [24]	
Study/Visit Day [1]	–30 to 0	1	4 [23] (±1d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	(±7d)	Refer to Footnote
Informed consent	X												
Medical history [2]	X												
Demographics	X												
AE assessment [3]		X		X	X	X			X			X	
Concomitant medications [4]	X	X		X	X	X			X			X	
HIV/CMV/ Hepatitis B, C	X												
CX-2009 administration [5]		X				X			X				
CT/MRI (chest, abdomen, pelvis) [6]	CT/MRI/Tumor assessment to be conducted every 8 (±1) weeks from the first dose of CX-2009 with assessment for response per RECIST Version 1.1												
Bone scan [7]	As clinically indicated												
ECG [8]	X	Day 1 of Cycles 1 and 3 and as clinically indicated for other visits										X	
Full physical examination [9]	X											X	
Targeted physical examination [10]		X		X	X	X			X				

Table 13. Schedule of Procedures: Parts A, A2, and B

Period/ Procedure	Screening	Treatment Period											FU/EOS [25]
		Cycle 1 DLT Assessment Day 1 to Day 21				Cycle 2			Cycle 3 & On [22]			EOT [24]	
Study/Visit Day [1]	–30 to 0	1	4 [23] (±1d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	(±7d)	Refer to footnote
Complete ophthalmology examination [11]	X	All subjects within 5 days prior to Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; and at the EOT Visit. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.											
Ocular symptom assessment [12]	X	X				X			X			X	
Vital signs	Refer to Table 17												
ECOG performance status [13]	X	X				X			X			X	
Hematology [14]	X	X		X	X	X	X	X	X	X	X	X	
Serum chemistry [15,16]	X	X		X	X	X	X	X	X	X	X	X	
Coagulation [17]	X	As clinically indicated										X	
Urinalysis [18]	X											X	
Pregnancy test [19]	X	X				X			X			X	X
Archival/baseline tumor biopsy	X												
Tumor markers [20]	As clinically indicated												
Biopsy (fixed and frozen) and plasma biomarker sample [21]	X (Parts A, B only)		X (3 to 5 days post C1D1)										
Plasma PK and ADA	Refer to Table 18 (Parts A and A2) and Table 19 (Part B)												

See footnotes on the following page.

Table 13. Schedule of Procedures: Parts A, A2, and B

Note: For Parts A, A2, and B, each cycle constitutes 21 days.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (eg, weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit or as otherwise specified in the Schedule of Procedures. Visits conducted outside the windows are to be discussed with the Medical Monitor or designee in advance.
2. Medical history to include confirmation of previous cancer diagnosis, and record cancer treatment history, current symptoms at baseline, and current medications, as well as those taken within 30 days of first dose of study drug. An ophthalmology history is also required.
3. AEs will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination.
4. Concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Changes in concomitant medications will be collected up to and including the EOT Visit. After EOT, only concomitant medications administered for irAEs occurring within 90 days after last dose will be recorded. Once a subject enters the Follow-Up Period, only new therapies for the treatment of their cancer should be recorded in the eCRFs.
5. CX-2009 will be administered by IV infusion every 21 days. There must be a **MINIMUM** of 21 days between infusions (a window of ±2 days may occur). CX-2009 will be administered over 90 (±10) minutes with careful monitoring of IRRs.
6. MRI (CT may also be acceptable) to be performed within 30 days prior to the first dose of CX-2009 as baseline and repeated for assessment of tumor response every 8 (±1) weeks from the first dose of CX-2009 as per NCCN Guidelines until progression. Scans will be performed at a regular interval, regardless if CX-2009 dosing is delayed or modified. Scans will also be repeated at the EOT Visit (if the subject has not experienced progression). Tumor measurements will be recorded at baseline and repeated at regular intervals, as per the NCCN Guidelines for the specific tumor type. CR or PR must be confirmed at a second tumor assessment obtained at ≥4 weeks from the assessment at which CR or PR was first observed. Tumor response will be evaluated using RECIST (v1.1). Skin lesions (whether measurable or not) should be photographed along with a ruler at all time points for tumor assessments. MRI (CT scan may also be acceptable) will be performed every 12 weeks for subjects who have been on study drug >12 months.
7. Bone scans will be performed as clinically indicated and at the discretion of the Investigator.
8. Twelve-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible), and archived, while supine at Screening (within 7 days prior to Cycle 1 Day 1), preinfusion and both 15 minutes and 1 hour post-EOI on Day 1 of Cycles 1 and 3 (only) and as clinically indicated, and at the EOT Visit.
9. A full physical examination should be performed at Screening, prior to infusion of CX-2009, and at the EOT Visit.
10. A targeted physical examination should be performed weekly during the DLT period, once each cycle, and as needed by subject symptoms or clinical observations, focused on key organ systems of interest (eg, CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings).
11. A complete ophthalmologic examination (including visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, corneal photography, and Schirmer's test) will be performed in all subjects at baseline (within 5 days prior to the first dose of CX-2009); within 5 days prior to Cycle 2, Day 1; Cycle 3, Day 1; and at the EOT Visit by an ophthalmologist. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.
12. The ocular symptom assessment will include assessment of blurred vision and ocular discomfort. The ocular symptom assessment will be performed at Screening, Day 1 of every cycle, and at the EOT Visit. If ocular toxicity occurs, see Section 5.5.3.2 and Section 5.5.4.1.
13. ECOG performance status should be assessed at Screening, Day 1 of every cycle, prior to each infusion, and at the EOT Visit.
14. Including CBC with differential, including platelet count and reticulocyte count, will be performed at Screening, preinfusion, weekly during treatment, and at the EOT Visit.
15. Serum chemistry will include ALP, AST/SGOT and ALT/SGPT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, magnesium, uric acid, LDH, and hemoglobin A1c, if clinically indicated. Blood glucose should be fasting at Screening and as indicated to evaluate possible hyperglycemia. Calculated creatinine clearance is required at Screening. Laboratory assessments drawn on the day of infusion should be drawn preinfusion.
16. Serum chemistry will only include electrolytes (potassium, sodium chloride, and magnesium) on Day 8 and Day 15 of every cycle.

Table 13. Schedule of Procedures: Parts A, A2, and B

17. Coagulation will include PT/aPTT/INR at Screening, the EOT Visit, and as clinically indicated. If results are abnormal at Screening, then repeat prior to dosing or as clinically indicated.
18. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at Screening and the EOT Visit.
19. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at Screening. If the Screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted. Urine pregnancy test (with serum test as needed for confirmation) should be obtained prior to each cycle of therapy, at the EOT Visit, and at FU/EOS Visits through 50 days after the last dose of CX-2009.
20. Tumor marker assessments should be scheduled concurrently with CT for PSA and CA125 for appropriate tumor types; all others as clinically indicated.
21. Biopsies in subjects participating in the Part A dose escalation schema will be optional. For the subjects who consent to pretreatment and on-treatment tumor biopsies during dose escalation (Part A), tumor biopsies (fixed and frozen) will be collected during the Screening Period and 3 to 5 days after the first dose of CX-2009. Biopsy collection for the purpose of determining eligibility for Part A2 is not permitted. For Part A2, tumor biopsies (fixed and frozen) are required 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician. Paired plasma samples will be obtained at the time of the tumor biopsies. The technical details for the collection of specimens will be outlined in the Laboratory Manual. Biopsy collection for the purpose of determining eligibility for Part B is not permitted. For the dose expansion (Part B), consent to pretreatment and on-treatment tumor biopsies will be mandatory in at least 7 subjects for each tumor type. For these subjects, tumor biopsies (fixed and frozen) will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician.
22. Day 8 and Day 15 Visits are not needed for subjects who have been on study drug >4 months and have no ongoing ≥Grade 2 adverse events.
23. Day 4 Visit and assessments only for subjects who participate in the on-treatment tumor biopsies.
24. An EOT Visit will be conducted 30 days (±7 days) after the last infusion of CX-2009.
25. Follow-Up and EOS:

- If subject had documented progression, the subject may continue in the study if experiencing clinical benefit (as assessed by the Investigator) following consultation with the Medical Monitor or designee; otherwise, 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.
- If subject has not had progression, imaging assessments will continue until progression is documented. Survival Follow-Up will be done every 3 months (±14 days) as described above.
- Women of childbearing potential will undergo pregnancy testing at FU/EOS Visits through 50 days after the last dose of CX-2009.

ADA = antidrug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA125 = cancer antigen 125; CBC = complete blood count; CMV = cytomegalovirus; C1D1 = Cycle 1 Day 1; CR = complete response; CT = computed tomography; CV = cardiovascular; d = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology group; eCRF = electronic case report form; EOI = end of infusion; EOS = end of study; EOT = end of treatment; FU = follow-up; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; IRR = infusion-related reaction; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PK = pharmacokinetic; PR = partial response; PSA = prostate-specific antigen; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumours; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Table 14. Schedule of Procedures: Parts C1 and C2

Period/ Procedure	Screening	Treatment Period														FU/EOS [25]
		Cycle 1 DLT Assessment Day 1 to Day 28					Cycle 2				Cycle 3 & On [22]				EOT [24]	
Study/Visit Day [1]	–30 to 0	1	4 [23] (±1d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	(±7d)	Refer to footnote
Informed consent	X															
Medical history [2]	X															
Demographics	X															
AE assessment [3]		X		X	X	X	X		X		X		X		X	
Concomitant medications [4]	X	X		X	X	X	X		X		X		X		X	
HIV/CMV/ Hepatitis B, C	X															
CX-2009 administration [5]		X			X		X		X		X		X			
CT/MRI (chest, abdomen, pelvis) [6]	CT/MRI/Tumor assessment to be conducted every 8 (±1) weeks from the first dose of CX-2009 with assessment for response per RECIST Version 1.1															
Bone scan [7]	As clinically indicated															
ECG [8]	X	Day 1 of Cycles 1 and 2 and as clinically indicated for other visits													X	
Full physical examination [9]	X														X	
Targeted physical examination [10]		X		X	X	X	X		X		X		X			

Table 14. Schedule of Procedures: Parts C1 and C2

Period/ Procedure	Screening	Treatment Period														
		Cycle 1 DLT Assessment Day 1 to Day 28					Cycle 2				Cycle 3 & On [22]				EOT [24]	FU/EOS [25]
Study/Visit Day [1]	-30 to 0	1	4 [23] (±1d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	(±7d)	Refer to Footnote
Complete ophthalmology examination [11]	X	All subjects within 5 days prior to Cycle 1, Day 1; Cycle 1 Day 15; Cycle 2, Day 1; and at the EOT Visit. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.														
Ocular symptom assessment [12]	X	X			X		X		X		X		X		X	
Vital signs	Refer to Table 17															
ECOG performance status [13]	X	X			X		X		X		X		X		X	
Hematology [14]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry [15,16]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation [17]	X	As clinically indicated													X	
Urinalysis [18]	X														X	
Pregnancy test [19]	X	X			X		X		X		X		X		X	X
Archival/ baseline tumor biopsy	X															
Tumor markers [20]	As clinically indicated															
Biopsy (fixed and frozen) and plasma biomarker sample [21]	X		X (3 to 5 days post C1D1)													
Plasma PK and ADA	Refer to Table 20 (Part C1) and Table 21 (Part C2)															

See footnotes on the following page.

Table 14. Schedule of Procedures: Parts C1 and C2

Note: For Parts C1 and C2, each cycle constitutes 28 days.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (eg, weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit or as otherwise specified in the Schedule of Procedures. Visits conducted outside the windows are to be discussed with the Medical Monitor or designee in advance.
2. Medical history to include confirmation of previous cancer diagnosis, and record cancer treatment history, current symptoms at baseline, and current medications, as well as those taken within 30 days of first dose of study drug. An ophthalmology history is also required.
3. AEs will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination.
4. Concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Changes in concomitant medications will be collected up to and including the EOT Visit. After EOT, only concomitant medications administered for irAEs occurring within 90 days after last dose will be recorded. Once a subject enters the Follow-Up Period, only new therapies for the treatment of their cancer should be recorded in the eCRFs.
5. CX-2009 will be administered by IV infusion every 14 days. There must be a **MINIMUM** of 14 days between infusions (a window of ±2 days may occur). CX-2009 will be administered over 90 (±10) minutes with careful monitoring of IRRs.
6. MRI (CT may also be acceptable) to be performed within 30 days prior to the first dose of CX-2009 as baseline and repeated for assessment of tumor response every 8 (±1) weeks from the first dose of CX-2009 as per NCCN Guidelines until progression. Scans will be performed at a regular interval, regardless if CX-2009 dosing is delayed or modified. Scans will also be repeated at the EOT Visit (if the subject has not experienced progression). Tumor measurements will be recorded at baseline and repeated at regular intervals, as per the NCCN Guidelines for the specific tumor type. Complete response or PR must be confirmed at a second tumor assessment obtained at ≥4 weeks from the assessment at which CR or PR was first observed. Tumor response will be evaluated using RECIST (v1.1). Skin lesions (whether measurable or not) should be photographed along with a ruler at all time points for tumor assessments. MRI (CT scan may also be acceptable) will be performed every 12 weeks for subjects who have been on study drug >12 months.
7. Bone scans will be performed as clinically indicated and at the discretion of the Investigator.
8. Twelve-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible), and archived, while supine at Screening (within 7 days prior to Cycle 1 Day 1), preinfusion and both 15 minutes and 1 hour post-EOI on Day 1 of Cycles 1 and 2 (only) and as clinically indicated, and at the EOT Visit.
9. A full physical examination should be performed at Screening, prior to infusion of CX-2009, and at the EOT Visit.
10. A targeted physical examination should be performed weekly during the DLT period, prior to each infusion, and as needed by subject symptoms or clinical observations, focused on key organ systems of interest (eg, CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings).
11. A complete ophthalmologic examination (including visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, corneal photography, and Schirmer's test) will be performed in all subjects at baseline (within 5 days prior to the first dose of CX-2009); within 5 days prior to Cycle 1, Day 1; Cycle 1 Day 15; Cycle 2, Day 1; and at the EOT Visit by an ophthalmologist. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.
12. The ocular symptom assessment will include assessment of blurred vision and ocular discomfort. The ocular symptom assessment will be performed at Screening, prior to each infusion, and at the EOT Visit. If ocular toxicity occurs, see Section 5.5.3.2 and Section 5.5.4.1.
13. ECOG performance status should be assessed at Screening, Day 1 of every cycle, prior to each infusion, and at the EOT Visit.
14. Including CBC with differential, including platelet count and reticulocyte count, will be performed at Screening, preinfusion, weekly during treatment, and at the EOT Visit.
15. Serum chemistry will include ALP, AST/SGOT and ALT/SGPT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, magnesium, uric acid, LDH, and hemoglobin A1c, if clinically indicated. Blood glucose should be fasting at Screening and as indicated to evaluate possible hyperglycemia. Calculated creatinine clearance is required at Screening. Laboratory assessments drawn on the day of infusion should be drawn preinfusion.
16. Serum chemistry will only include electrolytes (potassium, sodium chloride, and magnesium) on Days 8 and 22 of every cycle.

Table 14. Schedule of Procedures: Parts C1 and C2

17. Coagulation will include PT/aPTT/INR at Screening, the EOT Visit, and as clinically indicated. If results are abnormal at Screening, then repeat prior to dosing or as clinically indicated.
18. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at Screening and the EOT Visit.
19. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at Screening. If the Screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted. Urine pregnancy test (with serum test as needed for confirmation) should be obtained prior to each CX-2009 infusion, at the EOT Visit, and at FU/EOS Visits through 50 days after the last dose of CX-2009.
20. Tumor marker assessments should be scheduled concurrently with CT for PSA and CA125 for appropriate tumor types; all others as clinically indicated.
21. For Part C1, pretreatment and on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician. Biopsy collection for the purpose of determining eligibility for Part C1 is not permitted. For Part C2, pretreatment and on-treatment tumor biopsies will be mandatory in at least 7 subjects for each tumor type. For these subjects, tumor biopsies (fixed and frozen) will be collected during the Screening Period (baseline) and 3 to 5 days after the first dose of CX-2009, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician. Biopsy collection for the purpose of determining eligibility for Part C2 is not permitted.
22. Day 8 and Day 22 Visits are not needed for subjects who have been on study drug >4 months and have no ongoing ≥Grade 2 adverse events.
23. Day 4 Visit and assessments only for subjects who participate in the on-treatment tumor biopsies.
24. An EOT Visit will be conducted 30 days (±7 days) after the last infusion of CX-2009.
25. Follow-Up and EOS:

- If subject had documented progression, the subject may continue in the study if experiencing clinical benefit (as assessed by the Investigator) following consultation with the Medical Monitor or designee; otherwise, 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.
- If subject has not had progression, imaging assessments will continue until progression is documented. Survival Follow-Up will be done every 3 months (±14 days) as described above.
- Women of childbearing potential will undergo pregnancy testing at FU/EOS Visits through 50 days after the last dose of CX-2009.

ADA = antidrug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA125 = cancer antigen 125; CBC = complete blood count; CMV = cytomegalovirus; C1D1 = Cycle 1 Day 1; CR = complete response; CT = computed tomography; CV = cardiovascular; d = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern cooperative Oncology group; eCRF = electronic case report form; EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; FU = Follow-Up; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; IRR = infusion-related reaction; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PK = pharmacokinetic; PR = partial response; PSA = prostate-specific antigen; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumours; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Table 15. Schedule of Procedures: Parts D1 and D2

Period/Procedure	Screening	Treatment Period														FU/EOS [26]
		Cycle 1 DLT Assessment Day 1 to Day 28					Cycle 2				Cycle 3 & On [23]				EOT [25]	
Study/Visit Day [1]	–30 to 0	1	4 (±1d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	(±7d)	Refer to footnote
Informed consent	X															
Medical history [2]	X															
Demographics	X															
AE assessment [3]		X		X	X	X	X		X		X		X		X	
Concomitant medications [4]	X	X		X	X	X	X		X		X		X		X	
HIV/CMV/ Hepatitis B, C	X															
CX-2009 administration [5]		X			X		X		X		X		X			
CX-072 administration [6]		X			X		X		X		X		X			
CT/MRI (chest, abdomen, pelvis)[7]	CT/MRI/Tumor assessment to be conducted every 8 (±1) weeks from the first dose of study treatment with assessment for response per RECIST Version 1.1 and per irRECIST (Parts D1 and D2)															
Bone scan [8]	As clinically indicated															
ECG [9]	X	Day 1 of Cycles 1 and 2 and as clinically indicated for other visits													X	
Full physical examination [10]	X														X	
Targeted physical examination [11]		X		X	X	X	X		X		X		X			
Complete ophthalmology examination [12]	X	All subjects within 5 days prior to Cycle 1, Day 1; Cycle 1 Day 15; Cycle 2, Day 1; and at the EOT Visit. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.														

Table 15. Schedule of Procedures: Parts D1 and D2

Period/Procedure	Screening	Treatment Period														
		Cycle 1 DLT Assessment Day 1 to Day 28					Cycle 2				Cycle 3 & On [23]				EOT [25]	FU/EOS [26]
Study/Visit Day [1]	-30 to 0	1	4 (±1d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	22 (±2d)	(±7d)	Refer to footnote
Ocular symptom assessment [13]	X	X			X		X		X		X		X		X	
Vital signs	Refer to Table 17															
ECOG performance status [14]	X	X			X		X		X		X		X		X	
Hematology [15]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry [16,17]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation [18]	X	As clinically indicated													X	
Urinalysis [19]	X														X	
Pregnancy test [20]	X	X			X		X		X		X		X		X	X
Archival/ baseline tumor biopsy	X															
Tumor markers [21]	As clinically indicated															
Biopsy (fixed and frozen) and plasma biomarker sample [22]							X (3 to 5 days after C2D1)									
Plasma PK and ADA sample	Refer to Table 22 (Part D1) and Table 23 (Part D2)															

See footnotes on the following page.

Table 15. Schedule of Procedures: Parts D1 and D2

Note: For Parts D1 and D2, each cycle constitutes 28 days.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (eg, weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit or as otherwise specified in the Schedule of Procedures. Visits conducted outside the windows are to be discussed with the Medical Monitor or designee in advance.
2. Medical history to include confirmation of previous cancer diagnosis, and record cancer treatment history, current symptoms at baseline, and current medications, as well as those taken within 30 days of first dose of study drug. An ophthalmology history is also required.
3. AEs will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination.
4. Concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Changes in concomitant medications will be collected up to and including the EOT Visit. After EOT, only concomitant medications administered for irAEs occurring within 90 days after last dose will be recorded. Once a subject enters the Follow-Up Period, only new therapies for the treatment of their cancer should be recorded in the eCRFs.
5. CX-2009 will be administered by IV infusion every 14 days. There must be a **MINIMUM** of 14 days between infusions (a window of ±2 days may occur). CX-2009 will be administered over 90 (±10) minutes with careful monitoring of IRRs. When CX-2009 and CX-072 are administered on the same day, CX-072 is to be administered first, followed by a saline flush, followed by the CX-2009 infusion. CX-2009 is to be infused no sooner than 30 minutes after completion of the CX-072 infusion.
6. 800 mg CX-072 is to be administered over 60 (±10) minutes. When CX-2009 and CX-072 are administered on the same day, CX-072 is to be administered first, followed by a saline flush, followed by the CX-2009 infusion. CX-2009 is to be infused no sooner than 30 minutes after completion of the CX-072 infusion.
7. MRI (CT may also be acceptable) to be performed within 30 days prior to the first dose of study treatment as baseline and repeated for assessment of tumor response every 8 (±1) weeks from the first dose of study treatment as per NCCN Guidelines until progression. Scans will be performed at a regular interval, regardless if study treatment is delayed or modified. Scans will also be repeated at the EOT Visit (if the subject has not experienced progression). Tumor measurements will be recorded at baseline and repeated at regular intervals, as per the NCCN Guidelines for the specific tumor type. CR or PR must be confirmed at a second tumor assessment obtained at ≥4 weeks from the assessment at which CR or PR was first observed. Tumor response will be evaluated using RECIST (v1.1) and irRECIST (Parts D1 and D2). Skin lesions (whether measurable or not) should be photographed along with a ruler at all time points for tumor assessments. MRI (CT scan may also be acceptable) will be performed every 12 weeks for subjects who have been on study drug >12 months.
8. Bone scans will be performed as clinically indicated and at the discretion of the Investigator.
9. Twelve-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible), and archived, while supine at Screening (within 7 days prior to Cycle 1 Day 1), preinfusion and both 15 minutes and 1 hour post-EOI on Day 1 of Cycles 1 and 2 (only) and as clinically indicated, and at the EOT Visit.
10. A full physical examination should be performed at Screening, prior to infusion of study treatment, and at the EOT Visit.
11. A targeted physical examination should be performed weekly during the DLT period, prior to each infusion, and as needed by subject symptoms or clinical observations, focused on key organ systems of interest (eg, CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings).
12. A complete ophthalmologic examination (including visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, corneal photography, and Schirmer's test) will be performed in all subjects at baseline (within 5 days prior to the first dose of CX-2009); within 5 days prior to Cycle 1, Day 1; Cycle 1 Day 15; Cycle 2, Day 1; and at the EOT Visit by an ophthalmologist. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.
13. The ocular symptom assessment will include assessment of blurred vision and ocular discomfort. The ocular symptom assessment will be performed at Screening, prior to each infusion, and at the EOT Visit. If ocular toxicity occurs, see Section 5.5.3.2 and Section 5.5.4.1.
14. ECOG performance status should be assessed at Screening, Day 1 of every cycle, prior to each infusion, and at the EOT Visit.
15. Including CBC with differential, including platelet count and reticulocyte count, will be performed at Screening, preinfusion, weekly during treatment, and at the EOT Visit.

Table 15. Schedule of Procedures: Parts D1 and D2

16. Serum chemistry will include ALP, AST/SGOT and ALT/SGPT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, magnesium, uric acid, LDH, and hemoglobin A1c, if clinically indicated. Blood glucose should be fasting at Screening and as indicated to evaluate possible hyperglycemia. Calculated creatinine clearance is required at Screening. Laboratory assessments drawn on the day of infusion should be drawn preinfusion.
17. Serum chemistry will only include electrolytes (potassium, sodium chloride, and magnesium) on Days 8 and 22 of every cycle.
18. Coagulation will include PT/aPTT/INR at Screening, the EOT Visit, and as clinically indicated. If results are abnormal at Screening, then repeat prior to dosing or as clinically indicated.
19. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at Screening and the EOT Visit.
20. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at Screening. If the Screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted. Urine pregnancy test (with serum test as needed for confirmation) should be obtained prior to each study treatment infusion, at the EOT Visit, and at FU/EOS Visits through 50 days after the last dose of CX-2009 or 6 months after the last dose of CX-072, whichever is later.
21. Tumor marker assessments should be scheduled concurrently with CT for PSA and CA125 for appropriate tumor types; all others as clinically indicated.
22. For both Parts D1 and D2, on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected 3 to 5 days after the third dose of study treatment, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician. Biopsy collection for the purpose of determining eligibility for Part D1 or D2 is not permitted.
23. Day 8 and Day 22 Visits are not needed for subjects who have been on study drug >4 months and have no ongoing ≥Grade 2 adverse events.
24. An EOT Visit will be conducted 30 days (±7 days) after the last infusion of study treatment.
25. Follow-Up and EOS:

- If subject had documented progression, the subject may continue in the study if experiencing clinical benefit (as assessed by the Investigator) following consultation with the Medical Monitor or designee; otherwise, 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.
- If subject has not had progression, imaging assessments will continue until progression is documented. Survival Follow-Up will be done every 3 months (±14 days) as described above.
- Women of childbearing potential will undergo pregnancy testing at FU/EOS Visits through 50 days after the last dose of CX-2009 or 6 months after the last dose of CX-072, whichever is later.

ADA = antidrug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA125 = cancer antigen 125; CBC = complete blood count; CMV = cytomegalovirus; CR = complete response; CT = computed tomography; CV = cardiovascular; d = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern cooperative Oncology group; eCRF = electronic case report form; EOI = End of Infusion; EOS = End of Study; EOT = End of Treatment; FU = Follow-Up; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; IRR = infusion-related reaction; irRECIST = Immune-related Response Criteria in Solid Tumours; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PK = pharmacokinetic; PR = partial response; PSA = prostate-specific antigen; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumours; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Table 16. Schedule of Procedures: Parts E1 and E2

Period/ Procedure	Screening	Treatment Period											FU/EOS [25]
		Cycle 1 DLT Assessment Day 1 to Day 21				Cycle 2			Cycle 3 & On [23]			EOT [24]	
Study/Visit Day [1]	–30 to 0	1	4 [22] (±1d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	(±7d)	Refer to Footnote
Informed consent	X												
Medical history [2]	X												
Demographics	X												
AE assessment [3]		X		X	X	X			X			X	
Concomitant medications [4]	X	X		X	X	X			X			X	
HIV/CMV/ Hepatitis B, C	X												
CX-2009 administration [5]		X				X			X				
CX-072 administration [6]		X				X			X				
CT/MRI (chest, abdomen, pelvis) [7]	CT/MRI/Tumor assessment to be conducted every 8 (±1) weeks from the first dose of CX-2009 with assessment for response per RECIST Version 1.1 and per irRECIST (Parts E1 and E2)												
Bone scan [8]	As clinically indicated												
ECG [9]	X	Day 1 of Cycles 1 and 3 and as clinically indicated for other visits										X	
Full physical examination [10]	X											X	
Targeted physical examination [11]		X		X	X	X			X				

See footnotes on the following page.

Table 16. Schedule of Procedures: Parts E1 and E2

Period/ Procedure	Screening	Treatment Period											FU/EOS [25]
		Cycle 1 DLT Assessment Day 1 to Day 21				Cycle 2			Cycle 3 & On [23]			EOT [24]	
Study/Visit Day [1]	–30 to 0	1	4 (±1d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	1 (±2d)	8 (±2d)	15 (±2d)	(±7d)	Refer to footnote
Complete ophthalmology examination [12]	X	All subjects within 5 days prior to Cycle 1, Day 1; Cycle 2, Day 1; Cycle 3, Day 1; and at the EOT Visit. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.											
Ocular symptom assessment [13]	X	X				X			X			X	
Vital signs	Refer to Table 17												
ECOG performance status [14]	X	X				X			X			X	
Hematology [15]	X	X		X	X	X	X	X	X	X	X	X	
Serum chemistry [16,17]	X	X		X	X	X	X	X	X	X	X	X	
Coagulation [18]	X	As clinically indicated										X	
Urinalysis [19]	X											X	
Pregnancy test [20]	X	X				X			X			X	X
Archival/baseline tumor biopsy	X												
Tumor markers [21]	As clinically indicated												
Biopsy (fixed and frozen) and plasma biomarker sample [22]						X (3 to 5 days after C2D1)							
Plasma PK and ADA	Refer to Table 24 (Part E1) and Table 25 (Part E2)												

Table 16. Schedule of Procedures: Parts E1 and E2

Note: For Parts E1 and E2, each cycle constitutes 21 days.

1. Study visits that cannot occur on the scheduled day due to unforeseen circumstances other than toxicity (eg, weather or holidays) should be completed as close to the scheduled date as possible. Laboratory assessments may be performed up to 2 days prior to the visit or as otherwise specified in the Schedule of Procedures. Visits conducted outside the windows are to be discussed with the Medical Monitor or designee in advance.
2. Medical history to include confirmation of previous cancer diagnosis, and record cancer treatment history, current symptoms at baseline, and current medications, as well as those taken within 30 days of first dose of study drug. An ophthalmology history is also required.
3. AEs will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination.
4. Concomitant medications will be assessed and reviewed prior to infusion and at any other visit that includes a physical examination. Changes in concomitant medications will be collected up to and including the EOT Visit. After EOT, only concomitant medications administered for irAEs occurring within 90 days after last dose will be recorded. Once a subject enters the Follow-Up Period, only new therapies for the treatment of their cancer should be recorded in the eCRFs.
5. CX-2009 will be administered by IV infusion every 21 days. There must be a **MINIMUM** of 21 days between infusions (a window of ±2 days may occur). CX-2009 will be administered over 90 (±10) minutes with careful monitoring of IRRs. When CX-2009 and CX-072 are administered on the same day, CX-072 is to be administered first, followed by a saline flush, followed by the CX-2009 infusion. CX-2009 is to be infused no sooner than 30 minutes after completion of the CX-072 infusion.
6. 1200 mg CX-072 is to be administered over 60 (±10) minutes. When CX-2009 and CX-072 are administered on the same day, CX-072 is to be administered first, followed by a saline flush, followed by the CX-2009 infusion. CX-2009 is to be infused no sooner than 30 minutes after completion of the CX-072 infusion.
7. MRI (CT may also be acceptable) to be performed within 30 days prior to the first dose of CX-2009 as baseline and repeated for assessment of tumor response every 8 (±1) weeks from the first dose of study treatment as per NCCN Guidelines until progression. Scans will be performed at a regular interval, regardless if study treatment is delayed or modified. Scans will also be repeated at the EOT Visit (if the subject has not experienced progression). Tumor measurements will be recorded at baseline and repeated at regular intervals, as per the NCCN Guidelines for the specific tumor type. CR or PR must be confirmed at a second tumor assessment obtained at ≥4 weeks from the assessment at which CR or PR was first observed. Tumor response will be evaluated using RECIST (v1.1) and irRECIST (Parts E1 and E2). Skin lesions (whether measurable or not) should be photographed along with a ruler at all time points for tumor assessments. MRI (CT scan may also be acceptable) will be performed every 12 weeks for subjects who have been on study drug >12 months.
8. Bone scans will be performed as clinically indicated and at the discretion of the Investigator.
9. Twelve-lead ECGs should be obtained in triplicate (approximately 2 to 5 minutes apart), in digital format (when possible), and archived, while supine at Screening (within 7 days prior to Cycle 1 Day 1), preinfusion and both 15 minutes and 1 hour post-EOI on Day 1 of Cycles 1 and 3 (only) and as clinically indicated, and at the EOT Visit.
10. A full physical examination should be performed at Screening, prior to infusion of study treatment, and at the EOT Visit.
11. A targeted physical examination should be performed weekly during the DLT period, prior to infusion of study treatment, and as needed by subject symptoms or clinical observations, focused on key organ systems of interest (eg, CV, pulmonary, GI, skin, ophthalmic, endocrine, or any systems with previously noted abnormal findings).
12. A complete ophthalmologic examination (including visual acuity, indirect fundoscopy, slit lamp examination under dilatation, intraocular pressure measurement, corneal photography, and Schirmer's test) will be performed in all subjects at baseline (within 5 days prior to the first dose of CX-2009); within 5 days prior to Cycle 2, Day 1; Cycle 3, Day 1; and at the EOT Visit by an ophthalmologist. Subjects who report treatment-emergent changes in vision or other ocular symptoms will undergo repeat examinations prior to infusion every other cycle and as clinically indicated.
13. The ocular symptom assessment will include assessment of blurred vision and ocular discomfort. The ocular symptom assessment will be performed at Screening, prior to each infusion, and at the EOT Visit. If ocular toxicity occurs, see Section 5.5.3.2 and Section 5.5.4.1.
14. ECOG performance status should be assessed at Screening, Day 1 of every cycle, prior to each infusion, and at the EOT Visit.
15. Including CBC with differential, including platelet count and reticulocyte count, will be performed at Screening, preinfusion, weekly during treatment, and at the EOT Visit.

Table 16. Schedule of Procedures: Parts E1 and E2

16. Serum chemistry will include ALP, AST/SGOT and ALT/SGPT, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, magnesium, uric acid, LDH, and hemoglobin A1c, if clinically indicated. Blood glucose should be fasting at Screening and as indicated to evaluate possible hyperglycemia. Calculated creatinine clearance is required at Screening. Laboratory assessments drawn on the day of infusion should be drawn preinfusion.
17. Serum chemistry will only include electrolytes (potassium, sodium chloride, and magnesium) on Day 8 and Day 15 of every cycle.
18. Coagulation will include PT/aPTT/INR at Screening, the EOT Visit, and as clinically indicated. If results are abnormal at Screening, then repeat prior to dosing or as clinically indicated.
19. Urinalysis (including assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity) with microscopic examination at Screening and the EOT Visit.
20. Serum pregnancy test (HCG) should be evaluated in all women of childbearing potential at Screening. If the Screening serum pregnancy test is obtained within 7 days of first infusion, the Day 1 pregnancy test may be omitted. Urine pregnancy test (with serum test as needed for confirmation) should be obtained prior to each study treatment, at the EOT Visit, and at FU/EOS Visits through 50 days after the last dose of CX-2009 or 6 months after the last dose of CX-072, whichever is later.
21. Tumor marker assessments should be scheduled concurrently with CT for PSA and CA125 for appropriate tumor types; all others as clinically indicated.
22. For both Parts E1 and E2, on-treatment tumor biopsies will be optional. For the subjects who consent, tumor biopsies will be collected 3 to 5 days after the third dose of study treatment, provided that the tumor is accessible and a biopsy is deemed safe by the treating physician. Biopsy collection for the purpose of determining eligibility for Part E1 or E2 is not permitted.
23. Day 8 and Day 15 Visits are not needed for subjects who have been on study drug >4 months and have no ongoing ≥Grade 2 adverse events.
24. An EOT Visit will be conducted 30 days (±7 days) after the last infusion of study treatment.
25. Follow-Up and EOS:

- If subject had documented progression, the subject may continue in the study if experiencing clinical benefit (as assessed by the Investigator) following consultation with the Medical Monitor or designee; otherwise, 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.
- If subject has not had progression, imaging assessments will continue until progression is documented. Survival Follow-Up will be done every 3 months (±14 days) as described above.
- Women of childbearing potential will undergo pregnancy testing at FU/EOS Visits through 50 days after the last dose of CX-2009 or 6 months after the last dose of CX-072, whichever is later.

ADA = antidrug antibody; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA125 = cancer antigen 125; CBC = complete blood count; CMV = cytomegalovirus; CR = complete response; CT = computed tomography; CV = cardiovascular; d = day; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology group; eCRF = electronic case report form; EOI = end of infusion; EOS = end of study; EOT = end of treatment; FU = follow-up; GI = gastrointestinal; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; INR = international normalized ratio; IRR = infusion-related reaction; irRECIST = Immune-related Response Criteria in Solid Tumours; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PK = pharmacokinetic; PR = partial response; PSA = prostate-specific antigen; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumours; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Table 17. Schedule of Vital Signs Measurements: All Parts

Period/Procedure	Screening [a]	Cycles 1 to 6		Cycles 7 & On		EOT [b]
Time of Measurement		Preinfusion	EOI	Preinfusion	EOI	
Height	X					
Weight	X	X		X		X
Heart rate	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X
Temperature	X	X	X	X	X	X
Respiratory rate	X	X	X	X	X	X
Pulse oximetry	X	X	X	X	X	X

During the first 6 doses of study drug, vital signs should be measured within 60 minutes prior to infusion, every 15 (±5) minutes during infusion, at the EOI (±5 minutes), and approximately hourly for 4 hours after the completion of the infusion. On all other infusion days, vital signs should be measured within 60 minutes prior to infusion, at the EOI (±5 minutes), and 60 (±5) minutes after completion of the infusion (unless clinical signs require more frequent monitoring). Height should be measured at the Screening Visit only. Weight should be measured at Screening and Day 1 of each cycle. During an IRR, vital signs should be recorded every 2 to 5 minutes until stable.

[a] Screening Visit = Study Days -30 to -1.

[b] EOT Visit to be conducted 30 (±7) days after the last infusion of study treatment.

EOI = end of infusion; EOT = end of treatment; IRR = infusion-related reaction.

Table 18. Schedule of PK and ADA Assessments: Parts A and A2

Period/Procedure	Cycle 1							Cycles 2, 4, 6, 8, & Every 8 Cycles Thereafter	Cycle 3				EOT	Follow-up Visit 1
Cycle Day	1		2	3	4	8	15	1	1		8	15		
Time of Draw	Preinfusion	Post-EOI	DOV	DOV	DOV	DOV	DOV	Preinfusion	Preinfusion	Post-EOI	DOV	DOV	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X							X	X				X	X

Notes: Parts A and A2 cycle length is 21 days. Serial blood samples will be collected to characterize the PK of the Probody therapeutic in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 dosing and PK/ADA collection must be recorded.

[a] PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 1 Day 2 (±6 hours)
- Cycle 1 Day 3 (±12 hours)
- Cycle 1 Day 4 (±12 hours) – Day 4 PK samples only for subjects who participate in the on-treatment tumor biopsies
- Cycle 1 Day 8 (±1 day)
- Cycle 1 Day 15 (±1 day)
- Cycles 2, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- Cycle 3 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 3 Day 8 (±2 days)
- Cycle 3 Day 15 (±2 days)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

[b] ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycles 1, 2, 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

ADA = antidrug antibody; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 19. Schedule of PK and ADA Assessments: Part B

Period/Procedure	Cycle 1		Cycles 2, 4, 6, 8, & Every 8 Cycles Thereafter	Cycle 3		EOT	Follow- up Visit 1
Cycle Day	1		1	1			
Time of Draw	Preinfusion	Post-EOI	Preinfusion	Preinfusion	Post-EOI	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X		X	X		X	X

Notes: Part B cycle lengths are 21 days. Sparse blood samples will be collected to characterize the PK of the Probody therapeutic in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 dosing and PK/ADA collection must be recorded.

[a] PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycles 2, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- Cycle 3 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

[b] ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycles 1, 2, 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

ADA = antidrug antibody; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 20. Schedule of PK and ADA Assessments: Part C1

Period/ Procedure	Cycle 1							Cycle 2				Cycles 3, 4, 6, 8 & Every 8 Cycles Thereafter	EOT	Follow- up Visit 1
Cycle Day	1		2	3	4	8	15	1		8	15	1		
Time of Draw	Preinfusion	Post-EOI	DOV	DOV	DOV	DOV	Preinfusion	Preinfusion	Post-EOI	DOV	Preinfusion	Preinfusion	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X						X	X			X	X	X	X

Notes: Part C1 cycle length is 28 days. Serial blood samples will be collected to characterize the PK of the Probody therapeutic in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 dosing and PK/ADA collection must be recorded.

[a] PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 1 Day 2 (±6 hours)
- Cycle 1 Day 3 (±12 hours)
- Cycle 1 Day 4 (±12 hours) - Day 4 PK samples will be only drawn for subjects who participate in the on-treatment tumor biopsies.
- Cycle 1 Day 8 (±1 day)
- Cycle 1 Day 15: preinfusion (up to 1 day before infusion)
- Cycle 2 Day 1: preinfusion, 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 2 Day 8 (±2 days)
- Cycle 2 Day 15: preinfusion
- Cycles 3,4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion
- EOT
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

[b] ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycle 1 Day 1: preinfusion
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion
- Cycle 2 Day 15: preinfusion
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

ADA = antidrug antibody; D = day; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 21. Schedule of PK and ADA Assessments: Parts C2

Period/Procedure	Cycle 1			Cycle 2			Cycles 3, 4, 6, 8 & Every 8 Cycles Thereafter	EOT	Follow- up Visit 1
Cycle Day	1		15	1		15	1		
Time of Draw	Preinfusion	Post-EOI	Preinfusion	Preinfusion	Post-EOI	Preinfusion	Preinfusion	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X		X	X		X	X	X	X

Notes: Part C2 cycle length is 28 days. Sparse blood samples will be collected to characterize the PK of the Probody therapeutic in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 dosing and PK/ADA collection must be recorded.

[a] PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI
- Cycle 2 Day 15: preinfusion (up to 1 day before infusion)
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

[b] ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycle 1 Day 1: preinfusion
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion
- Cycle 2 Day 15: preinfusion (up to 1 day before infusion)
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009

ADA = antidrug antibody; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 22. Schedule of PK and ADA Assessments: Part D1

Period/Procedure	Cycle 1						Cycle 2				Cycles 3, 4, 6, 8 & Every 8 Cycles Thereafter	EOT	Follow-up Visit 1
Cycle Day	1		2	3	8	15	1		8	15	1		
Time of Draw	Preinfusion	Post-EOI	DOV	DOV	DOV	Preinfusion	Preinfusion	Post-EOI	DOV	Preinfusion	Preinfusion	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X					X	X			X	X	X	X
CX-072 PK [c]	X	X				X	X	X		X	X	X	X
CX-072 ADA [d]	X					X	X			X	X	X	X

Notes: Part D1 cycle length is 28 days. Serial blood samples will be collected to characterize the PK of the CX-2009 and CX-072 and all drug-related moieties in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 and CX-072 dosing and PK/ADA collection must be recorded.

[a] CX-2009 PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 1 Day 2 (±6 hours)
- Cycle 1 Day 3 (±12 hours)
- Cycle 1 Day 8 (±1 day)
- Cycle 1 Day 15 (±1 day)
- Cycle 2 Day 1: preinfusion, 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 2 Day 8 (±2 days)
- Cycle 2 Day 15 (±1 days): preinfusion
- Cycles 3,4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[b] CX-2009 ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycle 1 Day 1: preinfusion
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion
- Cycle 2 Day 15: preinfusion
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

Table 22. Schedule of PK and ADA Assessments: Part D1

[c] CX-072 PK samples will be drawn at the following times:
- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycle 2 Day 15: preinfusion
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion
- EOT
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[d] CX-072 ADA samples will be drawn at the following times (to coincide with PK collections):
- Cycle 1 Day 1: preinfusion
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion
- Cycle 2 Day 15: preinfusion
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion
- EOT
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

ADA = antidrug antibody; D = day; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 23. Schedule of PK and ADA Assessments: Part D2

Period/Procedure	Cycle 1			Cycle 2			Cycles 3, 4, 6, 8 & Every 8 Cycles Thereafter	EOT	Follow-up Visit 1
Cycle Day	1		15	1		15	1		
Time of Draw	Preinfusion	Post-EOI	Preinfusion	Preinfusion	Post-EOI	Preinfusion	Preinfusion	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X		X	X		X	X	X	X
CX-072 PK [a]	X	X	X	X	X	X	X	X	X
CX-072 ADA [b]	X		X	X		X	X	X	X

Notes: Part D2 cycle length is 28 days. Sparse blood samples will be collected to characterize the PK of the Probody therapeutic in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 and CX-072 dosing and PK/ADA collection must be recorded.

[a] CX-2009 and CX-072 PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycle 1 Day 15: preinfusion (up to 1 day before infusion)
- Cycle 2 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI
- Cycle 2 Day 15: preinfusion (up to 1 day before infusion)
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[b] CX-2009 and CX-072 ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycle 1 Day 1: preinfusion
- Cycle 1 Day 15: preinfusion
- Cycle 2 Day 1: preinfusion
- Cycle 2 Day 15: preinfusion
- Cycles 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

ADA = antidrug antibody; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 24. Schedule of PK and ADA Assessments: Part E1

Period/Procedure	Cycle 1						Cycles 2, 4, 6, 8 & Every 8 Cycles Thereafter	Cycle 3				EOT	Follow-up Visit 1
Cycle Day	1		2	3	8	15	1	1		8	15		
Time of Draw	Preinfusion	Post-EOI	DOV	DOV	DOV	DOV	Preinfusion	Preinfusion	Post-EOI	DOV	DOV	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X						X	X				X	X
CX-072 PK [c]	X	X					X	X	X			X	X
CX-072 ADA [d]	X						X	X				X	X

Notes: Part E1 cycle length is 21 days. Serial blood samples will be collected to characterize the PK of the CX-2009 and CX-072 and all drug-related moieties in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 and CX-072 dosing and PK/ADA collection must be recorded.

[a] PK samples will be drawn at the following times:

- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 1 Day 2 (±6 hours)
- Cycle 1 Day 3 (±12 hours)
- Cycle 1 Day 8 (±1 day)
- Cycle 1 Day 15 (±1 day)
- Cycles 2, 4, 6, 8, and every 8 cycles thereafter: Day 1: preinfusion (up to 2 days before infusion)
- Cycle 3 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI, and 1 hour (±10 minutes) post-EOI
- Cycle 3 Day 8 (±2 days)
- Cycle 3 Day 15 (±2 days)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[b] ADA samples will be drawn at the following times (to coincide with PK collections):

- Cycles 1, 2, 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

Table 24. Schedule of PK and ADA Assessments: Part E1

[c] PK samples will be drawn at the following times:
- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycles 2, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion
- Cycle 3 Day 1: preinfusion, 15 (±10) minutes post-EOI
- EOT
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[d] ADA samples will be drawn at the following times (to coincide with PK collections):
- Cycles 1, 2, 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

ADA = antidrug antibody; D = day; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Table 25. Schedule of PK and ADA Assessments: Part E2

Period/Procedure	Cycle 1		Cycles 2, 4, 6, 8 & Every 8 Cycles Thereafter	Cycle 3		EOT	Follow-up Visit 1
Cycle Day	1		1	1			
Time of Draw	Preinfusion	Post-EOI	Preinfusion	Preinfusion	Post-EOI	DOV	DOV
CX-2009 Plasma PK [a]	X	X	X	X	X	X	X
CX-2009 Serum ADA [b]	X		X	X		X	X
CX-072 PK [c]	X	X	X	X	X	X	X
CX-072 ADA [d]	X		X	X		X	X

Notes: Part E2 cycle length is 21 days. Sparse blood samples will be collected to characterize the PK of the Probody therapeutic in all subjects. Blood samples will be collected to assess the extent of ADA response to the Probody therapeutic. Actual times of CX-2009 and CX-072 dosing and PK/ADA collection must be recorded.

[a] PK samples will be drawn at the following times:
- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycles 2, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- Cycle 3 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[b] ADA samples will be drawn at the following times (to coincide with PK collections):
- Cycles 1, 2, 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[c] PK samples will be drawn at the following times:
- Cycle 1 Day 1: preinfusion, 15 (±10) minutes post-EOI
- Cycles 2, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- Cycle 3 Day 1: preinfusion (up to 2 days before infusion), 15 (±10) minutes post-EOI
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

[d] ADA samples will be drawn at the following times (to coincide with PK collections):
- Cycles 1, 2, 3, 4, 6, 8, and every 8 cycles thereafter: Day 1 preinfusion (up to 2 days before infusion)
- EOT (DOV)
- Follow-up Visit 1: Once any time >90 days after the last dose of CX-2009 or CX-072, whichever comes later

ADA = antidrug antibody; DOV = day of visit; EOI = end of infusion; EOT = end of treatment; PK = pharmacokinetic.

Appendix C: Synopsis of the mTPI-2 Design

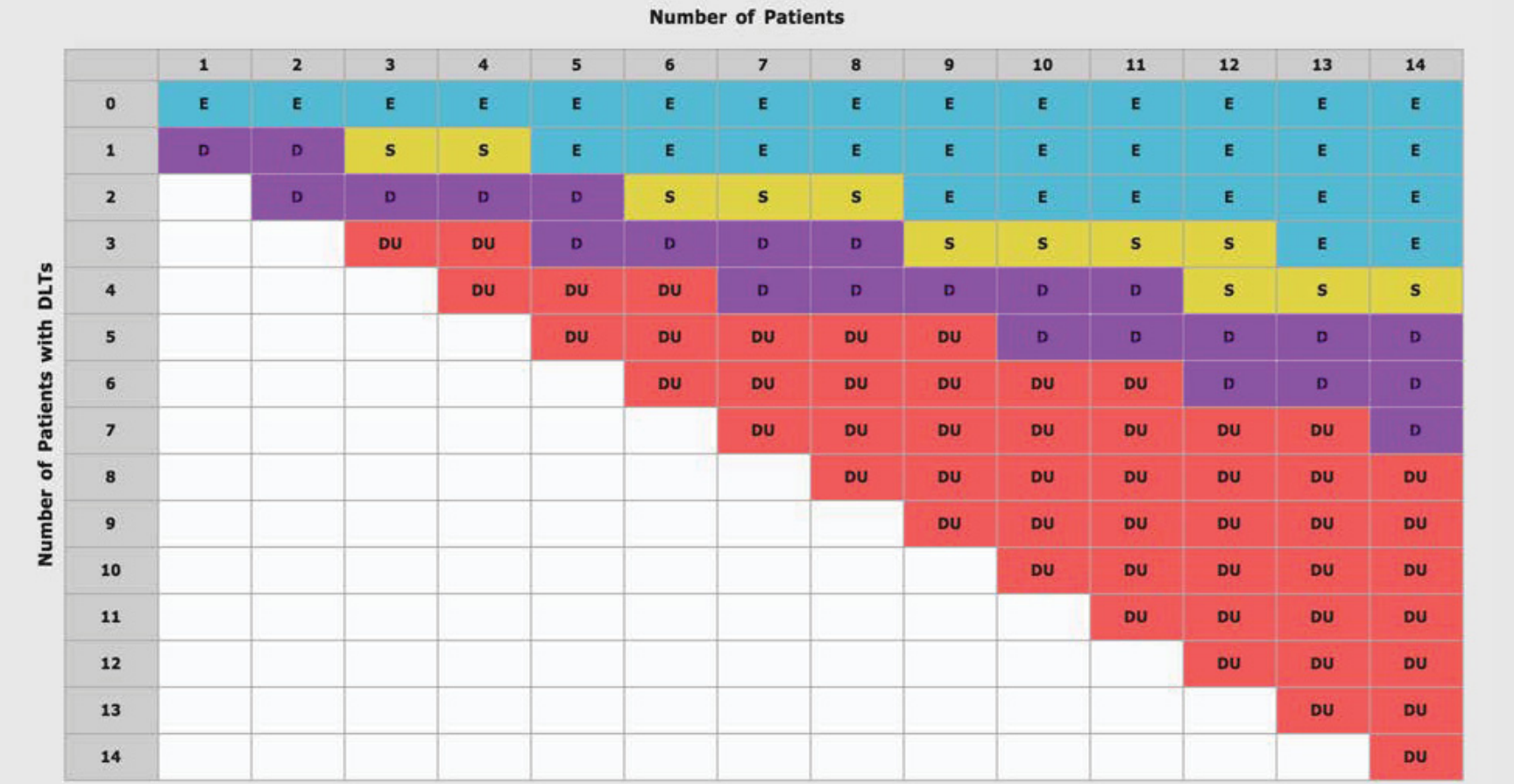
The modified toxicity probability interval 2 (mTPI-2) design (Guo 2017) is an interval-based Phase 1 dose-finding design for guiding subject allocation from observed safety outcomes at different dose levels, and deciding the maximum tolerated dose (MTD) at the end of the trial. It is an improvement over the mTPI design (Ji 2010, Ji 2013, Yang 2015).

The mTPI design assesses the probabilities that the toxicity rate p_i of dose level i falls into 3 intervals $(0, p_T - \varepsilon_1)$, $(p_T - \varepsilon_1, p_T + \varepsilon_2)$, and $(p_T + \varepsilon_2, 1)$, where p_T is the target toxicity probability (say, $p_T = 0.3$) for the MTD, ε_1 and ε_2 specify the length of toxicity interval. For example, when $p_T = 0.3$, $\varepsilon_1 = 0.05$, and $\varepsilon_2 = 0.05$, the 3 toxicity intervals are (0.24), (0.25, 0.35), and (0.36, 1) and represent scenarios of underdosing, proper dosing, and overdosing. Similarly, when $p_T = 0.2$, $\varepsilon_1 = 0.05$, and $\varepsilon_2 = 0.05$, the respective toxicity intervals are (0.14), (0.15, 0.25), and (0.26, 1). The mTPI-2 design selects the interval with the maximum probability and recommends decision to escalate, stay at the current dose level, or de-escalate, accordingly. In the previous example, if (0.25, 0.35) has the maximum probability, the design recommends to stay at the current dose level.

The mTPI-2 design improves over the mTPI design by blunting the Ockham's razor that leads to some statistically sound, but practically undesirable, decisions in the original mTPI design. Case in point: with a target toxicity probability of $p_T = 0.3$, the original mTPI design would recommend no dose change even if 3 of 6 subjects experienced dose-limiting toxicities (DLTs) at a given dose. To improve upon the original mTPI design, mTPI-2 divides the intervals $(0, p_T - \varepsilon_1)$ and $(p_T + \varepsilon_2, 1)$ into shorter subintervals and makes recommendations based on these finer subintervals. The simulation study by Guo et al (Guo 2017) has shown that the mTPI-2 design minimizes the risk of wrong dose allocations, particularly with small-sample inferences common in dose-finding studies.

Both mTPI and mTPI-2 designs are transparent and user-friendly to both statisticians and clinicians, as all the decisions can be tabulated for examination prior to the trial. Figure 6 and Figure 7 are dose-finding decision tables for up to 14 subjects with target toxicity probability of 30.0% and 20.0%, respectively. In these tables, the columns represent the number of subjects treated at the current dose and rows denote the number of subjects experiencing DLT at that dose. The table enumerates all the possible dose-finding decisions, and therefore can be used to design and conduct the trial conveniently.

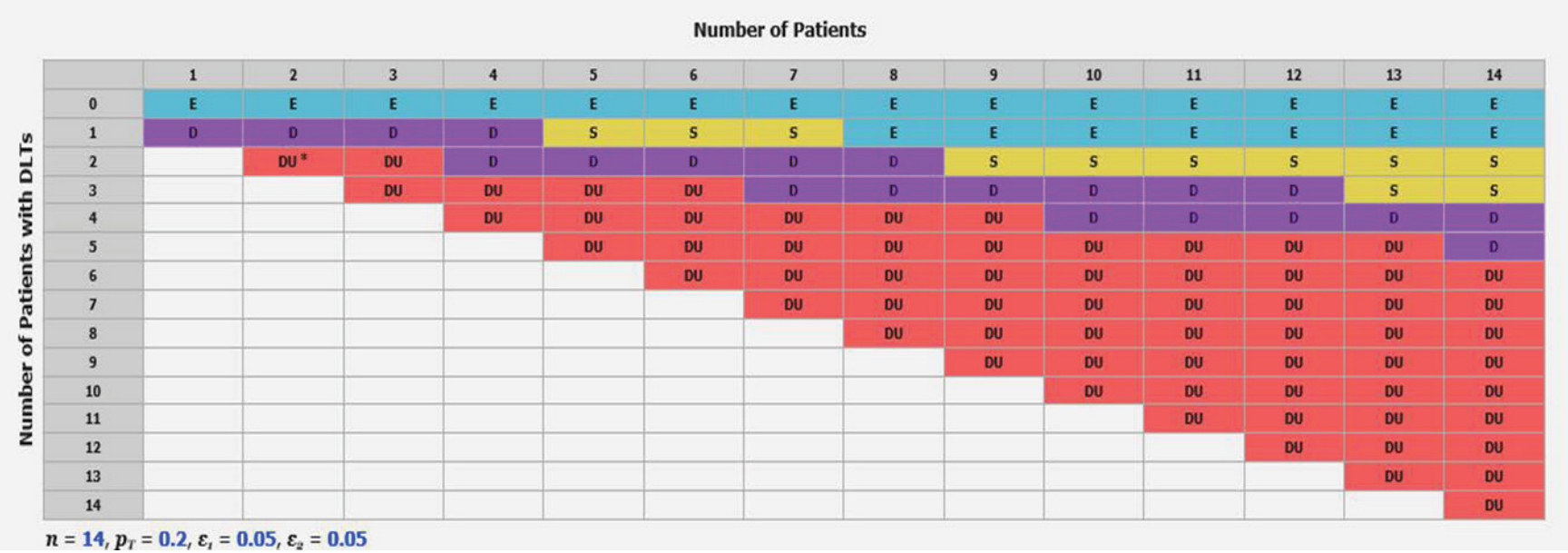
Figure 6. Decision Table for mTPI-2 Cohort (Target Toxicity Probability = 30.0%)



A decision table of the mTPI-2 design, with 14 subjects, the target probability of $p_T = 0.3$ and 2 values $\varepsilon_1 = \varepsilon_2 = 0.05$.

D = de-escalate to a lower dose; DLT = dose-limiting toxicity; DU = de-escalate to a lower dose and the current dose will never be used again in the study; E = escalate to the next higher dose; mTPI-2 = modified toxicity probability interval 2; S = stay at the same dose.

Figure 7. Decision Table for mTPI-2 Cohort (Target Toxicity Probability = 20.0%)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	D	D	S	S	S	E	E	E	E	E	E	E
2		DU *	DU	D	D	D	D	D	S	S	S	S	S	S
3			DU	DU	DU	DU	D	D	D	D	D	D	S	S
4				DU	DU	DU	DU	DU	DU	D	D	D	D	D
5					DU	DU	DU	DU	DU	DU	DU	DU	DU	D
6						DU	DU	DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU
11											DU	DU	DU	DU
12												DU	DU	DU
13													DU	DU
14														DU

A decision table of the mTPI-2 design, with 14 subjects, the target probability of $p_T = 0.2$ and 2 values $\varepsilon_1 = \varepsilon_2 = 0.05$.

D = de-escalate to a lower dose; DLT = dose-limiting toxicity; DU = de-escalate to a lower dose and the current dose will never be used again in the study; E = escalate to the next higher dose; mTPI-2 = modified toxicity probability interval 2; S = stay at the same dose.

*: If at the first dose level, users can choose to early-terminate the study or not based on their own discretion.

Appendix D: Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) has been established for the study. The DSMB will consist of individuals with pertinent expertise in clinical trials in oncology, immunology, and statistics who will review, on a regular basis, accumulating safety data from this ongoing study. The DSMB will also be notified of Module amendments. The DSMB will be charged with responsibility to advise CytomX Therapeutics, Inc. with regard to:

- The continuing safety of current and future participants in the study; and
- The continuing validity and scientific merit of the study.

The DSMB will convene every 6 months in accord with meetings scheduled to review the overall CX-2009 program; a change in the frequency of meetings will be dictated by the availability and severity of ongoing safety information. Meetings will be held with the appointed representatives of the Statistical and Medical Groups from CytomX Therapeutics, Inc. The DSMB will review all safety information to determine whether the study will continue unchanged or whether Module modifications are required to ensure subject safety. Recommendations for closing should be on the basis of excessive toxicity in the statistics report or the aggregated safety data. This determination will be documented by a letter from the DSMB. In the event that the DSMB advises a major change in the study design or conduct, such as early termination, this advice will be transmitted to Sponsor Steering Committee. The Sponsor Steering Committee will consist of representatives of senior management of CytomX Therapeutics, Inc., including Chief Medical Officer, Chief Legal Counsel, and Chief Executive Officer.

The DSMB will consist of at least 3 members. Data Safety Monitoring Board member(s) who withdraw prior to completion of the project will be replaced. Should it become necessary to expand the number of DSMB members, CytomX Therapeutics, Inc. will appoint additional members. The responsibilities of the DSMB for this trial will end 6 months after last subject is enrolled or upon submission of a final study report.

Appendix E: Safety Review Committee

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 Therapeutics, Inc. who will review on a regular basis, the cumulative safety data from each cohort in the study in order to:

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

Actions taken regarding dose escalation or amendments to the Module will be documented and stored in the trial master file for the study.

Appendix F: Adjusted Ideal Body Weight Calculation

The total dose of drug will be calculated based on each subject's adjusted body weight using the following formula:

Adjusted Ideal Body Weight (AIBW)

IBW [a] + 0.4 (Actual Weight-IBW [a])

Where:

Ideal Body Weight (IBW)

IBW [a] (male) = $0.9H^1 - 88$

IBW [a] (female) = $0.9H^1 - 92$

[a] H = height in cm; W = weight in kg.

Appendix G: List of Concomitant Medications Representing Inhibitors of CYP3A

Table 26. List of Concomitant Medications Representing Inhibitors of CYP3A

CYP Enzymes	Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors
CYP3A	Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevi, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

CYP = cytochrome P450.

Source: United States Food and Drug Administration web site: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers: Table 3-2. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table. Accessed 19 November 2019.

Appendix H: List of Concomitant Medications Requiring Avoidance

Table 27. List of Concomitant Medications Requiring Avoidance

CYP Enzymes	Sensitive Substrates	Substrates With Narrow Therapeutic Range
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, primozide, quinidine, sirolimus, tacrolimus, terfenadine

CYP = cytochrome P450.

Source: United States Food and Drug Administration web site: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers: Table 3-1. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1. Accessed 19 November 2019.

Appendix I: Description of Criteria to Assess CD166 Immunohistochemistry Staining

High cluster of differentiation 166 (CD166) expression is defined as immunohistochemistry (IHC) staining of ≥50.0% of tumor cell staining at 3+ intensity. Only membrane-associated staining within tumor cells will be evaluated. The cytoplasmic staining in tumor cells or the staining in non-tumor cells (ie, normal epithelium or immune cells) will not be considered for scoring. Scoring will be attributed following a pathologist's visual assessment of the membrane-associated staining intensity on tumor cells using the following criteria: 0 = no staining, 1+ = weak staining, 2+ = moderate staining, 3+ = strong staining. Subjects (except those with hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer) will be required to have demonstrated high CD166 expression (3+) in archival tumor tissue, as measured by a qualified IHC assay using a clinical trial assay performed in a central Clinical Laboratory Improvement Amendments of 1998 (CLIA)-certified laboratory.

Appendix J: Prior Lines of Therapy Counting Rule Guidance

Therapy administered in the neoadjuvant or adjuvant setting do not count as a regimen to determine eligibility in this module. Therapy(ies) following surgery for locally advanced breast cancer (BC) (eg, Stage IIIA with T3 N1 M0) will count as adjuvant therapy. All classes of systemic antineoplastic drugs count when administered for advanced or metastatic BC (hormonal, biological, cytotoxic, immunotherapeutic, antibody drug conjugates, chemo-radiation, etc) will count as a regimen, whether administered as single-agent or in combination.

Following are examples of what does NOT count as a separate regimen:

- Substitution within a class due to toxicity;
- Retreatment with the same agent without interval progression;
- Continuation of 1 drug within a combination regimen;
- Planned sequential dosing (1 drug followed by a second drug without interval progression); or
- Local therapy (eg, intratumor injection).