STATISTICAL ANALYSIS PLAN

Study Title:	An Open-Label, Dose-Finding and Proof of Concept Study of the PD-L1 Probody™ Therapeutic, CX-072, as Monotherapy and in Combination with Vervoy® (Ipilimumab) or with Zelboraf® (Vemurafenib) in Subjects with Advanced or Recurrent Solid Tumors or Lymphomas
Phase:	1/2a
Protocol No:	CTMX-M-071-001 (PROCLAIM-0001: Probody Clinical Assessment in Man CX-072 Clinical Trial 001)
Protocol Version (Date):	Amendment 8 (04 June 2020)
Analysis Plan Version (Date):	3.0 (03NOV2020)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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STATISTICAL ANALYSIS PLAN REVISION HISTORY

Revision Date (DD MMM YYYY)	Version	Summary of Revision	Reason for Revision
-	1.0	-	-
12AUG2018	2.0		Updated to include protocol amendments through Amendment 5 (18APR2020)
01SEP2020	3.0		Updated to include protocol amendments through Amendment 8 (04JUN2020)

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GLOSSARY OF ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen
CI	confidence interval
CR	complete response
cSCC	cutaneous squamous cell carcinoma
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DI	dose intensity
DLT	dose limiting toxicity
DOR	duration of response
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
ER	emergency room
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
hTMB	high tumor mutational burden
ID	identification
INR	international normalized ratio
ir	immune-related
irAE	immune-related adverse event
IRR	infusion related reaction
ITT	intent to treat
IV	intravenous
LLT	lower-level term
LOQ	limit of quantitation
MAD	maximum achieved dose
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities

NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PDI	planned dose intensity
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
q 14 days	every 14 days
q 21 days	every 21 days
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
REP	response evaluable population
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SD	stable disease
SOC	system organ class
StD	standard deviation
SOC	system organ class
SUV	standardized uptake value
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TET	thymic epithelial tumor
TMTB	total measured tumor burden
TFLs	tables, figures, and listings
TNBC	triple negative breast cancer
TRAE	treatment-related treatment-emergent adverse event
TTR	time to response
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma
WHODrug	World Health Organization Drug Dictionary

1. PURPOSE

This statistical analysis plan (SAP) describes the statistical methodology and data handling for Study CTMX-M-072-001. This SAP is based upon the following study documents:

- Protocol Core Amendment 2 (11-MAY-2018)
- Protocol Module Amendment 8 (04-JUN-2020)

The analyses specified in this SAP will be used to support safety reviews, publications, and FDA submissions. The SAP will be finalized prior to database lock. In instances where the SAP might contradict the analyses specified in the Common Core Document, the SAP supersedes the Common Core Document. If sample size is inadequate for a particular analysis, the analysis described in this document may not be performed.

ICH-E3 "Structure and Content of Clinical Study Reports" was used as guidance in producing this SAP.

2. STUDY POPULATION

This is a FIH, Phase 1/2a, open-label, multicenter, dose escalation, multidose study of CX-072. The study will evaluate the safety, tolerability, and preliminary efficacy of multiple doses of CX-072, administered as monotherapy or in combination with ipilimumab or vemurafenib to subjects with metastatic or locally advanced unresectable solid tumors or lymphomas. Inclusion and exclusion criteria are detailed in Sections 10.1 and 10.2 of the study protocol.

3. STUDY OBJECTIVES

The study objectives per Protocol Module Amendment 8 are as follows.

3.1. Primary Objectives

3.1.1. Primary Objectives for Parts A Through C

The primary objectives for Parts A through C of the study are:

1. Evaluate the safety and tolerability of multiple doses of CX-072, administered as monotherapy or in combination with ipilimumab or vemurafenib to subjects with metastatic or locally advanced unresectable solid tumors or lymphomas; and
2. Determine the MTD and DLTs of:
   - CX-072 as a monotherapy administered to PD-1/PD-L1 naive subjects,
   - CX-072 in combination with ipilimumab administered to PD-1/PD-L1 and CTLA-4 inhibitor naive subjects,
   - CX-072 in combination with ipilimumab administered to subjects that have had prior treatment with a PD-1/PD-L1 inhibitor, and
   - CX-072 in combination with vemurafenib administered to PD-1/PD-L1 naive subjects.

3.1.2. Primary Objectives for Parts D [redacted]

The primary objective of Parts D [redacted] of the study is to obtain preliminary and confirmatory evidence of the efficacy of CX-072 monotherapy, respectively, via the objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) (tumor types include: UPS, small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, TNBC with skin lesions, and hTMB [Part D only]), as assessed by Investigator (Part D) [redacted]. As of Amendment 08, Parts A-[redacted] are closed, and the long-term extension part of the study will begin (see Section 19 of the study protocol). [redacted]

3.2. Secondary Objectives

3.2.1. Secondary Objectives for Parts A Through C

The secondary objectives for Parts A through C of the study are:

1. Obtain preliminary evidence of anti-cancer activity for the following endpoints in subjects treated with CX-072 as monotherapy or when administered in combination with ipilimumab or vemurafenib:
   - ORR by RECIST v 1.1

- ORR by modified immune-related response criteria as defined in the Common Core Document or Modified Cheson/Lugano Classification for Lymphomas
- Time to response (TTR)
- Duration of response (DOR)
- Progression-free survival (PFS)

2. Characterize the incidence of ADA against CX-072 and ipilimumab
3. Characterize the single and multidose PK profile of CX-072 when administered alone, and CX-072, ipilimumab, and vemurafenib when administered in combination
4. Assess overall survival (OS) in subjects receiving CX-072

3.2.2. Secondary Objectives for Parts D

The secondary objectives for Part D of the study are:

5. Further characterize the efficacy of CX-072 monotherapy as evidenced by:
   - DOR as assessed by Investigator (Part D)
   - ORR by modified immune-related (ir) RECIST as defined in the Common Core Document
   - PFS
6. Evaluate safety and tolerability of CX-072, administered as monotherapy
7. Characterize the incidence of ADAs against CX-072
8. Characterize the PK profile of CX-072
9. Assess OS in subjects receiving CX-072

3.3. Exploratory Objectives

[redacted]

[redacted]

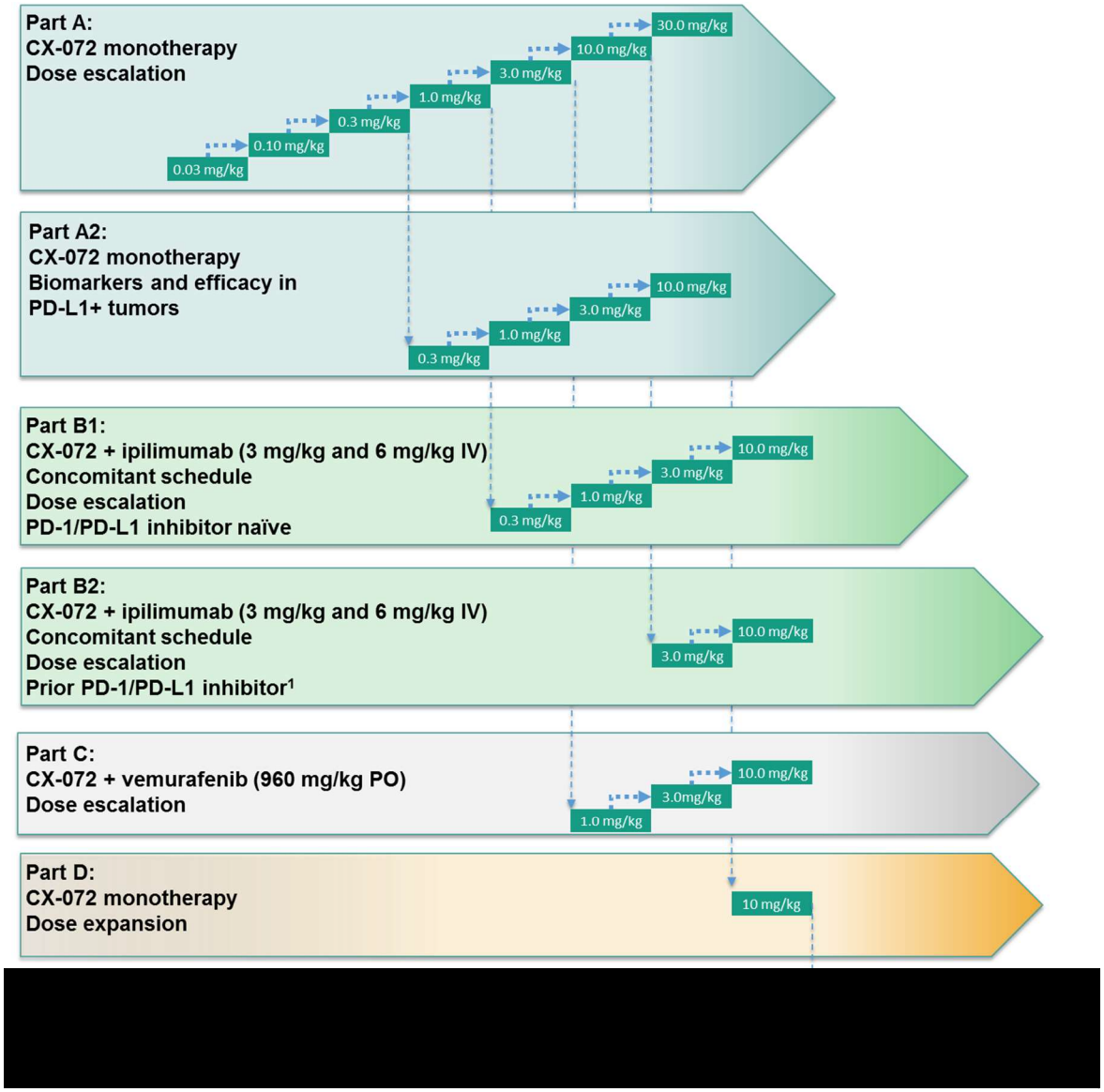
4. STUDY METHODS

4.1. Overview of Study Design

This is a FIH, Phase 1/2a, open-label, multicenter, dose escalation, multidose study of CX-072. Approximately 60 study sites will be utilized. Parts A through C are designed to evaluate the safety and determine the MTD and/or MAD of CX-072 as monotherapy and in combination with ipilimumab or vemurafenib (see Figure 1). Parts D [redacted] are designed to obtain preliminary and confirmatory evidence of anti-cancer activity, respectively. The doses to be tested in each part of the study and the dose escalation schema are outlined in Table 1 and Figure 2, respectively. [redacted] As of Amendment 08, Parts A-[redacted] are closed, and the long-term extension part of the study will begin (see Section 19 of the study protocol).

All subjects in Part A2 (CX-072 monotherapy), subjects in Part B2 receiving CX-072 + 3 mg/kg ipilimumab (but not subjects receiving 6 mg/kg ipilimumab), TNBC with skin lesions cohorts in Parts D [redacted].

Figure 1: Study Diagram



[1]Subjects discontinued prior PD-1/PD-L1 for reasons other than toxicity.
IV = intravenous; PD-1 = programmed cell death; PD-L1 = programmed cell death ligand 1; PO = oral.

Notes:
In Part A, an expansion cohort of up to 22 additional subjects is planned to be enrolled for an imaging substudy conducted in the Netherlands.

As of Amendment 08, Parts A-[redacted] are closed, and the long-term extension part of the study will begin (see Section 19 of the study protocol). [redacted]

The study is divided into 7 parts:

- Part A: CX-072 monotherapy dose escalation and imaging substudy
  - Any metastatic or advanced unresectable solid tumor or lymphoma ($n \leq 33$), measurable or nonmeasurable disease
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
  - CX-072 monotherapy (0.03, 0.1, 0.3, 1, 3, 10, and 30 mg/kg) IV every 14 days (q2wk)
  - Expansion cohort of up to 22 additional subjects (10 mg/kg CX-072 monotherapy) for an imaging substudy conducted in the Netherlands
- Part A2: CX-072 monotherapy dose effect
  - Any metastatic or advanced unresectable solid tumor or lymphoma (at least 2 subjects in each cohort with TET) ($n \leq 24$), measurable disease, relapsed or refractory
  - Tumor proportion score (TPS) ≥ 1% membranous staining based on the DAKO PD-L1 Immunohistochemistry (IHC) 22C3 pharmDx
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
  - Participation in biomarker analysis and biopsies
  - CX-072 monotherapy (0.3, 1, 3, and 10 mg/kg) IV q2wk
  - Initiation of each cohort's enrollment requires successful completion of the Part A CX-072 monotherapy at that dose level
- Part B1: CX-072 plus ipilimumab combination dose escalation (PD-1/PD-L1 inhibitor naive)
  - Any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) ($n \leq 30$), measurable or nonmeasurable disease
  - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available for their specific disease in the country where they are being treated)
  - CX-072 (0.3, 1, 3, and 10 mg/kg) in combination with ipilimumab (3 or 6 mg/kg) IV q3wk × 4 doses in a concomitant schedule followed by CX-072 monotherapy IV q2wk
  - Initiation of cohort enrollment requires successful completion of the subsequent CX-072 monotherapy dose level tested in Part A

- Part B2: CX-072 plus ipilimumab combination dose escalation (prior PD-1/PD-L1 inhibitor)
    - Any metastatic or advanced unresectable solid tumor or lymphoma (excluding TET) (n ≤ 18), measurable disease
    - Prior therapy with PD-1/PD-L1 inhibitors, discontinued for reasons other than toxicity
    - CTLA-4 inhibitor naive
    - CX-072 (3 and 10 mg/kg) in combination with ipilimumab (3 or 6 mg/kg) IV q3wk × 4 doses in a concomitant schedule followed by CX-072 monotherapy IV q2wk
    - Initiation of cohort enrollment requires successful completion of the subsequent CX-072 monotherapy dose level tested in Part A
    - Participation in biomarker analysis and biopsies (only in cohorts receiving CX-072 + 3 mg/kg ipilimumab [but not 6 mg/kg ipilimumab]) is mandatory
- Part C: CX-072 plus vemurafenib combination dose escalation
    - BRAF V600E mutation-positive metastatic or advanced unresectable melanoma (n ≤ 18), measurable or nonmeasurable disease
    - BRAF-inhibitor naive
    - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy is not available to the subject)
    - CX-072 (1, 3, and 10 mg/kg) IV q2wk in combination with vemurafenib 960 mg PO twice daily (approximately every 12 hours [q12h]), concomitant schedule
    - Initiation of cohort enrollment requires successful completion of the subsequent CX-072 monotherapy dose level tested in Part A
- Part D: Expansion cohort for safety and efficacy at CX-072 10 mg/kg administered as monotherapy
    - Subjects with metastatic or locally advanced unresectable tumor types of UPS (n ≤ 20), small bowel adenocarcinoma (n ≤ 25), cSCC (n ≤ 25), MCC (n ≤ 25), TET (n ≤ 25), anal SCC (n ≤ 25), TNBC with skin lesions (n ≤ 25), and hTMB (n ≤ 25) measurable disease, that have failed to respond or showed tumor progression despite SOC therapy, are not candidates for SOC therapy, are unwilling to undergo SOC therapy, or for whom no available therapy is expected to convey clinical benefit
    - Immunotherapy naive, including PD-1/PD-L1 and CTLA-4 inhibitor therapy naive (where there is no immunotherapy or PD-1/PD-L1 and CTLA-4 inhibitor therapy available to the subject)

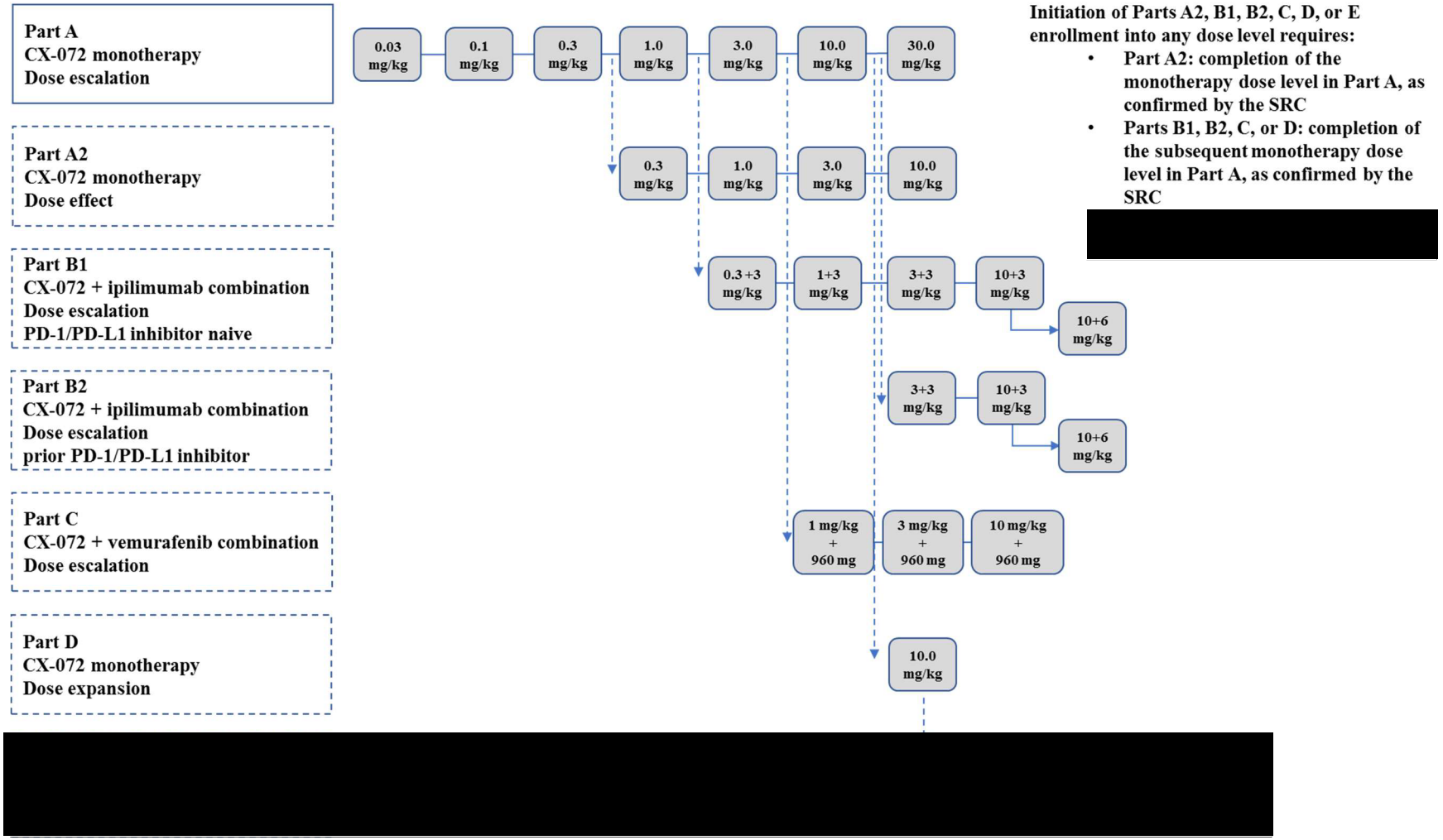
- [redacted]

Table 1: Doses to be Tested [1]

Dose CX-072 (mg/kg)	Cohort #	Part A Dose Escalation CX-072 (mg/kg) Monotherapy	Cohort #	Part A2 Dose Effect CX-072 (mg/kg) Monotherapy	Cohort #	Part B1 CX-072 + Ipilimumab Combination Dose Ipilimumab	Cohort #	Part B2 CX-072 + Ipilimumab Combination Dose Ipilimumab	Cohort #	Part C Dose Escalation CX-072 + Vemurafenib Combination Dose Vemurafenib PO q12h	Part D Dose Expansion
0.03	1A	0.03									10 mg/kg
0.1	2A	0.1									
0.3	3A	0.3	3A2	0.3	3B1	+ 3 mg/kg ipi					
1	4A	1	4A2	1	4B1	+ 3 mg/kg ipi			4C	+ 960 mg q12h vem	
3	5A	3	5A2	3	5B1	+ 3 mg/kg ipi	5B2	+ 3 mg/kg ipi	5C	+ 960 mg q12h vem	
10	6A	10	6A2	10	6B1	+ 3 mg/kg ipi	6B2	+ 3 mg/kg ipi	6C	+ 960 mg q12h vem	
30	7A	30									
10					7B1	+ 6 mg/kg ipi	7B2	+ 6 mg/kg ipi			

[1]The Sponsor in consultation with the SRC may modify the doses of study drug in response to DLTs observed during the study.

Figure 2: Phase 1/2a Dose Escalation, Dose Expansion, and Response Evaluation Schema



PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; q2wk = every 2 weeks; SRC = Safety Review Committee.

4.2. Subject Eligibility and Enrollment

After signing the informed consent form (ICF) subjects will be evaluated for CTMX-M-072-001 study eligibility during the Screening Period (no more than 30 days before study drug administration). All subjects must have histologically confirmed diagnosis of metastatic or locally advanced unresectable tumors that progressed or are intolerant to standard therapy as defined in Section 10.1 of the study protocol. Subjects who fulfill any of the exclusion criteria at screening (outlined in Section 10.2 of the study protocol) will not be eligible for admission into the study.

Up to 123 subjects may be enrolled into the dose escalation cohorts (Parts A through C) and 195 subjects into the expansion cohort (Part D), [redacted] In Part A, an expansion cohort of up to 22 additional subjects is planned to be enrolled for an imaging substudy conducted in the Netherlands.

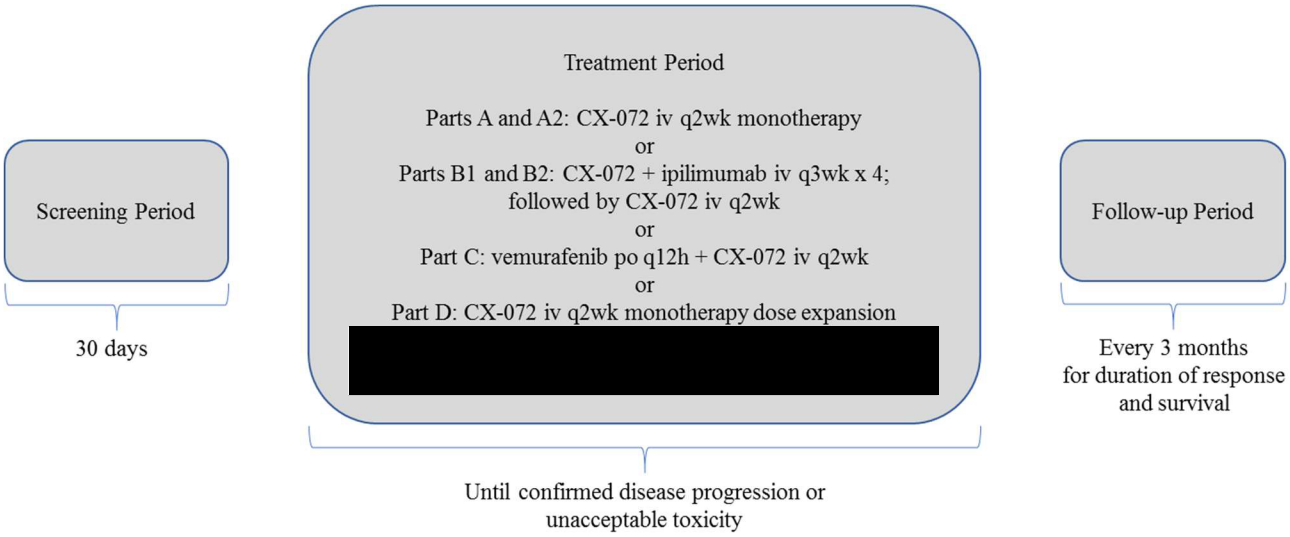
4.3. Study Periods and Follow-Up

The study is divided into periods with associated evaluations and procedures that must be performed at specific time points (see Figure 3). The schedule of study procedures summarizes the frequency and timing of efficacy, safety, and other study measurements. Results of tumor assessments must be reviewed and documented before administering the next study treatment.

A subject who is withdrawn from the study during a DLT assessment period before the completion of the assessment period for a reason other than DLT will be replaced.

An individual subject's participation in the study Parts A[redacted] is approximately 2 years. Upon activation of Amendment 08, Investigators may elect to allow subjects who continue to receive clinical benefit to continue to receive study drug if permitted by the Sponsor (see Section 19, Section 20, and Section 21 of the protocol).

Figure 3: Study Periods



iv = intravenous; po = oral; qXd = every X days; qXwk = every X weeks.

Following the completion of study treatment, subjects with progressive disease will enter the follow-up period for monitoring of survival; subjects with SD, PR, or CR will enter the follow-up period for monitoring of DOR and PFS. Once a subject experiences a withdrawal criterion (see Section 4.5), they will continue to be monitored for survival.

Once Protocol Amendment 8 is approved at a site, subjects receiving study treatment will be eligible to roll over to the long-term extension part of the study (protocol Sections 19 through 27). Subjects who are no longer receiving study treatment but are in the follow-up period for Parts A[redacted] will have concluded their participation in the study due to Sponsor termination. Follow-up for survival will no longer be performed.

4.4. Study Drug Administration

CX-072 is a Probody therapeutic derived from a proprietary human anti–PD-L1 mAb. In subjects with various cancers, conventional anti–PD-L1 mAb (atezolizumab, avelumab, and durvalumab) and anti–PD-1 mAb (nivolumab and pembrolizumab) have demonstrated clinical effectiveness as monotherapy and/or in combination with other immunotherapies.

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

Administration of the 0.03 and 0.1 mg/kg dose levels will be limited to sites in the US.

[redacted]

[redacted]

4.5. Discontinuation of Subjects from Treatment

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

- The subject experiences progression of disease by either RECIST or irRECIST guidelines; for a subject with a single observation of disease progression, the subject may continue until the next scheduled radiological assessment. If continued progression (>20% increase in target lesions, unequivocal progression in non-target lesions or new lesion(s) assessed by the Principal Investigator as likely representing new site(s) of malignant disease), the subject must be discontinued from the trial.
- 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 AE related to study drug(s) which precludes further administration of the study drug(s).
- The subject experiences a prolonged treatment delay (defined in protocol Section 12).
- The subject becomes pregnant, either prior to the first dose of study drug or at any time during treatment.
- In the Investigator's judgment, the subject should discontinue treatment.
- The Sponsor terminates the study.

Subjects who discontinue study drug administration for reasons other than DLT may be replaced to ensure the minimum number of subjects required for DLT evaluation is enrolled. Subjects who have enrolled in the study and have withdrawn prior to receiving the first dose will be designated as screen failures. These subjects, as well as those who withdraw prior to completion of the DLT period for reasons other than toxicity, may be replaced.

4.6. Study Completion

Once Protocol Amendment 8 is approved at a site, subjects receiving CX-072 study treatment will be eligible to roll over to the long-term extension part of the study, and Parts A-D of

Study CTMX-M-072-001 will be considered to be terminated by the Sponsor for subjects who are currently in the follow-up phase.

5. STUDY ENDPOINTS

5.1. Primary Safety Domains

The safety and tolerability of multiple doses of CX-072 administered as monotherapy or in combination with ipilimumab or vemurafenib to subjects with metastatic or locally advanced unresectable solid tumors or lymphomas, will be evaluated for the following:

- DLTs
- AEs and SAEs (assessed via NCI CTCAE version 4.03)
- Physical examinations
- Triplicate electrocardiograms (ECGs)
- Clinical laboratory evaluations
- Treatment discontinuation due to toxicity

5.2. Primary Efficacy Endpoint

Objective response rate (ORR) is the primary efficacy endpoint in Parts C and D. For solid tumors, response evaluation will be based upon RECIST criteria (version 1.1). ORR is defined as the proportion of subjects with complete response (CR) or partial responses (PR) on two consecutive tumor assessments at least 4 weeks apart. For lymphomas, objective response will be evaluated by Modified Cheson/Lugano Classification for Lymphomas.

5.3. Secondary Efficacy

The secondary efficacy endpoints include:

- Duration of response (DOR)
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)

[redacted]

6. DATA CAPTURE AND PROCESSING

Data will be recorded on electronic case report forms (eCRFs) and maintained in a Medidata Rave clinical database. All data will undergo rigorous review processes including electronic and manual data checks. Periodic data quality reviews will also be conducted to minimize errors and omissions.

7. ANALYSIS AND REPORTING

7.1. Interim Analyses

7.1.1. Safety Review Committee (SRC)

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

(1) Approve dose escalation to the next cohort in each part of the study

(2) Recommend modifications to the dose or schedule as it pertains to subject safety

(3) Recommend modifications to the protocol related to subject oversight (e.g., additional safety monitoring, changes to inclusion/exclusion criteria, etc.)

(4) Evaluate combination schedules to recommend modifications to the combination dosing schedule/regimen

7.1.2. Data Safety Monitoring Board (DSMB)

A DSMB has been established for the study. The DSMB will monitor the safety of the study for Cohorts A-D. The DSMB will consist of individuals in relevant fields of expertise. It will convene on a regular basis (at least twice per year) and will review all safety and efficacy 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 3 of the study protocol and a separate DSMB charter. The DSMB will make recommendations to the Sponsor, who will make ultimate decisions regarding study modification or discontinuation.

7.2. Final Analysis

The final efficacy and safety analyses will be conducted once all subjects have progressed or for those deriving continued benefit, are placed in a rollover study so that efficacy and safety data continue to be collected.

7.3. Follow-up Analysis

After the final analysis, additional supplemental analyses of efficacy and safety may be performed to satisfy regulatory requirements or to perform long-term efficacy (e.g., overall survival) and follow-up safety assessments.

8. SAMPLE SIZE DETERMINATION

Cohorts of 1, 3, or 6 subjects may be treated at each dose level for Part A, B1, B2, or C in the 3+3 design. The ultimate number enrolled to each study Part, will depend upon the observed safety of each cohort, where enrollment of additional subjects (up to 6) may be required, as per protocol, to further elucidate the safety profile at a given dose level. Additionally, escalation may be halted before the highest planned dosing cohort is enrolled, should the MTD be defined at a lower dose.

The maximum number of subjects enrolled in this study is as follows:

- In Part A, 15 to 33 subjects may be enrolled (1 to 6 subjects per cohort, up to 7 cohorts)
- In Part A2, 24 subjects may be enrolled (6 subjects per cohort, up to 4 cohorts)
- In Part B1, 18 to 36 subjects may be enrolled (3 to 6 subjects per cohort, up to 6 cohorts)
- In Part B2, 12 to 24 subjects may be enrolled (3 to 6 subjects per cohort, up to 4 cohorts)
- In Part C, 9 to 18 subjects may be enrolled (3 to 6 subjects per cohort, up to 3 cohorts)

For Part A, an expansion cohort of up to 22 additional subjects is planned to be enrolled for an imaging substudy conducted in the Netherlands.

[redacted]

[redacted]

For the expansion cohort (Part D), potentially eligible subjects will be those with:

- Undifferentiated pleomorphic sarcoma (UPS)
- Small bowel adenocarcinoma

- Cutaneous squamous cell carcinoma (cSCC)
- Merkel cell carcinoma (MCC)
- Thymic carcinoma (TET)
- Anal squamous cell carcinoma (anal SCC)
- Triple negative breast cancer (TNBC)
- High tumor mutational burden (hTMB)

for the purposes of providing a preliminary assessment of tumor response, as well as additional safety assessment at doses of 10 mg/kg. The expansion cohorts are enrolled in a gated fashion as explained below. The number of subjects in the following discussion refers to treated subjects with measurable disease at baseline per RECIST v1.1. Response refers to confirmed objective response.

A total of 20 subjects will be evaluated for UPS. Initially, 14 subjects will be evaluated for small bowel adenocarcinoma, cSCC, MCC, TET, anal SCC, TNBC with skin lesions, and hTMB.

9. ANALYSIS POPULATIONS

Analysis populations for tabulations and figures are defined below for the following populations: safety analysis population (SP), the response evaluable population (REP), and the imaging assessment population (IAP). Subject disposition will be based upon the number of enrolled subjects. Enrolled subjects are those subjects that have provided informed consent and who have had a cohort assigned.

9.1. Safety Analysis Population (SP)

The safety analysis population includes all enrolled subjects who receive at least one dose of study drug. The SP will be used for evaluating subject characteristics, treatment administration, and safety endpoints.

9.2. Response Evaluable Population (REP)

The response evaluable population (REP) includes all subjects in the safety analysis population who have an adequate (i.e. evaluable) baseline disease assessment. The REP is used for efficacy analyses related to objective response, including objective response rate (ORR), time to response (TTR), and duration of response (DOR). Subjects who discontinue study treatment without adequate post-baseline disease assessments will be counted as non-responders. For interim reporting purposes only, subjects who are ongoing without adequate post-baseline disease assessments will be excluded from the REP.

9.3. Response Evaluable Population with Post-Baseline Disease Assessment (REP-PBDA)

The REP-PBDA includes all subjects in the REP who have an adequate disease assessment at baseline and at least one post-baseline assessment. The REP-PBDA is used for efficacy sensitivity analyses related to objective response.

9.4. Imaging Assessment Population (IAP)

The imaging assessment population (IAP) consists of all subjects in whom at least one ^{89}Zr-CX-072-PET scan has been performed. Subjects who have enrolled in the substudy and have withdrawn prior to completing the PET scan series may be replaced.

10. GENERAL STATISTICAL CONSIDERATIONS

10.1. General Statistical Considerations

Data will be analyzed using SAS (Version 9.4 or higher). All subjects who sign an ICF are identified by an 8-digit subject number where the first 4 digits are for site identification and the last 4 digits are the sequential enrollment within a site (e.g. 1013-0001).

The planned study cohorts are as follows:

- Part A: Cohort identifiers 1A to 7A, receiving CX-072 doses (mg/kg) 0.03, 0.1, 0.3, 1, 3, 10, and 30 IV q 14 days, respectively
- Part A2: Cohort identifiers 3A2 to 6A2, receiving CX-072 doses (mg/kg) 0.3, 1, 3, and 10 IV q 14 days, respectively
- Part B1: Cohort identifiers 3B1 to 9B1, receiving CX-072 and Ipilimumab shown in the following table:

Cohort Identifier	CX-072 Dose (mg/kg)	Ipilimumab Dose (mg/kg)
3B1	0.3	3
4B1	1	3
5B1	3	3
6B1	10	3
7B1	10	6
8B1	10	10

- Part B2: Cohort identifiers 5B2 to 8B2, receiving CX-072 and Ipilimumab shown in the following table:

Cohort Identifier	CX-072 Dose (mg/kg)	Ipilimumab Dose (mg/kg)
5B2	3	3
6B2	10	3
7B2	10	6
8B2	10	10

- Part C: Cohort identifier 4C to 6C, receiving CX-072 (1, 3, 10 mg/kg) IV q 14 days + vemurafenib 960 mg PO twice daily, respectively.
- Part D: CX-072 IV q 14 days with doses up to the MTD/MAD (the recommended Phase II dose [RP2D] is 10 mg/kg effective 02JUL2018).

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages
- Continuous data will be summarized using number of non-missing values (n), mean, median, standard deviation, first quartile (Q1), third quartile (Q3), minimum, and maximum.

10.1.1. Handling of Missing Data

All data will be analyzed as they were collected in the database. Missing data, other than as described in Section 10.1.2, will not be imputed.

10.1.2. Derived and Computed Variables

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

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

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

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

Except for dates associated with prior cancer regimens or procedures, no other missing date components will be imputed. However, AEs with missing or incomplete start dates (and times, in the case of infusion-related reaction) will be attributed to treatment (i.e. TEAEs) according to the following algorithm:

- No date or no date/time is reported: The event will be considered treatment emergent
- Only the year is reported: If the year is after or the same as the year component of the first dose date, the event will be considered treatment-emergent

- Only the month and year are reported: If the month and year are after or the same as the month and year of the first dose date, the event will be considered treatment emergent.

- When date and time are required data elements, but time is missing: If the event occurred on or after the day of the first dose in the treatment period, then the event will be considered treatment emergent.

10.1.2.2. Study Days Relative to First Infusion of Study Medication

Study Day 1 is the day of the first infusion; negative Study Days occur prior to first infusion of study medication; and positive Study Days are those after the first infusion (e.g. Study Day -1 is the day immediately preceding the day of first infusion and Study Day 2 is the day immediately following the day of first infusion).

10.1.2.3. Treatment Duration

Study treatment duration, CX-072 monotherapy (in weeks) is:

$$\frac{(Stop\ date\ of\ last\ study\ drug\ infusion - Start\ date\ of\ initial\ study\ drug\ infusion) + 14}{(\frac{365.25}{52})}.$$

Combination therapy CX-072 and Ipilimumab duration of treatment (in weeks) is the sum of the following two parts divided by $(\frac{365.25}{52})$.

(1) For Cycles 1 and 2, the first 4 administrations of CX-072 and ipilimumab have a treatment duration (in days) determined by

$$(Stop\ date\ of\ last\ study\ drug\ infusion\ in\ Cycle\ 1\ or\ 2 - Start\ date\ of\ initial\ study\ drug\ infusion) + 21$$

(2) For Cycle 3 and beyond, ipilimumab is discontinued and treatment duration (in days) is determined strictly by administration of CX-072

$$(Stop\ date\ of\ last\ study\ drug\ infusion - Start\ date\ of\ Cycle\ 3\ drug\ infusion) + 14\ .$$

For combination therapy, CX-072 and vemurafenib duration of treatment (in weeks) when the patient stops vemurafenib before CX-072 is

$$\frac{(Stop\ date\ of\ last\ study\ drug\ administration - Start\ date\ of\ initial\ study\ drug\ administration) + 1}{(\frac{365.25}{52})}.$$

For combination therapy, CX-072 and Vemurafenib duration of treatment (in weeks) when the patient stops CX-072 prior to Vemurafenib is

$$\frac{(Stop\ date\ of\ last\ study\ drug\ administration - Start\ date\ of\ initial\ study\ drug\ administration) + 14}{(\frac{365.25}{52})}.$$

10.1.2.4. Percent of Dose of Each Study Drug

For each study medication, the percent of each dose received will be calculated using the following formula rounded to one decimal place:

$$100 \times \frac{Total\ dose\ of\ study\ drug\ administered}{Total\ planned\ dose\ of\ study\ drug},$$

For study drugs CX-072 and ipilimumab, this statistic will be computed based upon dose units of mg/kg. For vemurafenib, the percent of dose of study drug will be based upon dose units of milligrams.

10.1.2.5. Dose Intensity (DI) of Each Study Drug

For each study medication, the dose intensity is computed as

$$\frac{Cumulative\ dose\ of\ study\ drug}{Treatment\ duration\ (weeks)\ for\ study\ drug}.$$

For CX-072, cumulative dose will be computed based upon administered CX-072 in units of mg/kg over the treatment duration of CX-072 (as shown in Section 10.1.2.3 CX-072 monotherapy). For ipilimumab, dose intensity (mg/kg/week) will be computed based upon administration during Cycles 1 and 2 where treatment duration is Part 1 in Section 10.1.2.3. For vemurafenib, cumulative dose (mg) will be determined by daily ingestion of the oral tablets. Treatment duration will be based upon initiation and last dose of vemurafenib.

10.1.2.6. Planned Dose Intensity (PDI)

For each study medication, the planned dose intensity is determined by:

$$\frac{Cumulative\ planned\ dose\ of\ study\ medication}{Planned\ treatment\ duration\ (weeks)}.$$

PDI is computed in a similar manner to DI based upon initiation and last dose of each study drug per protocol.

10.1.2.7. Relative Dose Intensity (RDI)

For each study medication, the relative dose intensity (%) is evaluated as:

$$100 \times \frac{DI}{PDI} .$$

10.1.2.8. Duration of Infusion (minutes)

For each IV study medication, the duration of infusion, in minutes, will be computed as follows:

$$\frac{(Infusion\ stop\ time - Infusion\ start\ time) + 1}{60} .$$

10.1.2.9. Time Since Prior Regimens or Procedures

Time since prior regimens or procedures (weeks) is calculated as:

$$\frac{First\ infusion\ date - End\ date\ of\ the\ last\ prior\ regimen\ or\ procedure\ (relative\ to\ study)}{7} .$$

When only the month and year components of regimen or procedure end dates are reported, the day will be imputed to the 15th of the month. If only the year is reported, then the end date will not be imputed, and the regimen or procedure will not be eligible for selection as the last prior regimen or procedure.

10.1.2.10. Time Since Initial Histopathological Diagnosis

Time since initial histopathological diagnosis (years) is calculated as:

$$\frac{Informed\ consent\ date - Date\ of\ initial\ histopathological\ diagnosis}{365.25} .$$

10.1.2.11. Time Since Most Recent Disease Recurrence/Progression

Time since most recent disease recurrence/progression (years) is calculated as:

$$\frac{Informed\ consent\ date - Date\ of\ most\ recent\ disease\ recurrence/progression}{365.25} .$$

10.1.2.12. AEs with Missing Relationship

Every attempt will be made to obtain complete information for AEs regarding relationship to study treatment, however in the case of missing data:

> AEs with missing relationship designations will be considered "Related" to study treatment provided the AE onset date/time occurs on or after initiating exposure to study treatment (e.g. CX-072 infusion start date/time).

10.1.2.13. Baseline Measurement

A baseline measurement is defined as the last non-missing value prior to the start of study treatment.

10.2. Data Handling Conventions and Transformations

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

If statistical methods based upon assumptions of normally distributed data are inappropriate, analyses may be performed on transformed data or alternative nonparametric methods may be implemented.

10.3. Definition of Study Day

Study day will be calculated from the first dosing (infusion) date of study drug and derived as follows:

- Study days prior to first dose (which are less than
- For post dose study days: Assessment Date – First Dosing Date] + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

10.4. Analysis Visit Windows

The nominal visit as recorded on the eCRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to initial treatment with study drug will be included in the determination of the baseline value.

- Unscheduled visits after the initial treatment with study drug will be included in determining the maximum post baseline toxicity grade as well as determining efficacy outcomes (e.g. best percentage change from baseline in target lesions or best overall response).

- For subjects who prematurely discontinue from the study, end of treatment data will be summarized as a separate visit, labeled as "End of Treatment Visit".

- Data collected at follow-up visits will be summarized as separate visits

11. SUBJECT CHARACTERISTICS AND DEMOGRAPHICS

Subject characteristics and demographics tables will be presented for the following groupings:

- Parts A and A2 combined
- Part B1
- Part B2
- Part C
- CX-072 monotherapy (10 mg/kg) combining subjects in Parts A and A2 and stratifying subjects in Part D by tumor type

11.1. Subject Enrollment and Disposition

A summary table of all subjects enrolled will be presented. This table will include the following elements:

- Number of subjects enrolled
- Number and percentage of subjects in each analysis population
- Number of subjects treated and their study status (on treatment, off treatment, in follow-up or off study)
- Number of subjects terminating treatment
    - Frequency distribution of treatment discontinuation reasons
- Number of subjects discontinuing the study
    - Frequency distribution of study discontinuation reasons
- Duration of follow-up

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

The subject enrollment and disposition tables will be supported with a by-subject listing (sorted by subject identifier in ascending order) of the reasons for premature study drug or study discontinuation.

11.2. Protocol Deviations

Subjects in the Safety Population who did not meet eligibility criteria to participate in the study but were enrolled and treated in the study will be summarized. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations documented during routine monitoring will be summarized for the Safety Population. The frequency and percentage of subjects with important protocol deviations by study treatment and deviation reason (e.g. nonadherence to study drug, violation of select inclusion/exclusion criteria). A by-subject listing will be provided for those subjects with important protocol deviations.

11.3. Demographics and Baseline Characteristics

Descriptive statistics will be generated for all demographic and baseline characteristics by the groupings described in Section 11. Each summary table will include the following elements:

Demographics:

- Age at enrollment (years)
- Gender
- Race
- Ethnicity

Baseline subject characteristics:

- Cigarette smoking history:
  - Current versus former smoker
- Subject cancer type and characterization:
  - Cancer type
  - Baseline ECOG
  - Subject PD-L1 expression status at baseline by local testing
- Subject prior cancer treatment:
  - Total number of prior regimens per subject (including regimens given for early and advanced malignancies)
  - Time since last cancer treatment end (weeks)
  - Prior radiotherapy

Other prior cancer treatment information including the regimen or procedure, treatment duration (weeks), best overall response, and reason for end of therapy will be captured in a listing.

12. SAFETY AND TOLERABILITY ANALYSIS

The primary objective of the study is to evaluate the safety and tolerability of multiple doses of CX-072, administered as monotherapy or in combination with ipilimumab or vemurafenib to subjects with metastatic or locally advanced unresectable solid tumors or lymphomas and to determine the MTD and DLTs of those regimens.

Safety will be assessed via AEs, clinical laboratory data, vital signs, ECG parameters, and physical examinations. Dosing and exposure to CX-072 will be presented.

Safety analyses include all subjects in the SP from Parts A, A2, B1, B2, C, D, and the IAP. The summaries will include the following groupings:

- Parts A and A2 combined
- Part B1
- Part B2
- Part C
- CX-072 monotherapy (10 mg/kg) combining subjects in Parts A and A2 and stratifying subjects in Part D by tumor type

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

12.1. Adverse Events, Serious Adverse Events and Deaths

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

AEs occurring during the follow-up period (up to and including 30 days after administration of the last dose of study drug for all adverse events and up to and including 90 days after administration of the last dose of study drug for all SAEs and immune-related adverse events (irAES) should be followed until resolution to baseline status, initiation of a new therapy, or stabilization. With the activation of Amendment 08 and enrollment into the long-term extension part of the study, irAEs, SAEs and possible episodes of Hy's Law (as described in Section 16.7 of the protocol) are reportable.

12.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. System organ class (SOC),

high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

12.1.2. Adverse Event Severity

Adverse events are graded by the Investigator as Grade 1, 2, 3, 4, or 5 according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03. If the Investigator did not record or assess the severity grade of an event, then the event will be categorized as "missing" for tabular summaries and data listings. The "missing" category will be listed last in summary presentations.

12.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the Investigator selected "Related" on the AE eCRF to the question of "Related to CX-072." Relatedness will always default to the Investigator's assessment, not that of the Medical Monitor. Events for which the Investigator did not record or assess the relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will display the relationship as missing.

12.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs meet the definition of SAE that is specified in the study protocol. SAEs captured in the clinical database will be reconciled with the SAE database prior to database lock.

12.1.5. Treatment-Emergent Adverse Events

12.1.5.1. Definition of Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is an event that emerges during treatment having been absent pre-treatment of worsens relative to the pre-treatment state. AE presentation will include incidence, grade (per NCI-CTCAE criteria), and relationship to study drug.

For infusion related reactions (IRRs), the start time of the AE is also recorded. For such records, the IRR will be considered treatment-emergent if the start date and time is on or after initial study drug dosing date and time.

12.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days (90 days for irAEs) after the date of the last dose of study drug

An AE with completely missing onset and stop dates or with the onset date missing and a stop date after initial study drug dosing date will be considered treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the initial study drug dosing date will be considered treatment emergent.

If only the start time of the IRR is missing and the event occurred on or after the day of the first dose of study drug, then the event will be regarded as treatment emergent.

12.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based upon the Safety Population. Only TEAEs occurring while on treatment and up to and including 30 days after the last dose of study drug (up to and including 90 days after last dose for irAEs) will be included in the adverse events summaries. SAEs occurring between informed consent and first dose as well as any AEs occurring more than 90 days after last study drug dose will be listed.

All TEAEs with PT "Malignant neoplasm progression" unrelated to study drug will be excluded from the AE summaries. These AEs represent the clinical efficacy endpoint of disease progression and will be included within the efficacy analyses.

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

12.1.6.1. Summaries of AE Incidence by Severity

The number and percentage of subjects who experienced AEs described below will be provided and summarized by SOC and PT unless otherwise indicated:

- TEAEs

- TEAEs of Grade 3 or higher (by SOC, PT and maximum severity)

- Treatment-related TEAEs (TRAEs) stratified by study drug (combination therapy)
- TRAEs of Grade 3 or higher (by SOC, PT and maximum severity) stratified by study drug (combination therapy)
- Serious TEAEs
- Serious TRAEs stratified by study drug (combination therapy)
- TEAEs leading to discontinuation of study drug stratified by study drug (combination therapy)
- TEAEs leading to death
- AESIs
- Treatment emergent irAEs
- Treatment emergent irAEs of Grade 3 or higher

A brief, high-level summary of AEs described above will be provided by the number and percentage of subjects who experienced the above AEs. Furthermore, the summary will also include the number and percentage of subjects who experienced infusion related reactions (IRRs), both any grade and Grade 3 or higher.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a particular subject during the study.

In addition to the above summary tables, TEAEs, TEAEs of Grade 3 or higher, TRAEs, TRAEs of Grade 3 or higher, serious TEAEs, TEAEs leading to discontinuation of study drug, and AESIs will be summarized by PT only in descending order of total frequency within indication.

Furthermore, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- Treatment-related AEs

- Treatment-related AEs of Grade 3 or higher
- IRRs
- AESIs
- SAEs
- AEs leading to death (i.e. outcome of death)
- AEs leading to discontinuation of study drug

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

12.2. Study Drug Administration and Exposure

Drug exposure will be summarized by part and dose cohort using the SP. The number of doses administered for CX-072 and each combination with be summarized categorically and continuously. The duration of treatment (in months) will be summarized continuously as will the percent of dose of each study drug. The number and percent of subjects who were administered a dose different from the planned total dose and the reason they received a dose different from the planned total dose will be summarized.

The numbers and percentages of subjects who missed Vemurafenib doses will be summarized.

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

12.3. Prior and Concomitant Medications

All medications taken within 30 days before the administration of study drug and all concomitant medications and therapies administered during the study will be recorded on the relevant eCRF. Summaries will be based on the SP. No formal statistical testing is planned. All medications will be coded using the World Health Organization Drug Dictionary (WHODrug) version dated March 2020 (B3).

Prior and concomitant medications will be summarized by Anatomic Therapeutic Classification (ATC) Level 4 within ATC Level 2 by part and dose level. Each subject will only be counted once within each level of the summary (ATC level 2 or ATC level 4). A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The

summary will be ordered alphabetically by ATC medical class and then by standardized medication name in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be alphabetical.

12.3.1. Prior Non-Anticancer Medications

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

12.3.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

12.4. Prior Anticancer Therapy and Procedures

The number of prior regimens, time since the completion of last prior regimen, time since the last prior procedure, and time since progression in the last regimen will be summarized by indication using descriptive statistics based on the SP.

In deriving the time since the completion of last prior regimen and the time since the last prior procedure, all partial dates will be identified, and the partial dates will be imputed as follows:

- If day is missing but the month and year are available, then the imputed day will be the 15th of the month.

A partial date will not be imputed if the year and/or month is missing.

Prior cancer treatment information including the regimen or procedure, treatment duration, best overall response, reason for therapy ended, and time since disease progression will be listed.

12.5. Clinical Laboratory Tests

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the SP. The analyses will be based on values reported in standard units. When values are below the LOQ, they will be listed as such, and the number associated with the inequality sign will be used for statistical calculations as specified in Section 10.2.

The following laboratory tests are specified in the study protocol:

- Hematology: red blood cells, hemoglobin, hematocrit, platelet, white blood cells, WBC absolute neutrophils, neutrophils, absolute lymphocyte, lymphocyte, absolute monocyte, monocyte, absolute basophils, basophils, absolute eosinophils, eosinophils, blast count.

- Blood chemistry: albumin, protein, uric acid, sodium, potassium, chloride, calcium, phosphorus, chloride, bicarbonate, CO2, blood urea nitrogen (BUN), urea, creatinine, lipase, amylase, magnesium, glucose, lactate dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase.

- Coagulation: Prothrombin time (sec), activated partial thromboplastin time (sec), international normalized ratio (INR)

- Urinalysis:

    - Blood, protein, glucose as negative, trace, positive, 0, +, ++, +++, >+++

    - Specific gravity, pH, Leukocytes, ketones, urobilinogen: Low, normal, high

- Thyroid: thyroid stimulating hormone (TSH), free T3, free T4

- Serology: Anti-Hepatitis C antibody, Hepatitis B virus surface antigen, Hepatitis B core antibody, human immunodeficiency virus (HIV) status

Select laboratory results will be graded based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Laboratory results will be graded only if the criteria do not require clinical findings data. The following laboratory parameters will be

graded: ALT, alkaline phosphatase, AST, bilirubin, lymphocytes, LDH, creatinine, hemoglobin, neutrophils, platelets, WBCs, and lactate dehydrogenase.

A by-subject listing for laboratory test results with at least a CTCAE grade of 2 will be provided by subject identifier and sample collection date in chronological order for hematology, serum chemistry, and urinalysis separately.

No formal statistical testing is planned.

12.5.1. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- AST: (a) > 3 times of the upper limit of normal reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the SP who have non-missing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

12.5.2. Shifts Relative to the Baseline Value

For lab tests that have toxicity grades assigned according to CTCAE version 4.03, shift tables will be presented by showing change in severity grade from baseline to maximum postbaseline severity.

For all other lab tests, shift tables will be presented by showing changes in results from baseline value (low, normal, and high) to the worst postbaseline result (low, normal, high, or low and high). A subject would have a worst postbaseline result of normal if all postbaseline

results are within the normal reference range. The value of "low and high" would be used if the subject has postbaseline values that are below the normal reference range at one visit and above the normal reference range at another visit.

12.6. Other Safety Measures

12.6.1. Vital Signs

Graphical summaries of vital signs data over the course of the study will be prepared by subject within each part and dose cohort. Baseline will be defined as the non-missing assessment attained before and closest to the date/time of first dose of study treatment.

12.6.2. ECGs

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

13. EFFICACY ANALYSES

Efficacy analyses will be limited to subjects who received 10 mg/kg CX-072 IV q2wk monotherapy during the study. This efficacy subset includes subjects from Parts A, A2 and D. Efficacy summaries will include the following:

- Parts A and A2 combined
- Parts A, A2, and D stratified by tumor types specified in Part D:
    - Anal small cell carcinoma
    - Cutaneous small cell carcinoma
    - High tumor mutational burden
    - Small bowel adenocarcinoma
    - Thymoma
    - Triple negative breast cancer
    - Undifferentiated pleomorphic sarcoma

13.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be evaluated via the REP who received 10 mg/kg CX-072 IV q2wk monotherapy during the study. The REP is used for efficacy analyses related to objective tumor response, i.e. ORR, TTR, and DOR.

13.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is ORR where tumor assessments are evaluated by study investigators per RECIST (RECIST v1.1). ORR is defined as the proportion of subjects with CR or partial response PR on two consecutive tumor assessments with scan dates at least 4 weeks apart. For lymphomas, objective response would have been evaluated by Modified Cheson/Lugano Classification for Lymphomas if patients with this tumor type were enrolled in the study.

Subjects who received anticancer therapy other than the study treatment prior to achieving CR or PR, will be considered non-responders and will be included in the denominators in calculations of response rates.

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

In the case of stable disease (SD), measurements must meet SD criteria at least once after study entry with a minimum interval of 7 weeks. If the first post-baseline response

assessment is SD and the assessment occurs less than 7 weeks from first dose of study drug, then the response would be changed to NE.

13.1.2. Best Overall Response

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

When no imaging nor measurements occur at a particular time point, the subject is deemed not evaluable (NE) at the time point. If only a subset of lesion measurements are obtained at an assessment, usually the case is also considered NE at the time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (e.g. in the case of an assessment of PD).

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as per protocol (i.e. ~8 weeks later and no earlier than 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

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

Table 3: Best Overall Response Algorithm

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

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
NE	NE	NE

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = Not Evaluable.

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

Tumor burden assessed using RECIST v1.1 will be calculated as the sum of the longest diameter of target non-nodal lesions plus the short axis of target nodal lesions. Change, percent change, and maximum percent change from baseline will be calculated. The percent changed from baseline will be plotted by time on study via a spider plot. The maximum percent change from baseline will be plotted in a waterfall plot. The spider and waterfall plots will include all visits regardless of whether a response assessment has been recorded (provided that all baseline target lesions were measured at the visit). Complete response is defined as the disappearance of all target lesions. The only exception is pathological lymph nodes (whether target or non-target) which must have reduction in short axis to < 10 mm.

13.1.3. Analysis of the Primary Efficacy Endpoint

The primary efficacy analysis will be based upon the REP. A pooled estimate of ORR will be computed from subjects allocated to Parts A and A2. In addition, ORR estimates will be determined for each tumor type represented in Part D. Exact 95% CIs for ORR will be derived via the Clopper-Pearson method.

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

13.2. Secondary Efficacy Endpoints

13.2.1. Definition of Secondary Efficacy Endpoints

13.2.1.1. Duration of Response (DOR)

DOR is defined as the time from the first documentation of objective response (i.e. ORR = CR or PR) that is subsequently confirmed to the first documentation of disease progression or death due to any cause on study, whichever occurs first. DOR is determined for subjects in the REP who have a confirmed objective tumor response. Subjects who neither progress nor

die will be censored on the date of their last tumor assessment. Subjects who start subsequent anti-cancer therapy prior to progression will be censored on the date of their last tumor assessment prior to the initiation of subsequent anti-cancer therapy. These situations and how censoring is employed are displayed in Table 4.

Table 4: Date of Censoring - DOR

Situation Description	Date of Progression or Censoring	Outcome
No disease progression nor death on-study	Date of last tumor assessment	Censored
Subjects who commence anti-cancer therapy prior to disease progression	Date of last tumor assessment prior to initiation of subsequent anti-cancer therapy	Censored

13.2.1.2. Time to Response (TTR)

Time to Response (TTR) is defined as the time from the date of the first dose of study drug to the first documentation of confirmed objective tumor response. TTR is only determined for subjects who have a confirmed objective tumor response.

13.2.1.3. Progression-Free Survival (PFS)

PFS is defined as the time from the date of the first dose of study drug to the date of first documentation of objective tumor progression (PD) or death due to any cause, whichever occurs first. PFS is determined for the SP. 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 the commencement date of study treatment. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last tumor assessment prior to the initiation of subsequent anti-cancer therapy. These situations are outlined in Table 5.

Table 5. Date of Progression or Censoring - PFS

Situation Description	Date of Progression or Censoring	Outcome
No baseline disease assessments	Date of initiation of study drug	Censored
No on-study tumor assessments and did not die	Date of initiation of study drug	Censored
No disease progression nor death on-study	Date of last tumor assessment with a response assessment other than not evaluable (NE)	Censored
Subjects who started anti-cancer therapy without a prior reported progression	Date of their last tumor assessment with a response assessment other than NE prior to the initiation of subsequent anti-cancer therapy	Censored
Died or progressed (on treatment*) after 2 or more consecutive missed assessments	Date of their last tumor assessment with a response assessment other than NE prior to the consecutive missed assessments	Censored
Died or progressed in follow-up	Date of last tumor assessment with a response assessment other than NE	Censored
Death before first disease assessment	Date of death	Progressed
Death without a reported progression	Date of death	Progressed
Disease progression (on treatment*) without missed assessments	Date of progression	Progressed
Died or progressed (on treatment*) after a single missed assessment	Date of death or disease progression	Progressed

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

13.2.1.1. Overall Survival (OS)

OS is defined as the time from the date of the first dose of study drug to the date of death due to any cause (as captured on the Study Discontinuation, Treatment Termination, Survival

Status and/or AE CRF pages). OS is determined for the SP. Censoring rules for OS appear in Table 6 below.

Table 6: Date of Censoring - OS

Situation Description	Date of Progression or Censoring	Outcome
Last known to be alive and/or lost to follow-up	Date of last contact (noted eCRF pages) • Discontinuation Call • Study Discontinuation • Substudy Discontinuation • Survival Status • Treatment Termination	Censored

13.2.2. Analysis Methods for Secondary Efficacy Endpoints

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

The median and its associated 95% CI for DOR, TTR, PFS, and OS will be determined via Brookmeyer and Crowley (1982). The range of TTR, PFS and OS will also be computed. Frequencies and percentages will be summarized for event rates and censored observations of the time-to-event endpoints. Six- and twelve-month and 2-year survival rates will be computed. The number and percentage of disease progressions and deaths will be included (replacing the event rate) in the PFS summary.

13.2.3. Efficacy Measure During Follow-Up

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

13.2.4. Eastern Cooperative Oncology Group (ECOG) Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2, 3, 4, and 5) will be summarized over time by protocol-specified visits.

14. PHARMACOKINETIC, IMMUNOGENICITY, AND PHARMACODYNAMIC ASSESSMENTS

Pharmacokinetic, immunogenicity, and pharmacodynamic analyses include all subjects in the SP from Parts A, A2, B1, B2, C, D, and the IAP. The summaries will include the following groupings:

- Parts A and A2 combined
- Part B1
- Part B2
- Part C
- CX-072 monotherapy (10 mg/kg) combining subjects in Parts A and A2 and stratifying subjects in Part D by tumor type
- IAP

14.1. PK Assessments

Details of the PK analyses will be provided in a separate PK analysis plan.

14.2. Immunogenicity Assessments

Serum samples will be collected from study participants, as described in the protocol, to assess the immunogenicity of CX-072. Samples will be initially screened for anti-drug antibodies (ADA). If the sample is found to be ADA positive in the screening assay, a confirmatory assay and a titer assay will be performed to further characterize antidrug antibodies.

Immunogenicity analyses will be listed based upon the groupings specified above (Section 14).

15. EXPLORATORY ANALYSES

[redacted]

16. IMAGING SUBSTUDY

This is an open-label, single-arm substudy designed to evaluate the whole body distribution of 89Zr-CX-072 in subjects with locally advanced or metastatic solid tumors or malignant lymphoma prior to treatment with CX-072 on the main study Protocol Module CTMX-M-072-001. The substudy will be conducted at up to 3 sites.

The imaging substudy consists of two parts:

(1) Part I-1, optimal protein dose of CX-072 and the optimal interval between 89Zr-CX-072 injection and scanning will be assessed.
(2) Part I-2, subjects will undergo 89Zr-CX-072-positron emission tomography (PET) imaging at the optimal 89Zr-CX-072 protein dose and optimal scanning schedule determined in Substudy Part I-1 to evaluate the whole body distribution of 89Zr-CX-072 in subjects with locally advanced or metastatic solid tumors or malignant lymphoma.

16.1. Substudy Objectives and Statistical Analyses

16.1.1. Primary Objectives

The primary objective of the substudy is to evaluate the whole body distribution of 89Zr-CX-072 in subjects with locally advanced or metastatic solid tumors or malignant lymphoma.

All subjects in the IAPl be included in the analyses. All PET data will be centrally analyzed. ^{89}Zr-CX-072 tumor uptake and whole body distribution will be scored visually and quantitatively. Quantification of ^{89}Zr-CX-072 distribution will be performed using AMIDE software (Stanford University, Palo Alto, CA, USA). ^{89}Zr-CX-072 uptake will be corrected for body weight and injected dose and assessed using SUV. The SUV of all tumor lesions and relevant normal tissues will be determined for all PET-CT scans.

A summary table including summary statistics of SUV by organ and imaging time point will be determined. A listing of the ^{89}Zr-CX-072-PET scan results will be provided.

16.1.2. Secondary Objectives

The secondary objectives of the substudy are:

(1) To evaluate the correlation of ^{89}Zr-CX-072 tumor uptake with PD-L1 expression as assessed in archival or fresh tumor tissue
(2) To assess the heterogeneity of ^{89}Zr-CX-072 tumor uptake within and between subjects
(3) To describe the safety of ^{89}Zr-CX-072 alone or in combination with CX-072

(4) To evaluate the relationship between tumor uptake of ^{89}Zr-CX-072 and subject response as measured by overall response rate (ORR) in the main study (CTMX-M-072-001)
(5) To characterize the incidence of anti-drug antibodies (ADA) against CX-072
(6) To characterize the PK profile of ^{89}Zr-CX-072 and CX-072

The imaging substudy analyses will be completed outside of this analysis plan. The results will be summarized in the appendix of the clinical study report.

17. REFERENCES

Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics. 1982; 38:29-41. doi:10.2307/2530286.

18. SOFTWARE

SAS® Software Version 9.4M5. SAS Institute Inc., Cary, NC, USA.

19. APPENDIX 1 - ADVERSE EVENTS OF SPECIAL INTEREST AND POTENTIAL IMMUNE-RELATED ADVERSE EVENTS

The following are considered AESIs:

AEs that potentially meet dose limiting toxicity (DLT) criteria are:

- Infusion related reactions ≥ 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 of the following irAEs defined as: AEs requiring the use of systemic corticosteroids within 30 days after the AE onset date with no clear alternate etiology, or requiring the use of systemic hormonal supplementation:
  - Pneumonitis
  - Colitis
  - Hepatitis (including AST or ALT elevations > 3 · ULN or bilirubin > 1.5 · ULN)
  - Nephritis (including serum creatinine > 1.5 · ULN)
  - Pancreatitis
  - Motor and sensory neuropathy
  - Myocarditis
  - Encephalitis
  - Endocrinopathies (including but not limited to hypothyroidism, hyperthyroidism, hypophysitis, diabetes mellitus, and adrenal insufficiency)
  - Ocular toxicities (e.g. uveitis)
  - Skin reactions including Stevens-Johnson syndrome or toxic epidermal necrolysis
  - Diarrhea.

The following table includes all preferred terms that are considered potential irAEs:

Alanine aminotransferase increased	Febrile neutropenia	Pneumonitis
Arthralgia	Guillain-Barre syndrome	Pruritus
Aspartate aminotransferase increased	Hyperthyroidism	Rash
Autoimmune hypothyroidism	Hypophysitis	Rash macular
Blood bilirubin increased	Hypothyroidism	Rash maculo-papular
Colitis	Immune-mediated hepatitis	Thrombocytopenia
Diarrhoea	Myocarditis	Thyroiditis acute
Drug eruption	Neutropenia	Transaminases increased

Potential irAEs that are considered related to CX-072 are reviewed by the CytomX Safety group to determine if the AE requiring the use of systemic corticosteroids within 30 days after the AE onset date with no clear alternate etiology, or requiring the use of systemic hormonal supplementation. If so, then the AE is considered irAE.