Official Title of Study: A First-in-Human, Multicenter, Phase 1/2, Open-Label Study of XTX202 in Patients with Advanced Solid Tumors

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STUDY PROTOCOL

XTX202-01/02-001

A First-in-Human, Multicenter, Phase 1/2, Open-Label Study of XTX202 in Patients with Advanced Solid Tumors

Protocol Number:	XTX202-01/02-001
Phase:	1/2
Date of Protocol:	07 February 2024
Version:	6.0 (Amendment 5)
Previous Version:	20 April 2023 (Amendment 4)
Sponsor:	Xilio Development, Inc. 828 Winter Street Waltham, MA 02451
Medical Monitor:	[redacted]

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SPONSOR PROTOCOL APPROVAL

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements, including 21 CFR parts 11, 50, 54, 56, and 312.

I have read this protocol and approve the design of this study:

[redacted]

[redacted] Signature Date

Chief Medical Officer
Xilio Development, Inc.

INVESTIGATOR PROTOCOL APPROVAL

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to principles of Good Clinical Practice and local regulations and requirements.

Institution/Clinic: _____

Principal Investigator

Print Name: _____

Signature: _____

Date (dd/mm/yyyy): _____

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Xilio Development, Inc.	828 Winter Street Waltham, MA 02451	[redacted]
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1. SYNOPSIS

Name of Sponsor/Company: Xilio Development, Inc.		
Name of Investigational Product: XTX202		
Name of Active Ingredient: XTX202 is a fully human, masked and modified fragment crystallizable (Fc) fusion, recombinant human interleukin-2 (IL-2) protein.		
Protocol Number: XTX202-01/02-001	**Phase:** 1/2	**Country:** United States
Title of Study: A First-in-Human, Multicenter, Phase 1/2, Open-Label Study of XTX202 in Patients with Advanced Solid Tumors		
Study Center(s): Phase 1 and Phase 2: up to 40 sites in the United States and globally		
Studied Period (Years): Estimated date first patient enrolled: January 2022 Estimated date last patient completed: December 2025		
Study Duration: Patients will remain on XTX202 until disease progression, unacceptable toxicity, 3 cycles after confirmed complete response (CR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (provided they have been treated for at least 8 cycles), completion of 24 months of study therapy, termination of the study by Sponsor, death, or withdrawal of consent. [redacted] Patients may continue study treatment beyond the durations noted in the protocol if recommended by the Investigator to be in the best interest of the patient and approved by the Sponsor. Each patient treated on study in Phase 2 will be followed for survival for 24 months after his or her first dose of study drug, until the last patient completes study treatment, or the study is terminated by the Sponsor, whichever comes first.		
Objectives (Phase 1: Part 1a and Part 1b): **Primary** • To evaluate the safety and tolerability of XTX202 monotherapy in patients with advanced solid tumors • To determine the recommended Phase 2 dose(s) (RP2D[s]) and schedule of XTX202 monotherapy **Secondary** • To characterize the pharmacokinetic (PK) profile of XTX202 • To evaluate the immunogenicity of XTX202 • To evaluate the preliminary antitumor activity of XTX202 monotherapy in patients with advanced solid tumors		

[redacted]

Objectives (Phase 2):

Primary

- To evaluate the efficacy of XTX202 monotherapy in patients with metastatic renal cell carcinoma (RCC) and patients with unresectable or metastatic melanoma

Secondary

- To evaluate the safety and tolerability of XTX202 monotherapy in patients with metastatic RCC and patients with unresectable or metastatic melanoma
- To characterize the PK profile of XTX202 in patients with metastatic RCC and patients with unresectable or metastatic melanoma
- To evaluate the immunogenicity of XTX202 in patients with metastatic RCC and patients with unresectable or metastatic melanoma
- To further evaluate the efficacy of XTX202 monotherapy in patients with metastatic RCC and patients with unresectable or metastatic melanoma

[redacted]

Methodology:

General Study Design

This is a first-in-human, Phase 1/2, multicenter, open-label study designed to evaluate the safety, tolerability, and efficacy of XTX202, an engineered IL-2 prodrug with its activity masked, as monotherapy in patients with advanced solid tumors.

Phase 1 will consist of 2 parts:

- Part 1a will examine XTX202 monotherapy in an accelerated and standard 3+3 dose escalation design. Based on the results of Part 1a, patients with select advanced solid tumors will be enrolled in Part 1b.
- Part 1b will evaluate XTX202 monotherapy in relation to specific PD biomarkers; patients in Part 1b will be required to have fresh tumor biopsies predose and postdose. [redacted]

A schedule of assessments for Part 1a is provided in Table 1 and for Part 1b in Table 3.

Phase 2 will consist of 2 parts:

- Part 2a will enroll patients with metastatic RCC who have received a tyrosine kinase inhibitor (TKI) therapy and also have been treated and progressed on an anti-PD-1 therapy to determine the efficacy of XTX202 monotherapy in this population
- Part 2b will enroll patients with unresectable or metastatic melanoma who have received immune-checkpoint therapy with an anti-PD-1 therapy to determine the efficacy of XTX202 monotherapy in this population

A schedule of assessments for Phase 2 is provided in Table 3.

Note: Based on the January 2023 Food and Drug Administration (FDA) draft guidance, "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases," (US FDA 2023) the Safety Review Committee (SRC) may recommend more than 1 dose to be evaluated in the Phase 2 portion of the study in order to identify the optimal XTX202 dose for further development. The SRC may recommend each RP2D based on the totality of the data (safety, efficacy, and available PK and PD data), and Phase 2 may open in parallel with ongoing dose escalation in Part 1a prior to reaching the maximum tolerated dose (MTD). Once more than 1 RP2D is defined, patients in Phase 2 will be allocated to a dose level by the Sponsor.

Once an RP2D is defined based on SRC recommendation, any patient in the study remaining on treatment at a dose level lower than the highest RP2D without a treatment response after at least 3 cycles of therapy may have their dose escalated to a previously cleared dose level, if recommended by their treating investigator.

[redacted]

Phase 1 (Part 1a) (XTX202 Monotherapy Dose Escalation)

Part 1a will evaluate ascending doses of XTX202 monotherapy administered via intravenous (IV) infusion every 3 weeks (Q3W). Part 1a will employ a single-patient accelerated 100% dose escalation design. If a Grade ≥ 2 adverse event (AE) or any dose-limiting toxicity (DLT) is observed, then the study will transition to a 3+3 dose escalation that will include a 40% increase over the previous dose.

[redacted]

Beginning with dose level (DL) 6 in the 100% dose escalation design (8.0 mg/kg), the study will automatically transition to a conventional 3+3 design with a 40% dose increase independent of whether a Grade ≥ 2 AE or DLT is observed at the preceding dose level.

[redacted]

[redacted]

Abbreviations: AE = adverse event; DL = dose level; DLT = dose limiting toxicity; Q3W = every 3 weeks; SRC = safety review committee.

Note: Additional dosing schedules may be explored at any DL based on recommendation of the SRC and confirmation from the Sponsor. Intermediate DLs may be explored during dose escalation if approved by the SRC; lower DLs may be explored as additional DLs based on results of escalation and if approved by the SRC and Sponsor.

A patient will be enrolled at DL1 and monitored for 21 days postdose (the DLT Observation Period). If no Grade ≥ 2 AE or DLT is observed, then dose escalation will proceed to the next DL. Dose escalation will continue with a naïve single patient at each DL up to DL6 in the 100% dose escalation design (8.0 mg/kg) as long as no patient experiences a Grade ≥ 2 AE or DLT. If a Grade ≥ 2 AE or a DLT is observed in any patient, dose escalation will proceed with a 40% increase over the previous dose and transition to a conventional 3+3 design. Grade ≥ 2 AEs assessed by the SRC to have an etiology completely unrelated to study drug will not trigger a transition to 3+3 dose escalation.

[redacted]

Starting at DL6 in the 100% dose escalation design (8.0 mg/kg), Part 1a will transition to a conventional 3+3 design with a 40% dose escalation independent of whether any Grade ≥ 2 AE or DLT is observed at the preceding dose levels. Under the 3+3 design, if no patients experience a DLT, escalation will continue to the next DL; if 1 of the first 3 patients at a given DL has a DLT, then an additional 3 patients will be enrolled at that DL; if ≥ 2 patients have a DLT during the DLT Observation Period (21 days), dose escalation will be stopped and the DL immediately below this level will be considered the MTD.

After all naïve patients within a given DL have been followed for at least 21 days after first dose, the SRC will review all accumulated safety data and available laboratory and PK data. Initiation of the next DL will commence upon recommendation by the SRC and agreement from the Sponsor.

Dose escalation will continue until either an MTD is determined and/or the highest RP2D is defined.

Up to [redacted] additional patients may be enrolled at any DL with < 2 DLTs. These additional patients will not be considered for defining the MTD but will contribute to the overall safety assessment and PK/PD profile at that DL. The RP2D(s) selected for evaluation in Phase 2 will be based upon review of the cumulative safety, PK, PD, and available preliminary antitumor activity observed.

Phase 1 (Part 1b) (Pharmacodynamic Tumor Evaluation)

Based on the results from Part 1a, Part 1b will be initiated to further examine XTX202 as monotherapy in patients with select advanced solid tumors and to further characterize XTX202. Part 1b will require mandatory fresh tumor biopsies predose and postdose to fully characterize the PD profile of XTX202.

Phase 2

Part 2a (Patients with RCC)

Part 2a will include up to [redacted] patients with metastatic RCC in an optimal Simon's 2-stage design; patients will be treated with XTX202 monotherapy at the RP2D(s) until progression of disease, unacceptable toxicity, 3 cycles after CR, (provided they have been treated for at least 8 cycles), or 24 months of total study therapy.

Part 2b (Patients with Melanoma)

Part 2b will include up to [redacted] patients with unresectable or metastatic melanoma in an optimal Simon's 2-stage design; patients will be treated with XTX202 monotherapy at the RP2D(s) until progression of disease, unacceptable toxicity, 3 cycles after CR (provided they have been treated for at least 8 cycles), or 24 months of total study therapy.

DLT Criteria (Part 1a only)

DLTs will be evaluated during Part 1a (monotherapy dose escalation). The DLT Observation Period will include the first cycle of XTX202 and will run for approximately 21 days, beginning at Cycle 1, Day 1 (C1D1) and ending just prior to the second dose of the study drug at C2D1. No patient with a DLT will be replaced. For any patient in a dose hold prior to C2D1, the DLT Observation Period may be extended up to 7 days (28 days total) to confirm the evaluation of potentially ongoing DLTs.

A patient will be considered non-evaluable for DLT assessment if, for any reason other than an XTX202-related AE, the patient is unable to complete the DLT Observation Period (Days 1 to 21). Patients in Part 1a who are considered non-evaluable may be replaced after consultation between the Investigator and Sponsor.

DLTs are any of the toxicities listed below occurring during the DLT Observation Period, except those attributable solely to disease progression, intercurrent illness, or concomitant medications. Grade 3 or 4 laboratory abnormalities that occur without clinical sequelae, do not require hospitalization, last < 72 hours, and resolve spontaneously or to conventional medical interventions, will not be considered DLTs. Any Grade 3 or 4 neutropenia or lymphopenia lasting < 7 days is not considered a DLT if the above clinical criteria also apply. More information on DLT criteria is provided in Section 6.4.1.

Any AE that meets DLT criteria but occurs after the DLT Observation Period may be considered by the SRC for the selection of the RP2D(s). All toxicities (AEs) will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 based on Investigator assessment.

DLTs for Part 1a are defined as the following:

- Any treatment-related Grade ≥ 3 toxicity
- Any Grade febrile neutropenia
- The following nonhematologic exceptions:
  - Grade 3 nausea or vomiting lasting < 3 days
  - Grade 3 fatigue lasting < 7 days
- Any treatment-related toxicity that results in a treatment delay of ≥ 7 days

After a DLT has occurred, if the Investigator determines that continued treatment with XTX202 is in the patient's best interest, treatment with XTX202 at a reduced dose may resume after consultation with the Medical Monitor.

General Study Conduct

Schedules of assessments are provided in Table 1 and Table 3. If the patient is unable to attend a visit in person for medical reasons or due to circumstances outside of his or her control, alternative means of performing study assessments may be implemented by the site or Sponsor that may include telemedicine, local testing facilities, or deploying trained staff to the patient's home to perform protocol-required assessments.

Assessment of Safety

Safety will be assessed through the monitoring of AEs (including DLTs), physical examinations, and regular clinical laboratory evaluations.

Patients will be monitored continuously for toxicity while on treatment until the Safety Follow-up Visit (90 days after the last dose). AE severity will be assessed using the NCI-CTCAE version 5.0. Dose modifications will be applied for AEs assessed as related to XTX202 and of particular severity according to the guidelines set forth in the study protocol (Section 10.2).

Assessment of Efficacy

Imaging by computed tomography or magnetic resonance imaging as appropriate to anatomical regions of disease involvement will be conducted using a consistent modality to enable response assessment according to RECIST 1.1 (Eisenhauer 2009). Adjunctive imaging by positron emission tomography is permitted. The frequency of efficacy assessment is outlined in Table 1 and Table 3.

Assessment of Pharmacokinetic and Pharmacodynamic Activity

Blood samples for PK assessment will be collected in all parts of the study, at the schedules outlined in Table 1, Table 2, Table 3, and Table 4.

Plasma will be collected to determine the circulating levels of XTX202, and serum will be collected for the assessment of immunogenicity. Peripheral blood will be collected for immunophenotyping analysis to assess T-cell subsets and their activation states and for the analysis of immune-related gene expression.

In both Part 1a and Phase 2, archival tumor samples or fresh tumor biopsies will be collected to characterize potential biomarkers of response.

In Part 1b, mandatory fresh tumor biopsy samples (predose and postdose) will be used for PD assessment, including immunohistochemistry for tumor-infiltrating lymphocytes (TILs) and changes in immune-related gene expression.

Number of Patients (Planned):

It is anticipated the study may enroll up to approximately [redacted] across all parts of the study:

- Phase 1 – Dose Escalation and PD Expansion: [redacted]
  - Part 1a – Dose Escalation: up to [redacted]
  - Part 1b – PD Dose Expansion: [redacted]
- Phase 2 – Dose Expansion: [redacted]
  - Part 2a: up to [redacted] with metastatic RCC
  - Part 2b: up to [redacted] with unresectable or metastatic melanoma

Diagnosis and Main Criteria for Inclusion:

Patients are eligible for inclusion if all the following criteria are met:

1. Must be ≥ 18 years of age on day of signing informed consent
2. Disease criteria
   a. Phase 1, Part 1a: Any histologically or cytologically confirmed solid tumor malignancy that is locally advanced or metastatic and has failed standard therapy, or standard therapy is not curative or available
   b. Phase 1, Part 1b: Histologically or cytologically confirmed solid tumor malignancy with 1 of the following tumor histologies:
      i. RCC of clear cell histology only
      ii. Melanoma
      iii. Squamous cell skin carcinoma
      iv. Ovarian cancer
      v. Non-small cell lung cancer
      vi. Additional tumor types for which the Investigator believes there is scientific rationale to expect potential benefit, upon Sponsor approval

      Notes for Part 1b:

      Patients enrolled in Part 1b must have been previously treated with available standard therapy. Those patients who previously received immunotherapy must have, based on Investigator judgment, derived benefit from this treatment (examples would include achieving a complete or partial response, or prolonged stable disease while on immunotherapy).

      [redacted]

[redacted]

c. Phase 2, Part 2a: Patients with metastatic RCC who have previously been treated with an anti-programmed cell death protein 1 (PD-1) and a TKI per local and institutional standard of care. Patients must have progressed on treatment with an anti-PD-1 monoclonal antibody (mAb) administered either as monotherapy or in combination with other therapies.

d. Phase 2, Part 2b: Patients with unresectable or metastatic melanoma who have previously been treated with at least 1 prior line of therapy in the recurrent or metastatic setting. Prior therapy must have included an anti-PD-1 alone or in combination per local and institutional standard of care, and patient must have progressed on checkpoint inhibitor therapy. Patients with BRAF V600-activating mutation must have previously received targeted therapy per local and institutional standard of care.

[redacted]

3. Phase 2: measurable disease per RECIST 1.1

[redacted]

5. Eastern Cooperative Oncology Group performance status of 0 or 1
6. Adequate organ function, [redacted]

[redacted]

7. For Part 1b only: Tumor tissue samples: Patients must have lesions amenable to biopsy and be willing and able to provide fresh tumor biopsies (core, incisional, or excisional biopsy) before and after initiation of study treatment. [redacted]

[redacted]

11. Women of childbearing potential (WOCBP) (i.e. those not surgically sterile or postmenopausal) and male patients must be willing to abstain from sexual activity or use an approved contraceptive method for the duration of the study and for 3 months after the last administration of the study drug. WOCBP must have a negative serum pregnancy test at the time of study enrollment and prior to first dose of the study drug
12. Provide written informed consent and willing and able to comply with requirements of the study protocol

Exclusion Criteria

Eligible patients must not meet any of the following criteria:

1. Prior treatment with IL-2 therapy
2. History of or active autoimmune disorder that requires immunosuppressive therapy

   [redacted]
3. Anticipated to require another antineoplastic therapy during the course of the study
4. History of significant pulmonary disease including interstitial lung disease or pulmonary fibrosis
5. History of clinically significant cardiovascular disease including myocardial infarction, unstable angina, or coronary artery bypass grafting/angioplasty within the past 6 months; uncontrolled hypertension; ventricular arrhythmias requiring treatment; symptomatic congestive heart failure; symptomatic valvular heart disease; or myocarditis
6. [redacted]
7. For Part 1a only: Evidence of significant coronary artery disease on cardiac imaging performed during the screening period. The choice of appropriate imaging, such as stress echocardiography or nuclear perfusion scan, should be per standard local practice, with cardiology consultation as needed
8. [redacted]

[redacted]

9. Has an active autoimmune disease that has required systemic treatment in past 2 years, including the use of disease-modifying agents, corticosteroids, or immunosuppressive drugs

[redacted]

10. Has an active infection requiring systemic therapy within 4 weeks prior to study treatment.

[redacted]

14. Pregnant or breastfeeding

[redacted]

Investigational Product, Dosage, and Mode of Administration:

XTX202 will be administered by IV infusion at a starting dose of 0.27 mg/kg Q3W as outlined in Table 5. As of the writing of Protocol Amendment 5, 2 RP2Ds for XTX202 monotherapy have been defined at 1.4 mg/kg Q3W and 4 mg/kg Q3W.

Duration of Treatment:

XTX202 will be administered until disease progression, unacceptable toxicity, 3 cycles after confirmed CR per RECIST version 1.1 (provided they have been treated for at least 8 cycles), completion of 24 months of study therapy, termination of the study by Sponsor, death, or withdrawal of consent. [redacted]

Endpoints:

Primary (Phase 1)

- Incidence of DLTs (Part 1a only)
- Incidence of treatment-emergent AEs (TEAEs) and changes in clinical laboratory values

Secondary (Phase 1)

- Plasma concentrations of XTX202 (total and intact), including maximum observed serum concentration (C_{max}), time of maximum observed concentration (T_{max}), trough concentration (C_{trough}), area under the curve (AUC), half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd)
- Antidrug antibody (ADA) occurrence and titer in serum
- Investigator-assessed objective response rate (ORR) per RECIST 1.1

Primary (Phase 2)

- Investigator-assessed ORR per RECIST 1.1

Secondary (Phase 2)

- Incidence of TEAEs and changes in clinical laboratory values
- Plasma concentrations of XTX202 (total and intact), including C_{max}, T_{max}, C_{trough}, AUC, $t_{1/2}$, CL, and Vd
- Incidence and persistence of ADAs (including neutralizing ADAs) and titers, and their potential impact on PK, activity, and safety associated with XTX202
- Duration of response (DOR), defined as the time from first documented response to first documented disease progression
- Disease control rate, defined as the percent of patients who achieve a CR, partial response (PR), or stable disease (SD)
- Progression-free survival (PFS), defined as the time from first dose to first documented disease progression or death
- Overall survival (OS), defined as the time from first dose to death due to any cause

[redacted]

Statistical Methods:

No hypothesis will be formally tested in the Phase 1 dose escalation study, and the statistical methods will be primarily descriptive. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (n), mean, standard deviation, median, and range (minimum and maximum). Within each part, the analyses will be by dose group. Across different parts of the study, patients on the same DL may be pooled together, if specified.

A formal statistical analysis plan will be developed and finalized prior to study database lock.

Sample Size Determination

Phase 1 may enroll up to [redacted] during dose escalation and PD expansion. The number of patients treated in Phase 1 of the study will be based on safety and tolerability observed during dose escalation.

- Part 1a: with up to 14 dose cohorts planned, Part 1a may enroll up to [redacted] during dose escalation.
- Part 1b may enroll up to [redacted]

In Phase 2, Part 2a and Part 2b will each enroll up to [redacted] at the RP2D(s) in a Simon's 2-stage design to exclude an ORR < 5%.

Statistical Analysis

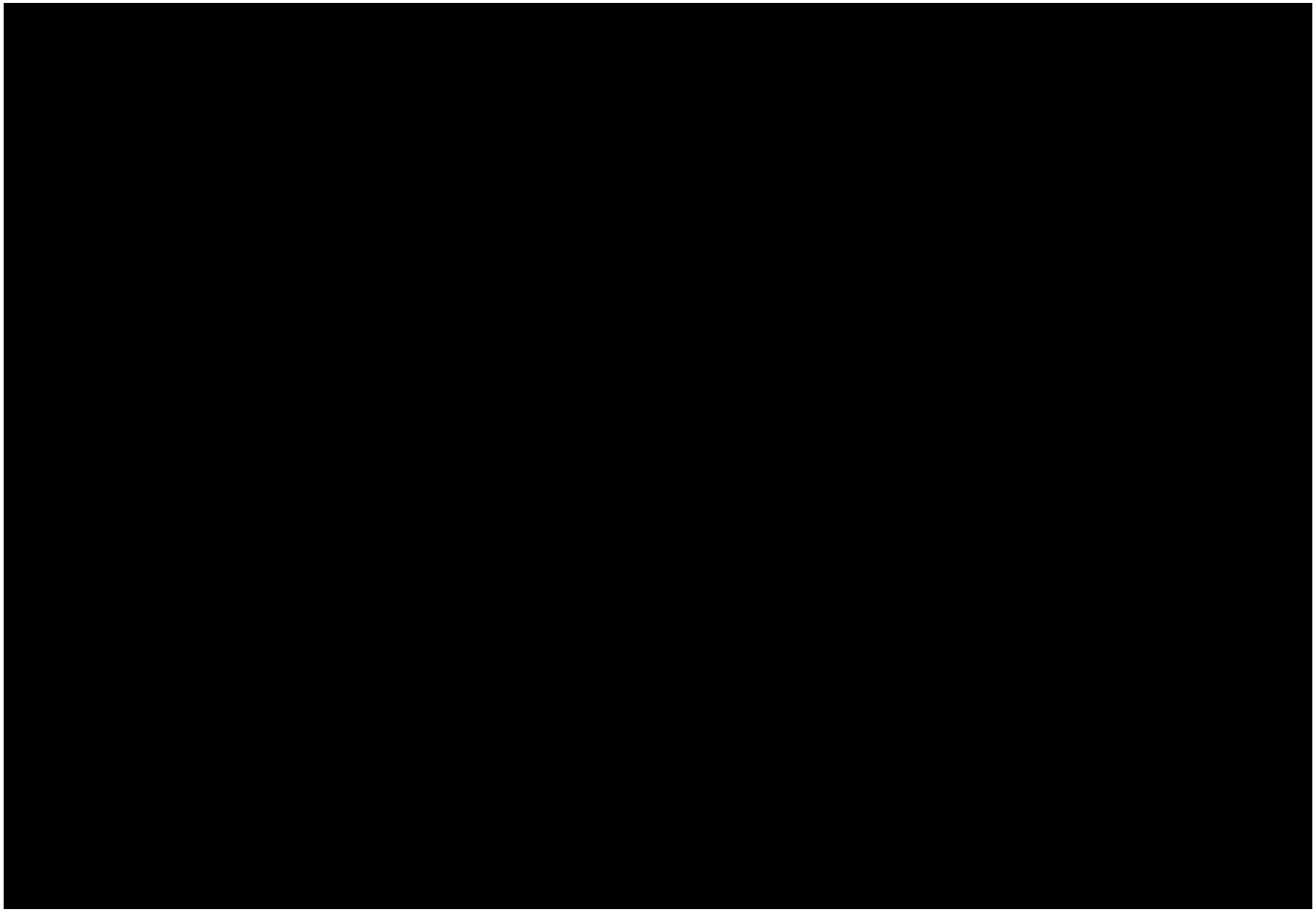
For Phase 1, Part 1a the number and type of DLTs experienced by patients will be summarized for each DL, accompanied by a by-patient listing of DLT events. The listing will include the description, severity, and relationship of the events to XTX202.

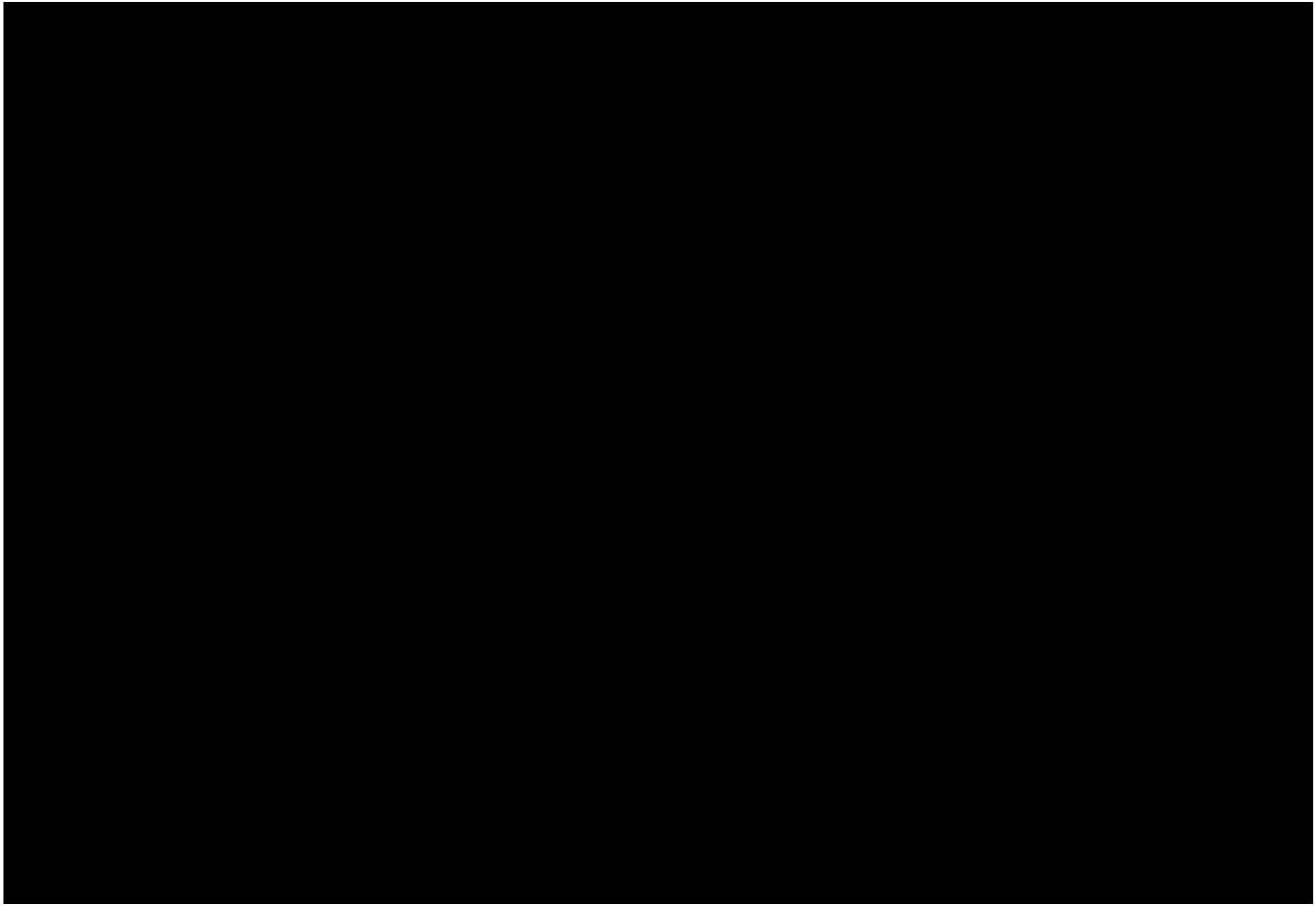
In all parts of the study, safety data, including vital signs, electrocardiograms (ECGs), laboratory test results, physical examinations, and AEs, will be summarized by dose and assessment timepoints, as appropriate. Change from baseline will be included in summary tables for laboratory, ECG, and vital sign parameters. Shifts in grade from baseline to maximum post-baseline grade will be summarized for each DL, as appropriate, for applicable laboratory data. Summaries of patients with AEs Grade ≥ 3 or laboratory values Grade ≥ 3 will be tabulated by DL, as appropriate.

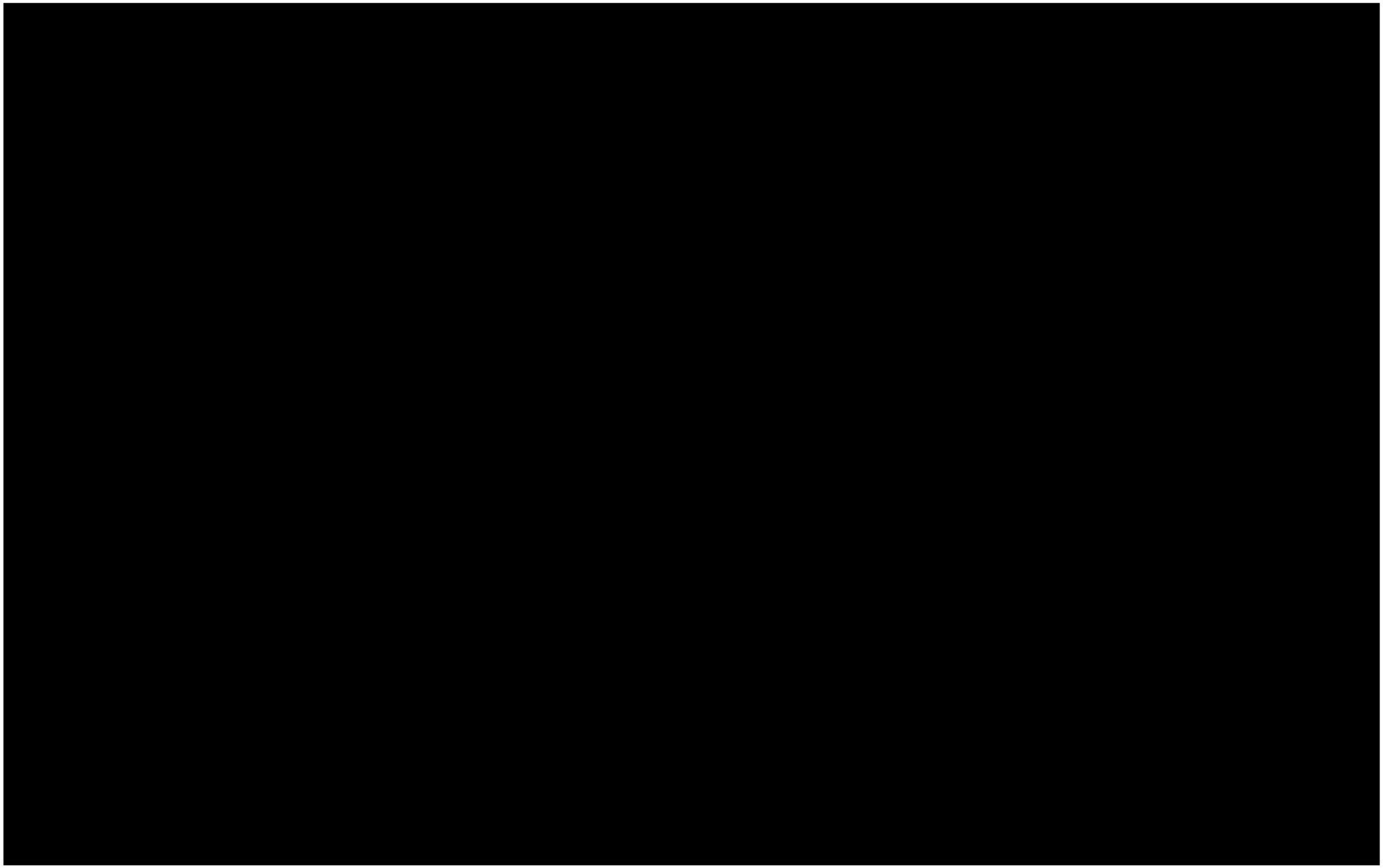
ORR will be assessed according to RECIST 1.1 (Eisenhauer 2009) and will be reported with category (CR, PR, SD, progressive disease, and not evaluable), counts by DL, percentage, and 95% confidence interval. The number and percentage of patients in each response category will be summarized by the efficacy assessment visit. The ORR will be presented by each tumor type, and by dose levels.

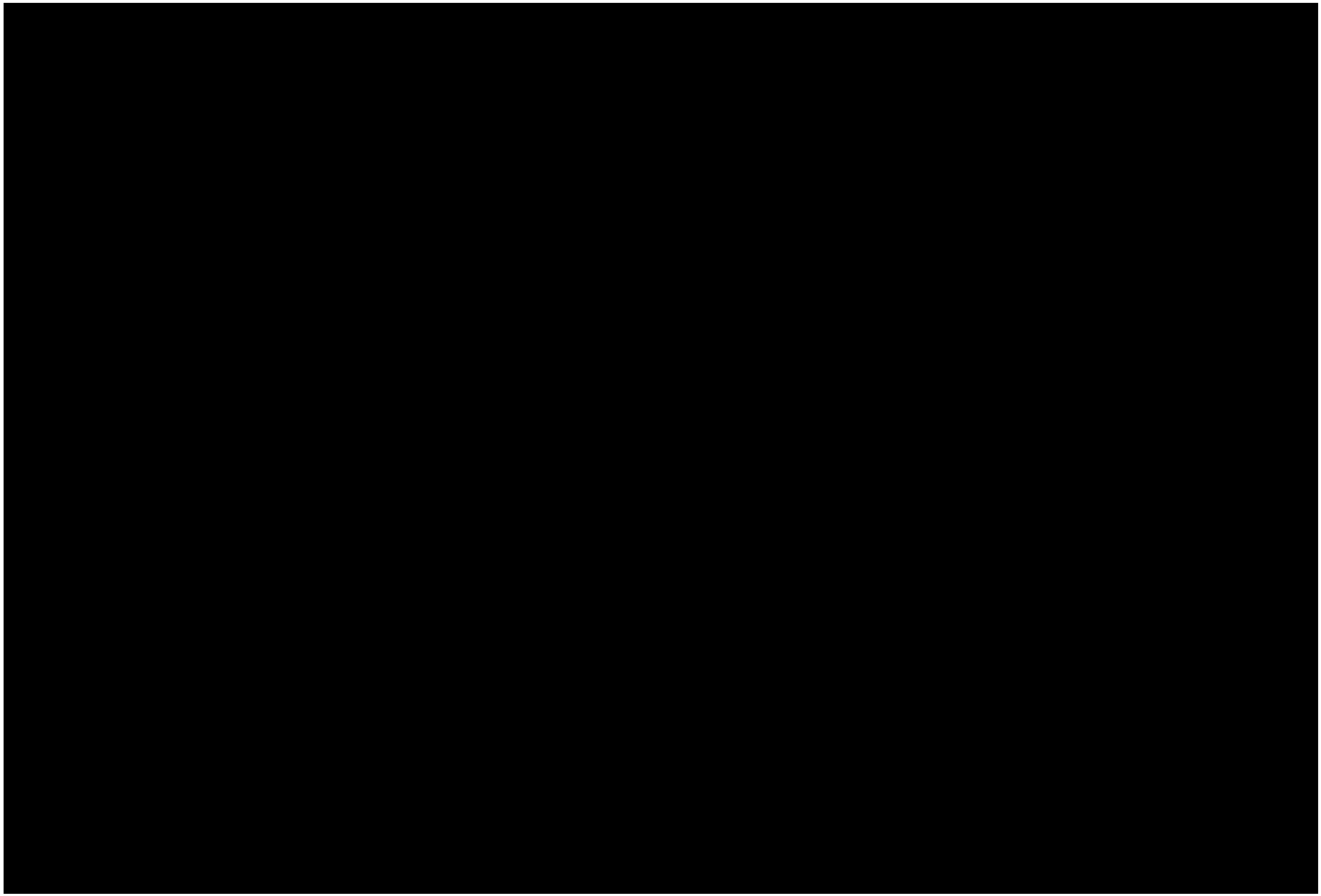
PK and PD endpoints, including PK parameters, peripheral blood immune cells, serum cytokines, and tumor tissue cellular subpopulations and biomarker expression, will be summarized and tabulated. PK parameters will be summarized by visit, overall, and by DL. PK/PD relationships and association with response will be explored.

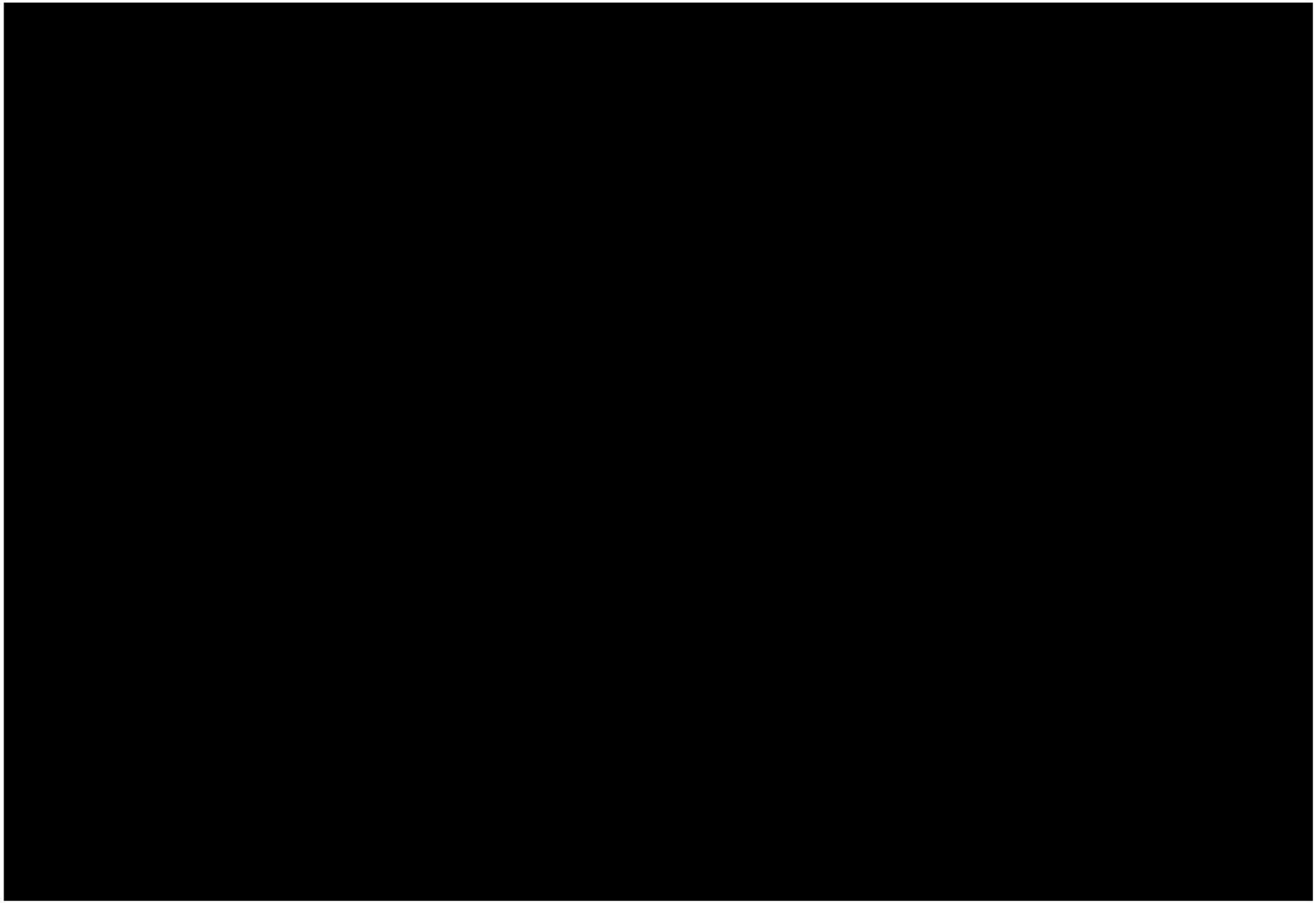
In Phase 2, time to event efficacy endpoints (DOR, PFS, and OS) will be analyzed using Kaplan-Meier methods.

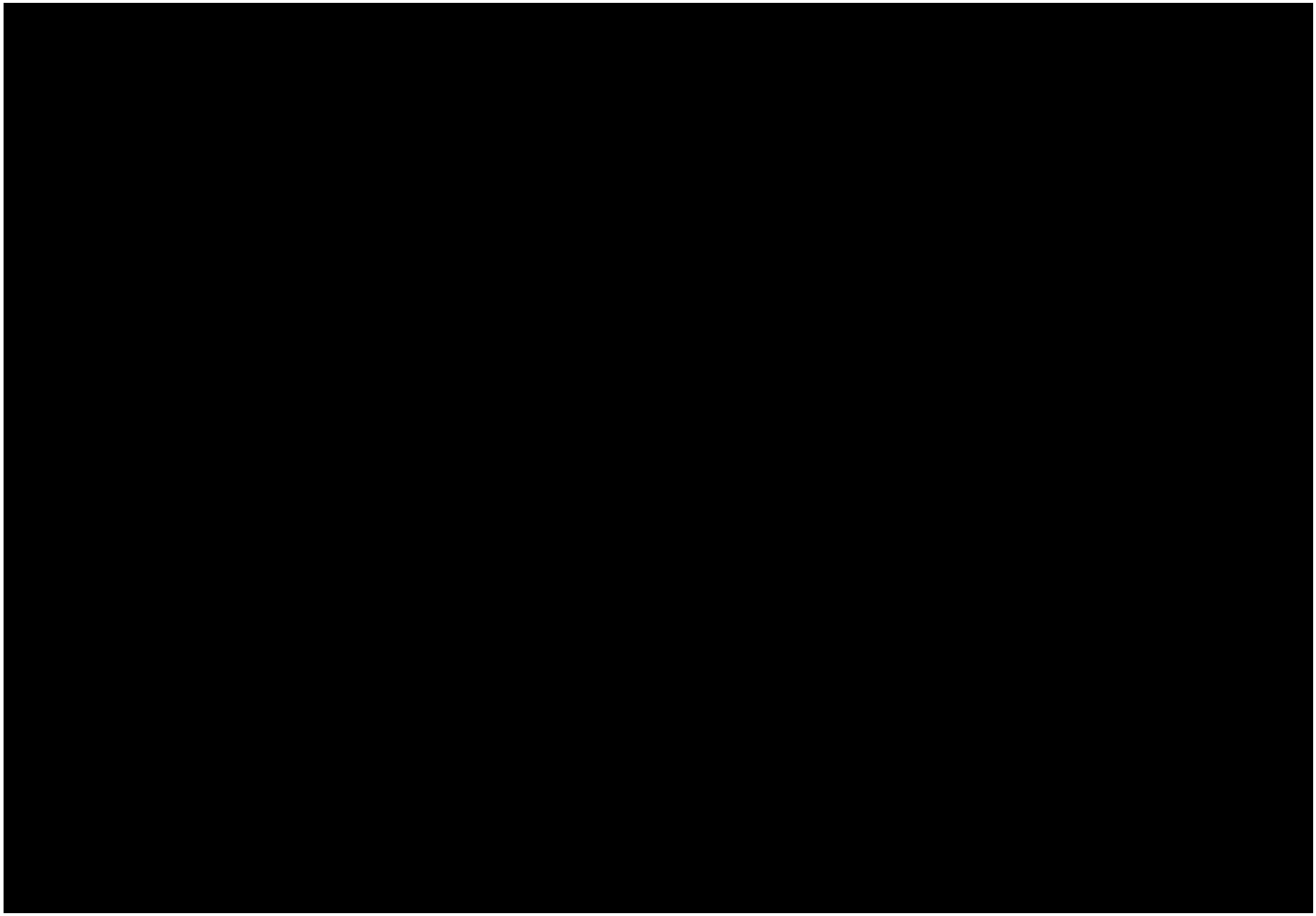






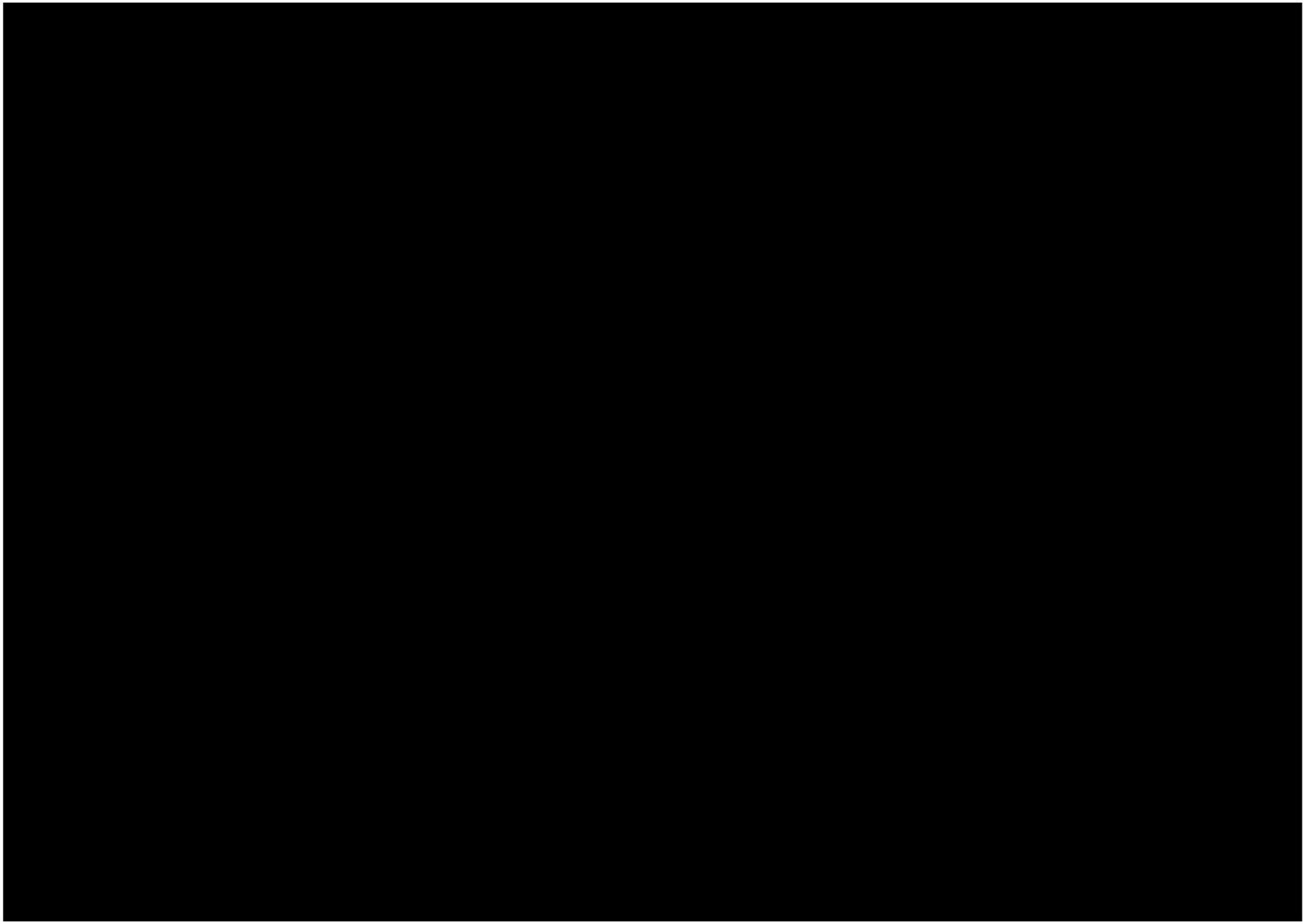






g When conducting the 12-lead ECG and PK blood draws at the same visit, the 12-lead ECG should be conducted before the blood draws. The 12-lead ECG

[redacted]



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Acronyms	Definitions
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
C1D1	Cycle 1, Day 1
CD4	CD4 molecule; used to identify T helper cells
CD8	CD8a molecule; used to identify cytotoxic T cells
CL	systemic clearance
CLS	capillary leak syndrome
C_{max}	maximum observed serum concentration
CNS	central nervous system
COVID-19	severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CR	complete response
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated protein 4
C_{trough}	trough concentration
DL	dose level
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End-of-Treatment
Fc	fragment crystallizable
FDA	Food and Drug Administration

Acronyms	Definitions
FIH	first-in-human
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (EU)
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HD	high dose
HED	human equivalent dose
hFcRn	human neonatal Fc receptor
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	interferon
IL-2	interleukin 2
IRB	Institutional Review Board
IV	intravenous(ly)
KM	Kaplan Meier
LEC	Local Ethics Committee
mAb	monoclonal antibody
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PD-1	programmed cell death-protein 1
PD-L1	programmed death ligand-1
PE	physical examination
PFS	progression-free survival

Acronyms	Definitions
PK	pharmacokinetic(s)
PR	partial response
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SRC	Safety Review Committee
STAT5	signal transducer and activator of transcription 5
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
T_{max}	time of maximum observed concentration
TME	tumor microenvironment
Treg	regulatory T cell
ULN	upper limit of normal
Vd	volume of distribution
WOCBP	women of childbearing potential
WT	wild type

2. BACKGROUND

2.1. INTERLEUKIN-2

2.1.1. Cytokines

Cytokines, small proteins that carry messages between cells, regulate the body's immune system. There are multiple cytokines, including interferon (IFN) alpha (α), beta (β), and gamma (γ), as well as interleukin-2 (IL-2), that have been approved across a range of oncology and other indications (Floros 2015). IL-2 is a master regulator of immune responses and has been investigated extensively as a potential anticancer immunotherapy, as IL-2 supports the function, survival, and proliferation of T cells, including the subset of T cells known as CD8+ T cells that are most closely linked to antitumor immunity. However, cytokine therapy has not achieved therapeutic success in a broad population of patients because its use has been limited by severe toxicity, including fatal outcomes (Rosenberg 2014).

2.1.2. Interleukin-2

2.1.2.1. Background

IL-2 activity is driven by 2 classes of receptor complexes, the high-affinity αβγ receptor that contains 3 subunits, and the intermediate-affinity βγ receptor that lacks the α-chain, a receptor known as CD25. The receptor complexes are differentially expressed on different cell types. The immune activating CD8+ T cells and natural killer (NK) cells primarily express βγ, and the immune suppressive regulatory T cells (Tregs) express the αβγ receptor. A wild-type (WT) IL-2 binds preferentially to the αβγ receptor and therefore strongly stimulates Tregs, thus limiting the immune activating effect of WT IL-2. Moreover, the presence of the high-affinity αβγ receptor on Tregs allows these cells to act as scavengers of WT IL-2 and reduce the availability of WT IL-2 for stimulation of CD8+ or NK cells. By contrast, non-α IL-2 does not bind to the α receptor component of the αβγ complex and therefore binds equally to CD8+, NK, and Treg cells. This shifts the balance of activity for non-α IL-2 away from Tregs and allows more effective activation of CD8+ and NK cells. In addition, non-α IL-2 is not subject to scavenging by Tregs since it does not bind to the αβγ high-affinity receptor and only binds to the intermediate affinity βγ receptor. By not being subject to scavenging by Tregs, the levels of non-α IL-2 are not reduced. Therefore, non-α IL-2 is available at higher concentrations to activate signaling through the βγ receptor on CD8+ and NK cells (Mitra 2018). As a result, non-α IL-2 is expected to be more effective at promoting antitumor immune response, thus inhibiting tumor growth more than WT IL-2.

2.1.2.2. Effective for the Treatment for Cancer

IL-2 also stimulates a variety of other immune cells, including NK cells, monocytes, and macrophages, either directly or indirectly by inducing T-cell secretion of potent cytokines such as tumor necrosis factor and IFN-γ. Due to its many immune system-stimulating activities, therapeutic IL-2 has shown efficacy in diverse cancers. High-dose (HD) IL-2 has been approved

in metastatic renal cell carcinoma (RCC) and unresectable or metastatic melanoma and can result in durable complete responses (CRs) and even cures. Specifically, the approved IL-2 treatment aldesleukin, an HD IL-2 therapy initially approved in 1992 as a monotherapy, produced overall response rates of 15% to 16% in metastatic RCC and unresectable or metastatic melanoma in clinical trials. Remarkably, 6% to 7% of patients achieved CR and functional cures (Proleukin® 2019).

2.1.2.3. Safety Concerns

Cytokine therapy has not achieved therapeutic success in a broad population of patients because its use has been limited by severe toxicity, including fatal outcomes.

Historical use of IL-2 in cancer has been accompanied by severe toxicity, and while the IL-2 is promising, its use has been greatly reduced due to these toxicities. When administered locally, IL-2 has been shown to be clinically active and well-tolerated, shrinking local cancerous lesions and reducing malignant effusions. However, when administered systemically, treatment with IL-2 has been shown to induce severe toxicities, including capillary leak syndrome (CLS), cytokine release syndrome (CRS), myocardial infarction (heart attack), acute renal failure, and immune-mediated neuropathy, and this toxicity profile greatly limits its current use (Dutcher 2014).

To avoid systemic toxicity, IL-2 has been directly injected into tumors, which has resulted in meaningful response rates in a range of tumors. However, while systemic toxicity has been minimized, intratumoral injections do not address the systemic nature of metastatic disease; therefore, these approaches have not solved the underlying therapeutic index problem for IL-2 (Den Otter 2008). It follows that engineering a form of IL-2 that can minimize the systemic effects while harnessing and directing the activity to the tumor microenvironment (TME) is the goal to benefit patients.

2.2. XTX202

XTX202 is a fully human masked, modified IL-2 fragment crystallizable (Fc) fusion protein, for the treatment of patients with metastatic or advanced solid tumors. The clinical development program of XTX202 will build upon the experience with prior IL-2 therapeutics, specifically aldesleukin (Proleukin®). XTX202 has been designed to limit systemic off-target activation, thereby potentially reducing adverse reactions while enhancing antitumor activity. Thus, XTX202 has the potential to extend the therapeutic benefit of IL-2 therapy to a broader patient population, enable administration of higher, more efficacious doses, and extend the duration of treatment. The initial proposed indication for XTX202 is for treatment of patients with metastatic RCC or metastatic or unresectable melanoma who have failed prior anti-programmed cell death-protein 1 (PD-1) therapy.

XTX202 contains 3 domains: a modified IL-2 domain, an Fc region domain, and a masking domain. The modified IL-2 domain is designed to exhibit reduced binding to the high-affinity IL-2 receptor while maintaining binding to the intermediate-affinity IL-2 receptor, thereby decreasing activation of Tregs relative to WT IL-2 while still activating effector T cells (Mitra

2018). In addition, the Fc fusion protein is intended to extend the half-life of IL-2. A masking domain based on IL-2Rβ (CD122) is linked to the Fc fusion protein and is designed to pharmacologically inactivate IL-2. XTX202 is activated by matrix metalloproteinases (MMPs) that are enriched in the TME. Cleavage at a protease cleavage site in XTX202 by MMPs results in an active IL-2 moiety when the masking domain is released. Thus, XTX202 is intended to have preferential bioactivity in tumor tissues compared with peripheral nontumor tissues, thereby preserving the antitumor activity of IL-2 while reducing its systemic toxicity.

Activation of signal transducer and activator of transcription 5 (STAT5)-mediated transcriptional processes are vital to the biological actions of IL-2, including T-cell proliferation, the differentiation of CD4+ T cells into multiple helper T-cell populations, the differentiation of CD8+ T cells into memory T cells, and induction of proinflammatory cytokine secretion (Ross 2018). After proteolytic cleavage, XTX202 is intended to engage the intermediate-affinity IL-2 receptor and promote STAT5-mediated transcriptional activity.

2.2.1. Nonclinical Summary

2.2.1.1. Nonclinical Pharmacology

In vitro studies have demonstrated that XTX202 is proteolytically cleaved and activated by multiple classes of recombinant human MMPs, which are highly expressed in the TME. The masking domain of XTX202 functions as intended by inhibiting STAT5 activation via the IL-2 receptor; full recovery of IL-2 signaling activity of XTX202 and STAT5 activation is achieved following proteolytic cleavage of the masking domain. In contrast to recombinant human IL-2, which is a more potent activator of Tregs than CD8+ T cells, the modified IL-2 domain is similarly potent in activating CD8+ T cells and Tregs.

There was no significant ex vivo cleavage of XTX202 in the reference plasma matrices at any timepoint, indicating that cleavage during the incubation period was minimal.

The antitumor efficacy of XTX202 (2 mg/kg dosed every 2 days) was determined in Tg32 transgenic mice bearing the murine MB49 bladder carcinoma model. Tg32 transgenic mice express human neonatal Fc receptor (hFcRn) and were selected for this study because they have been shown to better predict human pharmacokinetics (PK) of Fc-containing molecules than WT mice (Avery 2016). The efficacy, tolerability, and peripheral immune effects of XTX202 were compared with the effects of XTX200 (unmasked XTX202) and aldesleukin in hFcRn-expressing mice bearing MB49 tumors. Treatment with XTX202 resulted in tumor growth inhibition, which was similar to that observed with the unmasked version of XTX202, XTX200. However, in contrast to XTX200 and aldesleukin, XTX202 did not induce body weight loss, splenomegaly, lung edema, or peripheral immune cell activation or animal deaths.

Please see the Investigator's Brochure for more information.

2.2.1.2. Nonclinical Pharmacokinetics

Single dose, non-Good Laboratory Practice (GLP) PK studies have been completed in a nontumor-bearing and tumor-bearing murine model and in cynomolgus monkeys. Preliminary

PK data support the proposed dosing schedule of every 3 weeks (Q3W) in this proposed Phase 1 study.

Please see the Investigator's Brochure for more information.

[redacted]

2.3. RATIONALE FOR CURRENT STUDY

The objectives of this study are to evaluate the safety and tolerability of XTX202 monotherapy and determine the recommended Phase 2 dose(s) (RP2D[s]) and schedule suitable for advancing into further clinical studies.

Phase 1, Part 1a will evaluate ascending fixed doses of XTX202 monotherapy in a single-patient accelerated 100% dose escalation design based on dose-limiting toxicities (DLTs), overall safety, and the PK/pharmacodynamic (PD) profile. The first dose levels will employ this single-patient accelerated 100% dose escalation design to minimize the number of patients likely treated at subtherapeutic doses. If a Grade $\geq$ 2 adverse event (AE) or any DLT is observed, then the study will transition to a 3+3 dose escalation that will include a 40% increase over the previous dose. Up to [redacted] may be enrolled at any dose level with < 2 DLTs. These additional patients will not be considered evaluable for defining the maximum tolerated dose (MTD) but will contribute to the overall safety assessment and PK/PD profile at that dose level.

[redacted] he Part 1b patient population will focus on select tumor histologies that have been previously shown to potentially respond to IL-2 based therapies (Grande 2006).

[redacted]

Phase 2 will consist of 2 disease-specific expansion cohorts, 2a for patients with metastatic RCC and 2b with patients of unresectable or metastatic melanoma, using the RP2D(s) from Phase 1.

2.3.1. Starting Dose Rationale

The FIH dose of XTX202 is based on the human equivalent dose of the HNSTD in cynomolgus monkey, the most sensitive species in the GLP toxicology program.

2.3.2. Background on Renal Cell Carcinoma

RCC accounts for 2% of global cancer diagnoses and deaths annually, with an increasing incidence globally, and is the 10th most common cancer in the United States, with approximately 73,750 new cases and approximately 14,800 deaths projected in 2020. Most cases of RCC are discovered incidentally on imaging, and approximately one-third of cases are advanced or metastatic at the time of diagnosis. Survival is highly dependent on the stage at diagnosis, with metastatic disease having a 5-year survival rate of only 12% (Padala 2020). The landscape of therapeutic options has rapidly evolved such that the treatment goal, even in the metastatic setting, is to cure patients or ensure their long-term survival. Systemic frontline therapy options now include combinations of checkpoint inhibitors and tyrosine kinase inhibitors (TKIs) such as pembrolizumab and axitinib, nivolumab and ipilimumab, and avelumab and axitinib. Despite these recent approvals, there remains a pressing need to identify new therapeutic targets and effective treatments since the substantial majority of patients continue to experience relapses and progression and ultimately succumb to their cancer. As a result, cures are not commonly achieved, as in the example of pembrolizumab combined with vascular endothelial growth factor receptor-targeted TKI. Most patients with metastatic RCC will eventually relapse even after treatment with sunitinib or pembrolizumab and axitinib, as the median time to progression-free survival (PFS) is 11.1 months and 15.1 months, respectively (Rini 2019).

There are very few treatment options for patients with metastatic RCC who progress after anti-PD-1 and TKI treatment. IL-2-directed therapy offers the opportunity for durable responses and cures, as was seen in the historical aldesleukin treatment data. While only 15% of metastatic RCC patients treated with HD IL-2 obtain an objective response, approximately half of these, or 7% of all patients treated, achieved a CR. The unique feature of HD IL-2 is that approximately 90% of patients with metastatic RCC who achieved a CR remained permanently disease-free and off treatment (Dutcher 2014, Klapper 2008, Proleukin® 2019). Therefore, treatment that offers the

efficacy potential seen with HD IL-2 but with a safety profile enabling treatment of a broad range of patients offers an opportunity to address a significant unmet medical need.

2.3.3. Background on Melanoma

Melanoma of the skin is a relatively rare disease as it occurs in only 22 out of 100,000 people in the United States. However, it is a very deadly disease, accounting for 75% of skin cancer deaths, and it was estimated that more than 7,000 people died from melanoma in 2019 (Davis 2019). While there have been substantial improvements in the treatment of metastatic melanoma, treatment of Stage III and IV melanoma remains suboptimal, as the majority of patients with metastatic disease still relapse and progress, and there is an urgent need for additional therapeutic options (Curti 2021).

Recombinant IL-2 produced an objective response rate (ORR) of 16% in metastatic melanoma and produced CRs and functional cures in 7% of patients in clinical trials. However, use of recombinant IL-2 has been limited by DLTs (Proleukin® 2019). Accordingly, in the last decade, treatments that target PD-1 and cytotoxic T lymphocyte associated protein 4 (CTLA-4) have grown to dominate the metastatic melanoma treatment landscape. However, many patients do not respond, and relapses are common, leading to a 5-year survival rate of around 50% in metastatic melanoma (Curti 2021). A safe and effective form of IL-2 may improve initial response rates and clinical outcomes when added to checkpoint inhibitor therapy and may maintain responses in patients with melanoma who have relapsed from checkpoint treatment. Importantly, HD IL-2 has shown a response rate, including CRs in patients with melanoma despite those patients having progressed on prior treatment with an anti–PD-1 therapy, showing the potential for IL-2 mechanism of action-based efficacy in patients who have previously been treated with an anti–PD-1 therapy.

3. INVESTIGATIONAL PLAN

3.1. STUDY OVERVIEW

This is an FIH, Phase 1/2, multicenter, open-label study designed to evaluate the safety and tolerability of XTX202 in patients with advanced solid tumors.

The Phase 1 primary objectives are to evaluate the safety and tolerability of XTX202 monotherapy and determine the dose(s) of XTX202 and regimens to be further examined in Phase 2. The preliminary clinical PK, PD, and immunogenicity of XTX202, along with clinical activity, will be characterized. The study will examine the effect of XTX202 on the generation of antidrug antibodies (ADAs); the number of different T-cell subsets and their activation states; gene expression; tumor biopsy cell subsets; and biomarkers.

Phase 2 will evaluate the efficacy and safety of the RP2D(s) of XTX202 in 2 disease-specific cohorts: Part 2a in metastatic RCC, and Part 2b in unresectable or metastatic melanoma. Any additional Phase 2 cohorts planned based on the data obtained in Phase 1 will be described in future protocol amendments.

Additional cohorts may examine XTX202 in combination with other therapies, for example an immune checkpoint inhibitor and TKI, after initial dose finding and demonstration of combination therapy tolerability. These cohorts may be added in future protocol amendments.

3.1.1. Selection of Patient Populations

Phase 1, Part 1a will enroll patients with any histologically or cytologically confirmed solid tumor malignancy that is locally advanced or metastatic and has failed standard therapy, or patients with advanced solid tumors who have limited available treatment options as determined by the Investigator. Patients with primary central nervous system (CNS) malignancy are not eligible.

Phase 1, Part 1b will enroll patients with histologically or cytologically confirmed solid tumors of select tumor histologies that have a potential to benefit from IL-2-based treatment, including RCC (clear cell histology only), melanoma, squamous cell skin cancer, ovarian cancer, and non-small cell lung cancer. Patients enrolled in Part 1b must have been previously treated with available standard therapy. [redacted]

For Phase 2, Part 2a will enroll up to [redacted] with metastatic RCC in an optimal Simon's 2-stage design. Eligible patients must have received a TKI and also have been treated with and progressed on an anti-PD-1 therapy. Part 2b will enroll up to [redacted] with unresectable or metastatic melanoma who have previously been treated with anti-PD-1 and progressed on checkpoint inhibitor therapy.

3.1.2. Benefit-Risk Assessment

Although this Phase 1/2 study is primarily designed to assess the safety and tolerability of XTX202, the study patient population includes those with advanced malignancies for which standard therapy has failed and effective treatment options are limited. These patients have progressed following standard-of-care treatment and have limited treatment options outside of conventional chemotherapy, which is cytotoxic and has not demonstrated meaningful clinical benefit in this setting. IL-2 has been validated as a treatment modality that has shown favorable benefit-risk ratio in several indications. [redacted] To mitigate the potential risks with XTX202, the study design includes close monitoring of patient safety by study Investigators. A Safety Review Committee (SRC) will review all available data at regular intervals to ensure the benefit/risk ratio continues to support the study of XTX202 in patients.

4. OBJECTIVES

4.1. PHASE 1 (PART 1A AND PART 1B) OBJECTIVES

4.1.1. Primary Objectives

- To evaluate the safety and tolerability of XTX202 monotherapy in patients with advanced solid tumors
- To determine the RP2D(s) and schedule of XTX202 monotherapy

4.1.2. Secondary Objectives

- To characterize the PK profile of XTX202
- To evaluate the immunogenicity of XTX202
- To evaluate the preliminary antitumor activity of XTX202 monotherapy in patients with advanced solid tumors

[redacted]

4.2. PHASE 2 OBJECTIVES

4.2.1. Primary Objective

- To evaluate the efficacy of XTX202 monotherapy in patients with metastatic RCC and patients with unresectable or metastatic melanoma

4.2.2. Secondary Objectives

- To evaluate the safety and tolerability of XTX202 monotherapy in patients with metastatic RCC and patients with unresectable or metastatic melanoma
- To characterize the PK profile of XTX202 in patients with metastatic RCC and patients with unresectable or metastatic melanoma
- To evaluate the immunogenicity of XTX202 in patients with metastatic RCC and patients with unresectable or metastatic melanoma
- To further evaluate the efficacy of XTX202 monotherapy in patients with metastatic RCC and patients with unresectable or metastatic melanoma

[redacted]

5. ENDPOINTS

5.1. PHASE 1 (PART 1A AND PART 1B)

5.1.1. Primary Endpoints

- Incidence of DLTs (Part 1a only)
- Incidence of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory values

5.1.2. Secondary Endpoints

- Plasma concentrations of XTX202 (total and intact), including maximum observed serum concentration (C_{max}), time of maximum observed concentration (T_{max}), trough concentration (C_{trough}), area under the curve (AUC), half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd)
- ADA occurrence and titer in serum
- Investigator-assessed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

[redacted]

5.2. PHASE 2

5.2.1. Primary Endpoints

- Investigator-assessed ORR per RECIST 1.1

5.2.2. Secondary Endpoints

- Incidence of TEAEs and changes in clinical laboratory values
- Plasma concentrations of XTX202 (total and intact), including C_{max}, T_{max}, C_{trough}, AUC, $t_{1/2}$, CL, and Vd
- Incidence and persistence of ADAs (including neutralizing ADAs) and titers, and their potential impact on PK, activity, and safety associated with XTX202
- Duration of response (DOR), defined as the time from first documented confirmed response to first documented disease progression

- Disease control date, defined as the percent of patients who achieve a complete CR, partial response (PR), or stable disease (SD)
- PFS, defined as the time from first dose to first documented disease progression or death
- Overall survival (OS), defined as the time from first dose to death due to any cause

6. STUDY DESIGN

This is an FIH, Phase 1/2, multicenter, open-label study designed to evaluate the safety, tolerability, and efficacy of XTX202, a tumor-selective, engineered IL-2 prodrug with its activity masked to keep it inactive until selectively activated in vivo in the TME.

Phase 1, Part 1a will examine XTX202 monotherapy in an accelerated and standard 3+3 dose escalation design to determine the RP2D(s) for Phase 2.

Based on the results of Part 1a, patients with select advanced solid tumors will be enrolled in Part 1b, which will evaluate XTX202 monotherapy in relation to specific PD biomarkers; patients in Part 1b will be required to have fresh tumor biopsies predose and postdose. [redacted]

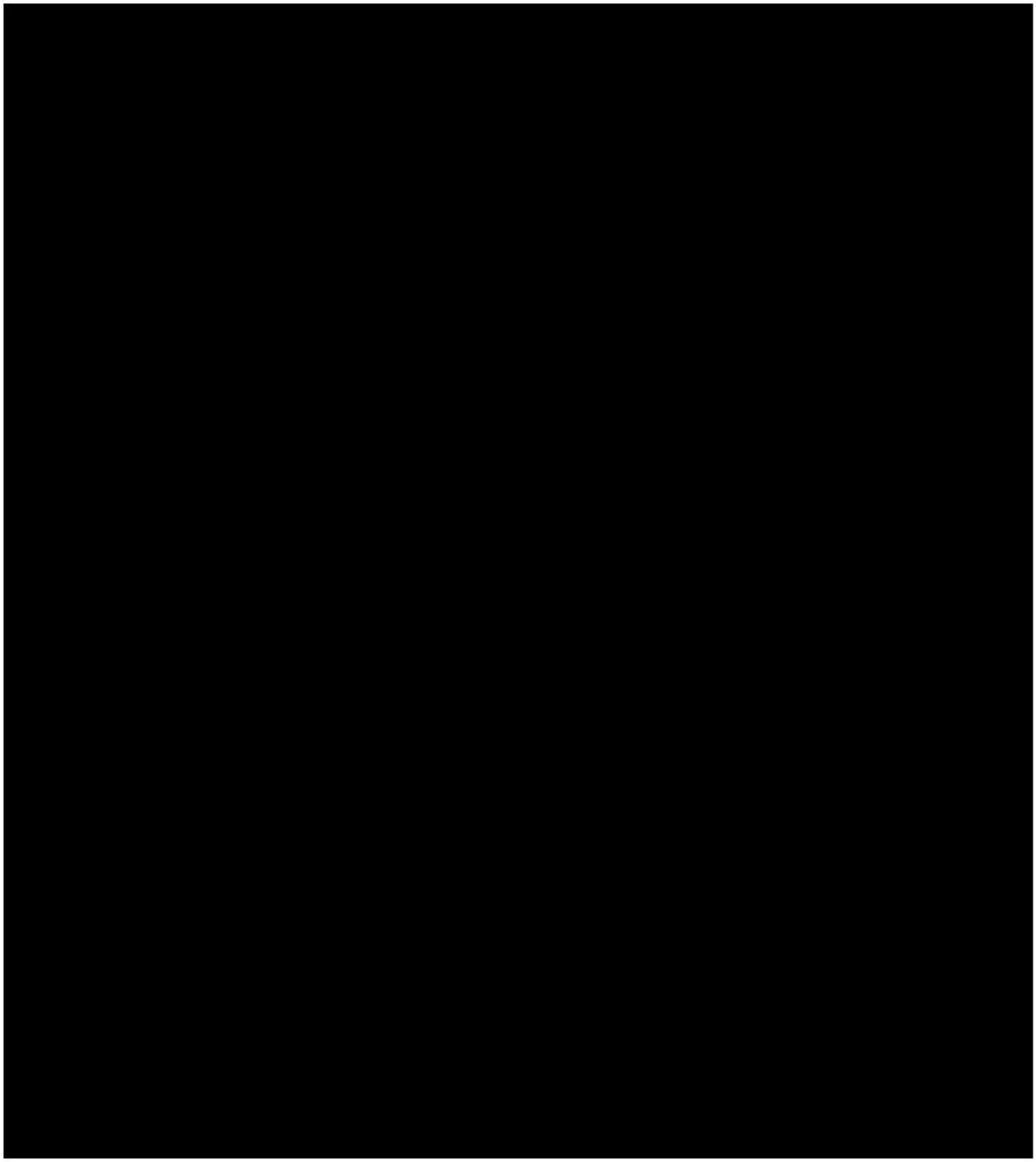
Phase 2 will examine the RP2D(s) of XTX202 in select indications to further evaluate the efficacy of XTX202. As of the writing of Protocol Amendment 5, 2 RP2Ds for XTX202 monotherapy have been defined at 1.4 mg/kg Q3W and 4 mg/kg Q3W.

Schedules of assessment are provided in Table 1 and Table 3. The study schematics for Phase 1 and Phase 2 are shown in Figure 1 and Figure 2, respectively.

Note: Based on the January 2023 Food and Drug Administration (FDA) draft guidance, "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases," (US FDA 2023) the SRC may recommend more than 1 dose to be evaluated in the Phase 2 portion of the study in order to identify the optimal XTX202 dose for further development. The SRC may recommend each RP2D based on the totality of the data (safety, efficacy, and available PK and PD data), and Phase 2 may open in parallel with ongoing dose escalation in Part 1a prior to reaching MTD. Once more than 1 RP2D is defined, patients in Phase 2 will be allocated to a dose level by the Sponsor.

Once an RP2D is defined based on SRC recommendation, any patient in the study remaining on treatment at a dose level lower than the highest RP2D without a treatment response after at least 3 cycles of therapy may have their dose escalated to a previously cleared dose level, if recommended by their treating investigator.

Additional cohorts may examine XTX202 in combination with other therapies, for example an immune checkpoint inhibitor and TKI, after initial dose finding and demonstration of combination therapy tolerability. These cohorts may be added in future protocol amendments.



6.1. PHASE 1

6.1.1. Part 1a (Dose Escalation)

Part 1a will evaluate ascending doses of XTX202 monotherapy administered via IV infusion Q3W. It will employ a single-patient accelerated 100% dose escalation design. If a Grade ≥ 2 AE or any DLT is observed, then the study will transition to a 3+3 dose escalation that will include a 40% increase over the previous dose. During the single-patient accelerated phase, the SRC will review all Grade ≥ 2 AEs that occur during the DLT Observation Period to determine their etiology relative to study drug. Any Grade ≥ 2 AE assessed by the SRC to have an etiology completely unrelated to study drug will not trigger a transition to 3+3 dose escalation.

Beginning with dose level (DL) 6 in the 100% dose escalation design (8.0 mg/kg), the study will automatically transition to a conventional 3+3 design with a 40% dose increase, independent of whether a Grade ≥ 2 AE or DLT is observed at the preceding dose level.

[redacted]

Abbreviations: AE = adverse event; DL = dose level; DLT = dose limiting toxicity; Q3W = every 3 weeks; SRC = safety review committee.

Note: Additional dosing schedules may be explored at any DL based on recommendation of the SRC and confirmation from the Sponsor. Intermediate DLs may be explored during dose escalation if approved by the SRC; lower DLs may be explored as additional DLs based on results of escalation and if approved by the SRC and Sponsor.

A patient will be enrolled at DL1 and monitored for 21 days postdose (the DLT Observation Period). If no Grade ≥ 2 AE or DLT is observed, then dose escalation will proceed to the next DL. Dose escalation will continue with a naïve single patient at each DL up to DL6 in the 100% dose escalation design (8.0 mg/kg) as long as no patient experiences a Grade ≥ 2 AE or DLT. If a Grade ≥ 2 AE or a DLT is observed in any patient, dose escalation will proceed with a 40% increase over the previous dose and transition to a conventional 3+3 design. Grade ≥ 2 AEs assessed by the SRC to have an etiology completely unrelated to study drug will not trigger a transition to 3+3 dose escalation.

[redacted]

[redacted]

Starting at DL6 in the 100% dose escalation design (8.0 mg/kg), Part 1a will transition to a conventional 3+3 design with a 40% dose escalation independent of whether any Grade ≥ 2 AE or DLT is observed at the preceding dose levels. Under the 3+3 design, if no patients experience a DLT, escalation will continue to the next DL; if 1 of the first 3 patients at a given DL has a DLT, then an additional 3 patients will be enrolled at that DL; if ≥ 2 patients have a DLT during the DLT Observation Period (21 days), dose escalation will be stopped and the DL immediately below this level will be considered the MTD.

After all naïve patients within a given DL have been followed for at least 21 days after first dose, the SRC will review all accumulated safety data and available laboratory and PK data. Initiation of the next DL will commence upon recommendation by the SRC and agreement from the Sponsor.

Dose escalation will continue until either an MTD is determined and/or the highest RP2D is defined.

Up to [redacted] additional patients may be enrolled at any DL with < 2 DLTs. These additional patients will not be considered for defining the MTD but will contribute to the overall safety assessment and PK/PD profile at that DL. The RP2D(s) selected for evaluation in Phase 2 will be based upon review of the cumulative safety, PK, PD, and available preliminary antitumor activity observed.

6.1.2. Part 1b (Pharmacodynamic Tumor Evaluation)

Based on the results from Part 1a, Part 1b will be initiated to further examine XTX202 as monotherapy in patients with select advanced solid tumors and to further characterize XTX202. Part 1b will require mandatory fresh tumor biopsies predose and postdose to fully characterize the PD profile of XTX202.

[redacted]

6.2. PHASE 2

6.2.1. Part 2a

Part 2a will include patients with metastatic RCC who have received a TKI therapy and also have been treated and progressed on an anti-PD-1 therapy. This part will employ an optimal Simon's 2-stage design using a one-sided type I error rate of < 0.05 and 80% power that will test the null hypothesis that $P \leq 0.05$ vs the alternative that $P \geq 0.20$, with a probability of early termination of 0.418. After evaluating the first [redacted] for efficacy in Stage 1, the study Part 2a will be terminated if no patient responds (CR or PR). If the study progresses to Stage 2, an additional [redacted] will be treated in Part 2a, for a total of up to [redacted] If at least 5 patients respond out of the total [redacted], there will be demonstration of efficacy of XTX202 within that population and the corresponding null hypothesis will be rejected.

6.2.2. Part 2b

Part 2b will include patients with unresectable or metastatic melanoma who have received immune checkpoint therapy with an anti-PD-1 therapy. This part will employ an optimal Simon's 2-stage design using a one-sided type I error rate of < 0.05 and 80% power that will test the null hypothesis that $P \leq 0.05$ vs the alternative that $P \geq 0.20$, with a probability of early termination of 0.418. After evaluating the first [redacted] for efficacy in Stage 1, the study Part 2b will be terminated if no patient responds (CR or PR). If the study progresses to Stage 2, an additional [redacted] will be treated in Part 2b, for a total of up to [redacted] If at least 5 patients respond out of the total [redacted] there will be demonstration of efficacy of XTX202 within that population and the corresponding null hypothesis will be rejected.

6.3. DOSING FREQUENCY

Patients will receive XTX202 IV Q3W at the assigned dose level until disease progression, unacceptable toxicity, 3 cycles after confirmed CR (provided they have been treated for at least 8 cycles), completion of 24 months of study therapy, termination of the study by Sponsor, death, or withdrawal of consent. Patients may continue study therapy beyond the treatment discontinuation criteria, as noted in Section 6.5, if recommended by the Investigator and approved by the Sponsor. Please see Section 13.9 for the specific requirements that need to be met for patients to receive treatment beyond disease progression. Alternate doses and/or dosing regimens may be explored upon review of initial PK, PD, safety, and tolerability data, and based upon recommendation from the SRC.

6.4. MONITORING OF ADVERSE EVENTS

Patients will be monitored continuously for AEs while receiving XTX202 and for 90 days after their last dose of XTX202. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (Appendix 2). Dose modification guidance for AEs possibly related to XTX202 is described in Section 10.2.

6.4.1. Dose-Limiting Toxicities

DLTs will be evaluated during Phase 1, Part 1a (monotherapy dose escalation). The DLT Observation Period will include the first cycle of XTX202 treatment and will run for approximately 21 days, beginning at Cycle 1, Day 1 (C1D1) and ending just prior to the second dose of the study drug at C2D1. No patient with a DLT will be replaced. For any patient in a dose hold prior to C2D1, the DLT Observation Period may be extended up to 7 days for a total of 28 days to confirm the evaluation of potentially ongoing DLTs.

A patient will be considered non-evaluable for DLT assessment if, for any reason other than an XTX202-related AE, the patient is unable to complete the DLT Observation Period (Days 1 to 21). Patients in Part 1a who are considered non-evaluable may be replaced after consultation between the Investigator and Sponsor.

DLTs are any of the toxicities listed below occurring during the DLT Observation Period, except those attributable solely to disease progression, intercurrent illness, or concomitant medications.

[redacted]

Any AE that meets DLT criteria but occurs after the DLT Observation Period may be considered by the SRC for the selection of the RP2D(s). All toxicities (AEs) will be graded using the NCI-CTCAE version 5.0 based on Investigator assessment.

DLTs for Part 1a are defined as the following:

- Any treatment-related Grade $\geq$ 3 toxicity
- Any Grade febrile neutropenia
- The following nonhematologic exceptions:
  - Grade 3 nausea or vomiting lasting < 3 days
  - Grade 3 fatigue lasting < 7 days
- Any treatment-related toxicity that results in a treatment delay of $\geq$ 7 days

After a DLT has occurred, if the Investigator determines that continued treatment with XTX202 is in the patient's best interest, treatment with XTX202 at a reduced dose may resume after consultation with the Medical Monitor.

6.4.1.1. Rationale for DLT Criteria

[redacted]

[redacted]

6.4.2. Safety Review Committee

This study will utilize an SRC that will meet regularly to review all accumulated data, including safety, PK, PD, and efficacy during dose escalation. More detailed information on the make-up of the SRC is available in the SRC Charter. The SRC will recommend all dose escalation decisions, and/or any changes to the dosing paradigm, based on review of the received data. Based on emerging data, the SRC can also recommend additional guidance for dose modification, premedication, and supportive care.

The SRC will also make all recommendations about the dose(s) selected for Phase 2 (dose expansion).

6.5. TREATMENT DISCONTINUATION

Discontinuation of study treatment does not represent withdrawal from the study.

A patient must be discontinued from study treatment and should continue to be monitored in the study for any of the following reasons:

- Discontinuation of treatment may be considered for patients who have attained a CR for at least 3 cycles and have been treated for at least 8 cycles (at least 24 weeks)[$]
- Completion of 24 months with study treatment[$]
- An AE that requires permanent discontinuation of study treatment*
- Disease progression as measured by the appropriate response criteria[$]
- Noncompliance to the protocol
- Investigator decision
- Patient becomes pregnant
- [redacted]

** Treatment-related TEAEs leading to the discontinuation of XTX202 will be followed until resolution, resolution to baseline, or until the event is considered stable or chronic.*

[$]Patients may continue on treatment beyond what is specified by these criteria if recommended by the Investigator to be in the best interest of the patient and approved by the Sponsor. Please see Section 13.9 for the specific requirements that need to be met for patients to receive treatment beyond disease progression.

The reason for treatment discontinuation should be documented.

Following treatment discontinuation, an EOT Visit should occur within 30 (± 7) days after the last dose of XTX202. The EOT assessment need not be performed if the patient has had the identical assessment within the previous 2 weeks or previous 30 days for disease response assessments, unless confirming response from a previous assessment. If a patient plans to start new anticancer therapy prior to the EOT Visit or 90-day Safety Follow-up Visit, these visits should occur prior to the initiation of new anticancer therapy, if possible.

All patients will have a final Safety Follow-up Visit approximately 90 (± 7) days after the last dose of XTX202, unless the patient withdraws from the study prematurely (Section 6.6). If the visit is completed in person, then all assessments should be performed. If follow-up is by phone, only AEs and concomitant medications will be collected.

All patients in Phase 2 who discontinue study treatment, and who have not withdrawn consent from the study, should enter Survival Follow-up (see Section 8.3).

6.5.1. Continued Access

[redacted]

6.6. STUDY WITHDRAWAL

Patients may voluntarily withdraw from the study at any time for any reason without prejudice.

Patients will be withdrawn from the study for any of the following reasons:

- Patient death
- Patient lost to follow-up
- Voluntary withdrawal of consent by patient
- Investigator's decision
- Termination of the study by Sponsor
- Patient no longer meets study requirements or is no longer eligible

If possible, prior to withdrawal, an EOT Visit should occur within 30 (± 7) days after the last dose of XTX202 and a final Safety Follow-up Visit approximately 90 (± 7) days after the last dose of XTX202. If the patient withdraws full consent from study participation (and not just study treatment), no further evaluations should be performed, and no attempts should be made to collect additional follow-up data.

7. STUDY POPULATION

7.1. INCLUSION CRITERIA

Patients are eligible for inclusion if all the following criteria are met:

1. Must be ≥ 18 years of age on day of signing informed consent
2. Disease criteria
    a. Phase 1, Part 1a: Any histologically or cytologically confirmed solid tumor malignancy that is locally advanced or metastatic and has failed standard therapy, or standard therapy is not curative or available
    b. Phase 1, Part 1b: Histologically or cytologically confirmed solid tumor malignancy with 1 of the following tumor histologies:
        i. RCC of clear cell histology only
        ii. Melanoma
        iii. Squamous cell skin carcinoma
        iv. Ovarian cancer
        v. Non-small cell lung cancer
        vi. Additional tumor types for which the Investigator believes there is scientific rationale to expect potential benefit, upon Sponsor approval

        Notes for Part 1b:

        Patients enrolled in Part 1b must have been previously treated with available standard therapy. Those patients who previously received immunotherapy must have, based on Investigator judgment, derived benefit from this treatment (examples would include achieving a complete or partial response, or prolonged stable disease while on immunotherapy).

        [redacted]

    c. Phase 2, Part 2a: Patients with metastatic RCC who have previously been treated with an anti-PD-1 and a TKI, per local and institutional standard of care. Patients must have progressed on treatment with an anti-PD-1 monoclonal antibody (mAb) administered either as monotherapy or in combination with other therapies.
    d. Phase 2, Part 2b: Patients with unresectable or metastatic melanoma who have previously been treated with at least 1 prior line of therapy in the recurrent or metastatic setting. Prior therapy must have included an anti-PD-1 alone or in combination per local and institutional standard of care, and patient must have progressed on checkpoint inhibitor therapy. Patients with BRAF V600-activating mutation must have previously received targeted therapy per local and institutional standard of care.

[redacted]

3. Phase 2: measurable disease per RECIST 1.1
4. [redacted]
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Adequate organ function, [redacted]
7. For Part 1b only: Tumor tissue samples: Patients must have lesions amenable to biopsy and be willing and able to provide fresh tumor biopsies (core, incisional, or excisional biopsy) before and after initiation of study treatment [redacted]

11. Women of childbearing potential (WOCBP) (i.e. those not surgically sterile or postmenopausal) and male patients must be willing to abstain from sexual activity or use an approved contraceptive method for the duration of the study and for 3 months after the last administration of the study drug. WOCBP must have a negative serum pregnancy test at the time of study enrollment and prior to first dose of the study drug
12. Provide written informed consent and willing and able to comply with requirements of the study protocol

7.2. EXCLUSION CRITERIA

Eligible patients must not meet any of the following criteria:

1. Prior treatment with IL-2 therapy
2. History of or active autoimmune disorder that requires immunosuppressive therapy [redacted]
3. Anticipated to require another antineoplastic therapy during the course of the study
4. History of significant pulmonary disease including interstitial lung disease or pulmonary fibrosis
5. History of clinically significant cardiovascular disease including myocardial infarction, unstable angina, or coronary artery bypass grafting/angioplasty within the past 6 months; uncontrolled hypertension; ventricular arrhythmias requiring treatment; symptomatic congestive heart failure; symptomatic valvular heart disease; or myocarditis
6. [redacted]
7. Part 1a only: Evidence of significant coronary artery disease on cardiac imaging performed within the screening period. The choice of appropriate imaging, such as stress echocardiography or nuclear perfusion scan, should be per standard local practice, with cardiology consultation as needed
8. [redacted]
9. Has an active autoimmune disease that has required systemic treatment in past 2 years, including the use of disease modifying agents, corticosteroids, or immunosuppressive drugs [redacted]
10. Has an active infection requiring systemic therapy within 4 weeks prior to study treatment. [redacted]

[redacted]

11. [redacted]

[redacted]

14. Pregnant or breastfeeding

15. [redacted]

[redacted]

8. STUDY PROCEDURES AND ASSESSMENTS

Timepoints for assessments to be collected throughout the study can be found in the Schedules of Assessments (Table 1 and Table 3). A brief description of each assessment can be found below.

If the patient is unable to attend a visit in person for medical reasons or due to circumstances outside of his or her control, alternative means of performing study assessments may be implemented by the site or Sponsor that may include telemedicine, local testing facilities, or deploying trained staff to the patient's home to perform protocol-required assessments.

8.1. SCREENING AND TREATMENT PROCEDURES AND ASSESSMENTS

8.1.1. Informed Consent

An informed consent form (ICF) must be signed by prospective patients prior to initiating any study-specific procedures. Standard of care assessments performed prior to ICF signing may fulfill study eligibility requirements if performed within the Screening Period.

8.1.2. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 7.1 and Section 7.2, respectively) will be reviewed for each potential patient. Eligibility will be documented in the electronic case report form (eCRF).

8.1.3. Medical History, Demographics, and Cancer History

Complete medical history will be obtained, including demographics, cancer history, and prior anticancer treatment history.

8.1.4. Previous and Concomitant Medications and Procedures

At Screening, previous and concomitant medications will be recorded. Assessment of any change in concomitant medications or procedures since the last visit will occur at all subsequent patient visits through safety follow-up.

8.1.5. Physical Examination and Vital Signs

A full physical examination (PE) or symptom-directed PE and vital signs check will be performed at the timepoints specified in the Schedules of Assessments (Table 1 and Table 3). PEs will also be conducted as clinically indicated.

A full PE will be performed at Screening and will include an assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory, abdomen, height, and weight. Vital signs will include temperature, blood pressure (sitting or semi-recumbent for 5 minutes), pulse rate, pulse oximetry, and respiratory rate. Weight will be taken prior to each XTX202 infusion. On days of infusion, vital signs are to be measured within 10 minutes prior to XTX202 infusion, every 15 (± 5) minutes during infusion, then hourly (± 10 minutes) for at least 6 hours in Part 1a and at least 3 hours in Part 1b and Phase 2 during the post-infusion observation period. Vital signs may

continue to be measured and assessed beyond the end of the observation period if the patient is not clinically stable. If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart.

During study treatment, PEs will be symptom directed. Any new clinically significant abnormality from baseline should be recorded as an AE.

8.1.6. Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be performed at the timepoints specified in the Schedules of Assessments (Table 1 and Table 3). Refer to Appendix 1 for a sample of the ECOG assessment.

8.1.7. Electrocardiogram

At the specified timepoints in the Schedule of Assessments, a standard 12-lead electrocardiogram (ECG) will be conducted following an approximate 10-minute rest period and obtained within an approximately 5-minute period at the timepoints outlined in Table 1 and Table 3.

When conducting the ECG and PK blood draws at the same visit, the ECG should be conducted before the blood draws. When applicable, ECGs will be performed prior to XTX202 administration and following completion of XTX202 infusion.

Any ECG findings assessed as clinically significant should be recorded as an AE. If any seriousness criteria are met, the event should be recorded and reported according to the serious adverse event (SAE) reporting process.

8.1.8. Cardiac Imaging

Cardiac imaging will be performed for patients in Phase 1, Part 1a at any point during screening prior to C1D1 to look for evidence of significant coronary artery disease. The choice of appropriate imaging, such as stress echocardiography or nuclear perfusion scan, should be per standard local practice, with cardiology consultation as needed.

8.1.9. Clinical Laboratory Tests

The following laboratory parameters will be measured at screening and at the timepoints specified in the Schedules of Assessments (Table 1 and Table 3) and will be analyzed locally:

- A serum pregnancy test within 7 days prior to the first dose for all WOCBP
- Urine or serum pregnancy testing for all WOCBP prior to each dose of XTX202 during treatment, at EOT, and Safety Follow-up visit
- Thyroid panel testing
  - Thyroid-stimulating hormone (TSH), triiodothyronine (T3) or free triiodothyronine (FT3), and free thyroxine (FT4) (or appropriate equivalent test per local and institutional standards)

- Hematology laboratory parameters including white blood cell count, hemoglobin, hematocrit, platelet count, and white blood cell differential
- Blood chemistry laboratory parameters including blood urea nitrogen, creatinine, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), amylase, lipase, albumin, magnesium, calcium, C-reactive protein, and phosphorus
- Coagulation laboratory parameters including prothrombin time, partial thromboplastin time or activated partial thromboplastin time, and international normalized ratio
- Complete urinalysis with qualitative analysis for protein (dipstick)
- Iron studies (serum ferritin and serum transferrin saturation)

Unscheduled assessments should be performed as clinically indicated.

Abnormal laboratory findings at screening should be recorded as medical history only if considered clinically significant.

Clinical laboratory assessments should be performed within 72 hours prior to XTX202 infusion when applicable. At C1D1 only, clinical laboratories collected for screening and within 7 days of the first XTX202 dose may be used as C1D1 laboratory values.

Laboratory findings assessed by the Investigator as clinically significant, including but not limited to those findings resulting in a drug interruption/hold/reduction/discontinuation or medical intervention, should be reported as AEs (see Section 11.1.1 for definition of an AE).

8.1.10. Tumor Evaluation and Response Assessment

Disease assessment by computed tomography (CT) or magnetic resonance imaging (MRI) as applicable for disease type and anatomic involvement will be performed at baseline (within 4 weeks prior to first dose) and during the study as outlined in Table 1, Table 3, and Appendix 3. Ongoing tumor evaluations to the same areas of disease involvement using the same method of scanning will be performed every 9 weeks from C1D1 (± 5 days) during the first 12 months, and then every 12 weeks (± 7 days) from 12 to 24 months until disease progression or the start of subsequent new anticancer therapy, including in patients who discontinue treatment for reasons other than disease progression. Unscheduled imaging is permitted if clinically indicated per the discretion of the Investigator.

Positron emission tomography imaging may be performed as adjunctive imaging.

The modality chosen (CT or MRI) to evaluate each individual patient should remain consistent for disease evaluation throughout the duration of the study.

Prior to treatment initiation, target and nontarget lesions will be identified by the Investigator per RECIST 1.1 (Appendix 3). During the study, disease response and progression will be determined by Investigator assessment per RECIST 1.1 (Appendix 3) at the time points indicated in Table 1 and Table 3.

Patients who achieve a CR or PR should undergo a follow-up response confirmation assessment (CT or MRI) ≥ 4 weeks after the first response. Patients will be expected to continue to follow the response assessment schedule as outlined in the schedule of events.

Appendix 3 show the criteria employed for lesion response assessment.

8.1.11. Tumor Biopsy

For patients in Part1a and Phase 2, documentation that archival tumor blocks or slides are available should be obtained during screening – if these are not available, a baseline fresh tumor biopsy should be obtained if this is considered safe and feasible. For patients in Part 1b, mandatory fresh tumor biopsies are required within 28 days prior to the first XTX202 dose and at the timepoints outlined in Table 1. [redacted] Fresh tumor biopsies are optional for Part 1a and Phase 2; if obtained, they should be within 28 days prior to first dose. See the XTX202-01/02-001 Laboratory Manual for specific instructions on fixation and processing of tumor tissue. Tumor biopsies should be core, incisional, or excisional biopsies, not fine needle aspirates. Additional tissue samples for exploratory PK or PD assessments will be obtained from patients undergoing a standard-of-care procedure that will involve a diagnostic tissue biopsy (including non-tumor tissue), if considered safe and feasible and if the patient consents to this additional collection.

8.1.12. XTX202 Administration and Post-Infusion Observation Period

XTX202 will be administered Q3W as outlined in Table 1 and Table 3. Weight will be taken prior to each XTX202 infusion. XTX202 will be administered on a mg/kg basis; if a patient's weight changes by > 10% (or per institutional standards), the administered dose should be modified accordingly. Detailed instructions on the administration of XTX202 can be found in Section 10.1.3.

[redacted]

[redacted]

Patient care and safety monitoring may be updated per the recommendation of the Investigator and/or SRC based on emerging safety data.

8.1.13. Pharmacokinetic Sampling

PK sample collection timepoints are shown in Table 2 and Table 4.

The date and time of each sample collection and the prior XTX202 dose must be recorded for all collected samples.

Additional PK samples, beyond those listed in Table 2 and Table 4, may be requested (when feasible) at the time of any unusual safety event, such as an AE different in type and severity from those expected in the setting of XTX202 use.

Refer to the XTX202-01/02-001 Laboratory Manual for details on processing, storage, and shipment of PK samples.

8.1.14. Immunogenicity Sampling and Assessments

As shown in Table 1 and Table 3, blood samples for immunogenicity assessments will be collected from all patients at multiple timepoints for analysis of ADA.

Refer to the XTX202-01/02-001 Laboratory Manual for immunogenicity sample handling procedures and shipping requirements.

8.1.15. Pharmacodynamic/Biomarker Sampling and Assessments

A variety of factors that may potentially predict clinical response to XTX202 will be assessed in peripheral blood and in tumor specimens. Data from these assessments will be evaluated for associations with biological effects and response or safety associated with XTX202.

Refer to the XTX202-01/02-001 Laboratory Manual for biomarker sample handling procedures. The timepoints for the collection of these assessments are outlined in Table 2, Table 3, and Table 4.

[redacted]

Samples collected during the study may be banked for up to 15 years. Any material left over may be used for bridging studies, repeat measurements, or to conduct research related to XTX202 pathways or to cancer biology in general.

Detailed instructions of the obtaining, processing, labeling, handling, storage, and shipment of these specimens will be provided in a XTX202-01/02-001 Laboratory Manual.

8.1.16. Adverse Events

Nonserious AEs should be captured on the eCRF from the time of signing of ICF through the Safety Follow-up Visit (90 days [± 7] after the last dose). AEs considered at least possibly related to XTX202 should be followed until resolution, return to baseline, or deemed chronic or stable.

After completion of the initial screening assessments, any new clinically significant findings for enrolled patients will be captured as an AE on the eCRF.

All SAEs will be reported within 24 hours to the Sponsor from the time of signing the ICF through the Safety Follow-up Visit or until the patient has been deemed to be a screen failure. After completion of the AE reporting period (i.e. Safety Follow-up Visit), only SAEs attributed to XTX202 must be reported to the Sponsor.

SARS-CoV-2 (COVID-19) infections confirmed during study participation will be captured on the COVID-19 eCRF.

See Section 11.2 for a full description of the collection and reporting of AEs during this study.

8.2. SAFETY FOLLOW-UP VISITS

All patients will have an EOT Visit 30 (± 7) days after last dose and a final Safety Follow-up Visit 90 (± 7) days after last dose of study treatment unless the patient withdraws from the study prematurely (Section 6.6). Ongoing AEs considered at least possibly related to XTX202 treatment should be followed until resolution, return to baseline, or are considered stable or chronic. If a patient plans to start new anticancer therapy prior to the 30-Day EOT Visit or Safety Follow-up Visit these visits should occur prior to the initiation of any new anticancer therapy, if possible. If the 90-Day Safety Follow-up Visit is completed in person, then all assessments should be performed. If the visit is done by phone, only AEs and concomitant medications will be collected.

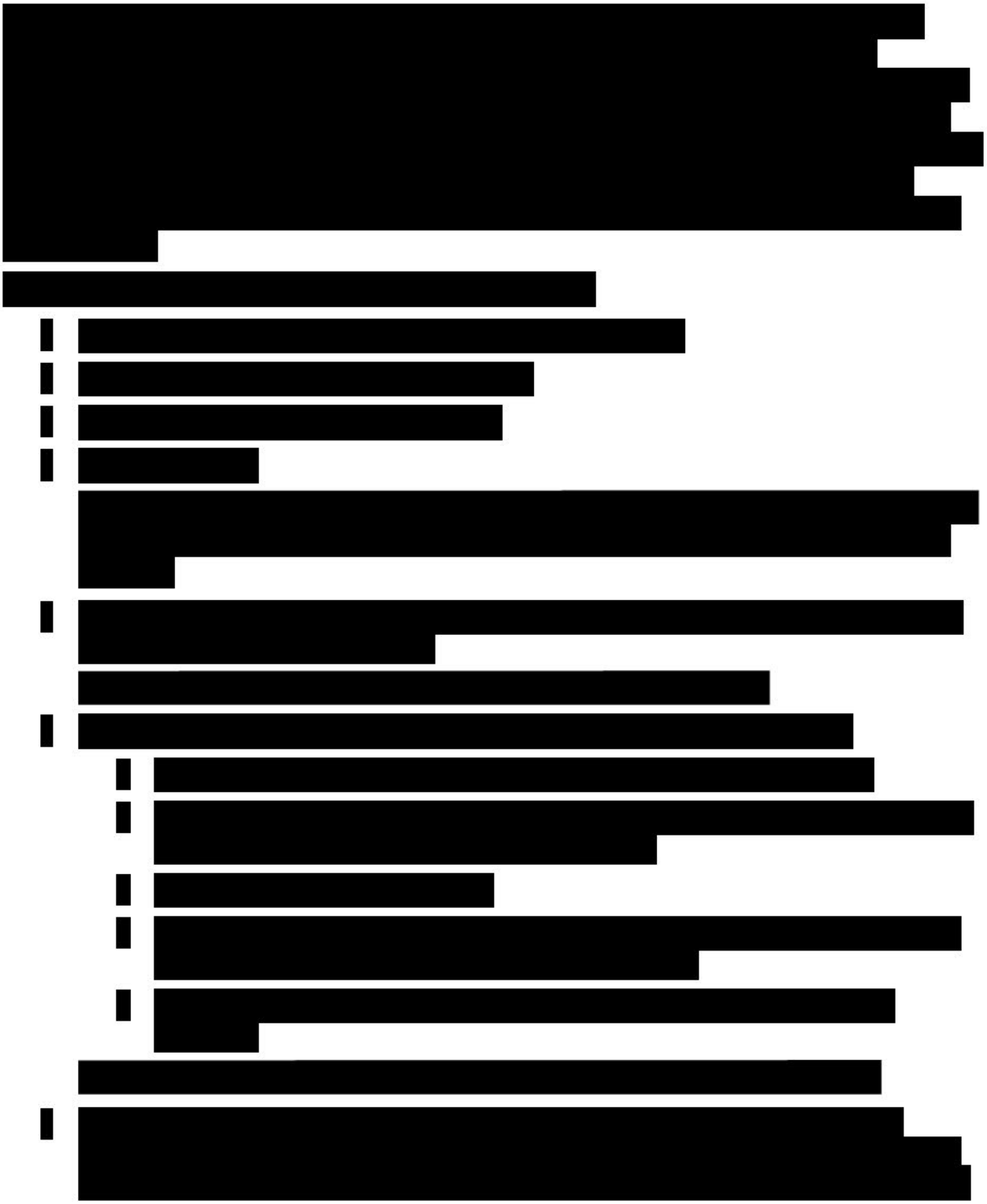
8.3. SURVIVAL FOLLOW-UP VISIT

In Phase 2 only, Survival Follow-up assessments following the 90-Day Safety Follow-up Visit will be collected every 3 months (± 2 weeks) for a total duration of 24 months from the first dose of XTX202, until the last patient completes study treatment, or the study is closed, whichever comes first. These assessments may be conducted by telephone interview. Information on the initiation of other anticancer therapy (including start date, therapy type/name, and response on treatment) may be collected. Additional survival follow-up calls may occur periodically if needed for data analysis.

9. STUDY MEDICATION

9.1. CONCOMITANT MEDICATIONS

9.1.1. Prohibited Medications



[redacted]

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator per standard of care.

All concomitant medication will be recorded on the eCRF including all prescription medications, over-the-counter products, vaccinations, herbal supplements, and IV fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 90 days after the last dose of study intervention at the Safety Follow-up Visit should be recorded. All concomitant medications administered during SAEs or Events of Clinical Interest (ECIs) are to be recorded. SAEs and ECIs are defined in Section 11.2.2.

9.1.2. Rescue Medications & Supportive Care

Study patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined, along with the dose modification guidelines, in Section 10.2.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

9.2. CONTRACEPTION AND PREGNANCY

The effects of XTX202 on conception, pregnancy, and lactation are unknown.

Female Patients

WOCBP must abstain from sexual activity, use an effective contraceptive method, or be surgically sterile from the time of signing the ICF through the duration of the study and for 3 months after the last administration of the study drug.

Effective contraception for WOCBP per World Health Organization criteria includes 1 "highly effective method" or 2 "effective" methods, as outlined in the Clinical Trial Facilitation and Coordination Group recommendations (CTFG 2020). WOCBP must have a negative serum pregnancy test at screening and negative urine tests prior to first dose of the study drug on C1D1 and throughout the study.

Highly Effective Methods (at least 1 required) (CTFG 2020)

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Effective Methods (at least 2 required) (CTFG 2020)

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

Note: combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

A WOCBP is defined as any woman in menarche who is not postmenopausal or permanently sterile. A postmenopausal woman must have had no menses for at least 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Male Patients

At Screening, all male patients who are not sterile (biologically or surgically) must commit to the use of a reliable and approved method of birth control (condoms with spermicide) from the signing of the ICF through the duration of the study and for 3 months after the last administration of the study drug.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Please see Section 11.2.7 for reporting of any pregnancy in patients receiving XTX202.

9.2.1. Pregnancy

If a patient inadvertently becomes pregnant while on study treatment, the patient will be immediately discontinued from study treatment. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy (including pregnancies in partners of male patients) and report the condition of the fetus or newborn to the Sponsor.

9.2.2. Use in Nursing Women

It is unknown whether XTX202 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breastfeeding are not eligible for enrollment.

9.3. DRUG ACCOUNTABILITY

The Investigator or designee is responsible for taking an inventory of each shipment of XTX202 received and comparing it with the accompanying drug order form. All unused XTX202 will be retained at the site until full drug accountability and reconciliation. After full drug accountability and reconciliation, the Investigator will dispose of any XTX202 at the study site per site procedures, or if necessary, all XTX202 will be returned to the Sponsor or its designee. Disposition of all XTX202 should be documented, including any XTX202 that is lost or damaged.

For more information on drug accountability, please see the XTX202-01/02-001 Pharmacy Manual.

9.4. ASSIGNMENT TO TREATMENT

All patients will receive open-label XTX202 at a dose and regimen based on the study design (see Section 6). Once enrolled, each patient will be assigned a unique subject identification number. This number will be recorded on the patient's eCRF pages and used to identify the patient throughout the study. Once a subject number is assigned, it cannot be reassigned to any other patient. Patients will be assigned to an XTX202 dose level based on the next available spot in the cohort(s) currently being enrolled.

10. XTX202 MATERIALS AND MANAGEMENT

10.1. XTX202

10.1.1. Description of XTX202

XTX202 is a tumor-selective, engineered IL-2 prodrug with its activity masked to keep it inactive until selectively activated within in the TME.

For more information on XTX202 concentration, formulation, and storage conditions, please see the XTX202-01/02-001 Pharmacy Manual and the Investigator's Brochure.

10.1.2. Packaging and Labeling

XTX202 will be supplied to the study site as open-label medication. Please refer to the XTX202-01/02-001 Pharmacy Manual for details regarding packaging and labeling of investigational product.

10.1.3. Dosage and Administration

10.1.4. Storage

XTX202 is supplied in vials for single use. Please see the XTX202-01/02-001 Pharmacy Manual for more details on storage.

10.1.4.1. Pre-Infusion Medications

Premedications are detailed in Section 10.2.1.

10.1.4.2. Post-Infusion Medications

No specific post-infusion medications are required for XTX202; however, post-infusion medications at Cycle 2 and beyond may be administered at the discretion of the Investigator.

10.2. DOSE HOLDS AND MODIFICATIONS

Patients will be monitored continuously for AEs while on study treatment. AE severity will be assessed using the NCI-CTCAE version 5.0 (Appendix 2).

It is anticipated that the specificity of cleavage of XTX202 within the TME will mitigate potential IL-2 mediated systemic adverse events. Nonetheless, careful monitoring of the patient in the initial post-infusion period is required for the initial dose (see Section 8.1.12). Most HD IL-2 related adverse events occur rapidly and typically peak 4 to 6 hours after a dose (Marabondo 2017). Prompt recognition and treatment of adverse events is critical. Doses of XTX202 should be held in the context of Grade $\geq$ 3 infusion-related reactions, with management of these events outlined in Section 10.2.1.

Dose reductions to previously evaluated dose levels are permitted.

If a patient experiences a treatment-related Grade $\geq$ 3 AE or any SAE, the start of the subsequent treatment cycle should be delayed until there is an acceptable resolution of the AE per the Investigator's clinical judgment. XTX202 may be withheld for up to 28 days for toxicity. Doses withheld for > 28 days due to treatment-related toxicity will result in permanent study treatment discontinuation. (If treatment had been withheld for reasons other than treatment-related toxicity, treatment may be reinitiated after consultation with the Medical Monitor.)

After experiencing a treatment-related Grade $\geq$ 3 AE or a treatment-related SAE, with the exception of infusion reactions (see Section 10.2.1 for infusion reaction management) and asymptomatic laboratory abnormalities, the dose of XTX202 administered in the subsequent cycle should be lowered to the next lowest dose level evaluated in the Phase 1 portion of the study. Up to 2 dose reductions are permitted in the study. If a patient experiences a treatment-related Grade $\geq$ 3 AE or a treatment-related SAE despite 2 dose reductions, treatment must be permanently discontinued.

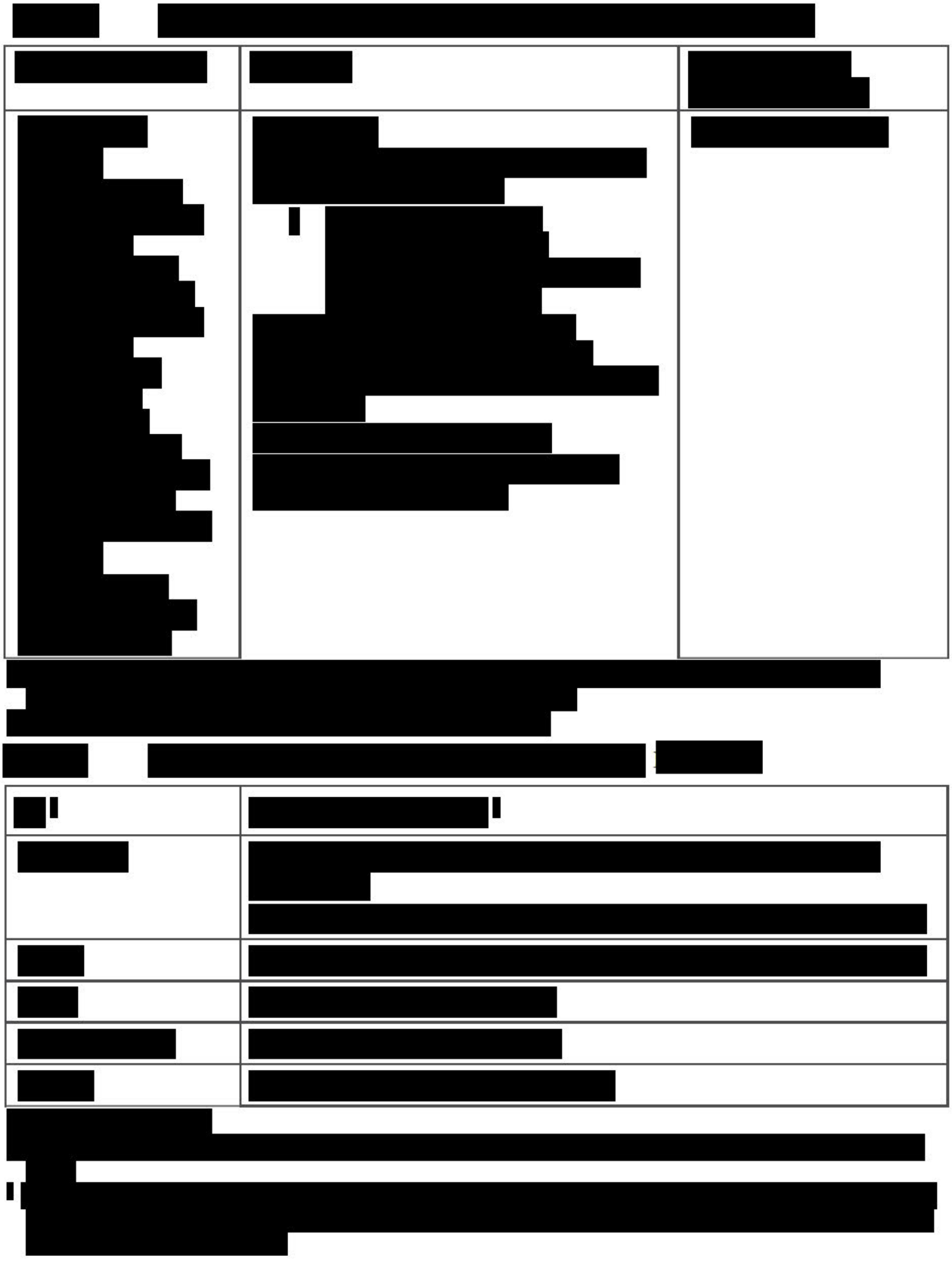
Based on emerging data, the SRC can recommend additional guidance for dose modification.

10.2.1. Infusion-Related Reactions

XTX202 may have the potential to cause reactions associated with the infusion, which may be severe or life-threatening (Dutcher 2014, Marabondo 2017). Signs and symptoms of infusion reactions or post-infusion AE(s) related to an increase in cytokines usually develop during or shortly after drug infusion and generally resolve quickly. [redacted]

Based on emerging data, the SRC can recommend additional guidance for dose modification, premedication, and supportive care for reactions associated with infusions.

[redacted]



11. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

11.1. ADVERSE EVENTS

11.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug, or with study participation, whether or not consider related to study treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs include worsening of a pre-existing medical condition as well as clinically significant changes from baseline laboratory values/conditions. Worsening of the pre-existing medical condition (e.g. diabetes, hypertension) means that it has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study is not considered an AE.

11.1.2. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF (as documented as medical history on the eCRF) is not considered an SAE
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is considered an important medical event
  - If an AE does not meet one of the serious criteria, but the Investigator or Sponsor considers an event to be clinically important, the event could be classified as an SAE under the criterion of “Important medical event.” Examples of such medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization.

11.1.3. Relationship to XTX202

The Investigator must assess the relationship between the AE and XTX202 as either "related to study drug (XTX202)" or "not related to study drug (XTX202)." The assessment of "related" must have a credible scientific basis. Although the temporal sequence of administration of the study drug and the subsequent occurrence of the AE may be supportive of a relationship, temporal sequence alone is an insufficient basis for an assessment of "related." Similarly, the elimination of other factors that may have been involved in the development of the AE cannot be the basis for an assessment of "related."

11.1.4. Adverse Event Severity

The Investigator will assess the grade of the AE per the NCI-CTCAE version 5.0 (Appendix 2). Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- 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 (ADL)
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE

Note: it is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity, whereas seriousness is classified by the criteria based on the regulatory definitions as described in Section 11.1.2 above.

11.2. PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS

11.2.1. Recording Adverse Events

Patients will be instructed to report all AEs and will be asked a general health status question at each study visit. All AEs and SAEs occurring in patients will be recorded in the eCRF from the time of signing the ICF through the Safety Follow-up Visit after the last dose of XTX202. An AE with causality related to study treatment will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition. All SAEs occurring from the signing of ICF through the Safety Follow-up Visit after the last dose of XTX202 will be processed as outlined in Section 11.2.6.

At each required visit during the trial, all AEs that have occurred since the previous visit must be reviewed by the Investigator. The Investigator must determine if the AE is serious or nonserious.

The Investigator must assign the following AE attributes:

- AE diagnosis or syndrome(s) if known
  - If not known at time of the report, record the signs and/or symptoms as AEs and provide an updated report with diagnosis when obtained
- Dates of onset and resolution
- Severity as defined per protocol
- Assessment of relatedness to each XTX202
- Action taken with each XTX202 as a result of the AE

In general, an AE that is the primary cause of subsequent events should be identified by the primary cause (e.g. for dehydration due to diarrhea, the AE would be diarrhea). However, AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events (e.g. sepsis secondary to pneumonia, both events should be recorded).

Concomitant illnesses that existed before entry into the study will not be considered an AE unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History page.

The signs and symptoms of progressive disease that meet the AE criteria should be reported as specific AEs, and not as disease progression.

11.2.2. Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

ECIs in this study include:

1. An overdose of investigational study medication as defined in Section 11.2.5 whether or not associated with clinical symptoms or abnormal laboratory results
2. Drug-induced liver injury
3. CRS

   Note: per the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading, defined as presented in Appendix 5 (Lee 2019). The clinical manifestations of CRS are varied and frequently involve multiple organ systems, with arrhythmia, cardiomyopathy, prolonged QTc, heart block, renal failure, pleural effusions, transaminitis, and coagulopathy a just a few of the significant complications of CRS. Per Lee et al., such significant events are uncommon in the absence of significant hypotension, hypoxia, or both. Thus, **hypotension** and **hypoxia** are the main determinants of the ASTCT consensus grading scale.

4. CLS

   Note: per NCI-CTCAE, defined as a disorder characterized by leakage of intravascular fluids into the extravascular space. CLS may result in hypotension and reduced organ perfusion, which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction,

respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

11.2.3. Abnormal Laboratory and Electrocardiogram Values

The Investigator is responsible for reviewing clinical laboratory tests and ECG results and determining whether an abnormal value represents a clinically significant change from the patient's baseline value. In general, abnormal laboratory findings and ECGs without clinical significance (based on the Investigator's judgment) should not be recorded as AEs. In general, an abnormal laboratory test and ECG results should be reported as an AE if the laboratory result:

- Requires an adjustment or discontinuation of XTX202
- Requires treatment or adjustment to concomitant medications
- Is considered to be an AE by the Investigator

11.2.4. Medication Errors, Misuse, and Abuse of XTX202

Overdose, medication error, misuse, and abuse are defined as follows:

- Overdose: refers to the administration of a quantity of XTX202 given per administration or cumulative, which is ≥ 50% above the planned dose according to the protocol
- Medication error: refers to an unintentional error in dispensing or administration of XTX202 not in accordance with the protocol
- Off-label use: refers to situations where XTX202 is intentionally used for medical purpose not in accordance with the protocol
- Misuse: refers to situations where XTX202 is intentionally and inappropriately used not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of XTX202, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to XTX202 because of one's professional or nonprofessional occupation

Overdoses, medication errors, abuse, or misuse will be collected as part of investigational medicinal product dosing information and/or as a protocol violation, as required.

11.2.5. Treatment of Overdose

For this study, an overdose of XTX202 will be defined as any dose ≥ 50% above the planned dose.

No specific information is available on the treatment of overdose of XTX202. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

11.2.6. Reporting of Serious Adverse Events

SAEs will be recorded on the appropriate eCRF within 24 hours of the Investigator's first knowledge of the event, even if the experience does not appear to be related to XTX202, from the time of signing ICF through the Safety Follow-up Visit after the last dose of XTX202.

The initial SAE eCRF must be as complete as possible, including details of the current illness and SAE, and an assessment of the relationship between the event and XTX202. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor or designee, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE considered related to XTX202 occurring more than 90 (± 7) days after the last dose of XTX202, the SAE must be reported as described above.

11.2.6.1. Reporting of Serious Adverse Events to Regulatory Authorities, Ethics Committee, and Institutional Review Board

The Sponsor or designee will determine expectedness of the Sponsor's product for each reported SAE based on the appropriate reference safety information per local requirements. The Sponsor or designee shall notify regulatory authorities of serious, unexpected, and related AEs or other AEs, per local requirements.

The Sponsor or designee shall notify the Investigator of serious, related, and unexpected AE(s) submitted to the regulatory agencies, per local country requirements.

The Investigator shall notify Central Ethics Committees of serious, related, and unexpected AE(s), or significant risks to patients, per country requirements.

The Investigator will notify the appropriate Institutional Review Board (IRB)/Local Ethics Committees (LECs) of serious, related, and unexpected AE(s), or significant risks to patients, per local country requirements. The Investigator must keep copies of all AE information on file, including correspondence with the Sponsor or IRBs/LECs.

11.2.7. Pregnancy and In Utero Drug Exposure

XTX202 has not been evaluated in pregnant or nursing women. Thus, pregnant women or WOCBP who are not using effective contraception are excluded from this study (see Section 9.2 and Section 8.1.9 for instructions on birth control and pregnancy testing, respectively).

Pregnancies occurring in patients or partners of male patients are considered immediately reportable events if the pregnancy occurs during the study treatment through the Safety Follow-up Visit after the patient's last dose of XTX202. If a pregnancy occurs in a patient, XTX202 must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. If a pregnancy occurs in the partner of a male patient, that partner should be consented, and the pregnancy followed as defined above.

The pregnancy must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the pregnancy by recording it on the appropriate eCRF.

The Investigator will follow the pregnant patient until completion of the pregnancy and must notify the Sponsor of the pregnancy outcome within 24 hours of the Investigator's knowledge of the outcome. The Investigator will provide this information by recording it on the appropriate eCRF. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant patient experiences an SAE during pregnancy, or the outcome of the pregnancy meets any of the serious criteria (i.e. spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e. report the event to the Sponsor or designee within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor or designee. In addition, any infant death or congenital anomaly occurring after 30 days that the Investigator suspects is related to the in-utero exposure to XTX202 should also be reported to the Sponsor or designee.

12. STATISTICAL METHODS

No hypothesis will be formally tested in the Phase 1 dose escalation study, and the statistical methods will be primarily descriptive. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (n), mean, standard deviation, median, and range (minimum and maximum). Within each part, the analyses will be by dose group. Across different parts of the study, patients on the same DL may be pooled together, if specified.

Details of the statistical methods for this study will be documented in a statistical analysis plan (SAP). When there is a difference between the final approved SAP and the protocol, the methods described in the final SAP will prevail.

12.1. SAMPLE SIZE

Phase 1, Part 1a and Part 1b may enroll up to [redacted] patients during dose escalation and PD expansion. The number of patients treated in Phase 1 of the study will be based on safety and tolerability observed during dose escalation.

In Phase 2, Part 2a and Part 2b will each enroll up to [redacted] at the RP2D(s) in a Simon's 2-stage design to exclude an ORR < 5%. The hypothesized response rate under treatment of ≥ 20% will be evaluated using a one-sided type I error rate of < 0.05 and 80% power. [redacted]

Note: The SRC may recommend more than 1 RP2D to be evaluated in the Phase 2 portion of the study to further characterize safety, efficacy, PK, PD and identify the optimal XTX202 dose for further development. The Sponsor will ensure that the dose allocation in Phase 2 will result in a sufficient dataset for the identification of the optimal dose in line with the January 2023 FDA draft guidance, "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases" (US FDA 2023). Details of the slot allocation process will be included in the operational manual. Descriptive statistics will be used to describe safety and efficacy of XTX202 for each Phase 2 dose level and each tumor type.

12.2. ANALYSIS SETS

The main analysis sets are defined in this section. Additional analysis sets may be defined in the SAP.

- **DLT-Evaluable Analysis Set:** all patients in Phase 1 (Dose Escalation Part 1a) who received at least 1 dose of XTX202 and either completed the DLT evaluation period or experienced a DLT during this period. This analysis set will be used to assess the tolerability of XTX202 in the dose escalation phase. Over the entire dose escalation phase, patients will be grouped based on the highest dose level each patient received.

- **All-Treated Analysis Set:** all patients who received any amount of XTX202, with treatment group based on the highest dose level received. This analysis set will be the primary analysis set for all safety endpoints, excluding DLT evaluation.
- **PK Analysis Set:** all enrolled patients who received at least 1 dose of XTX202 and have at least 1 postdose measurement of 1 analyte without protocol deviations or events affecting the validity of the PK results. This analysis set will be used for the analysis of PK parameters as further defined in the protocol. Exposure-response correlations may be performed. The PK exposure-response analysis will include patients who have both valid PK and valid response data.
- **Pharmacodynamic Analysis Set:** all enrolled patients who received at least 1 dose of XTX202 and have at least 1 postdose PD or biomarker measurement. This analysis set will be used for the analysis of PD endpoints as further defined in the protocol.
- **Response-Evaluable Analysis Set:** all patients with measurable disease at baseline who received any amount of XTX202 and had at least 1 post-baseline response assessment or discontinued treatment due to disease progression (including death caused by disease progression) prior the first efficacy evaluation. This analysis set will be the primary analysis set for efficacy endpoints.

12.3. REPLACEMENT OF PATIENTS

DLTs will be evaluated during Phase 1, Part 1a only, during the DLT Observation Period (C1D1 to C1D21) and ending just prior to C2D1. Patients with a DLT will not be replaced. Patients who discontinue treatment not due to a DLT or XTX202-related AE prior to completing the DLT Observation Period may be replaced. During Phase 2, unevaluable patients and patients who discontinue study prior to their first efficacy assessment due to reasons other than progressive disease or TEAEs may be replaced.

12.4. BACKGROUND CHARACTERISTICS

12.4.1. Patient Disposition

The number and percentage of patients in each disposition category (e.g. enrolled, included in each Analysis Set, discontinuing treatment, and discontinuing study, with a breakdown of the reasons for discontinuation) will be summarized by study part and dose level within study part.

For each part of the study, the All-Treated Analysis Set will be used as the basis for percentages, as appropriate.

12.4.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by study part and dose level within study part for the All-Treated Analysis Set: sex, race, age, type of cancer, tumor stage (tumor node metastases) at diagnosis and study entry, ECOG performance status, time elapsed since cancer diagnosis, and prior anticancer therapies. Additional parameters may be provided in the SAP.

12.5. XTX202 Exposure and Compliance

The summary statistics of exposure will be tabulated by study part and dose level within study part. In the summary, the following will be included:

- the cumulative number of days of exposure
- the number of doses completed
- the relative dose intensity

All variables are predefined:

- The cumulative number of days of exposure for each patient equal to the date of the last day of exposure minus the date of the first day of exposure plus 1
- For the number of doses started, if a patient has any record of starting administration number "X," the patient will be counted as completed administration X-1

All analyses within this section will be based on the All-Treated Analysis Set unless otherwise specified. Additional details are provided in the SAP.

12.6. Efficacy Analyses

Response will be based in Investigator assessment according to RECIST 1.1 (Appendix 3) and will be reported with response category (CR, PR, SD, progressive disease, and not evaluable) counts.

The first occurrence of CR or PR should be confirmed at a subsequent scan at least 4 weeks after the initial response determination.

For each patient, the best overall response is defined as the best overall response across all efficacy assessments and will be used to inform the ORR (CR and PR). The ORR, including total number of patients and percentages, will be calculated for each tumor type, by DL, and summarized by response category determined by the Investigator. The Clopper-Pearson 95% confidence interval will also be included in the summaries.

Time to event efficacy endpoints will be analyzed using Kaplan-Meier (KM) methods:

- DOR will be calculated for those patients with a CR or PR from the time of first response (of CR or PR) to disease progression (or censoring)
- PFS will be assessed from time of first treatment to disease progression (or censoring) as determined by the Investigator or death
- OS will be assessed from time of first XTX202 treatment to end of study (or censoring)

The relevant details for censoring will be described in the SAP. KM plots will be provided as appropriate for relevant endpoints.

All efficacy analyses will be based on the Response Evaluation Analysis Set unless otherwise specified.

12.7. SAFETY ANALYSES

The All-Treated Analysis Set will be used to evaluate all safety endpoints unless the endpoints are applicable to only select patients, such as the DLT evaluation.

For Phase 1, Part 1a, the number and type of DLTs experienced by patients will be summarized for each dose level, accompanied by a by-patient listing of DLT events. The listing will include the description, severity, and relationship of the events to XTX202.

In all parts of the study, safety data, including vital signs, ECGs, laboratory test results, and AEs, will be summarized by dose and assessment timepoints, as appropriate.

12.7.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or higher and will be graded according to the NCI-CTCAE version 5.0 (Appendix 2).

Summaries of AEs will include TEAEs. A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to the Safety Follow-up Visit after the last dose of XTX202.

AEs will be summarized by dose within cohort, if applicable.

TEAEs will be summarized by the frequency within MedDRA system organ class and preferred term. Separate tabulations will also be provided for TEAEs related to XTX202, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs Grade ≥ 3 in severity. Treatment-emergent SAEs and SAEs related to XTX202 will also be tabulated.

Detailed information of AEs will be included in a listing.

12.7.2. Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System units. All statistical analyses will be by cohort and by dose level within cohort, if applicable.

Summary statistics for laboratory values including change from baseline will be tabulated for scheduled visits. Shifts in grade from baseline to the maximum post-baseline (including unscheduled) grade will be summarized by number and percentage of patients within each category. Abnormality of laboratory data will be summarized and tabulated by number and percentage of patients with Grade ≥ 3 in severity.

A listing of individual patient hematology, blood chemistry, and coagulation values will be provided. This listing will include data from scheduled and unscheduled timepoints.

12.7.3. Immunogenicity

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those patients with at least 1 positive ADA assessment at any timepoint will be provided by dose regimen. The frequency of patients with at least 1 positive ADA assessment, and frequency of patients who develop ADA after a negative baseline

assessment will be provided by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of ECIs may be examined by overall immunogenicity status.

12.8. PHARMACOKINETIC ANALYSES

All PK analyses will be based on the PK Analysis Set. The raw PK data will be summarized by assessment visit. A noncompartmental model will be applied, and the following derived parameters will be summarized and plotted (as appropriate):

C_{max}	Maximum observed serum concentration
T_{max}	Time of maximum observed concentration
C_{trough}	Trough concentration
AUC	Area under the curve
$t_{1/2}$	Half-life
CL	Systemic clearance
Vd	Volume of distribution

Evaluations of PK data will include dose proportionality, accumulation upon multiple-dose administration, and PK/PD relationship. Additional details on the PK analyses will be provided in the PK/PD analysis plan.

12.9. PHARMACODYNAMIC ANALYSES

PD analyses involving changes in peripheral blood monocyte subpopulations, serum cytokines, and tumor tissue cellular subpopulations and biomarker expression will be descriptive in nature. Summary tabulations may be produced if data from enough patients are collected. Additional details on the PD analyses will be provided in the PK/PD analysis plan.

13. STUDY ADMINISTRATION

13.1. GOOD CLINICAL PRACTICE STATEMENT

This study is to be performed in accordance with the protocol, the Declaration of Helsinki 1996 version, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

General Guidance for Treatment Continuity Due to COVID-19

Prior to the utilization of any of the measures described below, discussion and approval must be obtained from the Sponsor/Contract Research Organization. It is expected that sites participating in this clinical study will make every effort to ensure proper monitoring of enrolled patients by adhering to safety monitoring as outlined in the protocol schedule of events. The use of local laboratories and local radiology centers to reduce the need for the patient to come to the study site are supported for the well-being of the patient.

A telemedicine solution that allows for continued monitoring of AEs, concomitant medications, protocol deviations, and other assessments may be used. Appropriate documentation of utilization should be captured at the site for review by the study monitor. General guidelines for patients with limited possibility to travel or restricted access to the study site:

- Conduct visit by phone or alternative location for assessment, i.e. local laboratory or imaging center.
  - Arrangements for the use of local laboratory or imaging center to be made by the site, including the reporting of results to the Principal Investigator for review.
- If reduced patient exposure in the clinic is necessary, in-person visits every other cycle are acceptable if there are no ongoing AEs or new AEs. These missed visits will be considered protocol deviations.
- Delay in study drug treatment is acceptable up for up to 30 days.

13.2. INFORMED CONSENT

The Sponsor or designee will provide a sample patient ICF for modification, as appropriate, by the Investigator. The ICF must include all elements required by ICH and GCP and must adhere to the IRB/Independent Ethics Committee (IEC) requirements and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator or designee will explain the nature of the study, its purpose and associated procedures, the expected duration, and the potential risks involved to the patient prior to enrollment. The Investigator or designee will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a patient will be asked if they are willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the

study. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol that necessitates a change to the content of the patient's informed consent. The Investigator will inform the patients of changes in a timely manner and will ask the patients to confirm continuation of their participation in the study by their signature on the revised ICF (if applicable). Any written ICF and written information must receive the approval/favorable opinion of the IRB/IEC in advance of use. Any additional approvals from the initial ICF should be forwarded to the Sponsor.

13.3. PATIENT CONFIDENTIALITY AND DATA PROTECTION

The written ICF will explain that study data will be stored in a database, maintaining confidentiality in accordance with national data legislation. All data processed by the Sponsor or its representative(s) will be identified by patient number and study code.

The written ICF will also explain that for data verification purposes, authorized representatives of the Sponsor, a regulatory authority, and an IRB/IEC may require direct access to parts of the hospital or clinic records relevant to the study that include the patient's medical history.

The Investigator must ensure that the patients' anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their assigned patient number and study code. Documents not for submission to the Sponsor, such as signed ICF, should be maintained in strict confidence by the Investigator.

13.3.1. General Data Protection Regulation (European Union)

The collection of data from European patients in the study constitutes a processing of personal data within the meaning of Article 4 of the General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (GDPR).

In this respect, the personal data collected will be processed in accordance with the GDPR as well as the local European laws applicable to study, including:

- Information will be delivered to patients accordingly to Article 13 of the GDPR
- Patients would be able to exercise their rights provided by the GDPR under Chapter III
- Transfers of patients' personal data outside of the European Union will be regulated in accordance with the provisions of Chapter V of the GDPR
- Patients' personal data will be processed by the Sponsor as required by GDPR

13.4. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE REQUIREMENTS

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC at each study site. The Principal Investigator must

submit written approval from the IRB to the Sponsor before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol. In addition, the IRB/IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB/IEC annually or as required by the IRB, regulations, and guidelines.

Progress reports and notifications of SAEs will be provided to the IRB/IEC according to regulations and guidelines.

13.5. CASE REPORT FORMS AND SOURCE DOCUMENTATION

Electronic CRFs will be provided for the recording of all data. The Principal Investigator/Sub-Investigator or designee will record data from all observations, tests, and assessments specified in the protocol on the eCRFs provided by the Sponsor.

13.6. SPONSOR MONITORING

Regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring methods to maintain oversight of the conduct of the study and study sites. Any restrictions in place at the trial site that will impact monitoring access to the site should be communicated to the Sponsor and Contract Research Organization.

Before the first patient signs consent to participate in the study, a representative of the Sponsor will visit the study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities regarding the protocol and the responsibilities of the Sponsor
- Confirm that the Investigator(s) (and other personnel involved with the study) have not invoked sanctions or demonstrated any scientific misconduct or fraud

During the conduct of the study, a representative of the Sponsor will have regular contact with the study site, and have regular visits to the study site to:

- Provide information and support the Investigator
- Confirm that the facilities remain acceptable
- Confirm that the study team is adhering to the protocol, data are being accurately recorded in the eCRFs, and the investigational product is being properly maintained and accountability records are current
- Perform source data verification with access to all original clinical records for each patient

13.7. QUALITY ASSURANCE

In compliance with GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IRB/IECs may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors to discuss findings and issues.

13.8. STUDY OR CLINICAL SITE TERMINATION

The Sponsor, or designee, reserves the right to terminate the study or a study site at any time. Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing the study treatment
- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the study site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If terminating the study, the Sponsor and the Investigator(s) will assure that adequate consideration is given to the protection of the patients' interests.

13.9. DURATION OF THE STUDY, EXPECTED DURATION OF PATIENT PARTICIPATION, AND END OF STUDY

Patients assigned to receive XTX202 must discontinue treatment for any of the reasons outlined in Section 6.5, unless otherwise noted. For a patient to continue to receive treatment beyond disease progression, there must be no decline in ECOG performance status and no clinically significant signs and symptoms of disease progression or any indication of rapidly progressing disease. In addition, patients with progressing tumors at critical anatomical sites (e.g. cord compression) that require alternative urgent medical intervention, should not receive additional treatment with XTX202.

The Investigator will have to counsel the patient about the potential risk and benefit of continuing study treatment beyond disease progression, and the patient's consent to continue with study treatment will have to be documented in the medical records.

Each patient treated on study in Phase 2 will be followed for survival for 24 months after his or her first dose of XTX202, until the last patient completes study treatment, or the study is terminated by the Sponsor, whichever comes first.

13.10. RECORDS RETENTION

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, SRC reviews, eCRFs, XTX202 inventory, IRB, and Sponsor correspondence pertaining to this study must be kept on file. All study documents must be kept secured for a period of 2 years after a marketing application is approved for XTX202, or until 2 years after shipment and delivery of the XTX202 for investigational use is discontinued or if required by local regulations, whichever is longer. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing or relocating study records for any reason.

13.11. FINANCING, LIABILITY, AND INSURANCE

The Sponsor may be required to submit reports on payments and transfers of value made to any Investigator or any other physician in compliance with the Physician Payments (Sunshine) Act. The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of the administration of the investigational product and procedures required by the protocol performed strictly in accordance with the scientific protocol as well as with applicable law.

13.12. PUBLICATIONS

All information regarding the investigational product supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Any publications arising from the study must be approved by the Sponsor in accordance with the Clinical Trial Agreement. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of XTX202 and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants as required.

This study will be registered in a publicly accessible database before the recruitment of the first patient. Results from the study will be disclosed in the database and will include negative and inconclusive, as well as positive results.

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15. APPENDICES

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Eastern Cooperative Oncology Group.
(Oken 1982)

APPENDIX 2. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0

CTCAE Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA lowest level term.

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- 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 ADL*.
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: life-threatening consequences; urgent intervention indicated.
- Grade 5: death related to AE.

A semi-colon indicates ‘or’ within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for grade selection. Grade 5 (death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

Publish date 27 November 2017
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

APPENDIX 3. RECIST RESPONSE CRITERIA

Response criteria were adapted from *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)* (Eisenhauer 2009).

A3-1. BASELINE EVALUATION

The baseline examination is to be done within 4 weeks of the start of XTX202.

A3-1.1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

Per RECIST version 1.1, a patient must have at least 1 radiologically measurable extracranial lesion. A measurable lesion is defined as one that can be accurately measured in at least 1 dimension by CT scan (CT scan slice thickness no greater than 5 mm) or MRI:

- Tumor lesions: long diameter ≥ 10 mm
- Pathologic lymph nodes: short diameter ≥ 15 mm

Non-measurable lesions are defined as all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 to < 15 mm) as well as truly non-measurable lesions, including, but not limited to, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, and lymphangitic involvement of skin or lung.

A3-1.2. SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

A3-1.2.1. Bone Lesions

Bone scan, positron emission tomography scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI, can be selected as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

A3-1.2.2. Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

A3-1.2.3. Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression of the lesion since the intervention.

A3-1.2.4. Baseline Documentation of Target and Non-Target Lesions

Baseline documentation of tumor sites may include imaging assessment of disease in the chest, abdomen, and pelvis. All baseline tumor measurements must be documented within 4 weeks before the start of therapy.

A3-1.2.5. Target Lesions

Up to a maximum of 5 measurable lesions total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibility should be selected. Per above, tumor or nodal lesions located in a previously irradiated area, or in an area subjected to other loco-regional therapy, should not be selected as target lesions unless there has been demonstrated progression in the lesion since the local therapy. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

A3-1.2.6. Nontarget Lesions

All other lesions (or sites of disease), including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed qualitatively as ‘present,’ ‘absent,’ or ‘unequivocal progression.’ In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (i.e. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

A3-2. TUMOR RESPONSE CRITERIA

A3-2.1. EVALUATION OF TARGET LESIONS

RECIST 1.1 CR, PR, progressive disease, and SD criteria are described as follows:

- CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
- Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum (i.e. nadir) on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  Note: the appearance of 1 or more new lesions is also considered progression
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

A3-2.2. EVALUATION OF NON-TARGET LESIONS

RECIST 1.1 CR, non-CR/non–progressive disease, and progressive disease criteria are described as follows:

- CR: disappearance of all nontarget lesions and, if appropriate, normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- Non-CR/non-progressive disease: persistence of 1 or more nontarget lesion(s).
- Progressive disease: unequivocal progression of existing nontarget lesion(s).

  Note: the appearance of 1 or more new lesions is also considered progression.

A3-2.3. DETERMINATION OF TUMOR RESPONSE

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Eisenhauer 2009
Note: Patients with a global deterioration of health status, requiring discontinuation of treatment without objective evidence of disease progression at that time, should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression, even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy), before confirming the CR status.

[redacted]

APPENDIX 5. CYTOKINE RELEASE SYNDROME RECOMMENDATIONS

A5-1. ASTCT CYTOKINE RELEASE SYNDROME CONSENSUS GRADING

Table 8: ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [1]	Temp. ≥ 38°C	Temp. ≥ 38°C	Temp. ≥ 38°C	Temp. ≥ 38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or [2]				
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula[3], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[1] Fever is defined as temperature 38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Source: Lee 2019