CTMX-M-072-002

A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX 072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors (PROCLAIM-CX-072)

NCT# 03993379

21/August/2019

PROCLAIM CLINICAL STUDY
MODULE CTMX-M-072-002

A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX 072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors

(PROCLAIM-CX-072)

Investigational Product:	CX-0729
Module Number:	CTMX-M-072-002
IND Number:	142922
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Date of Original Module:	18 April 2019
Date of Amendment 1:	24 May 2019
Date of Amendment 2:	21 August 2019

SIGNATURE PAGE

STUDY TITLE:
A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX-072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors (PROCLAIM-CX-072)

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

21 Aug 2019

Yifah Yaron, MD, PhD
Senior Medical Director
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-072-002, and any subsequent amendments. I will provide copies of this Module, which includes the Common Core, and access to all information furnished by CytomX Therapeutics, Inc. to 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 disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by CytomX Therapeutics, Inc., with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration regulations, Institutional Review Board/Independent Ethics Committee regulations, International Council for Harmonisation Guidelines for Good Clinical Practices (ICH GCP), and all other applicable regulatory requirements.

Investigator's Signature	Date

Investigator's Printed Name

SYNOPSIS

TITLE

A Phase 2, Open-Label, Multi-cohort Study of PD-L1 Probody™ Therapeutic CX-072 in Combination With Other Anticancer Therapy in Adults With Solid Tumors (PROCLAIM-CX-072)

STUDY NUMBER

CTMX-M-072-002

INVESTIGATIONAL PRODUCT

CX-072

PHASE

Phase 2

INDICATIONS

Solid tumors, including advanced/unresectable or metastatic cancer and neoadjuvant/resectable

ESTIMATED NUMBER OF SUBJECTS AND SITES

This is a global, multicenter study in approximately 40 sites and up to 162 subjects.

INTRODUCTION AND STUDY RATIONALE

CX-072 is a Probody™ therapeutic directed against programmed cell death ligand 1 (PD-L1) for the treatment of cancer. Like all Probody therapeutics, CX-072 is a fully recombinant monoclonal antibody (mAb) prodrug, designed to be preferentially activated by proteases associated with the tumor microenvironment (TME), and represents an approach that is expected to largely restrict drug activity to the TME by exploiting the dysregulation of tumor protease activity that is a hallmark of most cancers, and resulting in preferential activation and binding to tumor cells rather than healthy tissue. By localizing its activity to the TME, CX-072 is expected to reduce systemic toxicities, thereby expanding clinical opportunities for targeting the PD-1 (programmed death 1)/PD-L1 pathway, particularly when used in combination with ipilimumab. The clinical program to date has demonstrated activity of CX-072 in various tumor types, including as monotherapy and in dose escalation cohorts of CX-072 plus ipilimumab, with potential for increased tolerability compared with historical controls (Plummer 2018). Evidence that CX-072 circulates predominantly as the intact prodrug species (Boni 2018) and evidence of tumor binding in biopsy samples (Lyman 2018) have also been demonstrated.

This study is composed of 2 distinct documents:

- The Common Core Document (CTMX-C-001)
- This CX-072-specific Module (CTMX-M-072-002)

Briefly, the Common Core Document CTMX-C-001 (see Appendix A), or "Core," is a stable document that contains study design features typically included in a standard Phase 1-2 clinical study protocol, but without reference to a specific investigational medicinal product. The Core, which provides the basis for all first in human clinical studies with Probody therapeutics, describes general study procedures such as guidelines for drug accountability, efficacy and safety parameters, and study administrative procedures. The CX-072 Module for this Phase 2 study (this document) is customized for the assessment of the CX-072 Probody therapeutic in combination with ipilimumab at the designated combination doses and

provides all guidelines necessary to safely manage subject care. Familiarity with both documents is required for proper conduct of this study.

This core plus module system will enable a comprehensive clinical evaluation of Probody therapeutics within a unified clinical development program that has common components of study design, execution, and assessments, and common Investigator oversight. Where there are overlapping directives between the 2 documents, Investigators are instructed to follow the CX-072 Module regarding subject care guidelines. Refer to the Core (Appendix A) for a more detailed discussion of the core study design and rationale.

PRIMARY OBJECTIVES

Part A

- To obtain evidence of antitumor effect of CX-072 in combination with ipilimumab in subjects with solid tumors based on the objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1

Part B

- To obtain evidence of antitumor effect of CX-072 in combination with ipilimumab in subjects with solid tumors based on pathologic response following neoadjuvant administration of combination treatment

SECONDARY OBJECTIVES

Part A:

- Safety and tolerability of CX-072 in combination with ipilimumab in subjects with solid tumors
- Evaluate antitumor activity in subjects with solid tumors treated with CX-072 in combination with ipilimumab based on:
  - ORR by immune-related Response Criteria in Solid Tumours (irRECIST) as defined in the Core (Appendix A)
  - Duration of response (DOR)
  - Time to response (TTR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
- Characterize the pharmacokinetics (PK) of CX-072 and ipilimumab
- Characterize the incidence of CX-072 antidrug antibodies (ADAs) and ipilimumab ADAs

Part B:

- Safety and tolerability of CX-072 in combination with ipilimumab in subjects with solid tumors
- Evaluate antitumor activity in subjects with solid tumors treated with CX-072 in combination with ipilimumab based on:
  - ORR as defined by RECIST v1.1 prior to surgery
  - Relapse-free survival (RFS)
- Characterize the PK profile of CX-072 and ipilimumab
- Characterize the incidence of CX-072 ADAs and ipilimumab ADAs

EXPLORATORY OBJECTIVES

Parts A and B

- Evaluate biomarkers potentially capable of predicting a clinical response to combination treatment with CX-072 and ipilimumab
- Evaluate the relationship between CX-072 and ipilimumab combination treatment and exploratory biomarkers, safety, and antitumor activity

STUDY DESIGN AND DURATION

This is a Phase 2, multicenter, global, open-label, multi-cohort and parallel-cohort study of PD-L1 Probody therapeutic CX-072 in combination with ipilimumab designed to assess the antitumor effect of combination treatment and to characterize the safety, tolerability, PK, immunogenicity, and biomarkers of combination treatment in subjects with solid tumors.

This Module is comprised of 2 parts and 4 cohorts:

- **Part A:**
  - Cohort A1: Subjects with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma who have received no prior treatment for unresectable or metastatic melanoma
  - Cohort A2: Subjects with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma who have experienced progressive disease or relapse following treatment with a PD-1/PD-L1 immune checkpoint inhibitor
  - Cohort A3: Subjects with histologically or cytologically confirmed, advanced/unresectable or metastatic, transitional cell carcinoma of the urothelium who have experienced disease progression during or following treatment with platinum-based therapy
- **Part B:**
  - Cohort B1: Subjects with histologically confirmed resectable Stage III melanoma with palpable disease suitable for curative surgery

Enrollment into each cohort will occur in 2 stages:

- Cohorts A1, A3, and B1: Stage 1 will enroll and treat 14 subjects per cohort. Opening of Stage 2 for each cohort will be contingent on the number of confirmed objective responses (Part A) or pathologic responses (Part B) in Stage 1. Additional subjects will be added in Stage 2, for a total of approximately 40 subjects (range: 38 to 48) per cohort.
- Cohort A2: Stage 1 will enroll and treat 40 subjects. Opening of Stage 2 of Cohort A2 will require a subsequent amendment following a discussion with regulatory agencies to agree on success criteria to establish an appropriate sample size.

The study is comprised of 3 periods:

- The Screening Period begins within 30 days prior to the first dose of study treatment (ie, Cycle 1 Day 1 Visit).
- The Treatment Period begins with the first dose of study treatment (ie, Cycle 1 Day 1) and continues up to 30 days after the last dose of study treatment (ie, End of Treatment [EOT] Visit). All scheduling is relative to first dose of study treatment (ie, Cycle 1 Day 1).
- The Follow-up Period begins after the EOT Visit. The first Follow-up Visit will be 90 (±14) days after the last dose of study treatment and will continue every 90 (±14) days to collect survival information and subsequent cancer treatment information.

In Part A, tumor samples for biomarker assessments will be collected during Screening (archival or fresh biopsy). In Part B, archival tumor samples from the initial diagnostic biopsy will be collected during Screening. Tumor tissue from surgical resection (including resected lymph nodes) during the study will also be collected. The study assessments for each period are outlined in the Schedule of Assessments in Table 1 (Part A) and Table 2 (Part B).

In Part A, a subject's treatment may continue until confirmed disease progression (assessed by irRECIST), clinical deterioration as judged by the Investigator, withdrawal of consent, other study treatment withdrawal criteria are met, or until the study is terminated, whichever occurs first. In Part B, a subject's treatment duration will be up to approximately 15 months (including 1 year postsurgery). The end of the study (EOS) for an individual subject is defined as death, loss to follow-up, withdrawal of consent, or termination of the study.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION

Part A

- Combination treatment (intravenous [IV]): 800 mg CX-072 + 3 mg/kg ipilimumab, once every 3 weeks (q3w)
- Monotherapy treatment (IV): 800 mg CX-072, once every 2 weeks (q2w)

In Part A, subjects will be treated with 4 doses of 800 mg CX-072 IV plus 3 mg/kg ipilimumab IV combination therapy (ie, q3w on Cycle 1 Day 1, Cycle 1 Day 22, Cycle 2 Day 1 [Study Day 43], and Cycle 2 Day 22 [Study Day 64]; all ±2 days). Three weeks following receipt of the fourth dose of combination treatment (ie, Study Day 85 [±2 days]), subjects will receive 800 mg CX-072 IV monotherapy q2w until the occurrence of progressive disease by irRECIST, unacceptable toxicity, or the subject meets any of the other criterion for treatment discontinuation.

Part B

- Combination treatment (IV): 800 mg CX-072 + 1 mg/kg ipilimumab, q3w
- Monotherapy treatment (IV): 800 mg CX-072, q2w

In Part B, subjects will be treated with 2 doses of 800 mg CX-072 plus 1 mg/kg ipilimumab combination (ie, q3w on Cycle 1 Day 1, Cycle 1 Day 22; all ±2 days) followed by surgical resection of the tumor on Study Day 43 (–2/+7 days). An additional 2 doses of 800 mg CX-072 plus 1 mg/kg ipilimumab combination will be administered approximately 6 weeks postsurgery (ie, q3w on Cycle 2 Day 1 [Study Day 85 (±2 days)] and Cycle 2 Day 22 [Study Day 106 (±2 days)]). Three weeks following receipt of the fourth dose of combination treatment (ie, Study Day 127 [±2 days]), subjects will have the option to continue with 800 mg CX-072 monotherapy q2w following discussion and agreement of risk/benefit between the Investigator and the Sponsor Medical Monitor. Subjects may receive up to 1 year of CX-072 infusions postsurgery (including 2 postsurgery combination doses and then as monotherapy) until the occurrence of disease relapse, unacceptable toxicity, or the subject meets any other criterion for treatment discontinuation. A maximum of 4 doses of ipilimumab may be administered to any subject (Parts A and B).

RESPONSE VARIABLES

Part A: The primary criterion for defining evidence of anticancer activity is RECIST v1.1. The criterion for management of subject care and treatment discontinuation is irRECIST.

Part B: The primary criterion for defining evidence of anticancer activity is pathologic response based on central review of tumor sample from surgical resection. The criteria for management of subject care and treatment discontinuation are radiographic response assessment (prior to surgery), local pathologic assessment of surgical sample after surgery, or disease relapse. Tumor response as defined by RECIST v1.1 will be assessed prior to surgical resection; however, responses will not be confirmed, because the tumor assessment will be followed by surgical resection.

PHARMACOKINETIC, IMMUNOGENICITY, AND EXPLORATORY BIOMARKER VARIABLES

Pharmacokinetics: Concentration versus time data will be tabulated and plotted for the individual and mean serum total and Intact CX-072 moieties. Maximal plasma concentration (C_{max}) and minimal plasma concentration (C_{min}) will be tabulated individually and summarized using descriptive statistics (eg, mean, standard deviation, and coefficient of variation). Ipilimumab C_{max} and C_{min} will be summarized using descriptive statistics. Population PK (POPPK) analysis of the data may be performed as warranted by the data, and results of the analysis will be reported separately.

Immunogenicity: Serum samples will be collected to assess the immunogenicity of CX-072 and ipilimumab. All samples will be initially screened for ADAs. If the sample is found to be ADA positive in the screening assay, a confirmatory assay will be performed. Confirmed positive samples will be evaluated with a titer assay and may be further characterized for the presence of neutralizing or domain-specific ADA.

Exploratory Biomarkers: Exploratory studies will include the evaluation of the presence of PD-L1, tumor mutation burden (TMB), T cell receptor (TCR) repertoire, and circulating exploratory biomarkers including, but not limited to PD-L1.

SAFETY VARIABLES

Incidence and nature of adverse events (AEs) and serious adverse events (SAEs) (as assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0) as well as physical examinations, vital sign measurements, electrocardiograms (ECGs), clinical laboratory evaluations, and treatment discontinuation due to toxicity will be evaluated for safety assessment. Safety assessments will include tests for immunogenicity.

STATISTICAL ANALYSES

Analyses will be conducted by cohort and may be conducted overall. Statistical assessments/methods for safety, efficacy, PK/pharmacodynamics (PD), and immunogenicity are found in the Core. Additional endpoints will include, but are not limited to, frequency of AEs of special interest (AESIs) and percentage of reduction in tumor burden. For Part B1, the proportion of subjects with pathologic complete response (pCR), major pathologic response/near pCR, and pathologic partial response (pPR) will be summarized by count and percentage using the safety analysis population. RFS, assessed in subjects who have undergone surgical resection, is defined as the time from resection until the date of the first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurs first (Weber 2017). Censoring rules for the analysis of RFS are presented in Table 10.

SAMPLE SIZE DETERMINATION

The study is envisioned as a Simon's Two-Stage design (Simon 1989); assumptions used a targeted one-sided alpha of 5% and power of at least 80%. The Simon's Two-Stage design allows termination in a tumor type if CX-072 plus ipilimumab is ineffective based on an interim analysis at the end of Stage 1, which is anticipated to occur no earlier than 4 months after the first dose of study treatment of the last subject in Part A and no earlier than 7 months after the first dose of study treatment of the last subject in Part B (corresponding to 4 months after initiating the second dose of combination study treatment). Calculations were performed using EAST v6.4.1. The final (primary) analysis will be based on the entire study population, anticipated to occur 4 months after the first treatment of the last subject. The cohort will be considered a success if the number of responders meets or exceeds the specified success criteria in Table 9. For Cohort A2 under this amendment (Amendment 2), only Stage 1 is included (n = 40). Stage 2 of Cohort A2 will require a subsequent amendment following a discussion with regulatory agencies to agree on success criteria to establish an appropriate sample size. Enrollment in Cohort A2 cannot exceed the number specified in Stage 1 of the envisioned Simon 2-stage design as noted in Table 9.

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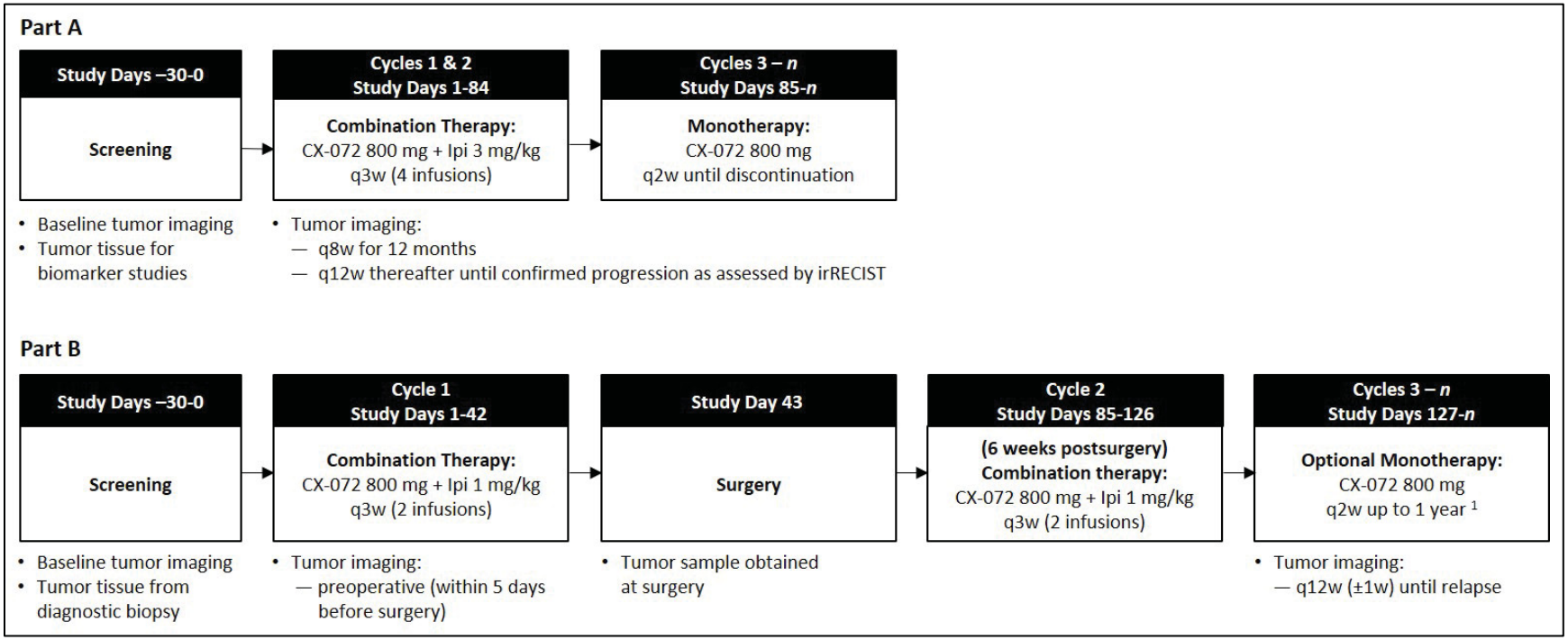
STUDY SCHEMATIC

Figure 1 Study Schematic (Parts A and B)



[1] May receive up to 1 year of CX-072 infusions postsurgery (including 2 postsurgery combination doses and then as monotherapy) until the occurrence of disease relapse, unacceptable toxicity, or the subject meets any other criterion for treatment discontinuation.

Note: Visit windows are noted in Schedules of Assessments (Table 1, Table 2).

Ipi = ipilimumab; irRECIST = immune-related Response Evaluation Criteria in Solid Tumours; q*x*w = once every *x* weeks; w = week.

SCHEDULE OF ASSESSMENTS – PART A

Refer to the footnotes below the table, applicable sections within this Module, and the Core (Appendix A) for descriptions of each assessment.

Table 1 Schedule of Assessments: Part A

Part A	**Screening**	**Treatment Period [1]**									
		Combo Cycle 1 (±2d)			**Combo Cycle 2 (±2d)**		**Mono Cycles 3 - *n* (±2d)**			**EOT**	**Follow-up [2]**
Cycle Day [3]	**Days –30 to 0**	**Day 1**	**Day 8**	**Day 22**	**Day 1**	**Day 22**	**Day 1**	**Day 15**	**Day 29**		
Study Day [3]	**–30 to 0**	**1**	**8**	**22**	**43**	**64**	**85, 127, then q42d**	**99, 141, then q42d**	**113, 155, then q42d**	**Last Tx Day +30d (-2/+7d)**	**Last Tx Day+90d then q90d (±14d)**
Informed Consent	X										
Medical History [4]	X										
Prior Cancer Tx	X										
Demographics	X										
AE Assessment	X [5]	X [6,7]									X [8]
Concomitant Medications [9]	X	X [6]									X
New Cancer Tx										X	X
Survival Status											X
Imaging											
Baseline Disease Assessment [10]	X										
Radiographic Tumor Assessment and Tumor Response Evaluation [10]	X	Scan q8w (±1w) for 12 months and q12w (±1w) thereafter until confirmed progression as assessed by irRECIST									
Clinical Procedures											
ECG [11]	X	X				X				X	
Physical Examination[12]	X	X [6]	X	X [6]	X [6]	X [6]	X [6]	X [6]	X [6]	X	
Vital Signs [13]	X	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X [6]	X	X [6]	X [6]	X [6]	X [6]	X [6]	X [6]	X	
Height, Weight [14]	X	X [6]		X [6]	X [6]	X [6]	X [6]			X	
Laboratory Assessments [3]											
ACTH	X										
Hematology [15]	X	X [6]	X	X [6]	X [6]	X [6]	X [6]	X [6]	X [6]	X	
Serum Chemistry [16]	X	X [6]	X	X [6]	X [6]	X [6]	X [6]	X [6]	X [6]	X	
Thyroid Function [17]		X [6]			X [6]		X [6]			X	
Coagulation [18]	X	X [6]			X [6]					X	
Urinalysis [19]	X	X [6]			X [6]		X [6]			X	

Part A	**Screening**	**Treatment Period [1]**									
		Combo Cycle 1 (±2d)			**Combo Cycle 2 (±2d)**		**Mono Cycles 3 - *n* (±2d)**			**EOT**	**Follow-up [2]**
Cycle Day [3]	**Days –30 to 0**	**Day 1**	**Day 8**	**Day 22**	**Day 1**	**Day 22**	**Day 1**	**Day 15**	**Day 29**		
Study Day [3]	**–30 to 0**	**1**	**8**	**22**	**43**	**64**	**85, 127, then q42d**	**99, 141, then q42d**	**113, 155, then q42d**	**Last Tx Day +30d (-2/+7d)**	**Last Tx Day+90d then q90d (±14d)**
Pregnancy Test [20]	X	X [6]		X [6]	X [6]	X [6]	X [6]	X [6]	X [6]	X	X [21]
Biomarker/PK/ADA Samples											
Tumor Tissue [22]	X										
Plasma for cfDNA	X	Collect at same time as tumor response assessment									
Circulating Serum Markers [23]	X	X [24]		X [24]	X [24]		C3, C4, C5 [24]				
PBMC for TCR	X	X [24]		X [24]	X [24]	X [24]	X [24]				
Plasma for Exosome		X [24]			X [24]						
Plasma for PK		Collect PK samples as shown in Table 3									
Serum for ADA to CX-072		X [24]		X [24]		X [24]	X [24,25]			X [24]	X [26]
Serum for ADA to Ipilimumab		X [24]				X [24]					
Study Treatment Administration											
CX-072 Infusion [27]		X		X	X	X	X	X	X		
Ipilimumab Infusion [27]		X		X	X	X					

1. Cycles are 6 weeks (42 days) each. Combination treatment cycles (Cycles 1 and 2) include 2 doses of CX-072 plus ipilimumab. Monotherapy treatment cycles (Cycles 3 and beyond) include 3 doses of CX-072. All scheduling is relative to first dose of study treatment (ie, Cycle 1 Day 1).
2. Subjects will be followed approximately every 90 (±14) days until withdrawal from study participation or death. Toxicity management may require additional visits at the discretion of the Investigator.
3. Laboratory assessments may be performed up to 2 days prior to the visit. Visits conducted outside the ±2-day windows noted are to be discussed with the Medical Monitor in advance.
4. Medical History: Include confirmation of previous cancer diagnosis and cancer treatment history, current symptoms at Screening, and prior or current medical conditions. For subjects with melanoma: if available, record findings from pathological diagnosis including but not limited to, melanoma subtype, margin status, Breslow thickness, Clark level, mitoses, ulceration status, and IHC marker information (eg, s-100, MART-1, HMB-45, SOCX10).
5. AEs: Record any nonserious AEs occurring after signing the ICF and prior to administration of the first dose of study treatment in the medical history eCRF. Record any SAEs occurring after signing the ICF in the AE eCRF.
6. Perform or assess prior to study treatment administration.
7. AEs: Record all AEs occurring up to 30 days after last dose of study treatment. Refer to Section 9 for AE reporting.
8. AEs: During the Follow-up Period, AE reporting is limited to irAEs, AEs ≥Grade 3, and SAEs occurring up to 90 days after last dose of study drug. After the AE reporting period (as defined in Section 9.1), all SAEs assessed as related to study treatment will be reported. Refer to Section 9 for AE reporting.
9. Concomitant Medications: Record medications taken within 30 days prior to the first dose of study treatment. Record concomitant medications and therapies administered during the study up to the EOT Visit. After EOT, record only concomitant medications administered for treatment of reported irAEs, AEs ≥Grade 3, and SAEs. Report all anticancer treatments until the end of the study.
10. Baseline Disease/Tumor Response Assessments: Refer to tumor-specific response criteria guidelines in Section 6 and the Core (Appendix A). Perform CT (with and/or without contrast) or MRI. Bone scans and PET scans may be performed if clinically indicated but may not be used to measure target lesions. Skin lesions must be

photographed along with a ruler at all time points for tumor assessments. Imaging methods will be employed consistently during the course of each subject's evaluation during the study. At the first progression, based on RECIST v1.1, the subject will be re-baselined according to irRECIST and should continue to be followed until irPD.

11. ECGs: Obtain 12-lead ECGs in triplicate (2 to 5 minutes apart) in digital format (when possible), and archived, while supine at Screening, 30 (±15) minutes before and after CX-072 infusion on Cycle 1 Day 1, Cycle 2 Day 22, at EOT, and as clinically indicated.
12. Physical Exam: See the Core (Section 10.1 in Appendix A).
13. Vital Signs: Include heart rate and blood pressure (supine), temperature, respiratory rate, and pulse oximetry. During the first 2 doses of combination treatment, measure vital signs within 60 minutes prior to infusion, every 15 (±5) minutes during infusion, at the EOI (±5 minutes), and every 60 (±15) minutes for 4 hours after the EOI. On all other infusion days, measure vital signs within 60 minutes prior to infusion, at the EOI (±15 minutes), and 60 (±15) minutes after the EOI (unless clinical signs require more frequent monitoring).
14. Measure height at Screening only; weigh at each visit indicated.
15. Hematology: CBC with differential prior to administration of study treatment; refer to hematology guidelines in the Core (Appendix A). CBC may be performed ≤7 days prior to Cycle 1 Day 1 and up to 2 days before subsequent study treatment administrations. Investigator should review results prior to administration of study treatment.
16. Serum Chemistry: Alkaline phosphatase, AST/SGOT and ALT/SGPT, GGT, amylase, lipase, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, magnesium, and LDH. Blood glucose should be fasting to evaluate possible hyperglycemia. Calculated creatinine clearance is required at Screening. Serum chemistry assessments may be performed ≤7 days prior to Cycle 1 Day 1 and up to 2 days before subsequent study treatment administrations. Laboratory assessments drawn on the day of infusion should be drawn prior to administration of study treatment.
17. Thyroid Function: TSH, free T4 and T3. May be performed at additional time points as clinically indicated.
18. Coagulation: PT/aPTT/INR. May be performed at additional time points as clinically indicated.
19. Urinalysis with microscopic examination: Protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity.
20. Pregnancy Test: Women of childbearing potential only. Perform serum pregnancy test (HCG) at Screening; if Screening test is obtained within 7 days of first dose of study treatment, the Day 1 test may be omitted. After Screening, perform serum pregnancy test on Day 1 of each cycle and perform either serum or urine pregnancy test (with serum test as needed for confirmation) at other required time points.
21. Follow-up Period Pregnancy Tests: Perform urine or serum pregnancy test at first and second Follow-up Visits only (ie, 3 and 6 months after the last dose of study treatment).
22. Tumor Tissue Sample: In cases where archival tumor sample is not available, biopsies for the purpose of providing tumor sample will be performed during Screening. If archival tumor sample is available from multiple time points, sample should be provided from the most recent time point.
23. Circulating Serum Markers: Include but are not limited to circulating tumor DNA and PD-L1 exosomes.
24. Biomarker/ADA Samples: Collect prior to study treatment administration on dosing days. At EOT, collect at study visit. Predose samples may be drawn at the time of other study-related blood draws taken prior to infusion.
25. ADAs to CX-072 Samples: Collect on Day 1 of every fourth cycle (starting from Cycle 4; ie, Cycle 8 Day 1, Cycle 12 Day 1, etc.).
26. ADAs to CX-072 Samples: Collect once at any time >90 days after last dose of CX-072.
27. If a ≥Grade 2 IRR is observed during or after an infusion, a local blood draw is required to measure tryptase, total immunoglobulin E, and complement C3a and C5 preferably within 2 hours and not more than 6 hours after the first signs/symptoms of the reaction.

ACTH = adrenocorticotropic hormone; ADA = antidrug antibody; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; cfDNA = cell-free DNA; C*x* = Cycle *x*; combo = combination treatment; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOI = end of infusion; EOT = end of treatment; GI = gastrointestinal; GGT = gamma glutamyltransferase; HCG = human chorionic gonadotropin; ICF = informed consent form; IHC = immunohistochemistry; INR = international normalized ratio; irAE = immune-related adverse event; IRR = infusion-related reaction; irRECIST = immune-related Response Evaluation Criteria in Solid Tumours; irPD = immune-related progressive disease; LDH = lactate dehydrogenase; mono = monotherapy;; MRI = magnetic resonance imaging; OS = overall survival; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PS = performance status; PT = prothrombin time; q*x*d = once every *x* days; q*x*w = once every *x* weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TCR = T cell receptor; TSH = thyroid-stimulating hormone; Tx = treatment.

SCHEDULE OF ASSESSMENTS – PART B

Refer to the footnotes below the table, applicable sections within this Module, and the Core (Appendix A) for descriptions of each assessment.

Table 2 Schedule of Assessments: Part B

Part B	**Screening**	**Treatment Period [1]**												**Follow-up [2]**
		Combo Cycle 1 (±2d)				**Surgery (-2/+7d)**	**Combo Cycle 2 (±2d)**		**Optional Mono Cycle 3 (±2d)**		**Optional Mono Cycles 4 – *n* (±2d) [3]**		**EOT**	
Cycle Day [4]	**Days –30 to 0**	**Day 1**	**Day 8**	**Day 22**	**Day 40 [5]**	**Day 43**	**Day 1**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 15**		
Study Day [4]	**–30 to 0**	**1**	**8**	**22**	**40**	**43**	**85**	**106**	**127**	**141**	**155, 183, then q14d**	**169, 197, then q14d**	**Last Tx Day +30d (-2/+7d)**	**Last Tx Day +90d then q90d (±14d)**
Informed Consent	X													
Medical History [6]	X													
Prior Cancer Tx	X													
Demographics	X													
AE Assessment	X [7]	X [8,9]												X [10]
Concomitant Medications [11]	X	X [8]					X [8]							X
New Cancer Tx													X	X
Survival Status														X
Imaging														
Baseline Disease Assessment [12]	X													
Radiographic Tumor Assessment and Tumor Response Evaluation [12]	X				X				Scan q12w (±1w) until relapse					
Surgical Resection						X								
Pathologic Response Assessment						X [13]								
Clinical Procedures														
ECG [14]	X	X			X			X					X	
Physical Examination[15]	X	X [8]	X	X [8]	X		X [8]	X [8]	X [8]	X [8]	X [8]	X [8]	X	
Vital Signs [16]	X	X	X	X	X		X	X	X	X	X	X	X	
ECOG PS	X	X [8]	X	X [8]	X		X [8]	X [8]	X [8]	X [8]	X [8]	X [8]	X	
Height, Weight [17]	X	X [8]		X [8]	X		X [8]	X [8]	X [8]		X [8]			

Part B	**Screening**	**Treatment Period [1]**												
		Combo Cycle 1 (±2d)				**Surgery (-2/+7d)**	**Combo Cycle 2 (±2d)**		**Optional Mono Cycle 3 (±2d)**		**Optional Mono Cycles 4 – *n* (±2d) [3]**		**EOT**	**Follow-up [2]**
Cycle Day [4]	**Days –30 to 0**	**Day 1**	**Day 8**	**Day 22**	**Day 40 [5]**	**Day 43**	**Day 1**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 15**		
Study Day [4]	**–30 to 0**	**1**	**8**	**22**	**40**	**43**	**85**	**106**	**127**	**141**	**155, 183, then q14d**	**169, 197, then q14d**	**Last Tx Day +30d (-2/+7d)**	**Last Tx Day +90d then q90d (±14d)**
Laboratory Assessments [4]														
ACTH	X													
Hematology [18]	X	X [8]	X [8]	X [8]	X		X [8]	X [8]	X [8]	X [8]	X [8]	X [8]	X	
Serum Chemistry [19]	X	X [8]	X [8]	X [8]	X		X [8]	X [8]	X [8]	X [8]	X [8]	X [8]	X	
Thyroid Function [20]		X [8]			X		X [8]		X [8]		X [8]		X	
Coagulation [21]	X	X [8]			X									
Urinalysis [22]	X	X [8]			X		X [8]		X [8]		X [8]			
Pregnancy Test [23]	X	X [8]		X [8]			X [8]	X [8]	X [8]	X [8]	X [8]	X [8]	X	X [24]
Biomarker/PK/ADA Samples														
Tumor Tissue	X [25]					X [26]								
Plasma for cfDNA	X													
Circulating Serum Markers [27]	X	X [28]		X [28]			X [28]	X [28]	X [28]		C4, C5 [28]			
PBMC for TCR	X	X [28]		X [28]			X [28]	X [28]						
Plasma for Exosome		X [28]			X [28]	X [28]								
Plasma for PK		Collect PK samples as shown in Table 3												
Serum for ADA to CX-072		X [28]		X [28]			X [28]	X [28]	X [28]		X [28,29]		X [29]	X [30]
Serum for ADA to Ipilimumab		X [28]						X [28]						
Study Treatment Administration														
CX-072 Infusion [31]		X		X			X	X	X	X	X	X		
Ipilimumab Infusion [31]		X		X			X	X						

1. Combination treatment cycles (Cycles 1 and 2) include 2 doses of CX-072 plus ipilimumab combination treatment and are 6 weeks (42 days) each. Optional monotherapy treatment cycles (Cycles 3 and beyond) include 2 doses of CX-072 and are 4 weeks (28 days) each. All scheduling is relative to first dose of study treatment (ie, Cycle 1 Day 1).
2. Subjects will be followed approximately every 90 (±14) days until withdrawal from study participation or death. Toxicity management may require additional visits at the discretion of the Investigator.
3. Subjects may receive up to 1 year of CX-072 infusions postsurgery (including 2 postsurgery combination doses and then as monotherapy) until the occurrence of disease relapse, unacceptable toxicity, or the subject meets any criterion for treatment discontinuation (Section 4.11).

4. Laboratory assessments may be performed up to 2 days prior to the visit, except for Cycle 2 Day 1 laboratory assessments, which should be performed within 7 days prior to Cycle 2 Day 1. Visits conducted outside the ±2-day windows are to be discussed with the Medical Monitor in advance.
5. Cycle 1 Day 40 assessments may be performed within 7 days prior to surgery; radiographic tumor assessment should be performed within 5 days prior to surgery. Any additional assessments performed as standard of care (eg, laboratory evaluations, AEs) presurgery or postsurgery, will be recorded in the eCRFs.
6. Medical History: Include confirmation of previous cancer diagnosis and cancer treatment history, current symptoms at Screening, and prior or current medical conditions. If available, record findings from pathological diagnosis including but not limited to, melanoma subtype, margin status, Breslow thickness, Clark level, mitosis, ulceration status, and IHC marker information (eg, s-100, MART-1, HMB-45, SOCX10).
7. AEs: Record any nonserious AEs occurring after signing the ICF and prior to administration of the first dose of study treatment in the medical history eCRF. Record any SAEs occurring after signing the ICF in the AE eCRF.
8. Perform or assess prior to study treatment administration.
9. AEs: Record all AEs occurring up to 30 days after last dose of study treatment. Refer to Section 9 for AE reporting.
10. AEs: During the Follow-up Period, AE reporting is limited to irAEs, AEs ≥Grade 3, and SAEs occurring up to 90 days after last dose of study drug. After the AE reporting period (as defined in Section 9.1), all SAEs assessed as related to study treatment will be reported. Refer to Section 9 for AE reporting.
11. Concomitant Medications: Record medications taken within 30 days prior to the first dose of study treatment. Record concomitant medications and therapies administered during the study up to the EOT Visit. After EOT, record only concomitant medications administered for treatment of reported irAEs, AEs ≥Grade 3, and SAEs. Report all anticancer treatments until the end of the study.
12. Baseline Disease/Tumor Assessments: Refer to tumor-specific response criteria guidelines in Section 6 and the Core (Appendix A). Bone scans and PET scans may be performed if clinically indicated but may not be used to measure target lesions. Skin lesions must be photographed along with a ruler at all time points for tumor assessments. Imaging methods will be employed consistently during the course of each subject's evaluation during the study. Presurgery tumor assessment will be performed according to RECIST v1.1. Postsurgery tumor assessments will be performed to monitor for disease relapse.
13. Pathologic Response Assessment: Perform after surgical resection in accordance with the laboratory manual. Pathologic response will be confirmed through a central pathology review.
14. ECGs: Obtain 12-lead ECGs in triplicate (2 to 5 minutes apart) in digital format (when possible), and archived, while supine at Screening, 30 (±15) minutes before and after CX-072 infusion on Cycle 1 Day 1, Cycle 1 Day 40, Cycle 2 Day 22, at EOT, and as clinically indicated.
15. Physical Exam: See the Core (Section 10.1 in Appendix A).
16. Vital Signs: Include heart rate and blood pressure (supine), temperature, respiratory rate, and pulse oximetry. During the first 2 doses of combination treatment, measure vital signs within 60 minutes prior to infusion, every 15 (±5) minutes during infusion, at the EOI (±5 minutes), and every 60 (±15) minutes for 4 hours after the EOI. On all other infusion days, measure vital signs within 60 minutes prior to infusion, at the EOI (±15 minutes), and 60 (±15) minutes after the EOI (unless clinical signs require more frequent monitoring).
17. Measure height at Screening only; weigh at each visit indicated.
18. Hematology: CBC with differential prior to administration of study treatment; refer to hematology guidelines in the Core (Appendix A). CBC may be performed ≤7 days prior to Cycle 1 Day 1 and Cycle 2 Day 1 and up to 2 days before subsequent study treatment administrations. Investigator should review results prior to administration of study treatment.
19. Serum Chemistry: Alkaline phosphatase, AST/SGOT and ALT/SGPT, GGT, amylase, lipase, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, magnesium, and LDH. Blood glucose should be fasting to evaluate possible hyperglycemia. Calculated creatinine clearance is required at Screening. Serum chemistry assessments may be performed ≤7 days prior to Cycle 1 Day 1 and Cycle 2 Day 1 and up to 2 days before subsequent study treatment administrations. Laboratory assessments drawn on the day of infusion should be drawn pre-dose.
20. Thyroid Function: TSH, free T4 and T3. May be performed at additional time points as clinically indicated.
21. Coagulation: PT/aPTT/INR. May be performed at additional time points as clinically indicated.
22. Urinalysis with microscopic examination: Protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, and specific gravity.
23. Pregnancy Test: Women of childbearing potential only. Perform serum pregnancy test (HCG) at Screening; if Screening test is obtained within 7 days of first dose of study treatment, the Day 1 test may be omitted. After Screening, perform serum pregnancy test on Day 1 of each cycle and perform either serum or urine pregnancy test (with serum test as needed for confirmation) at other required time points.
24. Follow-up Period Pregnancy Tests: Perform urine or serum pregnancy test at first and second Follow-up Visits only (ie, 3 and 6 months after the last dose of study treatment).

25. Tumor Biomarker Sample: Collect archival tumor samples from the initial diagnostic biopsy. In cases where archival tumor sample is not available, biopsies for the purpose of providing tumor sample will be performed during Screening. If archival tumor sample is available from multiple time points, sample should be provided from the most recent time point.
26. Tumor Tissue Sample: Collect tumor tissue from surgical resection (including resected lymph nodes) for pathologic response assessment and for biomarker analysis.
27. Circulating Serum Markers: Include but are not limited to circulating tumor DNA and PD-L1 exosomes.
28. Biomarker/ADA Samples: Collect prior to study treatment administration on dosing days. At surgery visit and EOT, collect at study visit. Predose samples may be drawn at the time of other study-related blood draws taken prior to infusion.
29. ADAs to CX-072 Samples: Collect on Day 1 of every fourth cycle (starting from Cycle 4; ie, Cycle 8 Day 1, Cycle 12 Day 1, etc.).
30. ADAs to CX-072 Samples: Collect once at any time >90 days after last dose of CX-072.
31. If a ≥Grade 2 IRR is observed during or after an infusion, a local blood draw is required to measure tryptase, total immunoglobulin E, and complement C3a and C5 preferably within 2 hours and not more than 6 hours after the first signs/symptoms of the reaction.

ACTH = adrenocorticotropic hormone; ADA = antidrug antibody; AE = adverse event; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; cfDNA = cell-free DNA; C*x* = Cycle *x*; combo = combination treatment; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOI = end of infusion; EOT = end of treatment; GI = gastrointestinal; GGT = gamma glutamyltransferase; HCG = human chorionic gonadotropin; ICF = informed consent form; INR = international normalized ratio; irAE = immune-related adverse event; IRR = infusion-related reaction; LDH = lactate dehydrogenase; mono = monotherapy; MRI = magnetic resonance imaging; OS = overall survival; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PS = performance status; PT = prothrombin time; q*x*d = once every *x* days; q*x*w = once every *x* weeks; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse event; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; TCR = T cell receptor; TSH = thyroid-stimulating hormone; Tx = treatment.

PHARMACOKINETIC PLASMA SAMPLING – PARTS A AND B

Table 3 Pharmacokinetic Plasma Sampling Schedule

Cycle Day or Visit [a]	Study Treatment	Part A [b,c]	Part B [b,c]
Cycle 1 Day 1	CX-072	0 h predose EOI	0 h predose EOI
Cycle 1 Day 1	Ipilimumab	0 h predose EOI	0 h predose EOI
Cycle 1 Day 22	CX-072	0 h predose	0 h predose
Cycle 1 Day 40	CX-072		At study visit
Cycle 2 Day 1	CX-072		0 h predose
Cycle 2 Day 22	CX-072	0 h predose EOI	0 h predose EOI
Cycle 2 Day 22	Ipilimumab	0 h predose EOI	0 h predose EOI
Cycle 3 Day 1	CX-072	0 h predose	0 h predose
Cycle 4 Day 1 and every 4 cycles thereafter	CX-072	0 h predose	0 h predose
EOT (-2/+7 days)	CX-072	At study visit	At study visit
Follow-up (±14 days)	CX-072	Once any time >90 days after last dose of CX-072	Once any time >90 days after last dose of CX-072

[a] A ±2-day window is allowed for each visit unless otherwise specified.

[b] Predose samples may be drawn at the time of other study-related blood draws taken prior to infusion.

[c] Collect EOI samples 30 (±10) minutes after EOI.

EOI = end of infusion; EOT = end of treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
a.m.	*ante meridian;* morning
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
cfDNA	cell-free DNA
CI	confidence interval
C_{max}	maximal plasma concentration
C_{min}	minimal plasma concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T lymphocyte–associated antigen 4
C*x*	Cycle *x*
d	day
dL	deciliter
DLP	data lock point
DLT	dose-limiting toxicity
DOR	duration of response
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation	Definition
EDC	electronic data capture
EOI	end of infusion
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
FT4	free thyroxine
g	gram
G1	Grade 1
GGT	gamma glutamyltransferase
GI	gastrointestinal
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
h	hour
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IgG_4	immunoglobulin G subclass 4
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application; United States)
INMC	International Neoadjuvant Melanoma Consortium
INR	international normalized ratio
Ipi	ipilimumab
irAE	immune-related adverse event
IRB	institutional review board

Abbreviation	Definition
irPD	immune-related progressive disease
IRR	infusion-related reaction
irRECIST	immune-related Response Evaluation Criteria in Solid Tumours
IU	International Unit
IV	intravenous(ly)
IXRS	interactive voice/web response system
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MEK	mitogen-activated protein kinase
mg	milligram
mIU	milli-international unit
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
MRI	magnetic resonance imaging
ms	millisecond
MTD	maximum tolerated dose
NA	not applicable
nivo	nivolumab
nM	nanomolar
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
pCR	pathologic complete response
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PD-1	programmed death 1

Abbreviation	Definition
PD-L1	programmed death ligand 1
PEF	peak expiratory flow
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
pNR	pathologic nonresponse
PO	*per os*; by mouth (oral)
POPPK	population pharmacokinetics
pPR	pathologic partial response
PS	performance status
PT	prothrombin time
QSP	quantitative systems pharmacology
QTc	corrected QT interval
q*x*d	once every *x* days
q*x*w	once every *x* weeks
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	relapse-free survival
RO	receptor occupancy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TBD	to be determined
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TMB	tumor mutation burden
TME	tumor microenvironment

Abbreviation	Definition
TNFα	tumor necrosis factor alpha
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
TTR	time to response
Tx	treatment
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
v	version
Vem	vemurafenib
w	week
WFI	water for injection
°C	degrees Celsius
°F	degrees Fahrenheit
µg	microgram
µmol	micromole

1 INTRODUCTION AND BACKGROUND INFORMATION

This study is composed of 2 distinct documents:

- The Common Core Document (CTMX-C-001)
- This CX-072-specific Module (CTMX-M-072-002)

Briefly, the Common Core Document CTMX-C-001 (see Appendix A), or "Core," is a stable document that contains all study design features typically included in a standard Phase 1-2 clinical study protocol, but without reference to a specific investigational medicinal product (IMP). The Core, which provides the basis for all first in human clinical studies with Probody™ therapeutics, describes general study procedures such as guidelines for drug accountability, efficacy and safety parameters, and study administrative procedures. The CX-072 Module for this Phase 2 study (this document) is customized for the assessment of the CX-072 Probody therapeutic in combination with ipilimumab at the designated combination doses and provides all guidelines necessary to safely manage subject care. Familiarity with both documents is required for proper conduct of this study.

This core plus module system will enable a comprehensive clinical evaluation of Probody therapeutics within a unified clinical development program that has common components of study design, execution, and assessments, and common Investigator oversight. Where there are overlapping directives between the 2 documents, Investigators are instructed to follow the CX-072 Module regarding subject care guidelines. Refer to the Core (Appendix A) for a more detailed discussion of the Core study design and rationale.

1.1 Immune Checkpoint Blockade in the Treatment of Cancer

Immunotherapy is emerging as a highly promising approach for the treatment of cancer through the mobilization of T cells that recognize cancer cells as foreign, resulting in potent and durable responses in many cancer types. T cell activity is regulated by both positive (costimulatory) and negative (coinhibitory) T cell surface molecules. Two important negative regulatory T cell surface molecules are programmed death 1 (PD-1) and cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), which act as checkpoints that downregulate the immune response, playing a protective role against autoimmunity in normal tissue but also inhibiting T cell reactivity against cancer cells in tumor tissue.

The normal role of PD-1 is to minimize immune-mediated damage to tissues under conditions of chronic T cell stimulation or from attack by autoreactive T cells. In many tumors, the ligand for PD-1, programmed death ligand 1 (PD-L1) is upregulated and is a dominant means by which tumors can evade the immune system.

Clinical trials have confirmed the capacity of checkpoint blockade to effectively restore the activity of tumor-specific immunity and have resulted in approval of agents that block PD-1/PD-L1 and CTLA-4 signaling in various types of malignancies (Herbst 2014,

Lipson 2015). Refer to the current local prescribing information for Bavencio (avelumab), Imfinzi (durvalumab), Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab), and Yervoy (ipilimumab).

However, despite the enormous potential of checkpoint blockade in the treatment of cancer, inhibitors of these pathways are not effective in all patients. Checkpoint inhibitors have shown clinical benefit in certain settings, including response rates ranging from 15% to 40% when administered as monotherapy.

In addition, checkpoint inhibitor therapies are not without safety liabilities. Because tumors use similar mechanisms to inhibit the immune system that the body uses to prevent immune-mediated damage to normal tissues, therapies that target immune inhibitory mechanisms relieve inhibition not only in the tumor, but also elsewhere in the body. This can result in systemic autoimmunity, including hepatitis, colitis, pneumonitis, diabetes, and endocrinopathies.

Current clinical strategies in immunotherapy for the treatment of cancer include exploring new, more potent combination therapies to increase the magnitude and duration of responses in a greater percentage of patients. Combining CTLA-4 signaling inhibition with PD-1/PD-L1 signaling inhibition has resulted in enhanced antitumor activity in various tumor types; however, the increased antitumor activity is associated with higher rates of toxicities that limit the clinical utility of combined checkpoint blockade. For example, in a Phase 3 study (CheckMate 067), when Opdivo (nivolumab), an anti-PD-1 monoclonal antibody (mAb), was administered in combination with Yervoy (ipilimumab), an anti-CTLA-4 mAb, in patients with advanced melanoma, both efficacy and toxicity increased compared with monotherapy treatment with either agent. Fifty-eight percent of the patients experienced objective responses with the combination compared with 19% and 41% for monotherapy ipilimumab and nivolumab, respectively, but 55% of the patients treated with the combination experienced Grade 3 or 4 treatment-related adverse events (TRAEs) compared with 16% and 27% for monotherapy ipilimumab and nivolumab, respectively (Larkin 2015). Presumably, because these agents are administered systemically, and because both the PD-L1 and CTLA-4 proteins are present on normal tissue, the synergy of effect between these 2 agents is not confined to the tumor, and inflammation in normal tissues can result in meaningful, sometimes life-threatening toxicity. The combination of checkpoint inhibitors that block the PD-1 pathway (eg, nivolumab) with inhibitors of CTLA-4 signaling (eg, ipilimumab), demonstrate synergistic effects in efficacy and toxicities that can be dose limiting.

Clinical approaches to addressing the safety challenges with these combinations include decreasing the dose of ipilimumab in the combination treatment to a dose below the approved monotherapy dose of ipilimumab in the advanced/metastatic setting; however, it is not yet known whether this approach is sufficient to improve safety in a meaningful way while maintaining efficacy in a majority of cancer types. In the setting of renal cell cancer (CheckMate 016 study), the combination of 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (Nivo 3 + Ipi 1) resulted in an objective response rate (ORR) equivalent to the combination of 1 mg/kg nivolumab plus 3 mg/kg

ipilimumab (Nivo 1 + Ipi 3), with decreased rates of toxicity noted in the combination containing 1 mg/kg ipilimumab. Median progression-free survival (PFS) was decreased in the Nivo 3 + Ipi 1 arm (7.7 months) compared with the Nivo 1 + Ipi 3 arm (9.4 months) (Hammers 2017) potentially pointing to the need of a higher than 1 mg/kg ipilimumab dose for sustained response. In CheckMate 032, a study assessing the combination of nivolumab plus ipilimumab versus nivolumab monotherapy in patients with esophagogastric cancer, toxicity was improved, although response rates decreased when the dose of ipilimumab used in combination with nivolumab was reduced: the investigator-assessed ORR was 12% with nivolumab 3 mg/kg monotherapy, 24% with Nivo 1 + Ipi 3, and 8% with Nivo 3 + Ipi 1. In these 3 treatment groups, Grade 3 or 4 TRAEs were reported in 17%, 47%, and 27% of patients, respectively (Jangigian 2018). These efficacy and safety results are indicative of a strong clinical need for less toxic checkpoint inhibitors for use in novel combinations for the treatment of cancer.

CX-072 is a Probody therapeutic directed against PD-L1 that is designed to be preferentially activated by proteases associated with the tumor microenvironment (TME) by exploiting the dysregulation of the tumor protease activity that is a hallmark of most cancers, and resulting in preferential activation and binding to tumor cells rather than healthy tissue. By localizing its activity to the TME, CX-072 is expected to reduce systemic toxicities, thereby expanding clinical opportunities for targeting the PD-1/PD-L1 pathway, particularly when used in combination with ipilimumab.

1.2 Cancer Types Assessed in This Combination Module

The following tumor types will be enrolled into parallel treatment arms of this Module:

- Part A:
  - Cohort A1: Subjects with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma who have received no prior treatment for unresectable or metastatic melanoma
  - Cohort A2: Subjects with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma who have experienced progressive disease or relapse following treatment with a PD-1/PD-L1 immune checkpoint inhibitor
  - Cohort A3: Subjects with histologically or cytologically confirmed, advanced/unresectable or metastatic, transitional cell carcinoma of the urothelium who have experienced disease progression during or following treatment with platinum-based therapy
- Part B :
  - Cohort B1: Subjects with histologically confirmed resectable Stage III melanoma with palpable disease

1.2.1 Melanoma

Melanoma is the most serious form of skin cancer. In the United States (US), it is the sixth most common cancer in men and the sixth in women (Siegel 2018); survival rates depend on the stage of the disease at the time of diagnosis. Treatment approaches depend on stage and other identified risk factors and include surgery, radiation therapy, and systemic therapy. In general, the prognosis is excellent for patients who present with localized disease and primary tumors ≤1.0 mm in thickness with >90% of patients experiencing 5-year survival. For patients with localized melanomas >1.0 mm in thickness, survival rates range from 50% to 90%, depending on tumor thickness, ulceration, and mitotic rate. In patients with clinically involved lymph nodes but no distant disease, therapeutic lymph node dissection is associated with 5-year survival rates of 30% to 50% (Balch 2009). Adjuvant radiation therapy may be considered for patients with high risk of recurrence, including patients with involved lymph nodes; however, controversy exists regarding the risk benefit of this approach (Burmeister 2012). Prior to the availability of checkpoint inhibitor therapy, the prognosis for patients with regional and distant metastatic melanoma (Stages III and IV, respectively) was generally poor, with 5-year survival rates for Stage III of 13% to 69% and as low as 6% in Stage IV (Karlsson 2017).

The prognosis of patients with metastatic melanoma has improved with the emergence of several effective systemic therapies. These approaches include immunotherapy (particularly with checkpoint inhibition) and targeted therapy that inhibits the mitogen-activated protein kinase pathway. However, despite these new novel therapies, a significant proportion of patients do not respond, and the majority eventually experience disease progression and die of their disease. In the KEYNOTE-006 study assessing Keytruda (pembrolizumab) versus ipilimumab in patients with advanced or metastatic melanoma and no prior checkpoint inhibitor therapy, 24-month overall survival (OS) rates were 55% in patients randomized to receive pembrolizumab and 43% in the ipilimumab group. In the Checkmate 067 study, the 4-year OS rates were 46% in the nivolumab group, 30% in the ipilimumab group, and 53% in the combination group (Hodi 2018).

Checkpoint inhibitors have also been found to be effective in advanced melanoma that has relapsed following frontline treatment with checkpoint inhibitor therapy, although the response rates are decreased compared to treatment in the frontline setting. Retrospective studies of patients treated with ipilimumab following progression on an anti-PD-1 agent have shown response rates to ipilimumab monotherapy ranging from 10% to 50% (Ochoa 2017). Randomized studies assessing pembrolizumab or nivolumab monotherapy following treatment failure with ipilimumab have shown response rates of 24% and 27%, respectively.

Ipilimumab, nivolumab, and pembrolizumab have all demonstrated clinical benefit and safety and are approved as monotherapy for the treatment of advanced/unresectable or metastatic melanoma (in the previously untreated and treated/relapsed setting). Ipilimumab in combination with nivolumab is approved for the treatment of unresectable or metastatic melanoma; however, concern over toxicity with this combination treatment may limit its use in some patients. Clinical

studies have also demonstrated benefit of adjuvant treatment with checkpoint inhibitor therapy in patients rendered disease free by surgery. High-dose ipilimumab is approved for adjuvant treatment in patients with pathologic involvement of regional lymph nodes of >1 mm who have undergone complete resection, including total lymphadenectomy (treatment for up to 3 years). Nivolumab is approved for treatment of patients with melanoma with lymph node involvement or metastatic disease who have undergone complete resection based on demonstrated improvement of relapse-free survival (RFS) compared with ipilimumab (treatment up to 1 year). In a recent clinical study (KEYNOTE-054), pembrolizumab demonstrated improved RFS compared with placebo in patients with completely resected Stage III melanoma (treatment up to 1 year). However, a significant proportion of patients remain at high risk of recurrence of their disease. In KEYNOTE-054, 12-month rate of RFS was 75.4% in the pembrolizumab group and 61.0% (95% CI, 56.5 to 65.1) in the placebo group and at 18 months, the rates of RFS were 71.4% (95% CI, 66.8 to 75.4) on pembrolizumab and 53.2% (95% CI, 47.9 to 58.2) on placebo. There were 78 patients (15.2%) in the pembrolizumab group in whom distant metastases developed (Eggermont 2018).

Neoadjuvant treatment of melanoma is not currently the standard of care; however, this approach is being assessed in clinical studies. In the melanoma neoadjuvant setting, Nivo 1 + Ipi 3 has been assessed in small studies, demonstrating a pathologic response rate of 78% and a pathologic complete response (pCR) of 33% reported in 1 study (Blank 2018) and a pCR of 45% reported in a second study (Amaria 2018). However, in both studies a high rate of Grade 3 or 4 AEs was reported (90% [Grade 3 or 4 AEs regardless of relationship] and 73% [treatment-related Grade 3 or 4 AEs] in each study, respectively). An ongoing study is currently assessing treatment with a lower dose of ipilimumab in combination with nivolumab (Nivo 3 + Ipi 1) in neoadjuvant melanoma.

1.2.2 Urothelial Carcinoma

Bladder cancer is the most common malignancy involving the urinary system. Urothelial (transitional cell) carcinoma is the predominant histologic type in the US and Europe, where it accounts for 90% of all bladder cancers (von der Maase 2000, von der Maase 2005). Urothelial cancer can also arise from the upper urinary tract and urethra. Approximately 25% of patients will have muscle-invasive disease and either present with or later develop metastases. Systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable locally advanced or metastatic urothelial malignancies. Although initial response rates are high, the median survival with multiagent chemotherapy is approximately 15 months. Second-line chemotherapy has had only a limited role with median OS with salvage chemotherapy, ranging from 5 to 7 months (Gopalakrishnan 2018).

Checkpoint inhibitors offer an additional treatment option for urothelial carcinoma patients with disease progression after initial systemic chemotherapy and for subsets of patients in the previously untreated setting. Multiple PD-1/PD-L1 inhibitors have been approved in the US

(accelerated approvals based on tumor response rate and duration of response) and European Union (full approvals) in various lines of therapy including cisplatin-ineligible and platinum-ineligible patients, and patients with disease progression after platinum therapy. Refer to the current local prescribing information for avelumab, durvalumab, pembrolizumab, nivolumab, and atezolizumab.

Combination checkpoint blockade with inhibitors of PD-1/PD-L1 and CTLA-4 is not currently part of standard of care for this disease; however, initial clinical data demonstrated increased efficacy when ipilimumab is added to nivolumab as assessed by response rate. A Phase 1-2 study of platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma showed a response rate of 38% and 26.9% in patients treated with Nivo 1 + Ipi 3 and Nivo 3 + Ipi 1, respectively. In the same study, patients treated with nivolumab monotherapy had an ORR of 25.6% (Rosenberg 2018). These data indicate a potential dose dependency of ipilimumab in the combination for obtaining clinical benefit in this malignancy. Grade 3 or 4 TRAEs occurred in 39% and 31% of patients in the respective dose groups. An ongoing study in previously untreated patients with advanced/unresectable of metastatic urothelial carcinoma is assessing Nivo 1 + Ipi 3. Given the demonstrated clinical efficacy of combined checkpoint blockade and the apparent dose dependency on ipilimumab, assessing effective and tolerable approaches for combined inhibition will provide additional options for patients.

1.3 CX-072 Overview

CX-072 is a Probody therapeutic being developed under the CytomX Therapeutics, Inc. (CytomX) Probody platform. Probody therapeutics are fully recombinant mAb prodrugs designed to be preferentially activated by proteases associated with the TME. They differ from unmodified mAbs by the recombinant addition of a cleavable prodomain composed of a mask and protease cleavable substrate at the amino terminus of the light chain, which blocks the antibody. This mask is designed to block binding to its target antigen until the prodomain can be removed by tumor-associated protease cleavage at the substrate and released in the presence of tumor-associated proteases. As such, Probody therapeutics are administered in a form designed to bind their target in tumor tissue but not in normal circulating cells or healthy tissues. In nonclinical models, Probody therapeutics, including those targeting PD-L1, have been shown to reduce toxicity of the relevant unmasked parent antibody while maintaining its antitumor activity. In patients, Probody therapeutics may be particularly useful in clinical settings where target binding in healthy tissue limits patient access to potent, efficacious regimens.

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

CX-072 is derived from a proprietary human anti-PD-L1 mAb and is designed to achieve efficacy comparable to other anti-PD-L1 mAbs but with reduced systemic immune activation

and immune-related toxicities, potentially enabling new, safer, or more effective combination therapies. Expression, purification, formulation, characterization, stability, and administration of CX-072 are similar to those of other mAbs.

1.3.1 Summary of CX-072 Nonclinical Safety Data

CX-072 was generally well tolerated in rats and cynomolgus monkeys following weekly intravenous (IV) infusion administered for 4 or 5 doses at 20 to 200 mg/kg/dose.

Good Laboratory Practice (GLP)-compliant 4-week repeat-dose general toxicity studies of CX-072 were conducted in rats and cynomolgus monkeys. In these studies, repeated weekly administration of CX-072 at doses of up to 200 mg/kg was well tolerated, with no overt signs of toxicity. Microscopic findings associated with CX-072 were suggestive of a general pro-inflammatory effect consistent with PD-L1 blockade and/or immune complex–mediated vascular injury in animals with antidrug antibodies (ADAs) rather than organ-specific toxicities.

In the rat GLP 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 animals in the mid dose and high-dose groups were 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 gastrointestinal 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 immune checkpoint inhibitors 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 for females and could not be determined for males (<20 mg/kg). The highest nonseverely toxic dose (HNSTD) in male and female monkeys was 200 mg/kg.

Additional information may be found in the CX-072 Investigator's Brochure (IB).

1.3.2 Summary of CX-072 Clinical Safety Data

Module CTMX-M-072-001, a first in human, Phase 1-2a study (enrollment initiated in January 2017), 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.

In Part B1, subjects receive CX-072 plus ipilimumab combination therapy in escalating dose cohorts of CX-072 (0.3, 1, 3, or 10 mg/kg) and ipilimumab (3 or 6 mg/kg). Combination treatment is administered once every 3 weeks (q3w) for 4 doses. Following combination treatment, subjects receive CX-072 monotherapy once every 2 weeks (q2w) until a protocol-defined criterion for discontinuation is met.

In Part B2, prior to implementation of Module CTMX-M-072-001 Amendment 6 (dated 02 November 2018), subjects received phased CX-072 plus ipilimumab (run-in of CX-072 monotherapy q2w for 4 doses followed by combination treatment with CX-072 [3 or 10 mg/kg] plus ipilimumab [3 or 6 mg/kg] q3w for 4 doses). Following combination treatment, subjects received CX-072 monotherapy q2w. Upon implementation of Amendment 6, the CX-072 run-in will be eliminated, and the CX-072 and ipilimumab will be administered concomitantly. As of the data lock point (DLP; 30 November 2018) for the CX-072 IB Edition 5, no subjects were enrolled in Part B2 under Amendment 6, and thus all subjects had received phased CX-072 plus ipilimumab. As of the DLP, Part A2 had completed enrollment; enrollment was ongoing in Parts A, B1, B2, C, and D; and enrollment in Part E had not yet been initiated.

As of the IB DLP, 149 unique subjects were exposed to CX-072 as monotherapy (108 subjects) and/or in combination with ipilimumab (30 subjects) and vemurafenib (11 subjects). In Parts A and A2 (CX-072 monotherapy dose escalation), 53 subjects were treated with CX-072 dose levels up to 30 mg/kg, and no maximum tolerated dose (MTD) was established. The recommended Phase 2 dose (RP2D) level for monotherapy was defined as 10 mg/kg or the equivalent of 800 mg fixed dosing.

In Part B1 (concomitant CX-072 plus ipilimumab combination therapy), subsequent to the DLP, the MTD for concomitant administration of CX-072 plus ipilimumab was defined as 10 mg/kg CX-072 plus 3 mg/kg ipilimumab. Two of 5 subjects treated with 10 mg/kg CX-072 plus 6 mg/kg ipilimumab experienced a dose-limiting toxicity (DLT) (Grade 3 colitis and Grade 3 alanine aminotransferase [ALT] increased [n = 1 each]), thus, this dose level was determined to have exceeded the MTD.

The CX-072 IB contains the clinical safety data for Parts A, B, C, and D of Module CTMX-M-072-001. An overview of treatment-emergent adverse events (TEAEs) in subjects receiving CX-072 monotherapy at the RP2D dose level of 10 mg/kg and subjects receiving concomitant treatment with CX-072 plus ipilimumab is as follows:

- Of the 71 subjects who received 10 mg/kg CX-072 monotherapy in Parts A and A2 (n = 16) and Part D (n = 55):
  - 59 (83%) experienced a TEAE (regardless of causality), 3 (4%) experienced a TRAE ≥Grade 3, and 2 (3%) experienced a treatment-related serious adverse event (SAE).
  - The most common TEAEs were anemia (14 [20%] subjects) and nausea (12 [17%] subjects).
- Of the 24 subjects who received concomitant treatment with CX-072 plus ipilimumab in Part B1 (all dose groups):
  - 24 (100%) experienced a TEAE (regardless of causality), 6 (25%) experienced a TRAE ≥Grade 3, and 6 (25%) experienced a treatment-related SAE.
  - The most common TEAEs were nausea (11 [46%] subjects) and decreased appetite, fatigue, and pruritus (8 [33%] subjects each).
- Across all treatment cohorts, 16 treatment-emergent SAEs were considered by the Investigator as related to CX-072 (Table 4).

Table 4: Treatment-emergent Serious Adverse Events Considered by the Investigator as Related to CX-072 in Module CTMX-M-072-001, by Preferred Term and Frequency

Preferred Term (Number of Subjects With Event)	Grade	CX-072 Dose (mg/kg)	Ipi Dose (mg/kg)	Vem Dose (mg)
Colitis (n = 3)	3	0.3	3	NA
	3	10	6	NA
	4 [a]	3	3	NA
Infusion related reaction (n = 2)	2	10	NA	NA
	4	1	NA	NA
Pyrexia (n = 2)	2	1	3	NA
	2	10	3	NA
Blood bilirubin increased (n = 1)	3	1	NA	960
Dyspnoea (n = 1)	3	0.3	3	NA
Enterocutaneous fistula (n = 1)	3	10	NA	NA
Febrile neutropenia (n = 1)	3	3	NA	NA
Hypophysitis (n = 1)	2	1	3	NA
Large intestine perforation (n = 1) [b]	5	3	3	NA
Myocarditis (n = 1)	3	10	NA	NA
Pneumonitis (n = 1)	3	3	NA	NA
Stress cardiomyopathy (n = 1)	3	1	NA	NA

[a] One subject with colitis was in Part B2 and the event occurred after the first dose of ipilimumab.

[b] Large intestine perforation was considered by the Investigator to be unrelated to ipilimumab and unrelated to CX-072. However, the Sponsor has conservatively assessed this event as a potential extension and outcome from the earlier autoimmune colitis event.

Notes: Adverse events were coded using Medical Dictionary for Regulatory Activities version 19.1. Table shows data as of 30 November 2018.

Ipi = ipilimumab; NA = not applicable; Vem = vemurafenib.

Source: Data on file at CytomX.

There were no Grade 5 TRAEs reported according to Investigator assessment; however, 1 subject in Part B2 (phased CX-072 plus ipilimumab) experienced a Grade 5 event of large intestine perforation that was conservatively assessed by the Sponsor as treatment related as a potential extension and outcome from an earlier event of autoimmune colitis.

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

1.4 Study Rationale

This Module will evaluate the antitumor effect of CX-072 in combination with ipilimumab and characterize the safety, tolerability, pharmacokinetics (PK), immunogenicity, and biomarkers of combination treatment in subjects with solid tumors.

Current clinical strategies in immunotherapy for the treatment of cancer include combined inhibition of CTLA-4 and PD-1/PD-L1 signaling. Clinical data described in Section 1.3.2 with nivolumab and ipilimumab demonstrate the synergistic effects of this combination with respect to both antitumor activity. However, the increased efficacy is associated with increased toxicity. Furthermore, the clinical data indicate that the dose of ipilimumab may be important for optimal antitumor activity.

Increased toxicity arising from combined checkpoint inhibition is largely due to the loss of protection from autoimmunity in normal tissues when both CTLA-4 and PD-1/PD-L1 pathways are blocked. CX-072, a PD-L1 inhibitor, is designed to be preferentially activated in the TME, enabling continued protection from autoimmunity via PD-L1 signaling in normal tissue while targeting combined checkpoint blockade in the tumor tissue. Combining ipilimumab with CX-072 is thus expected to improve tolerability while maintaining antitumor efficacy. The clinical program to date has demonstrated activity of CX-072 in various tumor types, including as monotherapy and in dose escalation cohorts of CX-072 plus ipilimumab with potential for increased tolerability compared with historical controls (Plummer 2018). Evidence that CX-072 circulates predominantly as the intact prodrug species (Boni 2018) and evidence of tumor binding in biopsy samples (Lyman 2018) have also been demonstrated.

The tumor types selected for this Module (ie, melanoma and urothelial carcinoma) are indications in which checkpoint inhibitor therapy is currently approved (PD-1/PD-L1 and/or CLTA-4) and in which combined checkpoint blockade has been shown to be effective, yet increased rates of Grade 3 or 4 AEs have also been noted when compared with checkpoint inhibitor monotherapy. Therefore, assessing potentially more tolerable combinations may be beneficial and could potentially lead to better options for cancer patients.

1.5 Rationale for Dose Selection

The doses of CX-072 and ipilimumab to be administered in this Module are:

- Part A:
  - Combination treatment: 800 mg CX-072+ 3 mg/kg ipilimumab q3w
  - Monotherapy treatment: 800 mg CX-072 q2w
- Part B:
  - Combination treatment: 800 mg CX-072 + 1 mg/kg ipilimumab q3w
  - Monotherapy treatment: 800 mg CX-072 q2w

The dose of CX-072 was selected based upon the totality of available nonclinical and preliminary clinical data from Module CTMX-M-072-001.

The dose of ipilimumab is selected based upon the approved dose in the advanced/metastatic cancer setting, available data from clinical studies of neoadjuvant ipilimumab in melanoma, and the MTD determination of the CX-072 plus ipilimumab combination from Part B1 of Module CTMX-M-072-001.

The combination dose of CX-072 plus ipilimumab in Part A of this Module is equivalent to the MTD of the combination of CX-072 plus ipilimumab determined in Part B1 of Module CTMX-M-072-001. The MTD of combination CX-072 plus ipilimumab was determined to be 10 mg/kg CX-072 plus 3 mg/kg ipilimumab. The dose level above the MTD (10 mg/kg CX-072 plus 6 mg/kg ipilimumab) was determined to have exceeded the MTD due to 2 of 5 subjects at this dose level experiencing a DLT (1 subject with Grade 3 colitis and 1 subject with Grade 3 AST increased). CX-072 at a fixed dose of 800 mg q2w is equivalent to the 10 mg/kg q2w weight-based dose and is the CX-072 dose that will be used in combination with ipilimumab.

In Part B, after receipt of the last dose of combination treatment, subjects will have the option to continue to receive CX-072 monotherapy following discussion and agreement of risk-benefit between the Investigator and Sponsor Medical Monitor. Subjects may receive up to 1 year of CX-072 infusions postsurgery (including 2 postsurgery combination doses and then as monotherapy). The 1-year treatment duration postsurgery corresponds to the 1-year treatment duration of nivolumab and pembrolizumab in the adjuvant melanoma setting.

1.5.1 Selection of CX-072 Fixed Dose

The fixed dose of 800 mg CX-072 q2w (equivalent to the 10 mg/kg q2w weight-based dose) for the CX-072 monotherapy treatments of Parts A and B was selected based upon the totality of available nonclinical and preliminary clinical data from Module CTMX-M-072-001. Published population PK (POPPK) and exposure-response analyses of Tecentriq (atezolizumab) suggested that patients receiving the labeled 1200 mg q3w dose surpassed a nonclinical trough target (minimal plasma concentration [C_{min}]) (based on assumed required PD-L1 receptor occupancy

(RO) of 95% for efficacy [Deng 2016]) and that, consistent with this observation, the probability of response did not depend on Cycle 1 C_{min} in these patients (Stroh 2017). A quantitative systems pharmacology (QSP) model was used to incorporate the effect of Probody therapeutic properties on the C_{min} required for 95% RO in the tumor for CX-072; the QSP model results suggested that the targeted C_{min} would span 13 to 99 nM (2 to 15 µg/mL) for Intact CX-072. Preliminary data from Module CTMX-M-072-001 suggest that ADAs have been observed in patients receiving CX-072, and that a fraction of patients receiving less than 10 mg/kg CX-072 q2w have not maintained targeted C_{min} with repeat dosing. Patients receiving 10 mg/kg CX-072 q2w have maintained C_{min} regardless of ADA status. A subsequent preliminary POPPK model was developed based on available preliminary CX-072 PK data from Module CTMX-M-072-001 as of October 2018. Simulations were conducted using this preliminary POPPK model with virtual patients administered either a weight-based 10 mg/kg dose or a fixed 800 mg dose q2w. The body weights considered in this evaluation were sampled from a distribution with the same geometric mean (76 kg) and standard deviation as the available patient data at the time of this evaluation; the fixed dose of 800 mg is based on this observed weight and rounded to permit an 80 mL dose of a 10 mg/mL solution of CX-072. The distribution of simulated Intact CX-072 area under the plasma concentration-time curve (AUC) and maximal plasma concentration (C_{max}) following the administration of fixed and weight-based exhibits considerable overlap following fixed or weight-based dosing with similar median predicted AUC and C_{max}.

These simulations further suggested that, as with 10 mg/kg CX-072 q2w, patients receiving 800 mg CX-072 q2w would meet or exceed the targeted C_{min} range regardless of ADA status. Collectively, this model-based evaluation does not suggest there would be a clinically meaningful change in exposure following the fixed dose of 800 mg CX-072 q2w (equivalent to the 10 mg/kg q2w weight-based dose) for further investigation.

The fixed dose of 800 mg CX-072 q3w for the CX-072 combination treatments of Parts A and B was informed by preliminary available PK data from Part B1 of Module CTMX-M-072-001, which suggest that patients receiving 10 mg/kg CX-072 q3w × 4 with 3 mg/kg ipilimumab q3w × 4 maintained targeted C_{min} of CX-072.

1.5.2 Selection of Ipilimumab Dose

For Part A (which will enroll subjects with advanced/unresectable or metastatic cancer), the dose of ipilimumab to be used in combination with CX-072 is 3 mg/kg q3w and is based on the MTD of the combination of CX-072 plus ipilimumab determined in Part B1 of Module CTMX-M-072-001 and the approved dose of ipilimumab for use in the advanced/metastatic setting.

For Part B (neoadjuvant design), the dose of ipilimumab to be administered in combination with CX-072 is 1 mg/kg and is based on the dose of ipilimumab currently being assessed in an ongoing study in the neoadjuvant melanoma setting (in combination with nivolumab 3 mg/kg) (Rozeman 2018). In 2 prior studies assessing combination ipilimumab plus nivolumab in the

neoadjuvant setting, the dose of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab resulted in a majority of subjects (90% [Blank 2018] and 73% [Amaria 2018]) experiencing Grade 3 or 4 TRAEs. To minimize risk of toxicity, the dose of ipilimumab that will be combined with CX-072 in the neoadjuvant setting (Part B) will be 1 mg/kg.

1.5.3 Rationale for Sample Size of Cohort A2

Cohort A2 under this amendment (Amendment 2) includes only Stage 1 (n = 40). Stage 2 of Cohort A2 will be implemented in a subsequent amendment after discussion with regulatory agencies to agree on success criteria to establish the proper sample size.

Patients with advanced unresectable or metastatic melanoma who progress on treatment with a PD-1 or PD-L1 checkpoint inhibitor represent an unmet medical need. Available treatment options after PD-1 antibody failure include ipilimumab with or without continued PD-1 inhibition. Prospective controlled data on melanoma treatment following progression on PD-1 inhibitors is lacking. Most of the available data come from retrospective observational studies (n < 100) showing response rates of 14% to 16% for patients treated with single agent ipilimumab and 21% for patients treated with ipilimumab and a PD-1 inhibitor (Long 2017; Zimmer 2017). An overall response rate of 45% was observed among 22 subjects treated with pembrolizumab in combination with ipilimumab. All subjects in the study had experienced prior disease progression during treatment with an anti-PD-1/PD-L1 antibody given as either a single agent or as a non-CTLA-4 antibody–containing combination (Olson 2018)

More recently, data from a prospective observational registration study of 200 melanoma patients who experienced treatment failure on single agent anti-PD-1 antibody were made available (Weichenthal 2019), showing responses in 4.2% of patients who were treated with single agent ipilimumab and in 19.5% of patients who were treated with ipilimumab plus nivolumab. The wide range of reported response rates highlights the uncertainty of determining the expected antitumor effect of CX-072 in combination with ipilimumab in this patient population. A sample size of 40 in Stage 1 of Cohort A2 permits better characterization of the ORR in a prospective manner and increases the power for rejecting the null hypothesis in Stage 1 (Table 9).

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Part A

The primary objective of Part A is to obtain evidence of antitumor effect of CX-072 in combination with ipilimumab in subjects with solid tumors based on ORR as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

2.1.2 Part B

The primary objective of Part B is to obtain evidence of antitumor effect of CX-072 in combination with ipilimumab in subjects with solid tumors based on pathologic response following neoadjuvant administration of combination treatment.

2.2 Secondary Objectives

Part A

The secondary objectives of Part A are to assess:

- Safety and tolerability of CX-072 in combination with ipilimumab in subjects with solid tumors
- Evaluate antitumor activity in subjects with solid tumors treated with CX-072 in combination with ipilimumab based on:
  - ORR by immune-related Response Criteria in Solid Tumours (irRECIST) as defined in the Core (Appendix A)
  - Duration of response (DOR)
  - Time to response (TTR)
  - PFS
  - OS
- Characterize the PK of CX-072 and ipilimumab
- Characterize the incidence of CX-072 ADAs and ipilimumab ADAs

2.2.1 Part B

The secondary objectives of Part B are to assess:

- Safety and tolerability of CX-072 in combination with ipilimumab in subjects with solid tumors
- Evaluate antitumor activity in subjects with solid tumors treated with CX-072 in combination with ipilimumab based on:
  - ORR as defined by RECIST v1.1 prior to surgery
  - RFS
  - OS
- Characterize the PK profile of CX-072 and ipilimumab
- Characterize the incidence of CX-072 ADAs and ipilimumab ADAs

2.3 Exploratory Objectives

The exploratory objectives of Parts A and B are to:

- Evaluate biomarkers potentially capable of predicting a clinical response to combination treatment with CX-072 and ipilimumab
- Evaluate the relationship between CX-072 and ipilimumab combination treatment and exploratory biomarkers, safety, and antitumor activity

3 STUDY DESCRIPTION

3.1 Study Design

This is a Phase 2, multicenter, global, open-label, multi-cohort and parallel-cohort study of PD-L1 Probody therapeutic CX-072 in combination with ipilimumab designed to assess the antitumor effect of combination treatment and to characterize the safety, tolerability, PK, immunogenicity, and biomarkers of combination treatment in subjects with solid tumors.

This Module is comprised of 2 parts and 4 cohorts as follows:

- Part A:
  - Cohort A1: Subjects with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma who have received no prior treatment for unresectable or metastatic melanoma
  - Cohort A2: Subjects with histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma who have experienced progressive disease or relapse following treatment with a PD-1/PD-L1 immune checkpoint inhibitor
  - Cohort A3: Subjects with histologically or cytologically confirmed, advanced/unresectable or metastatic, transitional cell carcinoma of the urothelium who have experienced disease progression during or following treatment with platinum-based therapy
- Part B :
  - Cohort B1: Subjects with histologically confirmed resectable Stage III melanoma with palpable disease suitable for curative surgery

See Figure 1 for a schematic representation of the study design.

3.2 Number of Sites and Subjects

This is a global, multicenter study in approximately 40 sites and up to 162 subjects.

3.3 Subject Enrollment

Enrollment into each cohort will occur in 2 stages:

- Cohorts A1, A3, and B1: Stage 1 will enroll and treat 14 subjects per cohort. Opening of Stage 2 for each cohort will be contingent on the number of confirmed objective responses (Part A) or pathologic responses (Part B) in Stage 1 (see Section 10.1). Additional subjects will be added in Stage 2, for a total of approximately 40 subjects (range: 38 to 48) per cohort.
- Cohort A2: Stage 1 will enroll and treat 40 subjects. Opening of Stage 2 of Cohort A2 will require a subsequent amendment following a discussion with regulatory agencies to agree on success criteria to establish an appropriate sample size.

Subjects will be enrolled using an interactive voice/web response system (IXRS). The investigative site will log into the IXRS to enroll a consented subject. Once assigned, numbers for any screening failures, nontreated, nonevaluable, or discontinued subjects will not be re-used.

3.4 Randomization and Blinding

This is an open-label study. No blinding is needed. Subjects will be enrolled into cohorts based on cancer type; no randomization will be conducted.

3.5 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) and will review all safety information to determine whether the study should continue unchanged or whether protocol modifications are required to ensure subject safety. Details on the DSMB are provided in Appendix B and in a separate DSMB charter. The DSMB will make recommendations to the Sponsor, who will make ultimate decisions regarding study alteration or discontinuation.

3.6 Safety Review Committee

Not applicable.

3.7 Estimated Treatment Duration and Study Periods

In Part A, a subject's treatment may continue until confirmed disease progression (assessed by irRECIST), clinical deterioration as defined by the Investigator, withdrawal of consent, other study treatment withdrawal criteria are met, or until the study is terminated, whichever occurs first. In Part B, a subject's treatment duration will continue until progression as defined by RECIST prior to surgery, disease relapse after surgery, clinical deterioration as defined by the Investigator, withdrawal of consent, other study treatment withdrawal criteria are met, the subject has received CX-072 for 1 year postsurgery, or until the study is terminated, whichever occurs first. In Part B, a subject's treatment duration will be up to approximately 15 months (including 1 year postsurgery).

This Module is comprised of 3 periods:

- The Screening Period begins within 30 days prior to the first dose of study treatment (ie, Cycle 1 Day 1 Visit). Subjects for whom consent is provided will undergo Screening Period assessments to determine eligibility for the study; assessments must be performed within 30 days prior to the first dose of study treatment unless otherwise stated in this Module. Subject evaluations and tests performed specifically to determine eligibility (ie, not performed as routine standard of care) may be performed only after the informed consent form (ICF) has been signed. Assessment(s) done per standard of care prior to signing the ICF may be used for eligibility determination if completed within 30 days prior to the first dose of study treatment. The study assessments to be followed are outlined in the Schedule of Assessments in Table 1 (Part A) and Table 2 (Part B).
- The Treatment Period begins with the first dose of study treatment (ie, Cycle 1 Day 1) and continues up to 30 days after the last dose of study treatment (ie, End of Treatment [EOT] Visit). All scheduling is relative to first dose of study treatment (ie, Cycle 1 Day 1).
- The Follow-up Period begins after the EOT Visit. The first Follow-up Visit will be 90 (±14) days after the last dose of study treatment and will continue every 90 (±14) days to collect survival information and subsequent cancer treatment information. After the first 2 Follow-up Visits, this information may be collected via telephone or e-mail with the subject, designated caregiver, or referring physician offices. Survival status or date of death may be collected from public documents if the subject's status is unknown and attempts to reach the subject are unanswered.

The end of the study (EOS) for an individual subject is defined as death, loss to follow-up, withdrawal of consent, or termination of the study.

Subjects who continue in the Follow-up Period after study completion may rollover to a companion protocol after their last Follow-up Visit, if one is available, for continued observation and follow-up.

3.8 Definition of Study Completion

The study will be completed when the Sponsor has determined that sufficient data have been collected to evaluate the primary and secondary study endpoints. This is anticipated to occur approximately 3 years from when the last subject is enrolled, or when the last subject has completed the EOT Visit.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria for All Subjects (Parts A and B)

Subjects must meet all of the following criteria at Screening to be eligible for admission into the study. See additional cohort-specific inclusion criteria in Sections 4.2, 4.3, 4.4, and 4.5.

1. At least 18 years of age
2. Measurable disease as defined by RECIST v1.1
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
4. Agree to provide tumor tissue and blood samples for biomarker assessment
   - Part A: Must agree to provide mandatory archival tumor tissue (formalin-fixed paraffin embedded tumor block or unstained slides) or undergo a new tumor biopsy
   - Part B: Must agree to provide tumor tissue from the initial diagnostic biopsy and prospectively agree to provide tumor tissue obtained from surgery on study for pathologic analysis and for biomarker assessment
5. Subjects with treated brain metastases are eligible **if** the brain metastases are stable (no magnetic resonance imaging [MRI] evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study treatment) and the subject does not require radiation therapy or steroids. Active screening for brain metastases (eg, brain computed tomography [CT] or MRI) is not required
6. Screening laboratory values must meet all of the following criteria:
   - White blood cells >2000/µL or 2.0×10^9/L
   - Neutrophils ≥1500/µL or 1.5×10^9/L
   - Platelets ≥100×10^3/µL or 100×10^9/L
   - Hemoglobin ≥9.0 g/dL (may have been transfused) or 90.0 g/L
   - Creatinine ≤2 mg/dL or 176.8 µmol/L OR measured or calculated creatinine clearance (glomerular filtration rate can also be used in place of creatinine or creatinine clearance) >50 mL/min
   - AST and ALT ≤2.5 × upper limit of normal (ULN)
   - Total bilirubin within ULN (unless diagnosed with Gilbert's syndrome, those subjects must have a total bilirubin <3.0 mg/dL or 51.3 µmol/L)
   - Amylase and lipase ≤1.5 × ULN
   - 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)
   - Serum albumin ≥2.5 g/dL

7. Females of childbearing potential and nonsterile males must agree to practice highly effective methods of birth control (as described in Appendix C) for the duration of the study and for 6 months after the last dose of study treatment
8. The ability to understand and the willingness to sign a written ICF and adhere to study schedule and prohibitions

4.2 Additional Inclusion Criteria for Cohort A1

9. Histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma
10. Must have BRAF V600 mutation status or consent to BRAF V600 mutation testing in accordance with local institutional standards during Screening Period
11. No prior systemic therapy for metastatic or unresectable disease and deemed to be intolerant to or refused standard first-line therapy for melanoma
    - Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to Screening, and all related AEs have either returned to baseline or stabilized. Prior adjuvant or neoadjuvant therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell costimulation or immune checkpoint pathways is not allowed.

4.3 Additional Inclusion Criteria for Cohort A2

12. Histologically or cytologically confirmed Stage III (unresectable) or Stage IV melanoma
13. Have experienced disease progression during treatment with an anti-PD-1/PD-L1 antibody (including bispecific antibodies) given as monotherapy or in a combination not containing anti-CTLA-4 antibody as the treatment regimen immediately prior to accrual to this study, or have experienced disease progression within 6 months of adjuvant or neoadjuvant anti-PD-1/PD-L1 antibody therapy
    - Progression is defined as radiographic progression, new lesion(s) (detected radiographically or by physical exam), or clinical progression per Investigator assessment
    - Subjects with radiographic progression prior to receiving at least 12 weeks of an anti-PD-1/PD-L1 therapy must have a confirmatory scan showing progression no sooner than 4 weeks after the initial radiographic progression

4.4 Additional Inclusion Criteria for Cohort A3

14. Histologically or cytologically confirmed advanced/unresectable or metastatic urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
15. Experienced disease progression during or after receipt of platinum-containing chemotherapy for metastatic disease or recurrence within 1 year of completing prior platinum-based neoadjuvant or adjuvant therapy. Only 1 prior line of platinum chemotherapy allowed. Subjects who received at least 1 cycle of a platinum-containing regimen but discontinued due to toxicity and who were deemed unsafe to continue with platinum therapy are also eligible.

4.5 Additional Inclusion Criteria for Cohort B1

16. Histologically or cytologically confirmed resectable Stage III melanoma with 1 or more macroscopic lymph node metastases (measurable according to RECIST v1.1) that can be biopsied and no history of in-transit metastases within the last 6 months
17. Lactate dehydrogenase (LDH) within normal range

4.6 Exclusion Criteria for All Subjects (Parts A and B)

Subjects who fulfill any of the following criteria at Screening will **not** be eligible for admission into the study. See additional cohort-specific exclusion criteria in Sections 4.7 and 4.8.

1. Treatment with cytotoxic chemotherapy, biologic agents, radiation, immunotherapy, or any investigational agent within 28 days prior to the first dose of study treatment. This interval can be reduced to 2 weeks for subjects who received bone-only radiation therapy or for subjects whose most recent prior therapy was a single-agent, small-molecule kinase inhibitor having a half-life of 3 days or less.
   – For Cohort A2: Prior anti-PD-1/PD-L1 antibody given as a single agent is not excluded within the 28 days prior to the first dose of study treatment. Time from last dose of prior anti-PD-1/PD-L1 inhibitor to first dose of study treatment must be at least the same length as the time interval of the prior PD-1/PD-L1 dosing schedule (eg, if prior PD-1/PD-L1 dosing was once every 14 days, then the last dose must have been at least 14 days prior to first dose of study treatment).
2. Prior therapy with a chimeric antigen receptor T cell–containing regimen
3. History of active autoimmune disease(s) including but not limited to inflammatory bowel diseases, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, systemic sclerosis, systemic lupus erythematosus, autoimmune vasculitis, autoimmune neuropathies, type 1 insulin-dependent diabetes mellitus
4. History of myocarditis regardless of the cause

5. History of intolerance to prior checkpoint inhibitor therapy defined as the need to discontinue treatment due to an irAE
6. History of toxic epidermal necrolysis or Stevens-Johnson syndrome
7. History of any syndrome or medical condition that required treatment with systemic steroids (≥10 mg daily prednisone equivalents) or immunosuppressive medications. However, subjects who required 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.
8. Baseline corrected QT interval (QTc) >470 ms. If a subject starts on a QTc prolonging drug(s), a series of electrocardiograms (ECGs) should be obtained to redefine the baseline QTc.
9. Unresolved acute toxicity Common Terminology Criteria for Adverse Events (CTCAE) v5.0 ≥Grade 1 (or baseline, whichever is greater) from prior anticancer therapy. Alopecia and other nonacute toxicities are acceptable. Hormone deficiency due to prior anticancer therapy, that is deemed stable with supplementation or does not require supplementation is allowed.
10. History of severe allergic or anaphylactic reactions to human mAb therapy or known hypersensitivity to any Probody therapeutic
11. Subjects with known human immunodeficiency virus, acquired immune deficiency syndrome, or any related illness
12. Subjects with acute or chronic hepatitis B or C
13. History of allogeneic tissue/solid organ transplant, stem cell transplant, or bone marrow transplant
14. Major surgery (eg, that required general anesthesia) within 4 weeks prior to the first dose of study treatment (and must be confirmed to be completely healed), or minor surgery (eg, not involving chest, abdomen, or intracranial structures) or gamma knife treatment (with adequate healing) within 14 days prior to first dose of study treatment (excluding biopsies conducted with local/topical anesthesia) if complete healing is confirmed
15. History of active malignancy not related to the cancer being treated within the previous 2 years, with the exception of localized cancers that are considered cured and, in the opinion of the Investigator, present a low risk for recurrence. These exceptions include, but are not limited to, basal or squamous cell skin cancer, superficial bladder cancer, and carcinoma in situ of the prostate, cervix, or breast.
16. Received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine.

17. Intercurrent illness including, but not limited to:
    - Ongoing severe aortic stenosis
    - Myocardial infarction or stroke within 24 weeks prior to first dose of study treatment
    - Any of the following within 12 weeks prior to first dose of study treatment: symptomatic congestive heart failure (ie, New York Heart Association Class III or IV), unstable angina pectoris, or clinically significant and uncontrolled cardiac arrhythmia
    - Nonhealing wound or ulcer within 4 weeks prior to Cycle 1 Day 1
    - Active infection requiring systemic antiviral, antibiotic, or antifungal therapy within 5 days prior to first dose of study treatment
18. Pleural or pericardial effusion or ascites requiring drainage ≥1 time(s) per month
19. History of multiple myeloma
20. Women who are pregnant or breastfeeding
21. Any condition, in the Investigator's opinion, that would limit the subject's compliance with study requirements
22. Participating in an ongoing interventional clinical study (eg, medication, radiation, procedures) unless the subject is only being followed for long-term outcomes

4.7 Additional Exclusion Criteria for Cohort A1

23. Prior systemic treatment for advanced unresectable or metastatic melanoma and/or deemed suitable for standard first-line therapy
24. Prior adjuvant or neoadjuvant therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T cell costimulation or immune checkpoint pathways
25. Prior adjuvant therapy with a BRAF or mitogen-activated protein kinase (MEK) inhibitor
26. Diagnosis of uveal, ocular, or mucosal melanoma

4.8 Additional Exclusion Criteria for Cohort A2

27. Prior treatment with an anti-CTLA-4 agent
28. Prior treatment with cell-based immunotherapy
29. More than 1 prior line of systemic anticancer therapy for unresectable or metastatic melanoma. Prior treatment with an anti-PD-1/PD-L1 antibody in both neoadjuvant/adjuvant and unresectable/metastatic settings is allowed.
30. Prior treatment with a BRAF or MEK inhibitor
31. Diagnosis of uveal, ocular, or mucocutaneous melanoma

4.9 Additional Exclusion Criteria for Cohort A3

32. Prior treatment with a PD-1/PD-L1 inhibitor or CTLA-4 inhibitor
33. More than 1 prior line of chemotherapy

4.10 Additional Exclusion Criteria for Cohort B1

34. Prior systemic treatment for melanoma
35. Diagnosis of uveal, ocular, or mucocutaneous melanoma

4.11 Study Treatment Discontinuation Criteria

Subjects MUST discontinue study treatment for any of the following reasons:

- The subject experiences confirmed disease progression as assessed by irRECIST (Part A) or disease progression prior to surgery or disease relapse after surgery (Part B)
- 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 adverse event (AE) that precludes further safe administration of study treatment (see also Section 5.3.1)
- The subject becomes pregnant at any time during the study, including prior to the first dose of study treatment
- In the Investigator's judgment, the subject should discontinue study treatment
- The Sponsor terminates the study
- The subject experiences an intercurrent illness that prevents further administration of study treatment
- The subject requires new/other anticancer treatment

5 TREATMENT OF SUBJECTS

5.1 Study Drugs

Study treatment consists of 2 study drugs, CX-072 and ipilimumab. CX-072 is a recombinant, protease-activatable immunoglobulin G subclass 4 (IgG_4) mAb prodrug (Probody therapeutic) that is derived from a human mAb against the ligand PD-L1 and is intended for use in oncology indications.

Ipilimumab is a human CTLA-4 blocking antibody approved for a variety of indications (see the local prescribing information for ipilimumab).

5.1.1 Formulation and Packaging

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 water for injection (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.

Ipilimumab

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for IV infusion, which may contain a small amount of visible translucent to white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL.

The vial and carton labels for each study drug will include standard product information in accordance with applicable regulatory requirements.

5.1.2 Storage and Accountability

It is the responsibility of the Investigator to ensure that the clinical supplies described below are stored as specified and in accordance with applicable regulatory requirements. Drug accountability details are provided in the Core (Appendix A).

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 original carton until time of use. Do not freeze.

Ipilimumab

Store vials upright under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect ipilimumab from light by storing in the original carton until time of use.

5.1.3 Study Drug Preparation and Dispensing

CX-072

In this study, CX-072 is administered at a fixed dose of 800 mg, which is equivalent to the 10 mg/kg weight-based dose. Detailed instructions for dose preparation and recommended devices for administration of CX-072 are described in the Pharmacy Manual.

Recommended safety measures for preparation and handling of CX-072 include laboratory coats and gloves. During dose preparation for IV administration, CX-072 may be stored at room temperature for a period of up to 8 hours under room light. Once CX-072 has been prepared for administration, the total storage time for CX-072 supports 4 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, because the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between CX-072 and polyolefin bags have been observed in compatibility testing.

Ipilimumab

Ipilimumab is supplied as a sterile, preservative-free solution in 10 mL (50 mg) and 40 mL (200 mg) vials at a concentration of 5 mg/mL. Ipilimumab dosing will be based on the subject's weight and dose level assignment. Ipilimumab may be diluted with 0.9% sodium chloride injection, United States Pharmacopoeia (USP) or 5% Dextrose Injection, USP to a final concentration ranging from 1 to 2 mg/mL. Follow the current local ipilimumab prescribing information for detailed instructions.

5.2 Study Drug Administration and Dosing Regimen

5.2.1 Study Drug Administration

800 mg CX-072 is to be infused over 60 minutes. When administered in combination, CX-072 is to be administered first, followed by a saline flush, and then followed by the ipilimumab infusion.

Ipilimumab is to be infused no sooner than 30 minutes after completion of the CX-072 infusion. Ipilimumab infusion times are according to the ipilimumab US package insert:

- 1 mg/kg ipilimumab is to be administered as a 30-minute IV infusion
- 3 mg/kg ipilimumab is to be administered as a 90-minute IV infusion

Study drugs are to 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. Study drugs must be administered under the supervision of a physician or other study personnel experienced in the use of IV agents. See Section 5.3.4.1 for monitoring of IRRs during and after each infusion.

All infusions are to be administered through a nonpyrogenic, low protein binding in-line filter (pore size of 0.2 µm). Following completion of the infusion, flush with an adequate amount of normal saline for infusion. Do not co-administer other drugs concurrently through the same IV line.

5.2.2 Study Treatment Dosing Regimen

CX-072 and ipilimumab are to be administered in this study as follows:

- Part A:
  - Combination treatment: 800 mg CX-072 + 3 mg/kg ipilimumab, q3w
  - Monotherapy treatment: 800 mg CX-072, q2w
- Part B:
  - Combination treatment: 800 mg CX-072 + 1 mg/kg ipilimumab, q3w
  - Monotherapy treatment: 800 mg CX-072, q2w

In Part A, subjects will be treated with 4 doses of 800 mg CX-072 IV plus 3 mg/kg ipilimumab IV combination therapy (ie, q3w on Cycle 1 Day 1, Cycle 1 Day 22, Cycle 2 Day 1 [Study Day 43], and Cycle 2 Day 22 [Study Day 64]; all ±2 days). Three weeks following receipt of the fourth dose of combination treatment (ie, Study Day 85 [±2 days]), subjects will receive 800 mg CX-072 IV monotherapy q2w until the occurrence of progressive disease by irRECIST, unacceptable toxicity, or the subject meets any other criterion for treatment discontinuation (Section 4.11).

In Part B, subjects will be treated with 2 doses of 800 mg CX-072 IV plus 1 mg/kg ipilimumab IV combination (ie, q3w on Cycle 1 Day 1, Cycle 1 Day 22; all ±2 days) followed by surgical resection of the tumor on Day 43 (-2/+7 days). An additional 2 doses of 800 mg CX-072 IV plus 1 mg/kg ipilimumab IV combination will be administered approximately 6 weeks postsurgery (ie, q3w on Cycle 2 Day 1 [Study Day 85 (±2 days)] and Cycle 2 Day 22 [Study Day 106 (±2 days)]). Three weeks following receipt of the fourth dose of combination treatment (ie, Study Day 127 [±2 days]), subjects will have the option to continue with 800 mg CX-072 IV monotherapy q2w following discussion and agreement of risk/benefit between the Investigator and the Sponsor Medical Monitor. Subjects may receive up to 1 year of CX-072 infusions postsurgery (including 2 postsurgery combination doses and then as monotherapy) until the occurrence of disease relapse, unacceptable toxicity, or the subject meets any other criterion for treatment discontinuation (Section 4.11).

A maximum of 4 doses of ipilimumab may be administered to any subject (Parts A and B).

5.3 Treatment Delays, Dose Modification, and Missed Doses

A minimum of 14 days is required between infusions of CX-072 and a minimum of 21 days between infusions of ipilimumab. In exceptional circumstances, an infusion may be delayed for up to 7 days. Infusions that cannot be administered in that time frame will be considered a missed dose, and the subject should come in for the next regularly scheduled visit relative to Day 1.

5.3.1 Dose Modification for Adverse Events

The following guidance is for dose modification of CX-072 and/or ipilimumab (ie, study treatment). Delays or permanent discontinuation of study treatment may be required as outlined in Table 5 and Section 5.3.2. Dose reduction of any study treatment 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.

Additional recommendations for interventions of irAEs depending on severity of the event are provided in Section 5.3.3.

Table 5 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 5.3.3.11	No action; G1 does not apply to severe cutaneous toxicities (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis).	Hold until recovery to ≤G1 or baseline.	Hold until recovery to ≤G1 or baseline. Consult with a dermatologist.	Permanently discontinue study treatment.
Colitis [a] See also Section 5.3.3.1	No action; may consider holding study treatment and resuming if toxicity does not exceed G1	Hold until recovery to ≤G1. Consider permanent discontinuation of ipilimumab. [b]	Hold until recovery to ≤G1. Consider permanent discontinuation of ipilimumab. [b]	Permanently discontinue study treatment.
Increased serum transaminases (AST/ALT) or total bilirubin See also Section 5.3.3.2	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 study treatment.	Permanently discontinue study treatment.
Pneumonitis See also Section 5.3.3.3	No action	Hold until recovery to ≤G1.	Permanently discontinue study treatment	Permanently discontinue study treatment.
Hypothyroidism or hyperthyroidism See also Section 5.3.3.4	No action	Hold until recovery to ≤G1 or baseline.	Hold until recovery to ≤G1 or baseline (with hormone replacement for hypothyroidism).	Permanently discontinue study treatment.
Adrenal insufficiency See also Section 5.3.3.6	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.	Hold until recovery to ≤G1 or baseline with hormone replacement
Hypophysitis See also Section 5.3.3.8	Consider holding study treatment 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.	Hold until recovery to ≤G1 or baseline with hormone replacement
Type 1 diabetes See also Section 5.3.3.7	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.	Hold until recovery to ≤G1 or baseline. Urgent endocrine consultation for all subjects. Initiate insulin therapy for all subjects.

Table 5 Dose Modifications for Select Adverse Events (continued)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	No action; consider holding treatment pending work-up.	Hold until recovery to ≤G1 or baseline. Consult nephrology.	Hold until recovery to ≤G1 or baseline. Permanently discontinue for Grade 3 nephritis.	Permanently discontinue study treatment.
Pancreatitis	Monitor for symptoms and laboratory abnormalities.	Hold until recovery to ≤G1 or baseline.	Hold until recovery to ≤G1 or baseline.	Permanently discontinue study treatment.
Myocarditis See also Section 5.3.3.5	NA	For any clinical suspicion, refer to cardiologist for workup, diagnosis, and treatment. Hold study treatment and contact Sponsor Medical Monitor to discuss discontinuation of study.		
Encephalitis or meningoencephalitis See also Section 5.3.3.10	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.			
Ocular inflammatory toxicity (eg, uveitis, conjunctivitis, orbital inflammation, episcleritis) See also Section 5.3.3.9	Refer to ophthalmology.	Hold until recovery to ≤G1 or baseline. Refer to ophthalmology.	Permanently discontinue study treatment. Refer to ophthalmology.	Permanently discontinue study treatment. Refer to ophthalmology.
Guillain-Barré 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 5.3.3.12	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 study treatment.

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

[b] After consultation with Sponsor Medical Monitor.

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

Delays in CX-072 treatment will also result in a delay of ipilimumab.

Resume study treatment in subjects whose adverse reactions recover to Grade ≤1 or baseline, at the discretion of the Investigator unless otherwise stated in Table 5 and/or Section 5.3.3.12.

Refer to the current local package insert for ipilimumab for common adverse reactions, black box warnings, dose modification, and other information pertaining to the management of AEs associated with ipilimumab treatment.

5.3.2 Study Treatment Discontinuation for Adverse Events

Permanent discontinuation of study treatment may be required as dictated in Table 5.

If CX-072 is discontinued, ipilimumab will also be discontinued.

If ipilimumab is discontinued, treatment with CX-072 may continue/resume after discussion and agreement between the Investigator and the Sponsor Medical Monitor that this would be in line with risk benefit for the individual subject.

Study treatment 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 treatment-related adverse reactions that do not recover to Grade ≤1 or baseline or resolve within 12 weeks after the last dose of study treatment

For adverse reactions that do not recover within 12 weeks, the Investigator must contact the Sponsor Medical Monitor to determine if the subject should be permanently withdrawn from study treatment or if a longer period of waiting for resolution is warranted.

5.3.3 Management of Immune-related Toxicity

All AEs should be monitored and managed according to standard of care. Refer to "Management of Immune-related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor 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 in accordance with standard of care.

5.3.3.1 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 of treatment to confirm toxicity does not exceed Grade 1. Withhold study treatment 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 and should consider permanent discontinuation of ipilimumab. 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 1.0 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, 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 treatment for Grade 4 or recurrent colitis upon restarting study treatment.

5.3.3.2 Immune-related Hepatitis

Monitor subjects for abnormal liver tests prior to and periodically during treatment. 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, hold study treatment, 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. Study treatment 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, 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 for Grade 3 or Grade 4 immune-related hepatitis.

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

5.3.3.3 Immune-related Pneumonitis

Monitor subjects for signs and symptoms of pneumonitis. Subjects with Grade 1 pneumonitis should be monitored weekly and treatment should be held if there is radiographic evidence of pneumonitis progression. Treatment 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 study treatment for Grade 2 immune-related pneumonitis and permanently discontinue treatment for Grade 3 or 4 or recurrent pneumonitis upon restarting study treatment.

5.3.3.4 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.

For Grade 1 hypothyroidism, treatment may be continued with close follow-up and monitoring of TSH and FT4. For Grade 2 hypothyroidism, treatment 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, treatment 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 treatment 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, study treatment 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, treatment 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.

5.3.3.5 Immune-related Myocarditis

Monitor subjects for myocarditis prior to and periodically during treatment. For all grades of myocarditis, permanent treatment discontinuation should be discussed. Cardiology should be consulted, 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 for any >Grade 2 myocarditis.

5.3.3.6 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 CT scan for metastasis/hemorrhage. For Grade 1 adrenal insufficiency, treatment may be held until subject is stabilized on replacement hormone. Withhold study treatment 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.

5.3.3.7 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 study treatment for Grade 2, Grade 3, or Grade 4 events, perform urgent endocrine consultation for all subjects, and initiate insulin therapy for all subjects. Hold treatment until glucose control is obtained on therapy with reduction of toxicity to ≤Grade 1.

5.3.3.8 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, FSH, LH, testosterone, estrogen) as clinically indicated. Consider brain imaging (pituitary/sellar cuts) if clinically indicated. Consider holding study treatment for Grade 1 events until subject is stabilized on replacement therapy. Withhold study treatment 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.

5.3.3.9 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 study treatment 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 study treatment after return to ≤Grade 1. Permanently discontinue for Grade 3 and Grade 4 uveitis or episcleritis. Blepharitis does not have a formal grading system. Treatment includes warm compresses and lubrication drops. Study treatment may continue unless the event is persistent and/or serious.

5.3.3.10 Immune-related Encephalitis or Meningoencephalitis

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

5.3.3.11 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.

5.3.3.12 Other Immune-related Adverse Reactions

For any suspected immune-related adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold study treatment, 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 study treatment 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.

5.3.4 Monitoring and Management of Infusion-related Reactions (IRRs)

5.3.4.1 Monitoring of IRRs

Subjects will be monitored for IRRs, including monitoring of vital signs as outlined in Footnote 13 of Table 1 (Part A) and Footnote 16 of Table 2 (Part B), during and after each study treatment infusion.

For the first 2 infusions of study treatment, subjects will be monitored for 4 hours after the completion of each infusion.

If no IRRs are noted during or after the first 2 infusions, monitoring for irAEs and vital signs will continue for 1 hour after the completion of each subsequent infusion.

After the first 2 infusions, monitoring beyond 1 hour after the infusion will be at the Investigator's discretion and in accordance with the investigational site's standard protocol.

5.3.4.2 Management of IRRs

Subjects should not receive any premedication prior to study treatment infusion, unless the Sponsor determines that the occurrence of IRRs warrants routine prophylactic treatment (which may include paracetamol/acetaminophen, histamine antagonists, and/or corticosteroids). Any subject who experiences an IRR should receive premedication (antipyretics and/or antihistamines) prior to receiving subsequent study treatment infusions. Additional premedication should be used only after review with the Medical Monitor.

Discontinue study treatment for a Grade 4 IRR or an IRR that is directly related to a Grade 4 AE.

If a ≥Grade 2 IRR is observed during or after an infusion, a local blood draw is required to measure tryptase, total immunoglobulin E, and complements C3a and C5, preferably within 2 hours and not more than 6 hours after the first signs/symptoms of the IRR.

For all allergic (hypersensitivity) reactions, including IRRs, that occur during or after study treatment administration, follow the guidelines in Table 6.

If anaphylaxis occurs (see diagnostic criteria in Appendix D), appropriate medical therapy in accordance with institutional standard of care must be administered immediately, and study treatment must be permanently discontinued.

Table 6 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 treatment 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 mg to 1000 mg PO; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. • Once symptoms have resolved, continuation of treatment is allowed with a 50% reduction of the original infusion rate; 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 treatment 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 treatment. Begin an IV infusion of normal saline, and treat the subject as follows: • Recommend **bronchodilators**, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10000 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 treatment 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.
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; PD-L1 = programmed death ligand 1; PO = *per os,* by mouth.

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).

5.4 Treatment Compliance

Study treatment will be administered only by qualified and trained study personnel at the study site. The infusion date and start and stop times will be recorded in the source documents and electronic case report form (eCRF).

5.5 Product Complaints

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

If the solution is cloudy, is discolored, or contains visible particulate matter, the product must be quarantined under the specified storage conditions, and the deficiency must be reported 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.

Return of the product must be recorded on the Drug Accountability Log to ensure complete tracking of drug supply.

5.6 Prior and Concomitant Medications and/or Procedures

Medications taken within 30 days prior to the administration of study treatment and all concomitant medications and therapies administered up to the EOT Visit will be recorded in the relevant eCRF. After EOT, only concomitant medications administered for treatment of reported irAEs, AEs ≥Grade 3, and SAEs will be recorded. All anticancer treatments will be reported until the end of the study.

1. 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 be at nonimmunosuppressive doses (<10 mg per day of prednisone or equivalent prior to the next study treatment administration). The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.
2. The use of herbal remedies for the purpose of treating the subject's cancer (eg, herbal preparation in Chinese traditional medicine), other marketed anticancer chemo/immunotherapy/hormonal drugs, or investigational drugs is not permitted.
3. Vitamins and nutritional supplements are not prohibited.
4. New chemotherapy, hormonal, radiation, or immunotherapy are not permitted during the screening or treatment periods.
5. Palliative/therapeutic therapies (eg, focal radiotherapy for pain, thoracentesis or paracentesis for comfort) are permitted after consultation with the Medical Monitor.

6. Co-administration of bisphosphonates and denosumab is permitted for subjects being administered bisphosphonates and denosumab prior to the study and confirmed to be on a stable dose. These drugs should be continued at the same dose during the study.
7. The use of live vaccines while on study treatment is prohibited. 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 Treatment Period must be documented on the subject's records and in the eCRF.

Any new anticancer therapies (eg, chemotherapy, biochemotherapy, radiation, immunotherapy, or any investigational treatment) for the treatment of the subject's cancer should be recorded in the eCRFs. Note that new anticancer therapies may only be administered after the last dose of study treatment.

6 RESPONSE ASSESSMENTS

Refer to Section 10.2 of the Core (Appendix A) for complete instructions regarding response assessments.

The Sponsor or designee will collect all study scans for possible independent review and analysis. Skin lesions must be photographed along with a ruler at all time points for tumor assessments.

6.1 Part A

- The primary criterion for defining evidence of anticancer activity is RECIST v1.1. The criterion for management of subject care and treatment discontinuation is irRECIST.
- Tumor assessments will be completed by CT or MRI at Screening, q8w (±1 week) from Cycle 1 Day 1 for 12 months, and q12w (±1 week) thereafter until confirmed progression as assessed by irRECIST.
- Any subject with a complete response or partial response is to have repeat assessments performed as early as 4 weeks after initial observation of response to confirm the response as defined by RECIST 1.1
- At the first occurrence of progressive disease, as defined by RECIST 1.1, the baseline is reset and overall response as assessed by irRECIST will be noted as immune-related stable disease. Immune-related progressive disease is determined only if an increase in tumor burden of 20% relative to the new baseline is observed on a subsequent tumor assessment.

6.2 Part B

- The primary criterion for defining evidence of anticancer activity is pathologic response based on central review of tumor sample from surgical resection. The criteria for management of subject care and treatment discontinuation are radiographic response assessment (prior to surgery), local pathologic assessment of surgical sample after surgery, or disease relapse. Tumor response, as defined by RECIST v1.1, will be assessed prior to surgical resection; however, responses will not be confirmed because the tumor assessment will be followed by surgical resection.
- Pathologic analysis of the resected tumor will be conducted by central review and according to the International Neoadjuvant Melanoma Consortium (INMC) scoring system (Tetzlaff 2018)
  - Pathologic complete response (pCR): Complete absence of viable tumor
  - Major pathologic response/near pCR: >0% but <10% of viable tumor in the treated tumor bed
  - Pathologic partial response (pPR): ≤50% of the treated tumor bed is occupied by viable tumor cells
  - Pathologic nonresponse (pNR): >50% of the tumor bed occupied by viable tumor cells
- Relapse is defined as the recurrence of melanoma locally, regionally, with distant metastasis, or with a new primary lesion
- Tumor assessments will be completed by CT or MRI at Screening, prior to scheduled surgical resection (ie, Cycle 1 Day 40 ±2 days), after completion of combination treatment following surgery (ie, Cycle 2 Day 22 [Study Day 106] ±2 days), and then every 12 (±1) weeks until relapse. After 3 years, tumor assessments will be performed according to standard of care.
- Prior to surgical resection, responses noted at the time of the tumor assessment will not be confirmed by a subsequent tumor assessment because the subject will undergo surgery following the presurgical tumor assessment

7 SAFETY ASSESSMENTS

Incidence and nature of AEs and SAEs (as assessed according to CTCAE Version 5.0) as well as physical examinations, vital sign measurements, ECGs, clinical laboratory evaluations, and treatment discontinuation due to toxicity will be evaluated for safety assessment. Safety assessments will also include tests for immunogenicity as described in Section 8.3.

Safety assessments will be performed in accordance with the Schedule of Assessments Table 1 (Part A) and Table 2 (Part B). Refer to the footnotes below the tables, applicable sections with this Module, and the Core (Appendix A) for a description of each procedure.

Subjects will continue to be monitored for irAEs, AEs ≥Grade 3, and SAEs up to 90 days following their last dose of study treatment. Toxicity management may require additional visits at the discretion of the Investigator. Additional follow-up will occur for subjects with ongoing AEs, SAEs, or AEs of special interest (AESIs) unless events have returned to baseline or stabilized.

8 PHARMACOKINETIC, IMMUNOGENICITY, AND EXPLORATORY BIOMARKER ASSESSMENTS

8.1 Pharmacokinetic Assessments

Concentration versus time data will be tabulated and plotted for the individual and mean serum total and intact CX-072 moieties. C_{max} and C_{min} will be tabulated individually and summarized using descriptive statistics (eg, mean, standard deviation, and coefficient of variation).

Ipilimumab C_{max} and C_{min} will be summarized using descriptive statistics.

Population PK (POPPK) analysis of the data may be performed as warranted by the data and results of the analysis will be reported separately.

8.2 Pharmacokinetic Sample Collection

Samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion (see Schedule of Assessments Table 1 [Part A] and Table 2 [Part B]). The schedule of PK blood sampling for both Part A and Part B can be found in Table 3; the times noted are predose or at the end of infusion (EOI).

The date and time of each dose administered and the times at which PK samples are collected must be recorded in the eCRF. If the infusion was interrupted, the reason for interruption will also be documented in the eCRF, and a sample will be collected at the EOI.

8.3 Immunogenicity Assessments

Serum samples will be collected to assess the immunogenicity of CX-072 and ipilimumab (Schedule of Assessments Table 1 [Part A] and Table 2 [Part B]). All samples will be initially screened for ADAs. If the sample is found to be ADA positive in the screening assay, a confirmatory assay will be performed. Confirmed ADA positive samples will be evaluated with a titer assay and may be further characterized for the presence of neutralizing or domain-specific ADA.

8.4 Exploratory Biomarker Assessments

The overall goal of the biomarker portion of Module CTMX-M-072-002 is to explore potential predictive markers associated with CX-072 clinical activity. Exploratory studies will evaluate the following:

- The presence of PD-L1 in tumors
- The tumor mutation burden (TMB) in circulating tumor DNA
- The T cell receptor (TCR) repertoire in peripheral blood mononuclear cells
- Circulating exploratory biomarkers including, but not limited to PD-L1 exosome

8.5 Exploratory Biomarker Collection

To address the above objectives, archival tumor tissue and blood samples will be collected at various time points as shown in the Schedule of Assessments Table 1 (Part A) and Table 2 (Part B).

8.5.1 Tumor Tissue

In Part A, tumor samples for biomarker assessments will be collected during Screening (archival or fresh biopsy). Fresh biopsies are required for subjects who do not have archival tumor samples and optional for subjects with accessible lesions that can be safely biopsied. The most recently obtained tumor sample should be provided for analysis.

In Part B, archival tumor samples from the initial diagnostic biopsy will be collected during Screening. Tumor tissue from surgical resection (including resected lymph nodes) during the study will also be collected.

Histopathology reports for the corresponding tumor samples will be collected. If available, findings from pathological diagnosis will be recorded, including but not limited to melanoma subtype, margin status, Breslow thickness, Clark level, mitoses, ulceration status, and IHC marker information (eg, s-100, MART-1, HMB-45, SOCX10).

8.5.2 Blood Samples

Blood collection is mandatory for all subjects. Samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. The full schedule of biomarker blood sampling can be found in Schedule of Assessments Table 1 (Part A) and Table 2 (Part B).

The date and time of each dose administered and the times at which blood biomarker samples are collected must be recorded in the eCRF.

The technical details for the collection of specimens are outlined in the study laboratory manual.

9 ADVERSE EVENTS/ SERIOUS ADVERSE EVENTS AND REPORTING

9.1 Adverse Events

An AE is defined as any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

All AEs within the reporting period (as defined below) are to be recorded in the AE eCRF. Nonserious AEs prior to initiation of study treatment will be recorded as medical history. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of terms relating to a diagnosis.

The reporting period for AEs is as follows:

- After the ICF is signed but prior to the initiation of study treatment, only SAEs will be reported
- After the ICF is signed and the first administration of study drug, all nonserious AEs and SAEs are reportable and continue to be reported up to 30 days after the last dose of study drug
- During the Follow-up Period, AE reporting is limited to irAEs, AEs ≥Grade 3, and SAEs occurring up to 90 days after last dose of study drug

After the defined AE reporting period, all SAEs assessed as related to study treatment will be reported to the Sponsor. At the last scheduled visit, the Investigator must instruct each subject to report to the Investigator and/or Sponsor or designee, any subsequent SAE that the subject's personal physician(s) believes might be related to prior study treatment. The Investigator must notify the study Sponsor or designee of any death or SAE that may have been related to prior study treatment.

For this Module, disease progression is an efficacy endpoint and in and of itself is not considered an AE or SAE unless disease progression results in death. Death that occurs during the AE reporting period (as defined above), that is attributed solely to disease progression of the

condition, will be recorded in the AE eCRF as a Grade 5 AE (regardless of attribution to study treatment). Deaths reported as SAEs due to progressive disease and considered not related to study treatment will be excluded from TEAE analysis.

All AEs (including SAEs), whether or not related to study drug, must be fully and completely documented using precise medical terminology in the applicable eCRFs (eg, AE eCRF, drug dispensation eCRF).

9.1.1 Serious Adverse Events

An SAE is any untoward medical occurrence with any of the following outcomes:

- Death
- Life-threatening: An AE 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 that, had it occurred in a more severe form, might have caused death.
- Requires or prolongs inpatient hospitalization
  - Note: examples of visits to a hospital facility that do not meet the seriousness criteria for hospitalization include outpatient surgery, preplanned or elective procedures, protocol-specified procedures (eg, administration of study drug)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect in the child or fetus of a subject exposed to the investigational product prior to conception or during pregnancy
- An important medical event, based on medical judgement, 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)

9.1.2 Unexpected Adverse Events

An AE is considered "unexpected" if either of the following occur:

- If the event is not listed in the IB or is not listed at the specificity or severity that has been observed
- If an IB is not required or available, the event is not consistent with the risk information described in the general investigational plan or elsewhere in the clinical trial 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. For this Module, unexpectedness will be determined by the Sponsor using the IB as a reference.

For ipilimumab, refer to the current local prescribing information (eg, US package insert Sections 5 and 6 or European Medicines Agency summary of product characteristics Section 4.8) for reference safety information and other information pertaining to AEs associated with ipilimumab treatment.

9.2 Adverse Event Classification

9.2.1 Relationship to Investigational Drug

The Investigator's assessment of causality must be provided for all AEs, serious and nonserious and recorded in the AE eCRF. The causality of each AE should be assessed and classified by the Investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). Several factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study drug(s)/study procedure
- Whether alternative etiology can be identified that could cause AE
- Mechanism of action of the study drugs
- Biological plausibility

9.2.2 Severity

The severity of an AE 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 CTCAE Version 5.0. If the CTCAE Version 5.0 does not apply, the severity descriptions in Table 7 will be used to determine the severity of the AE.

Table 7 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

9.3 Exposure In Utero

Subjects will be instructed to notify the Investigator if the subject or subject's partner becomes pregnant during the study or within 6 months after the last dose of study drug. The Investigator must notify the Sponsor within 24 hours via the Pregnancy Notification Form (preferred). If it is not possible to report the pregnancy via the Pregnancy Notification Form, telephone or email will be acceptable to meet the 24-hour reporting requirement. 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 and submitted to the Sponsor when the outcome of the pregnancy is known.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (eg, spontaneous abortion, elective abortion, or birth defect), the Investigator should follow the procedures for reporting an SAE.

9.4 Monitoring of Adverse Event Data

Individual subject safety will be assessed by the Investigator on an ongoing basis. AE data will be monitored and reviewed at regular intervals by the Sponsor to assess for any emerging safety signals or trends.

AEs occurring during the reporting period (defined in Section 9.5) should be followed until resolution to baseline status, stabilization, or initiation of a new anticancer therapy.

Proper instruction regarding AESIs will be provided to each site to ensure prompt reporting and communication between the Sponsor, Investigators, the US Food and Drug Administration (FDA), and other applicable regulatory agencies or health authorities.

For SAEs, the Investigator must complete the SAE form electronically in the electronic data capture (EDC) system for the study with as much information as possible and submit it within the time frame described in Section 9.6. 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, as applicable. 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 medical file.

All AEs considered to be related (definitely, probably, or possibly related) 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.

9.5 Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally to identify AEs during the course of the study. Any nonserious AEs occurring after signing the ICF and prior to administration of the first dose of study drug will be recorded in the medical history eCRF. Events occurring after administration of the first dose of study drug will be recorded in the AE eCRF. AEs that occur up to 30 days after administration of the last dose of study drug must be reported as AEs in the EDC system. Additionally, all irAEs, AEs ≥Grade 3, and SAEs that occur up to 90 days after administration of the last dose of study drug must be reported in the EDC system. See also Section 9.6 for reporting of SAEs.

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 in the AE eCRF. 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.

Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the AE eCRF. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus rather than hyperglycemia). 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
- The test finding is considered an AE by the Investigator

If an abnormal laboratory value is recorded as an AE, then the corresponding laboratory value must be marked clinically significant in the EDC system. Similarly, if an abnormal laboratory value is marked clinically significant in the EDC system, it should be recorded as an AE.

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 and the Core (Appendix A). Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (eg, diabetes mellitus rather than hyperglycemia).

9.6 Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction Reporting

Information on suspected unexpected serious adverse reactions (SUSARs) will be distributed to the relevant regulatory agencies, health authorities, institutional review board (IRB)/independent ethics committee (IEC), and investigational sites.

9.6.1 Investigator Reporting to the Sponsor

All SAEs that occur after the ICF is signed and up to 90 days after administration of the last dose of study drug must be recorded in the AE eCRF within 24 hours of knowledge of the occurrence (this refers to any AE that meets any of the criteria in Section 9.1.1, regardless if it is considered related to study drug). SAEs occurring more than 90 days after the last dose of study drug must be reported only if assessed as related to study drug.

To report the SAE, the Investigator must record the relevant information in the AE eCRF and any other applicable information in the relevant eCRF (eg, drug dispensation eCRF, applicable laboratory eCRF). If the event meets serious criteria and it is not possible for the site to access the EDC system, the site must complete the paper SAE reporting form and email or fax it to ICON Safety using the email or fax number listed in Table 8, all within 24 hours of awareness. When the EDC system becomes available, the site must enter the SAE information into the EDC, exactly as it was recorded on the paper SAE reporting form, within 24 hours of the system becoming available.

Table 8 Safety Contact Information: ICON Clinical Research

	Safety/SAE Hotline – USA	Safety/SAE Hotline – Europe/Asia Pacific
Telephone	+1 888-426-8801	+1 281-295-4889
Fax	+1 215-616-3096	+44 (0) 208-100-5005
e-mail	icon-mads@iconplc.com	icon-safety-centralreceipt@iconplc.com

For all SAEs, the Investigator is obligated to obtain and provide information to the Sponsor and ICON Safety in accordance with the time frames 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 in the AE eCRF or back-up paper 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 an 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 death certificate and summary of available autopsy findings (as applicable) must be submitted as soon as possible to the Sponsor or its designee.

9.6.2 Serious Adverse Event Follow-up

The Investigator must continue to follow the subject until the SAE has subsided; until the condition becomes chronic in nature or stabilizes (in the case of persistent impairment); until the subject withdraws consent, is lost to follow-up, or dies; or until it has been assessed that study treatment/procedure is not the cause of the SAEs.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system and, if requested, must submit any supporting documentation (eg, subject discharge summary or autopsy reports) to ICON Safety via Safety fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined in Section 9.6.1 for initial reporting of SAEs.

9.6.3 Reporting to Regulatory Agencies and Institutional Review Boards/Independent Ethics Committees

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

All other SUSARs will be reported to the FDA, competent authorities in all the countries concerned, and the central IRB/IEC, as applicable, as soon as possible but no later than 15 days after first knowledge by the Sponsor.

The Sponsor will inform all Investigators in accordance with applicable regulatory requirements, with instructions to submit to local IRBs/IECs in accordance with applicable requirements.

9.7 Rapid Notification of Adverse Events of Special Interest

In addition to SAEs, the following AESIs will be recorded in the AE eCRF within 24 hours of site awareness irrespective of seriousness, severity, or causality:

- IRRs ≥Grade 2
- Any potential Hy's Law case (>3 × ULN of either ALT/AST with concurrent >2 × ULN of total bilirubin and lack of alternate etiology)
- Any irAEs defined as AEs requiring the use of systemic corticosteroids (or other immune-suppressive therapy) within 30 days after the AE onset date with no clear alternative etiology, or requiring the use of systemic hormonal supplementation. Examples may include, but are not limited to:
  - 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)
  - Ocular toxicities (eg, uveitis)
  - Skin reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis
  - Diarrhea

Refer to Section 9.6 and the Core (Appendix A) for reporting SAEs and AESIs.

9.8 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 treatment administration) should be reported as AEs.

For this protocol, disease progression is an efficacy endpoint and in and of itself is not considered an AE or SAE unless disease progression results in death. Death that occurs during the AE reporting period (as defined above) that is attributed solely to disease progression of the condition will be recorded in the AE eCRF as a Grade 5 AE (regardless of attribution to study

treatment). Deaths reported as SAEs due to progressive disease and considered not related to study treatment will be excluded from TEAE analysis.

10 STATISTICAL METHODS AND CONSIDERATIONS

10.1 Sample Size Determination

The study is envisioned as a Simon's Two-Stage design (Simon 1989). Table 9 outlines the assumptions used for the Simon's Two-Stage design, with a targeted one-sided alpha of 5% and power of at least 80%. The Simon's Two-Stage design allows termination in a tumor type if CX-072 plus ipilimumab is ineffective based on an interim analysis at the end of Stage 1, which is anticipated to occur no earlier than 4 months after the first dose of study treatment of the last subject in Part A and no earlier than 7 months after the first dose of study treatment of the last subject in Part B (corresponding to 4 months after initiating the second dose of combination study treatment). Calculations were performed using EAST v6.4.1. The final (primary) analysis will be based on the entire study population, anticipated to occur 4 months after the first treatment of the last subject. The cohort will be considered a success if the number of responders meets or exceeds the specified success criteria in Table 9.

For Cohort A2 under this amendment (Amendment 2), only Stage 1 is included (n = 40). Stage 2 of Cohort A2 will require a subsequent amendment following a discussion with regulatory agencies to agree on success criteria to establish an appropriate sample size. Enrollment in Cohort A2 cannot exceed the number specified in Stage 1 of the envisioned Simon 2-stage design as noted in Table 9.

Table 9 Criteria for Expansion From Stage 1 to Stage 2 Under Simon's Two-Stage Design With 5% One-sided Alpha and ≥80% Power

Cohort	Null Hypothesis (ORR)	Alternative Hypothesis (ORR)	Power	Stage 1 Sample Size (n)	Stage 1 Rejection Criteria [a]	Entire Sample Size (n)	Study Success Criteria [b]
A1	28%	48%	80%	14	≤4	42	≥17
A2	10%	24%	98%	40	≤4	TBD [c]	TBD [c]
A3	15%	35%	85%	14	≤2	38	≥10
B1	61%	80%	80%	14	≤9	42	≥31

[a] Stage 1 rejection criteria means that if *x* or fewer responses are observed, enrollment in that indication is stopped.

[b] Study success criteria means that if *y* or more responses are observed, then the null hypothesis can be rejected.

[c] Stage 2 of Cohort A2 will require a subsequent amendment following discussion with regulatory agencies to agree on success criteria to establish an appropriate sample size.

Notes: Numbers refer to response-evaluable subjects. The design for Cohort A3 is based on an admissible design proposed by Jung et al (Jung 2004). All other designs are based on the optimal design proposed by Simon (Simon 1989).

ORR = objective response rate; TBD = to be determined.

10.2 Statistical Analyses

Analyses will be conducted by cohort and may be conducted overall. Statistical assessments/methods for safety, efficacy, PK/pharmacodynamics (PD), and immunogenicity are found in the Core (Appendix A). Additional endpoints will include, but are not limited to, the following endpoints: frequency of AESIs and percentage of reduction in tumor burden.

For Part B1, the proportion of subjects with pCR, major pathologic response/near pCR, and pPR will be summarized by count and percentage using the safety analysis population. In addition, a 95% CI based on the method of Koyama and Chen (Koyama 2008) will be provided. This method is appropriate because it is proposed for Simon's 2-stage design, accounting for the inherent futility analysis. Subjects who, after neoadjuvant therapy, are deemed by the Investigator to be ineligible for surgery due to progression or toxicity will be considered as non-responders.

RFS, assessed in subjects who undergo surgical resection, is defined as the time from resection until the date of the first recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurs first (Weber 2017). A subject who dies without reported recurrence will be considered to have recurred on the date of death. For subjects who remain alive and whose disease has not recurred, RFS will be censored on the date of last disease assessment. For those subjects who remain alive and have no recorded postsurgery disease assessment, RFS will be censored on the day of surgery. Censoring rules for the analysis of RFS are presented in Table 10. RFS curves, RFS medians with 95% CIs, and RFS rates at 6, 12, 18, 24, and 36 months with 95% CIs will be estimated using Kaplan-Meier methodology and may be stratified by PD-L1 status and/or disease stage.

Table 10 Censoring Scheme for Relapse-free Survival

Scenario	Date of Event of Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of surgery	Event
No postsurgery disease assessment	Date of surgery	Censored
No postsurgery disease assessments and no death	Date of surgery	Censored
No recurrence and no death	Date of last disease assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day of disease assessment	Date of last disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-melanoma primary cancer reported prior or on the same day of disease assessment	Date of last disease assessment prior to or on the same date of diagnosis of second nonmelanoma primary cancer	Censored

A separate statistical analysis plan (SAP) will be generated and additional details will be specified within the SAP. In instances where the SAP might contradict the analyses specified in this Module and/or the Core (Appendix A), the SAP supersedes the Module and Core.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

This study will be conducted in accordance with the current clinical protocol as approved by the applicable IRB/IEC, ICH Good Clinical Practice Guidelines, and other applicable regulatory requirements.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will meet all applicable regulatory requirements. governing IRBs.

The Investigator will provide the Sponsor or its designee with documentation of IRB/IEC approval of the following documents before the study begins at the study site(s) managed by the Investigator: Module, Core, ICF, and any other relevant materials intended for or directed to subjects (eg, subject diaries, advertisements). The Investigator will supply the Sponsor with documentation 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 using the ICF 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 applicable regulatory requirements for the protection of human subjects.

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 receipt of detailed information on the study. It is the responsibility of the Investigator to obtain consent 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 procedures performed under this protocol, including screening tests and evaluations.

All ICFs used for this Module 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.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Core or Module Amendments

Changes to the conduct of the study will be prepared by the Sponsor as an amendment to this Module and/or the Core (Appendix A) and will be implemented only upon joint approval of the Sponsor or its designee 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 study (eg, change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the change(s) and will subsequently notify the regulatory authorities and/or the IRB/IEC, as appropriate.

12.2 Address List

12.2.1 Sponsor

CytomX Therapeutics, Inc.
151 Oyster Point Boulevard, Suite 400
South San Francisco, CA 94080-1913
USA
Telephone: +1 650-515-3185
Fax: +1 650-351-0353

12.2.2 Contract Research Organizations

ICON Clinical Research Ltd
South County Business Park
Leopardstown
Dublin 18
D18 X5R3
Ireland

Syneos Health, LLC
1030 Sync Street
Morrisville, NC 27560
USA

13 REFERENCES

Amaria RN, Reddy SM, Tawbi HA, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. Nat Med. 2018;24(11):1649-1654.

Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36):6199-6206.

Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nat Med. 2018;24(11):1655-1661.

Boni V, Garcia-Corbacho J, Ott PA, et al. Preliminary results of PROCLAIM-CX-072: the first-in-human, dose-finding trial of PD-L1 Probody therapeutic CX-072 as monotherapy in patients with advanced solid tumors. Presented at: European Society for Medical Oncology (ESMO) Annual Congress; October 19-23, 2018; Munich, Germany.

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36(17):1714-1768.

Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol. 2012;13(6):589-597.

Clinical Trial Facilitation Group (CTFG). Heads of Medicines Agency (HMA) website. Recommendations related to contraception and pregnancy testing in clinical trials. 2014. Available at: http://www. hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. Accessed February 22, 2019.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs. 2016;8(3):593-603.

Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med. 2018;378(19):1789-1801.

Frazier KS, Engelhardt JA, Fant P, et al. Scientific and regulatory policy committee points-to-consider paper: drug-induced vascular injury associated with nonsmall molecule therapeutics in preclinical development: Part I. Biotherapeutics. Toxicol Pathol. 2015;43(7):915-934.

Gopalakrishnan D, Koshkin VS, Ornstein MC, Papatsoris A, Grivas P. Immune checkpoint inhibitors in urothelial cancer: recent updates and future outlook. Ther Clin Risk Manag. 2018;14:1019-1040.

Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. J Clin Oncol. 2017;35(34):3851-3858.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti–PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528): 563-567.

Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-1492.

Jangigian YY, Bendell J, Calvo E, et al. CheckMate-032 study: efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with metastatic esophagogastric cancer. J Clin Oncol. 2018;36(28):2836-2844.

Jung SH, Lee T, Kim K, George SL. Admissible two-stage designs for phase II cancer clinical trials. Stat Med. 2004;23:561-569.

Karlsson AK, Saleh SN. Checkpoint inhibitors for malignant melanoma: a systematic review and meta-analysis. Clin Cosmet Investig Dermatol. 2017;10:325-339.

Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008;27(16):3145-3154.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23-34.

LeBeau AM, Lee M, Murphy ST, et al. Imaging a functional tumorigenic biomarker in the transformed epithelium. Proc Natl Acad Sci U S A. 2013;110(1):93-98.

Lipson EJ, Forde PM, Hammers HJ, Emens LA, Taube JM, Topalian SL. Antagonists of PD-1 and PD-L1 in cancer treatment. Semin Oncol. 2015;42(4):587-600.

Long CV, Robert C, Arance A, et al. Antitumor activity of ipilimumab after pembrolizumab in patients with advanced melanoma in KEYNOTE-006. Eur J Cancer. 2017;72(Suppl 1):S128–S129.

Lyman SK, Gordon J, DuPage A, et al. Preliminary evidence of intratumoral activation and immunomodulatory effect of CX-072, a probody therapeutic antibody prodrug targeting PD-L1, in a phase 1/2 trial. Presented at: Society for Immunotherapy of Cancer (SITC) 33rd Annual Meeting; November 7-11, 2018; Washington, DC.

Ochoa CE, Joseph RW. Utility of ipilimumab in melanoma patients who progress on anti-PD-1 therapy. Melanoma Manag. 2017;4(3):143-145.

Olson D, Luke JJ, Hallmeyer S, et al. Phase II trial of pembrolizumab (pembro) plus 1 mg/kg ipilimumab (ipi) immediately following progression on anti-PD-1 Ab in melanoma (mel). J Clin Oncol. 2018;36(Suppl 15):9514-9514.

Overall CM, Kleifeld O. Tumour microenvironment - opinion: validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy. Nat Rev Cancer. 2006;6(3):227-239.

Plummer R, Sanborn RE, de Vries E, et al. Preliminary results of the first-in-human, dose-finding PROCLAIM-CX-072 trial evaluating the PD-L1 Probody therapeutic CX-072 in combination with ipilimumab in patients with advanced solid tumors. Presented at: European Society for Medical Oncology (ESMO) Annual Congress; October 19-23, 2018; Munich, Germany.

Rosenberg JI, Sharma P, de Braud FGM, et al. Nivolumab (N) alone or in combination with ipilimumab (I) in patients (pts) with platinum-pretreated metastatic urothelial carcinoma (mUCJ), including the nivolumab 1 mg/kg + ipilimumab 3 mg/kg expansion from CheckMate 032. Presented at: European Society for Medical Oncology (ESMO) 2018 Congress; October 20, 2018; Munich, Germany.

Rozeman EA, Menzies AM, van de Wiel BA, et al. OpACIN-neo: A multicenter phase 2 study to identify the optimal neo-adjuvant combination scheme of ipilimumab (IPI) and nivolumab (NIVO). Ann Oncol. 2018;29 suppl 8; abstr LBA42. Available at: https://www.esmo.org/Oncology-News/OpACIN-neo-optimal-neoadjuvant-combination-ipilimumab-nivolumab-Rozeman. Accessed April 12, 2019.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

Stroh M, Winter H, Marchand M, et al. Clinical pharmacokinetics and pharmacodynamics of atezolizumab in metastatic urothelial carcinoma. Clin Pharmacol Ther. 2017;102(2):305-312.

Tetzlaff MT, Messina JL, Stein JE, et al. Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma. Ann Oncol. 2018;29(8):1861-1868.

von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000;18(17):3068-3077.

von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005;23(21):4602-4608.

Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377:1824-1835.

Weichenthal M, Ugurel S, Leiter UM, et al. Salvage therapy after failure from anti-PD-1 single agent treatment: A Study by the German ADOReg melanoma registry. J Clin Oncol. 2019;37(Suppl 15):9505-9505.

Zimmer L, Apuri S, Eroglu Z, et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer. 2017;75:47-55.

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.

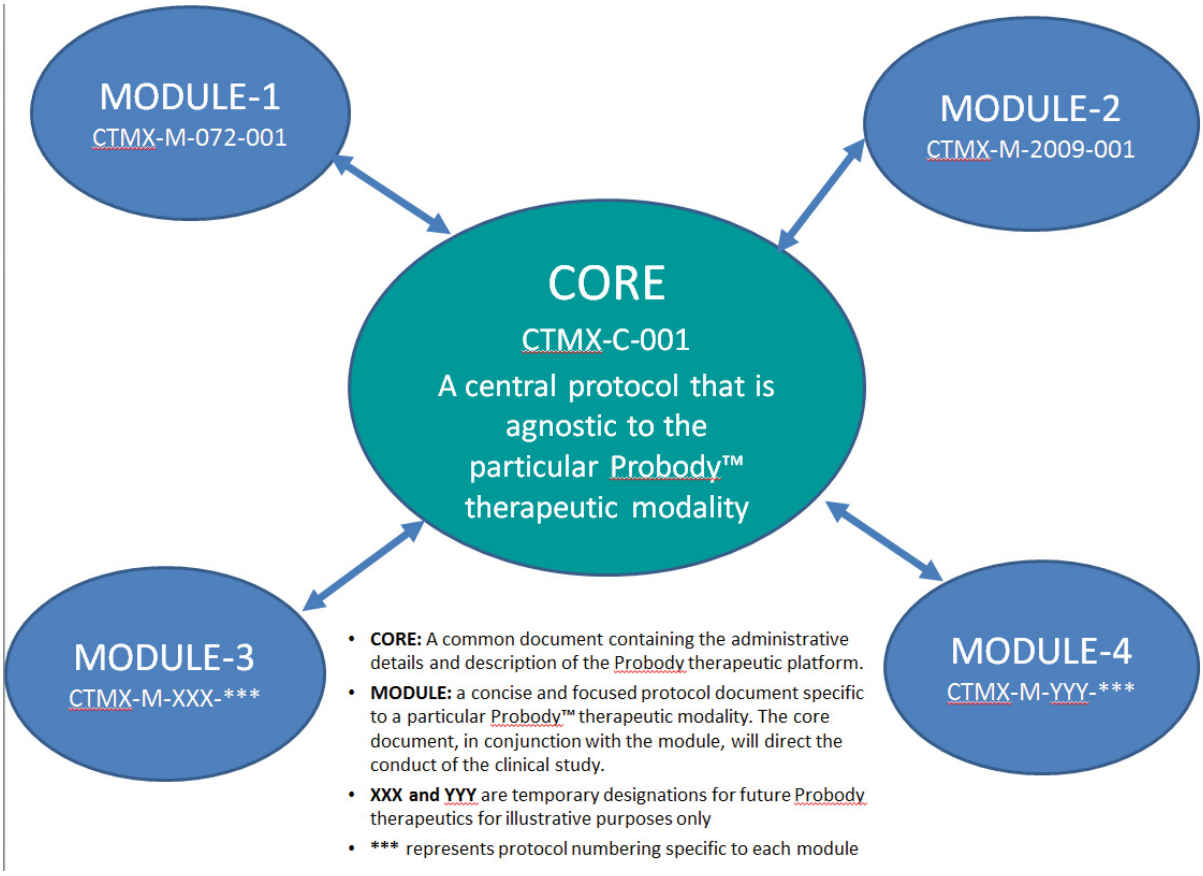
Finally, while the preclinical data show a characteristic level of activated Probody in the circulation of healthy animals, the extent of activation in subjects with concomitant morbidities will not be known until the clinical studies are initiated. A refined understanding of the subject population that 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

Annunziata CM, Kohn EC, LoRusso P, Houston ND, Coleman RL, et al. Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors. Invest New Drugs. 2013 Feb;31(1):77-84. PubMed PMID: 22370972.

Bohnsack O, Hoos A, Ludajic K. Adaptation of the Immune Related Response Criteria: irRECIST. Ann Oncol. 2014;25(4):iv361-iv372.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68. PubMed PMID: 25113753.

Cheson BD. Staging and response assessment in lymphomas: the new Lugano classification. Chin Clin Oncol. 2015 Mar;4(1):5. PubMed PMID: 25841712.

Chiou VL, Burotto M. Pseudoprogression and Immune-Related Response in Solid Tumors. J Clin Oncol. 2015 Nov 1;33(31):3541-3. PubMed PMID: 26261262.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 11). Eur J Cancer. 2009 Jan;45(2):228-47. PubMed PMID: 19097774.

Lutterbuese R, Raum T, Kischel R, Hoffmann P, Mangold S, et al. T cell-engaging BiTE antibodies specific for EGFR potently eliminate KRAS- and BRAF-mutated colorectal cancer cells. Proc Natl Acad Sci U S A. 2010 Jul 13;107(28):12605-10. PubMed PMID: 20616015.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009 Dec 1;15(23):7412-20. PubMed PMID: 19934295.

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: 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 or Core amendments. The DSMB will be charged with responsibility to advise CytomX Therapeutics, Inc. (CytomX) regarding:

- 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 at least 2 times per year in accord with meetings scheduled to review the overall CX-072 program; more frequent 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. The DSMB will review all safety information to determine whether the study will continue unchanged or whether protocol 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, including the Chief Medical Officer, Chief Legal Counsel, and Chief Executive Officer.

The DSMB will consist of at least 3 members. DSMB members who withdraw prior to completion of the project will be replaced. Should it become necessary to expand the number of DSMB members, CytomX will appoint additional members. The responsibilities of the DSMB for this study will end upon submission of a final clinical study report.

APPENDIX C: CONTRACEPTION GUIDELINES

The Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation:
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and if used this method must be used in combination with another acceptable method listed above.

Definition of Childbearing Potential

Childbearing potential is defined as being physiologically capable of becoming pregnant. No childbearing potential is defined as 1 or both of the following criteria:

- Surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥55 years of age with no spontaneous menses for ≥12 months, OR
  - <55 years of age with no spontaneous menses for ≥12 months AND with a postmenopausal follicle-stimulating hormone (FSH) concentration >30 IU/mL

Reference: Clinical Trial Facilitation Group (CTFG) 2014

APPENDIX D: DIAGNOSTIC CRITERIA FOR ANAPHYLAXIS

The clinical criteria for diagnosing anaphylaxis listed below are adapted from Sampson et al.

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (within minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips/tongue/uvula) and at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia);
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (generalized hives, itch/flush, swollen lips/ tongue/uvula);
   b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia);
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence);
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced BP after exposure to a known allergen for that subject (minutes to several hours):
   a. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person’s baseline.

Reference: Sampson 2006.