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)

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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-072
Module Number:	CTMX-M-072-002
IND Number:	142922
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Sponsor:	CytomX Therapeutics, Inc. 151 Oyster Point Boulevard, Suite 400 South San Francisco, CA 94080-1913 [redacted]
Medical Monitor/ Medical Expert:	[redacted], MD, PhD Senior Medical Director CytomX Therapeutics, Inc. [redacted]

Date of Original Module:	18 April 2019
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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.

[redacted] [redacted]

Senior Medical Director
CytomX Therapeutics, Inc.

INVESTIGATOR AGREEMENT

By signing below I agree that:

[redacted]
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 [redacted] documents:

- [redacted]
- This CX-072-specific Module (CTMX-M-072-002)

Briefly, the [redacted]

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. [redacted]

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

[redacted]

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.

[redacted]

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.

[redacted]

SPONSOR

CytomX Therapeutics, Inc.
151 Oyster Point Boulevard, Suite 400
South San Francisco, CA 94080-1913 USA
[redacted]

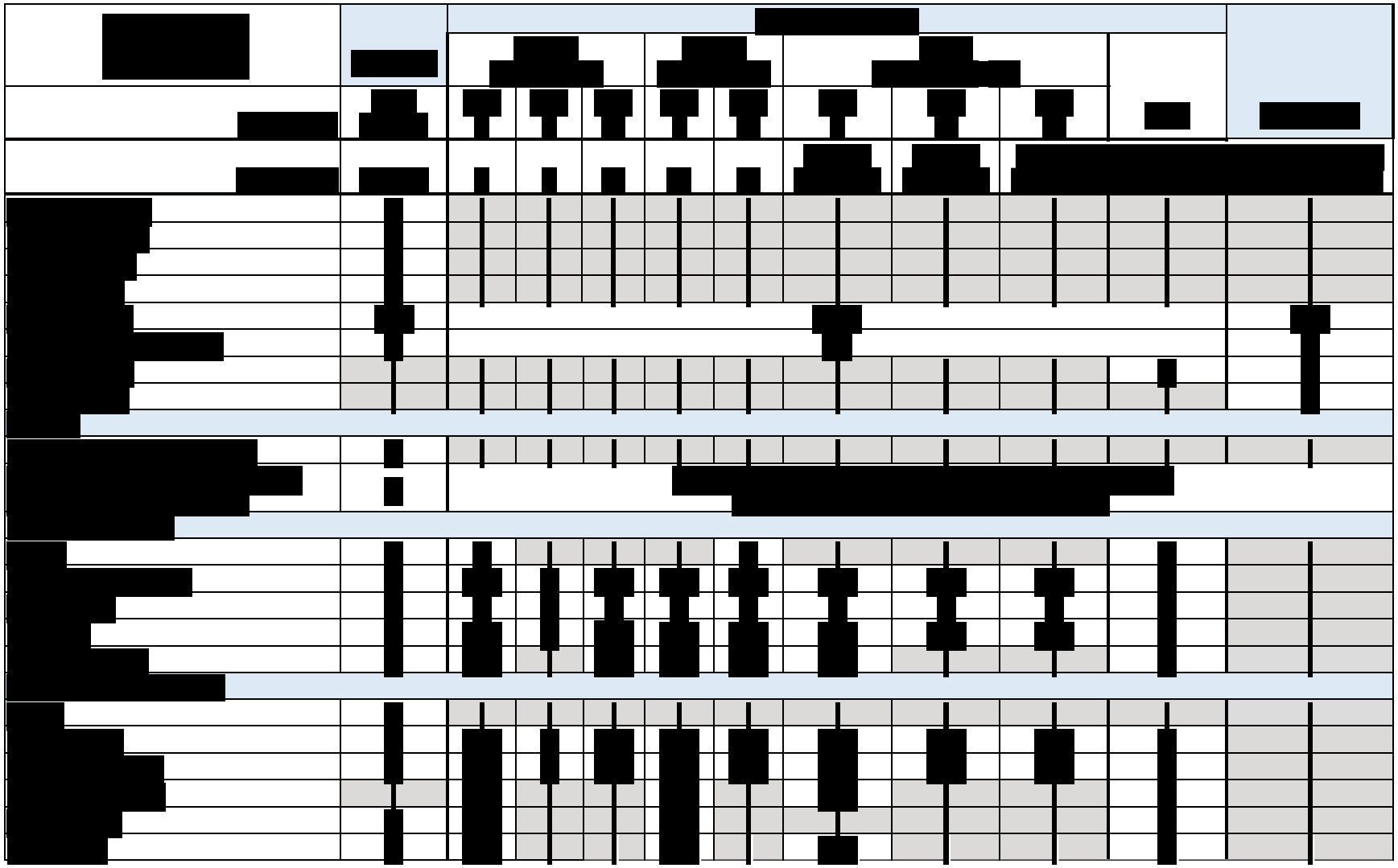
STUDY SCHEMATIC

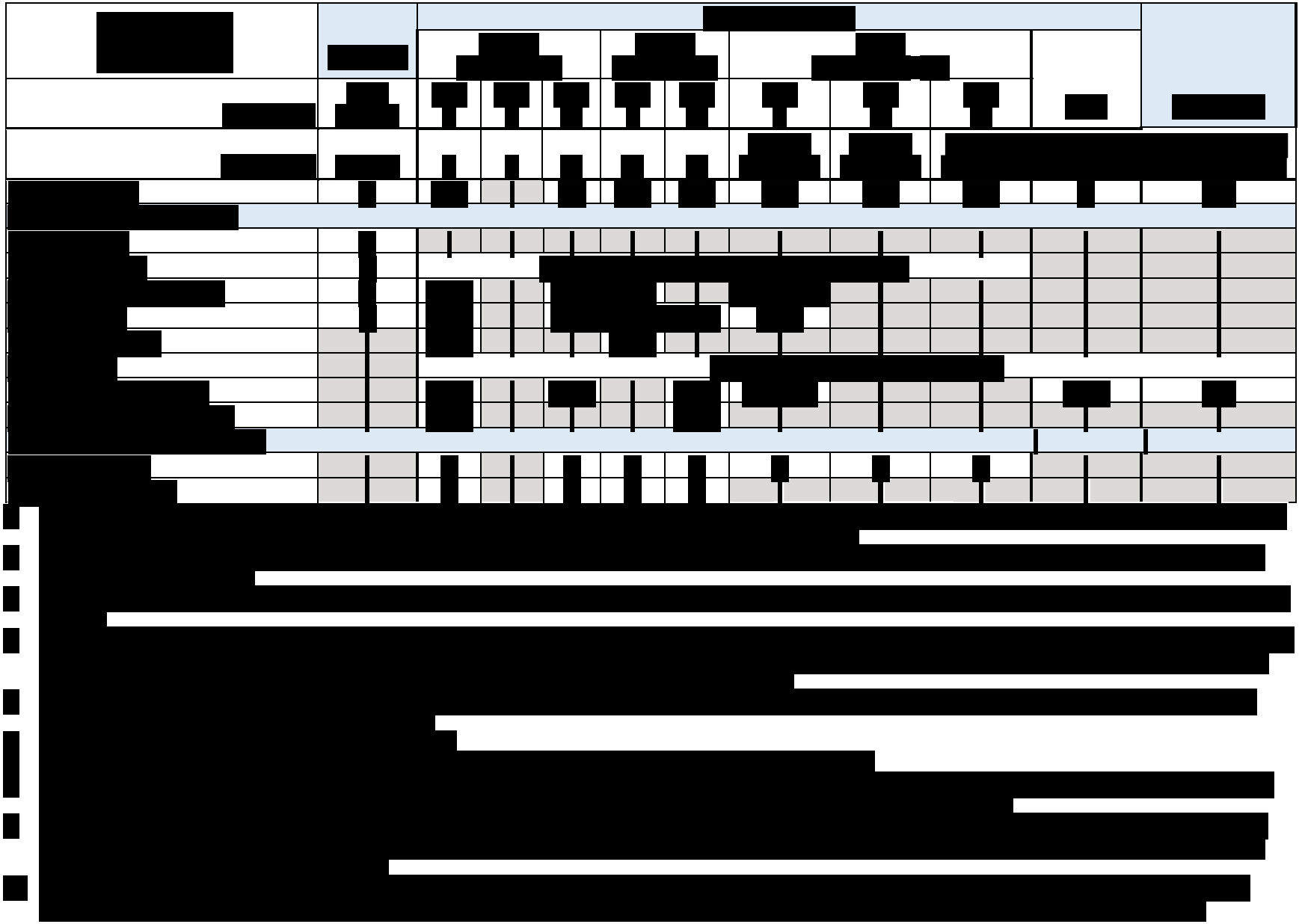
Figure 1 Study Schematic (Parts A and B)

SCHEDULE OF ASSESSMENTS – PART A

Refer to the footnotes below the table, applicable sections within this Module, [redacted] for descriptions of each assessment.

[redacted]

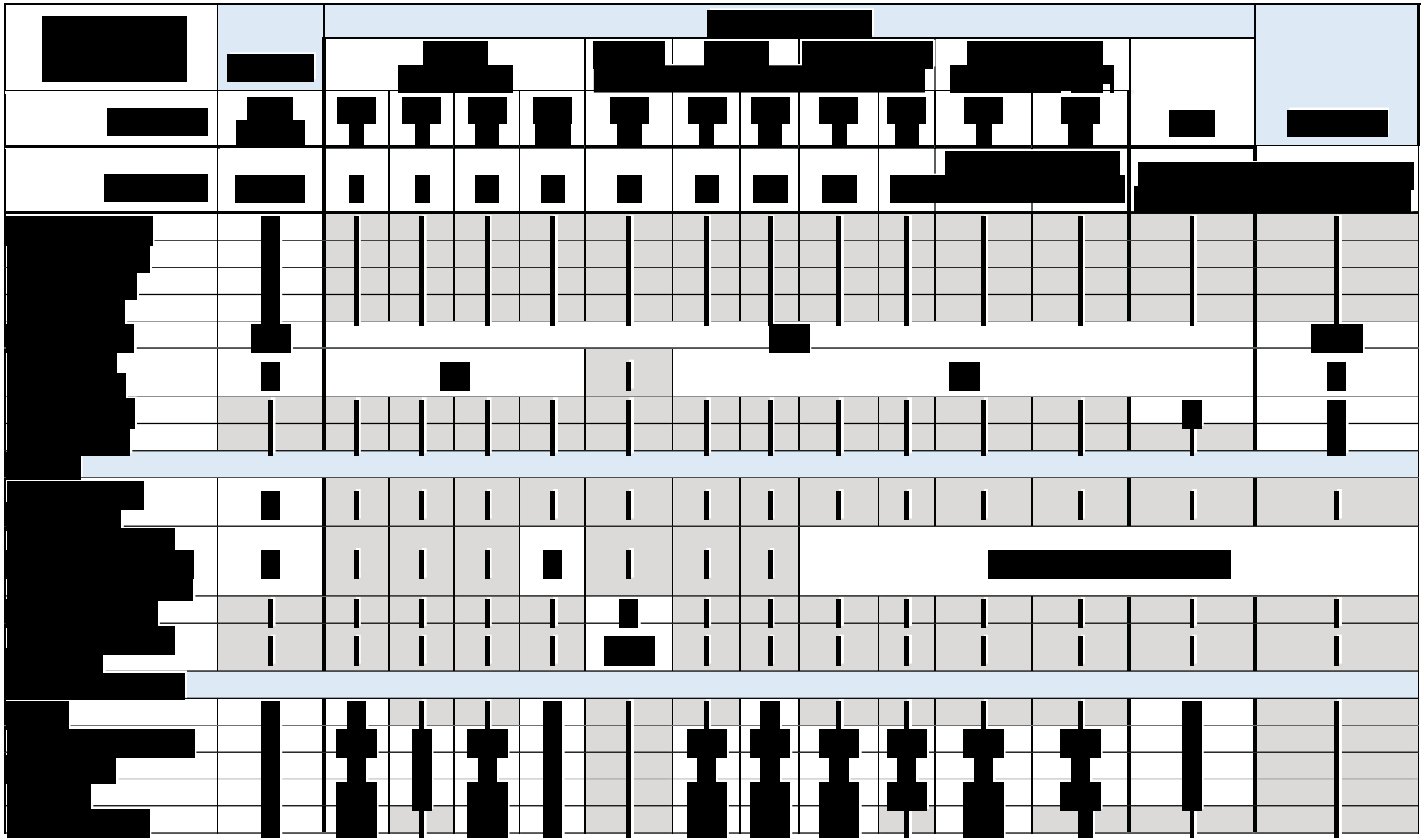


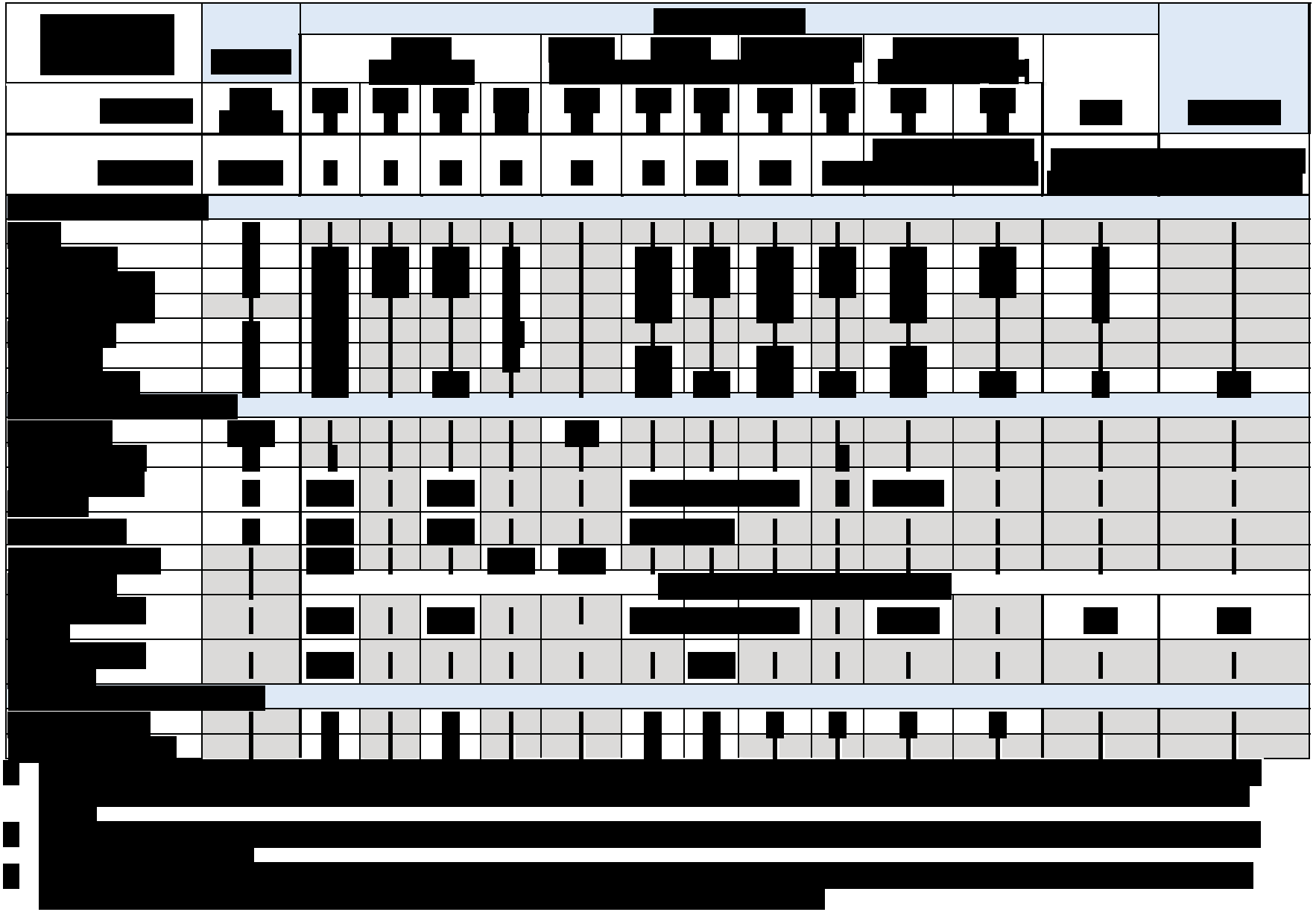


SCHEDULE OF ASSESSMENTS – PART B

Refer to the footnotes below the table, applicable sections within this Module, [redacted] for descriptions of each assessment.

Table 2 Schedule of Assessments: Part B





PHARMACOKINETIC PLASMA SAMPLING – PARTS A AND B

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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:

- [redacted]
- This CX-072-specific Module (CTMX-M-072-002)

Briefly, [redacted], or [redacted] 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. [redacted] 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.

[redacted]

1.3.2 Summary of CX-072 Clinical Safety Data

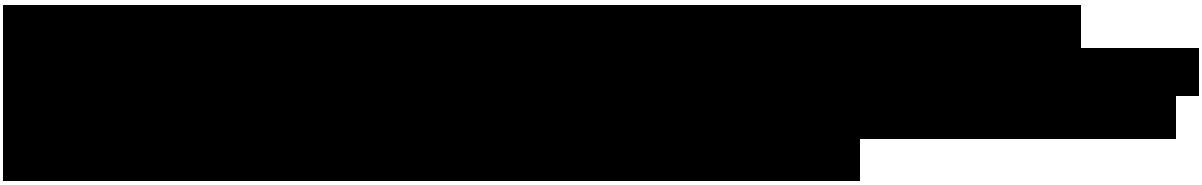
Module CTMX-M-072-001, a first in human, Phase 1-2a study (enrollment initiated in January 2017), is currently ongoing and is composed of 7 parts: Part A – monotherapy dose escalation, Part A2 – biomarker assessment and dose effect; Parts B1 and B2 – combination with ipilimumab; Part C – combination 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.



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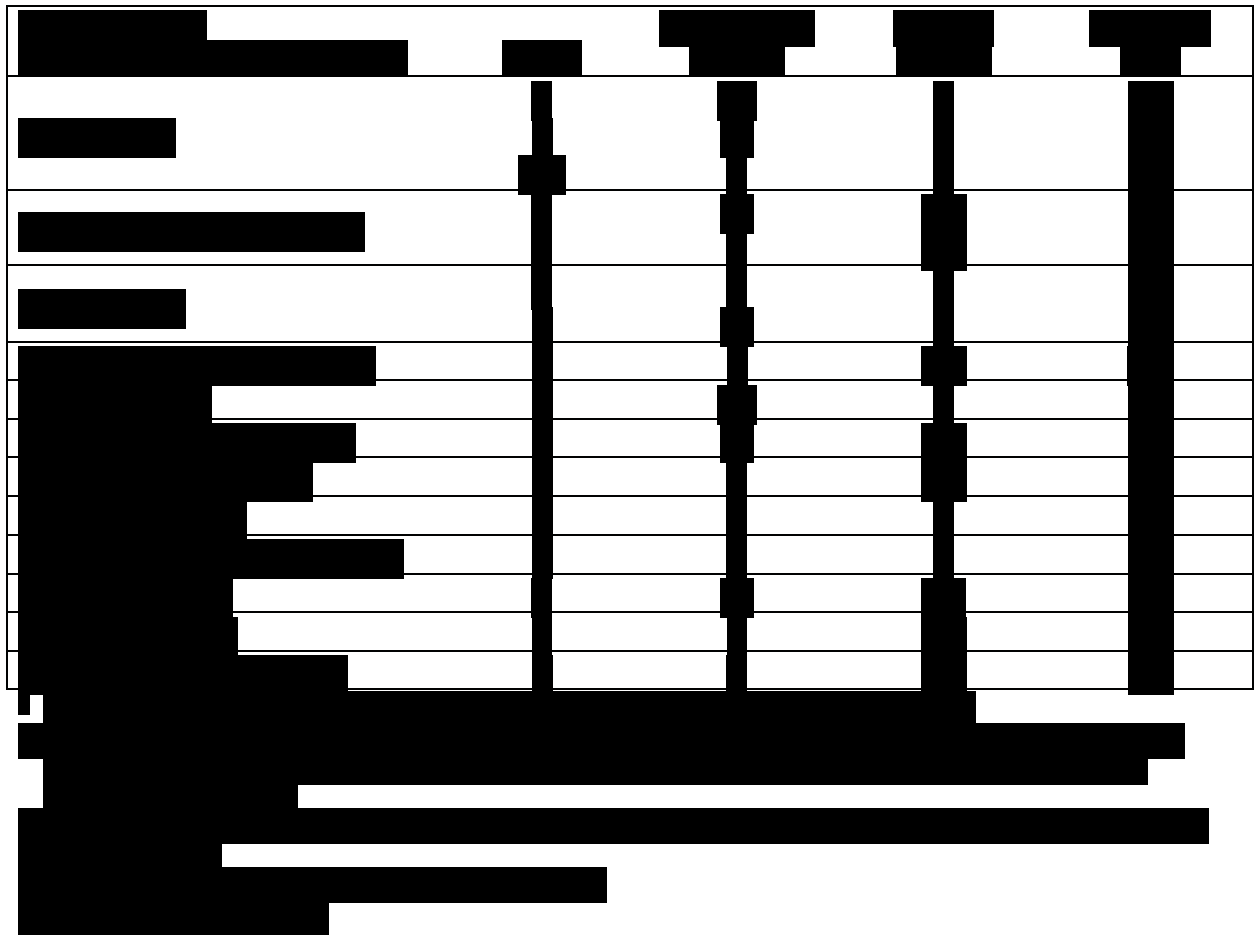

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1.4 Study Rationale

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.

[redacted]

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.

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

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 ([redacted]) 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

[redacted]

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).

[redacted]

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

[redacted]

5.2 Study Drug Administration and Dosing Regimen

5.2.1 Study Drug Administration

[redacted]

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.

[redacted]

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.

[redacted]

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).

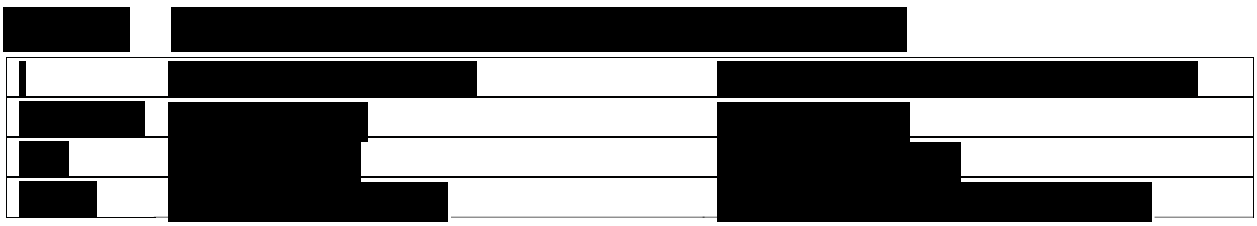
9.6 Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction Reporting

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.



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.

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 [redacted] 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

10.2 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 [redacted], the SAP supersedes the Module [redacted].

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 [redacted] 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
[redacted]

12.2.2 Contract Research Organizations

[redacted]

13 REFERENCES

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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 [redacted] mendments. 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.

[redacted] 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.