STUDY PROTOCOL

CTX-009-003

A Phase 2 Study of CTX-009 in Adult Patients with Metastatic Colorectal Cancer who have received Two or Three Prior Systemic Chemotherapy Regimens

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Phase:	2
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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): _____

SPONSOR PROTOCOL APPROVAL

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

DocuSigned by Minori Rosales
Minori Rosales | I approve this document
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PROTOCOL SYNOPSIS

Study Title: A Phase 2 Study of CTX-009 in Adult Patients with Metastatic Colorectal Cancer who have received Two or Three Prior Systemic Chemotherapy Regimens

Protocol Number:

CTX-009-003

Phase: 2

Study Rationale:

In the United States, patients with unresectable locally advanced and unresectable metastatic colorectal cancer are sequentially treated with various combinations or single agent courses of cytotoxic chemotherapy agents including 5-fluorouracil and its orally administered family members (capecitabine, TAS-102) oxaliplatin, and irinotecan, as well with targeted therapies such as bevacizumab or aflibercept (anti-VEGF), cetuximab or panitumumab (anti-EGFR), or multitargeted tyrosine kinase inhibitors (regorafenib). In subsets of patients who have had multigene panel testing done and whose tumors have been identified as having mutations that drive their disease such as defective mismatch repair, HER-2 overexpression, or NTRK fusions specific treatments with respectively PD-1 or PD-L1 inhibitors, traztuzumab or larotrectinib or entrectinib can also be used effectively. Despite the approval of multiple new agents in the past two decades, the goals of therapy are generally palliative although some patients will have long disease-free intervals when they respond to therapy. In the cases of patients whose disease has progressed, or who have not tolerated 2 or 3 prior lines of therapy, the expectation for tumor response with the available treatments are less than 5% and the median overall survival is approximately 6 months (for 3rd line therapy) or less (for 4th line therapy). In a Phase 1 study, responses have been seen in patients with colorectal cancers who were treated in the 4th line setting. Since CTX-009 targets tumor induced neoangiogenesis, and monoclonal antibodies that target vascular endothelial growth factor (VEGF) has been shown to extend the lives of patients with advanced colorectal cancer, testing of CTX-009 in the setting of advanced treatment refractory colorectal cancer is justified.

Investigational Product:

CTX-009 (also known as ABL001 and ES104) is a recombinant bispecific antibody that contains a single chain variable fragment (scFv) binding to human delta-like ligand-4 (DLL4) linked to the heavy chain that is based on the sequence of bevacizumab which binds to human VEGF.

Study Centers:

Enrollment is anticipated at approximately 10 clinical sites in the United States, Canada, South Korea, and/or China.

Objectives and Endpoints:

Primary:

Primary Objective	Primary Endpoints
To assess the efficacy of CTX-009 in patients with colorectal cancer (CRC) who have received two or three systemic therapies for advanced disease, as measured by Overall Response Rate (ORR).	Percentage of patients whose Best Overall Response (BOR) is assessed as Complete Response (CR) or Partial Response (PR) as assessed by RECIST v1.1

Secondary:

Secondary Objectives	Secondary Endpoints
To assess the efficacy of CTX-009 in patients with CRC as measured by Disease Control Rate (DCR)	Percentage of patients whose BOR is assessed as CR, PR, or Stable Disease (SD)
To assess the efficacy of CTX-009 in patients with CRC as measured by Duration of Response (DOR)	The number of days between the date of the radiological evaluation that first confirmed CR or PR and the date of the radiological evaluation that first confirmed Progressive Disease (PD) or the date of censoring
To assess the efficacy of CTX-009 in patients with CRC as measured by Progression Free Survival (PFS)	The number of days from Cycle 1 Day 1 (C1D1) until the date of objective PD (as assessed by an Independent Central Radiology (ICR) review and defined by RECIST v1.1) or the date of death (by any cause in the absence of disease progression) or the date of censoring
To assess the efficacy of CTX-009 in patients with CRC as measured by Overall Survival (OS).	The number of days from C1D1 until death by any cause. Patients who are still alive at the time of the analysis, or who have become lost to follow-up or withdrawn consent will be censored at their last date known to be alive.
To evaluate the safety profile of CTX-009, including immunogenicity of CTX-009 in treated patients	Incidence of Treatment Emergent Adverse Events (TEAEs) and changes in clinical abnormalities for all patients who received at least one dose of CTX-009

Pharmacokinetic Objective:

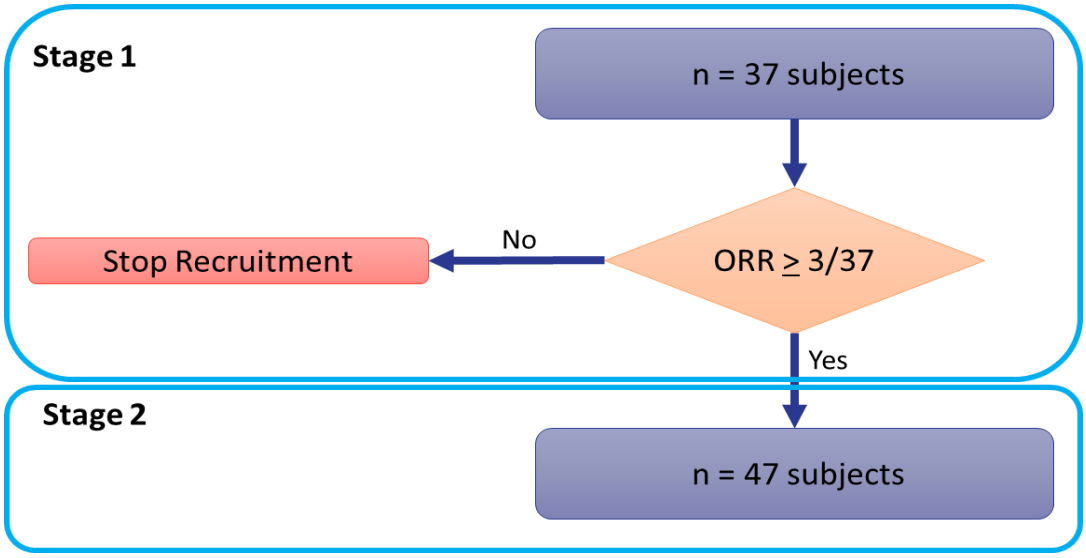
Objective	Endpoints
To characterize the pharmacokinetics of CTX-009 and explore exposure response by sparse population PK sampling	Serum concentrations of CTX-009 at specified timepoints

Exploratory Objective:

Objective	Endpoints
To evaluate Health Related Quality of Life in patients treated with CTX-009.	Changes in QoL scores from baseline

Study Design and Schema:

This study is designed as an open-label, adaptive Simon Two Stage study to evaluate the efficacy of CTX-009 in patients with metastatic CRC.



Simon 2 Stage Design

Assessment of Safety:

Safety will be assessed through the monitoring of adverse events (AEs) and clinical laboratory evaluations.

Patients will be monitored continuously for AEs while on treatment until 30 days after the last dose. Ongoing AEs considered at least possibly related to CTX-009 treatment should be followed until resolution, return to baseline or are considered stable or chronic. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher.

Number of Patients:

Approximately 37 patients will be enrolled into Stage 1, and if criteria are met to move to Stage 2, an additional 47 patients will be enrolled, for a total of approximately 84 patients.

Study Population:

Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. 18 years of age or older
2. Histologically or cytologically confirmed metastatic or recurrent colorectal cancers
3. The primary tumor must have been resected > 3 months prior to planned C1D1.
4. Patients who experienced progressive disease or relapse after receiving two or three prior lines of systemic therapy in the locally advanced or metastatic setting. Prior lines of systemic treatment must have included at least one fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab containing chemotherapy regimen (in any combination and may have been administered in the neoadjuvant or adjuvant setting).
    a. Patients whose tumor is not right sided and RAS wild type must also have received an anti-EGFR therapy.
    b. Patients with tumors harboring mutations or other alterations for which there are available targeted therapies (e.g., BRAF V600E, HER2-positive, MSI-H/dMMR, etc.) must have also received the relevant approved targeted therapies.
    c. If patient received peri-operative treatment (neoadjuvant and/or adjuvant), please consult the Sponsor Medical Monitor for review of prior treatment lines.
5. At least one lesion measurable as defined by RECIST v1.1
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
7. Predicted life expectancy of at least 12 weeks
8. Adequate hepatic and renal function within 14 days of C1D1 as described below:
    a. Total bilirubin ≤ 1.5 X upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤ 3.0 X ULN (≤ 5x ULN in case of hepatic metastasis)
    c. Estimated creatinine clearance ≥ 30 mL/min based on Cockcroft-Gault estimated creatinine clearance
    d. Urine protein ≤ 1+ by spot urinalysis (or, if > 1+ then 24 hr urine protein <1.0 g/24 hr)
9. Female patients who are women of childbearing potential (WCBP) must have a negative pregnancy test (serum-human chorionic gonadotropin [hCG] or urine-hCG) at Screening within 14 days of C1D1.
10. Female patients must be surgically sterile (or have a monogamous partner who is surgically sterile) or be at least 2 years postmenopausal or commit to use 2 acceptable forms of birth control (defined as the use of an intrauterine device (IUD), a barrier method with spermicide, condoms, any form of hormonal contraceptives, or abstinence) for the duration of the study and for 4 months following the last dose of study treatment. Male patients must be sterile (biologically or surgically) or commit to the use of a reliable method of birth control (condoms with spermicide) for the duration of the study and for 4 months following the last dose of study treatment.

11. Signed and dated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) before any protocol-directed screening procedures are performed.

Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. From the time point of signed informed consent,
    a. Less than 4 weeks have elapsed since patients had a surgery or major procedure
    b. Less than 2 weeks have elapsed from the last treatment date since patients had any radiation therapy
2. Prior to planned C1D1,
    a. Less than 4 weeks have elapsed since patients had chemotherapy or targeted therapy for colorectal cancer
    b. Less than 4 weeks have elapsed since patients had anticancer immunotherapy or investigational drug treatment
3. A history of the following cardiovascular diseases in past 5 years may be exclusionary, as determined by the Sponsor Medical Monitor:
    a. Congestive heart failure that corresponds to Class II or a higher class under New York Heart Association (NYHA) classification or less than 50% of left ventricular ejection fraction (LVEF)
    b. Uncontrolled hypertension (systolic blood pressure [SBP]/diastolic blood pressure [DBP] > 140/90 mmHg) (e.g., patient with SBP/DBP > 140/90 mmHg despite the best care including anti-hypertensive medications)
    c. Patients with a history of hypertensive crisis or pre-existing hypertensive encephalopathy
    d. Pulmonary hypertension
    e. Myocardial infarction
    f. Uncontrolled arrhythmia
    g. Unstable angina
    h. Patients with any significant vascular diseases (e.g., aortic aneurysm requiring surgery or recent peripheral artery thrombosis) within 6 months prior to the initial treatment of the investigational product
4. Symptomatic or uncontrolled central nervous system (CNS) metastasis (However, patients with asymptomatic CNS metastasis can participate provided that systemic corticosteroid treatment was discontinued at least 4 weeks prior to screening and that the patient is radiologically and neurologically stable or improving.)
5. A history of the following hemorrhage-related or gastroenterological disease:
    a. Active hemorrhage, hemorrhagic diathesis, coagulopathy or tumor invasion into great arteries
    b. History of clinically significant and active (within 6 months) gastroenterological disease, such as peptic ulcer, gastrointestinal (GI) bleeding, GI or non-GI fistula, perforation, abdominal abscess, clinical symptoms and signs of GI obstruction, need for parenteral hydration or nutrition, or inflammatory bowel disease.
6. Patients who received antiplatelet drugs (aspirin, clopidogrel, etc.) or anticoagulant drugs (warfarin, heparin, direct thrombin inhibitors, etc.) within 2 weeks prior to C1D1,

or are expected to need those drugs during the clinical study.

7. Patients requiring continuous treatment with systemic non-steroidal anti-inflammatory drugs (NSAIDs) or systemic corticosteroids (the following cases are permitted):
    a. NSAIDs: Up to 3 consecutive days' use is permitted.
    b. Corticosteroids: Topical use of corticosteroid, such as topical intra-articular injection, intranasal administration, eye drops, inhaler, etc., or temporary systemic corticosteroid use for treatment and prevention of patient's contrast media allergy, or adverse event, is permitted.
8. Severe infection requiring systemic antibiotics, antivirus drugs, etc., or other uncontrolled acute active infectious diseases
9. Patients with evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Inactive hepatitis B carriers who tested HBsAg positive may enroll provided that the patient's liver function values are normal. Also, patients with chronic HBV infection which has been controlled by the site's treatment guideline may enroll. HCV patients showing sustained viral response or patients with immunity to HBV infection may enroll.
10. Patients with other severe diseases or uncontrolled illnesses that warrant the exclusion from the study (permitted only if medically controlled) including but not limited to:
    a. Pre-existing hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 28 days prior to screening
    b. Major, unhealed injury, active ulcer or untreated fracture
    c. History of cerebrovascular incident (ischemic or hemorrhagic stroke), transient ischemic attack or subarachnoid hemorrhage within 6 months prior to screening 1.
    d. Moderate to severe ascites and/or pleural effusion.
11. Clinically significant abnormal electrocardiography (ECG) findings or history determined as clinically significant by the Investigator.
12. QT interval (Fridericia's formula) (QTcF) interval > 450 msec at the time of screening

Study Duration:

The study will consist of a Screening Period (up to 14 days), a Treatment Period (continuous treatment until disease progression, unacceptable toxicity, death, or withdrawal of consent), and a Follow-up Period (estimated 18 months from the first dose of CTX-009). Patients may continue on study treatment beyond disease progression if they are deriving clinical benefit.

It is estimated that the total study duration is approximately 18 months.

CTX-009 Administration:

CTX-009 will be administered at a dose of 10 mg/kg biweekly, on Day 1 and Day 15 of every 28 day cycle.

Treatment will continue until confirmed PD, unacceptable toxicity, withdrawal of consent, or other protocol-defined end of treatment criteria. A single dose reduction is permitted as described in the following Table:

Drug	Starting Dose	Dose Reduction
CTX-009	10.0 mg/kg	7.5 mg/kg

Administer on D1 and D15 of each treatment cycle		

Dose adjustments are permitted and required for specific adverse events, as detailed in the protocol. Patients must be evaluated for the dosing criteria specified in the protocol prior to each infusion.

Efficacy Assessment:

Anti-tumor activity is assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. The overall response rate (ORR), the primary efficacy endpoint, will be assessed by the Investigators.

1) Overall Response Rate (ORR)
   - Percentage of patients whose best overall response (BOR) is assessed as complete response (CR) or partial response (PR).
   - ORR= CR + PR

2) Disease Control Rate (DCR)
   - Percentage of patients whose best overall response (BOR) is assessed as complete response (CR), partial response (PR) or stable disease (SD)
   - DCR= CR + PR + SD

3) Duration of Response (DOR)
   - Time between the date of the radiological evaluation that first confirmed complete response (CR) or partial response (PR) and the date of the radiation evaluation that first confirmed the progressive disease (PD)

4) Progression-Free Survival (PFS)
   - Time between the date of C1D1 and the radiological evaluation confirming tumor progression or the date of death

5) Overall Survival (OS)
   - Time between the date of C1D1 and the date of death, or date of censoring

Statistical Methodology

Sample Size Determination

A sample size of 84 total patients (37 in Stage 1 and 47 additional in Stage 2) will have approximately 90% power on a two-sided alpha of 0.05 based on a Simon 2 Stage optimal design with a lower response rate bound of 5% and an upper bound of 15%.

Statistical Analysis:

The overall response rate (ORR, the proportion of subjects with CR or PR) will be summarized and tabulated along with the summary of BOR category (CR, PR, SD, or PD).

The safety data will be descriptively analyzed. All adverse events will be evaluated by CTCAE version 5.0 (or higher) and coded using MedDRA version 25.0 or later. Incidence of treatment

emergent adverse events (TEAEs) be summarized by system organ class, preferred term and by relatedness and severity.

Safety laboratory assessments and will be summarized by visit and evaluated by CTCAE version 5.0 grade. The CTCAE grade shifts from baseline will be summarized by post-baseline assessments for selected laboratory parameters.

Table 1: Schedule of Assessments

Assessment[1]	Screening	On Treatment				After Protocol Treatment Discontinuation		
		Cycle 1		Cycle 2 and Beyond		End of Treatment	Safety Follow Up	Survival Follow Up
		Day 1	Day 15	Day 1	Day 15			
Timing	≤ 14 Days Prior to C1D1	N/A	+/- 2 Days	+/- 3 Days		≤ 7 Days from Treatment Discontinuation	60 (+/-5) From EOT	Every 3 Months (+/- 7 Days)
Informed Consent and Eligibility Review[2]	X							
Medical History & Demographics	X							
Height	X							
Weight	X	X	X	X	X	X	X	
Vital Signs[3]	X	X	X	X	X	X	X	
Physical Examination[4]	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X		X		
12-lead Electrocardiogram[5]	X	X				X		
Echocardiogram[6]	X			X[6]		X		
Hepatitis B and C Serology	X							
Urinalysis[7]	X	X	X	X	X	X	X	
Blood Hematology[7]	X	X	X	X	X	X	X	
Blood Chemistry[7]	X	X	X	X	X	X	X	
Blood Coagulation Factors[7]	X	X		X		X	X	
Immunogenicity Blood Serum Sampling[7]	X	X		X		X		
PD/Biomarker Blood Sampling[7]	X	X		X		X		
PK Blood Sampling[7,8]		X	X	X		X		
Cardiac Assessments[7]	X	X	X	X	X	X	X	
Optional Archival Tumor Tissue Collection	X							
Pregnancy Test[7,9]	X	X		X		X		
EORTC QLQ[10]	X			X		X		
CTX-009 Treatment[11]		X	X	X	X			
Tumor Evaluation[12]	X	X				X	X	
Concomitant Drug and Procedures Review	X	X				X		
Adverse Event Assessment[13]	X	X				X	X	
Survival Assessment[14]							X	X

Footnotes:

1. For full details and descriptions of assessments, refer to Study Procedures section of the protocol.
2. Informed consent must be obtained prior to any protocol specific assessments and may be done up to 28 days from planned C1D1.
3. Vital signs should be collected prior to CTX-009 infusion.
4. A full physical exam will be conducted at Screening and EOT. Symptom-directed physical exams will be performed at other visits and as clinically indicated.
5. 12-lead ECG conducted following a 10-minute rest period and obtained within a 5-minute time period. QTc measurements will use the Fridericia's correction method (QTcF). ECGs will be read locally by the Investigator. At C1D1, complete within approximately 2 hours of completion of the infusion and as clinically indicated thereafter.
6. Echocardiogram required at screening may be performed up to 28 days prior to C1D1 to allow for additional scheduling time. Follow up echocardiograms should be done every 3 months (±7 days) thereafter; however if B-type natriuretic peptide (BNP) is elevated beyond the upper limit of normal range then an echocardiogram must be performed.
7. Clinical laboratory assessments should be collected prior to CTX-009 infusion.
8. PK collection to occur at pre-dose and post-dose of Day 1 of Cycles 1, 2, and 3, pre- and post-dose of Cycle 1 Day 15, and End of Treatment.
9. For women of childbearing potential only.
10. EORTC QLQ-30 must be completed during screening, Day 1 of cycles 3, 5, 7 and 9, and end of treatment. See Appendix 4 for the questionnaire.
11. CTX-009 will be administered 10mg/kg over approximately a 1 hour infusion.
12. Tumor evaluation via CT/MRI as applicable for disease type and anatomic involvement (at minimum, chest, abdomen, and pelvis). Tumor evaluation performed as standard of care can be used for screening purposes to confirm eligibility, however, the baseline study scan must occur within 14 days prior to C1D1. Ongoing tumor evaluations will be performed every 8 weeks (±7 days) from C1D1 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. All CT/MRIs will be collected for an Independent Central Radiology (ICR) review and read per RECIST v1.1.
13. For all patients, Adverse Events (AE), including Serious Adverse Events (SAEs), should be reported from signing of the ICF through 30-days after last dose or until the patient is determined to be a screen failure. AEs considered at least possibly related to CTX-009 should be followed until resolution, return to baseline, or deemed chronic or stable. The descriptions and grading scales found in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used for AE reporting.
14. Survival assessments include collection of any cancer treatments that occur following the discontinuation from study treatment. Survival assessments may occur over the phone.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Full Form
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BNP	brain natriuretic peptide
BOR	best overall response
C1D1	Cycle 1 Day 1
CI	confidence interval
CNS	central nervous system
CR	complete response
CRC	Colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DCR	disease control rate
DOR	duration of response
DLL	delta-like ligand
DNA	deoxyribonucleic acid
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	Epidermal Growth Factor Receptor
ELISA	enzyme-linked immunosorbent assay
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
hCG	human chorionic gonadotropin
hVEGF	human vascular endothelial growth factor
ICF	informed consent form
ICH	International Conference on Harmonisation
ICR	Independent Central Radiology
IEC	Independent Ethics Committee
IRB	institutional review board

Abbreviation	Full Form
IUD	intrauterine device
IV	intravenous
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
mDLL	mouse delta-like ligand
MedDRA	medical dictionary for regulatory activities
MGPT	multigene panel testing
min	minute
mL	milliliter
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NK_1	neurokinin-1
NSAIDs	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
PBS	phosphate buffered saline
PE	physical exam
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death-ligand
PFS	progression-free survival
PR	partial response
QTcF	corrected QT interval by Fredericia
RBC	red blood cell
RECIST	response evaluation criteria in solid tumors
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
scFv	single chain variable fragment
SCH	human stomach cancer (cell line)
SD	stable disease
TEAE	Treatment emergent adverse event
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
WBC	white blood cell
WCBP	women of child bearing potential

1. BACKGROUND OF DISEASE

1.1 Background of Conventional Treatment

1.1.1 Colorectal Cancer Statistics

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in the United States (US) and the second most common cause of cancer mortality both in the US and globally.[1] There have been refinements made to surgical and radiation techniques, and the discovery and testing of new drugs have led to better outcomes in individuals diagnosed with locally advanced and metastatic disease. Despite these improvements, in the US in 2021, nearly 150,000 people were diagnosed with CRC, and about one third of those, over 53,000 people, died of CRC. Death rates are significantly higher outside the US.[2] Additionally, the improvements in outcomes are not being seen across all demographic groups. In the US, the incidence rates in individuals diagnosed with CRC under age 50 have increased by 2% annually between 2012 and 2016, and it is estimated that by 2030, CRC will be the most common cause of cancer death in Americans under the age of 50. There are escalating research efforts to understand and cope with what is now often called the "young onset CRC epidemic".[3] In the US, the outcomes for racial minorities and rural dwelling populations tend to lag those of the Caucasian and urban dwelling demographic categories, a phenomenon that has spurred calls to eliminate such inequities.[4]

1.1.2 Therapeutic Options

Therapy for CRC depends on the stage of the individual patient's disease at diagnosis. Increasingly, multimodality and multidisciplinary approaches come into play when managing patients with both locally advanced and metastatic disease. While these approaches are saving lives, treatment options remain unsatisfactory for the subset of patients with treatment refractory metastatic disease who inevitably die of their disease. Despite the deployment of all of these resources for treatment, patients are still eager to find additional treatments to prolong their lives as they run out of standard therapeutic options.

Current treatment modalities relevant to the management of patients with CRC include:

- Surgery including minimally invasive surgical techniques
- Radiation therapies including focused techniques such as intensity modulated radiation therapies
- Locally directed therapies including ultrasonic and thermal catheter ablations, and chemo- and radioembolization
- Systemic therapies including:
    - Cytotoxic agents: 5-Fluorouracil (5-FU), capecitabine, TAS-102, oxaliplatin, irinotecan, liposome encapsulated irinotecan
    - Monoclonal Antibodies: bevacizumab, aflibercept, cetuximab, panitumumab
    - Immunotherapies: pembrolizumab, nivolumab, ipilimumab and others
    - Targeted therapies: regorafenib, entrectinib, larotrectinib, encorafenib, trastuzumab, lapatinib, ramucirumab

In the past two decades, multiple new agents have been approved by the Food and Drug Administration (FDA) for indications relevant to the management of CRC patients with metastatic disease. For most patients, chemotherapy with the cytotoxic agents 5-FU (and its orally administered analogues), oxaliplatin, and irinotecan, usually delivered as doublet or triplet combination regimens, are the mainstay of therapy.[5] The approach to therapy depends upon patient and physician preference, the patient's functional status (performance status), and the mutational profile of the tumor as assessed by multigene panel testing.

While there have been dozens of Phase III trials to define the optimal therapy for first- and second-line use in patients with metastatic CRC, there remains some controversy about how to best deploy the available therapies and patterns of practice are variable across the world. In the US, doublet chemotherapy is commonly prescribed for first- and second-line therapy, while in certain European countries (Italy in particular), triplet chemotherapy is favored.

The location of the primary tumor (left vs right colon) and the presence or absence of KRAS and BRAF mutations in the tumor often dictate whether a monoclonal antibody targeting Vascular Endothelial Growth Factor (VEGF) or the Epidermal Growth Factor Receptor (EGFR) pathways are added to the chemotherapy backbone.[6] In elderly patients or patients with poor performance status, sometimes a single agent such as capecitabine is used with or without a targeted therapy. More commonly patients receive doublet therapy with the oxaliplatin based FOLFOX (5-FU and oxaliplatin) or CapeOx (capecitabine and oxaliplatin) regimen, or the irinotecan based FOLFIRI (5-FU and irinotecan) regimen with bevacizumab, panitumumab, or cetuximab. As noted, some physicians prefer to administer all three chemotherapy drugs (5-FU, oxaliplatin, and irinotecan) together in a regimen known as FOLFOXIRI +/- bevacizumab or panitumumab or cetuximab. While refinements in these regimens have led to increases in the median overall survival of treated populations with metastatic CRC, from 12 months in the era of single agent 5-FU to more than 30 months in the era of multiagent regimens combined with targeted agents, very few patients with advanced disease are cured with drug therapy.

In the past two decades, the understanding of the heterogeneity of CRC has been elucidated using several FDA approved multigene panel testing (MGPT) platforms that look for the driver mutations in individual tumors. When tumors are found to have mutations, these can often be used to select specific agents that target these abnormalities or to eliminate drugs from consideration when a mutation that conveys resistance to a specific approach is discovered. An American Society of Clinical Oncology provisional clinical opinion published in June of 2022 recommends that all patients with advanced cancer receive MGPT if there is the potential to discern whether the findings could identify targeted therapies that impact treatment decisions.[7] This applies to all patients with metastatic CRC. In CRC and other tumors with a defect in the deoxyribonucleic acid (DNA) repair pathway known as the Mismatch Repair pathway, treatment with a monoclonal antibody targeting programmed cell death protein-1 (PD-1) or programmed cell death-ligand (PD-L1) such as pembrolizumab or nivolumab can lead to long term remissions of disease even when tumors are refractory to conventional agents.[8,9] Additional specific albeit rare mutations such as NTRK fusions or HER2 overexpression will lead medical teams to use specific agents that target those abnormalities.[10] In contrast, when a tumor is noted to have any RAS mutation or a BRAF mutation then treatment with panitumumab or cetuximab is ineffective and can be avoided.[11,12]

1.1.3 Drug Treatment for Treatment Refractory Disease

Once patients are deemed refractory to, or intolerant of chemotherapy regimens with or without targeted agents that are typically delivered in the first- or second lines of therapy, there are now additional options available from which they may benefit. Regorafenib is a multi-targeted kinase inhibitor that is approved for third-line therapy. In the Phase 3 CORRECT trial, the regorafinib treated cohort had an overall survival (OS) of 6.4 months versus 5.0 months for the cohort that received placebo plus best supportive care (HR 0.77; P=.005).[13] Trifluridine-tipiracil (TAS-102) is an oral combination chemotherapy drug approved by the FDA as indicated for patients who have progressed on at least two prior regimens. In the Phase 3 RECOURSE trial, the TAS-102 treated cohort demonstrated an OS of 7.1 months versus 5.3 months for the placebo treated cohort. (Hazard Ratio 0.68; P<.001).[14] While both regorafenib and TAS-102 prolonged the time both to tumor progression and OS, very few patients on either agent manifested a partial or complete response as measured by the RECIST criteria. The overall response rate (ORR) to regorafenib as 1% and the ORR to TAS-102 was 1.6%. Despite the availability of these two agents for patients who are refractory to chemotherapy, there remains significant unmet needs that underscore the need for additional effective agents for treatment of patients with metastatic disease that is refractory to currently available agents.

1.1.4 Evaluating the Efficacy of Anti-Tumor Drugs in Clinical Trials

Evaluation of treatment efficacy in the management of CRC is becoming more complex as more treatment options become available. With opportunities for more lines of therapy and for patients to obtain agents that are part of multidrug regimens being tested in the first line setting later in their continuum of care, response rates (RR) and progression free survival (PFS) are often designated as the primary study endpoints.

1.1.5 Response Rates in Patients with Metastatic CRC

The highest RR in patients with metastatic CRC have been reported for first line therapy with FOLFOXIRI plus bevacizumab, and approach 65%.[15] In second line studies, RR as high as 35% with a combination of chemotherapy plus a biologic agent have been reported in patients with progressive disease after treatment with FOLFOX who enrolled in a randomized study of FOLFIRI with or without panitumumab. Of note, the RR to FOLFIRI alone was 10% in this Phase III randomized study.[16] In a Cochrane meta-analysis that included 34 randomized clinical trials in patients with metastatic CRC treated in the second line setting, the RR when similar trials were combined was between 20-23%.[17] In the setting of third line therapy, the only data available to date come from two large randomized trials, the CORRECT trial that evaluated regorafenib showed a RR of 1%, and the RECOURSE study that evaluated TAS-102 showed a RR of 1.6%.[14,15] There are no current randomized trials beyond the third line setting that can be used to set benchmark expectations for RR beyond third line therapy.

1.2 CTX-009: Investigational Product Profile

Investigational drug CTX-009 (formally known as NOV1501 and also known as ABL001 or ES104), is a recombinant bispecific antibody produced from Chinese hamster ovary cells. It is a single chain fragment (scFv) that binds to human delta-like ligand 4 (DLL4) connected via a

peptide-linker to a moiety based on the heavy chain of bevacizumab that binds to human VEGF-A. Antibodies binding to VEGF and DLL4 were developed and the DLL4-binding antibody was connected via a peptide linker ($(Gly4Ser)_3$ linker) to the heavy chain C-terminal of bevacizumab. Binding to each target antigen (DLL4 and VEGF) was verified through Biacore analysis and enzyme-linked immunosorbent assay (ELISA) analysis. Further the ability of CTX-009 to inhibit the downstream signaling of each pathway, and functionally, to inhibit measures of angiogenesis (endothelial cell proliferation, vessel sprouting, etc.) was confirmed through an in vitro cell-based assay.[19]

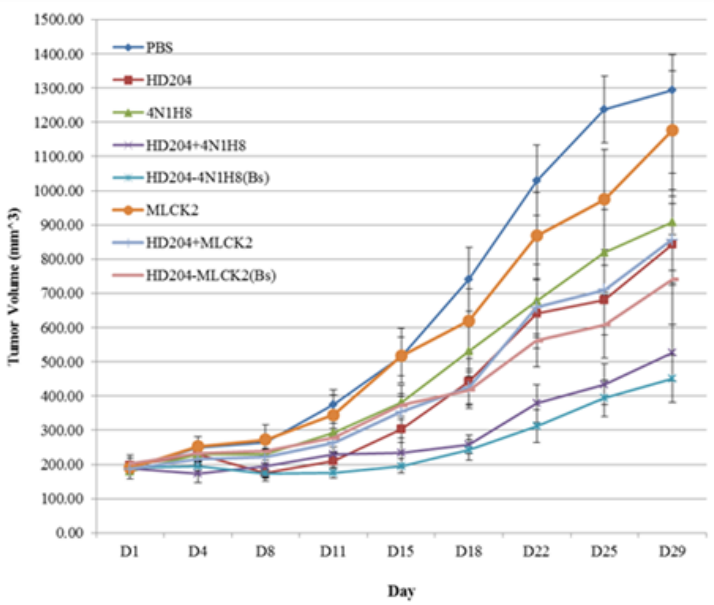
1.2.1 Results of Prior Non-Clinical Studies

Preliminary studies suggested that CTX-009 manifested improved antitumor activity compared to bevacizumab in preclinical tumor models.[20] These data are summarized in the current version of the CTX-009 Investigator's Brochure. The ability of a murine bispecific antibody version of CTX-009, referred to as Surrogate CTX-009 to inhibit the growth of established tumors in nude mice was studied using several human cell lines. Individual experimental results are summarized below.

1.2.1.1 Evaluating the Effects of Surrogate CTX-009 on Tumor Growth in Human Lung Cancer Cell (A549) Xenograft Mouse Model

The effect of surrogate CTX-009 on tumor growth was evaluated in an A549 (human lung cancer cell line) xenograft mouse model. A549 cells in Matrigel were injected subcutaneously in the right dorsal flank of BALB/c nude mice. When the average tumor size reached 150 mm^3, animals were grouped into treatment cohorts of 8 mice/group and treated twice weekly with intraperitoneal injections of either phosphate buffered saline (PBS), single antigen targeting antibody (2.5 mg/kg) and combinations thereof, or mouse surrogate bispecific antibody (surrogate CTX-009, 3.25 mg/kg). Tumor volume was measured twice a week for the duration of the study When the average tumor size of the PBS control group reached 1,500–2,000 mm^3, the study was terminated, the mice were sacrificed, and the final tumor weights were determined. The average tumor size on the final day of measurement (Day 29) was 1294.49±104.41 mm^3 in the PBS treatment group, 842.58±119.65 mm^3 in the anti-hVEGF antibody treatment group, 908.82±142.18 mm^3 in the anti-mDLL4 antibody treatment group, and 450.35±69.65 mm^3 in the surrogate CTX-009 treatment group (Figure 1). The reduction in tumor size on Day 29 for the surrogate CTX-009 and the anti-hVEGF plus anti-mDLL4 combination was statistically significant when compared to the PBS-treated cohort (One-way ANOVA, $P<0.001$). In this xenograft model, the mouse surrogate CTX-009 antibody suppressed tumor progression more effectively (74%) as compared to single antigen targeting antibodies, anti-VEGF (50%) or anti-mouse DLL4 antibody alone (50%), or the combination.

Figure 1: Suppression of tumor progression in human A549 lung cancer xenograft models by CTX-009 bispecific antibody mCTX-009 (anti-mDLL4/hVEGF bispecific antibody).



After a single injection of test article, tumor size was twice measured weekly. Each measured value was expressed as mean (±SE). Day 29 was the final measurement. Tumor size (mm^3) = 0.5x(long axis) x $(short\ axis)^2$.
HD204=anti-hVEGF; 41H8=anti-mDLL4; HD204-MLCK2(Bs) = CTX-009; HD204-4N1H8 = Surrogate CTX-009 (anti-mDLL4/hVEGF); MLCK2 = Anti-hDLL4 monoclonal antibody

1.2.1.2 Evaluating the Effects of Surrogate CTX-009 on Cancer Growth in Human Stomach Cancer Cell Xenograft Mouse Model

The effect of surrogate CTX-009 on tumor growth was evaluated by measuring tumor volume after administering PBS, single antigen targeting antibody (anti-hVEGF antibody, anti-mDLL4 antibody), and surrogate CTX-009 to a human stomach cancer (SCH) cell line xenograft mouse model.[20]

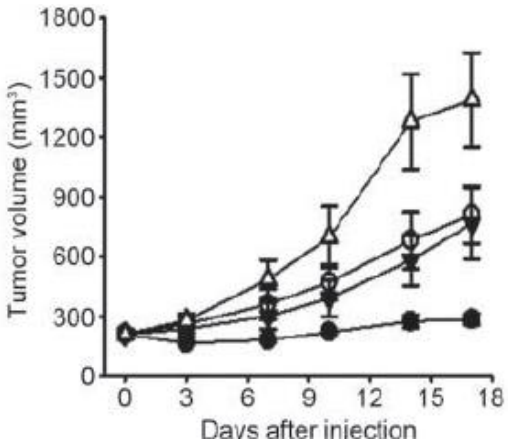
After administering the SCH cell line (1×107 cells/head) subcutaneously to the dorsal flank of BALB/c nude mice (8 weeks old, female), the mice were grouped into treatment cohorts of 6-7 mice/group. When the tumor grew to an average volume of 150-200 mm^3, mice were intraperitoneally administrated surrogate CTX-009 at 3.25 mg/kg, or 2.5 mg/kg of anti-hVEGF antibody or anti-mDLL4 antibody (represents an equimolar amount for each antibody) once a week. The tumor size was measured twice per week and calculated by using the formula:

Tumor size (mm^3) = 0.5 × (long axis) × $(short\ axis)^2$.

When the average tumor size of the control group reached 1,500–2,000 mm^3, the treatment was terminated, and the mice were sacrificed to measure tumor weights.

The surrogate CTX-009 treatment group had 89% inhibition of tumor growth, in contrast to 50% inhibition seen with the anti-hVEGF and anti-mDLL4 antibodies (Figure 2).

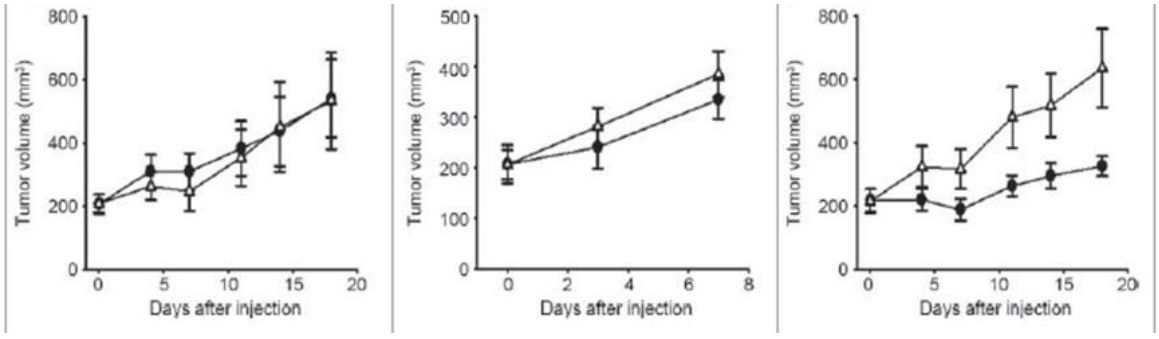
Figure 2: Suppression of tumor progression in human SCH gastric cancer xenograft models by mCTX-009 (anti-mDLL4/hVEGF bispecific antibody) bispecific antibody.



PBS (open triangle), anti-hVEGF antibody (2.5 mg/kg, open circle), an anti-mDLL4 antibody (2.5 mg/kg, closed triangle), or surrogate CTX-009 (3.25 mg/kg, closed circle).

After confirming the anti-tumor effect of CTX-009 in a human SCH xenograft mouse model, additional studies using other stomach cancer cell lines with different DLL4 expression levels (MKN-74, SNU-5, and SNU-16) were conducted to evaluate the anti-tumor effect of CTX-009 administered 6.5 mg/kg once per week, intraperitoneally (Figure 3). CTX-009 exhibited variable efficacy against the different cell lines, possibly due to the expression levels of DLL4 and Notch receptor, which are lower on MKN-74 and SNU-5 cell lines when compared to SCH and SNU-16 cell lines (Figure 3).

Figure 3: Suppression of tumor progression in human gastric xenograft models, including MKN-74 (A), SNU-5 (B), SNU-16 (C) by mCTX-009 bispecific antibody.



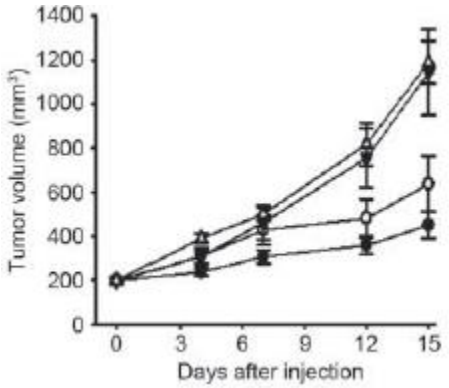
CTX-009 surrogate antibody (6.5 mg/kg, closed circle).

1.2.1.3 Evaluating the Dose-dependent Effects of surrogate CTX-009 on Tumor Growth in a Human Stomach Cell (SCH) Xenograft Mouse Model

A study was conducted to assess the dose-dependent efficacy of CTX-009 bispecific antibody in a human stomach cancer cell xenograft mouse model.[20] After mice were anesthetized, 1.0×107 SCH cells were transplanted subcutaneously to the dorsal flank of female BALB/c nude mice. The mice were then administered surrogate CTX-009 intraperitoneally at doses of 0.361 mg/kg, 1.083 mg/kg and 3.25 mg/kg, once per week.

Administration of surrogate CTX-009 at 0.361, 1.083 and 3.25 mg/kg demonstrated a dose dependent inhibition of tumor progression in a SCH gastric cancer xenograft model (Figure 4).

Figure 4: Suppression of Tumor Progression in Human Gastric Xenograft Model (SCH) by CTX-009 in a Dose Dependent Manner



PBS (open triangle); surrogate CTX-009 (0.361 mg/kg, closed triangle; 1.083 mg/kg, open circle; 3.25 mg/kg, closed circle) was intraperitoneally injected once per week.

1.2.2 Results of Prior Clinical Studies

Two phase 1 clinical trials with CTX-009, administered either as a monotherapy (NOV150101-101, NCT03292783) or in combination with chemotherapy (CTX-009-001, NCT04492033), were conducted in patients with advanced solid tumors. An ongoing Phase 2/3 trial (CTX-009-002, NCT05506943) is being conducted in patients with biliary tract cancers, however, data are not yet available.

1.2.2.1 Phase 1 Monotherapy Dose-Escalation Study

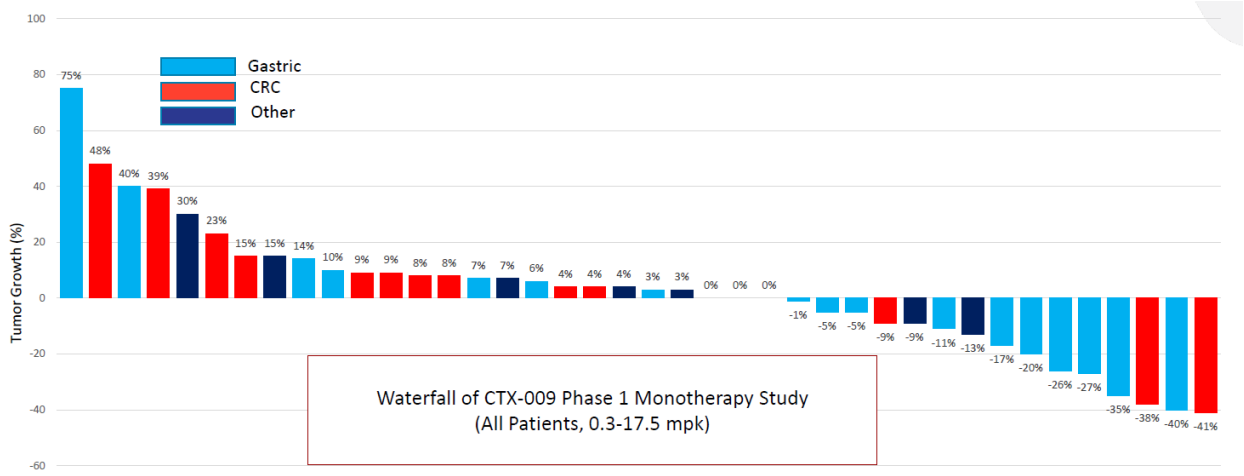
The Phase 1 clinical trial to evaluate the safety and tolerability and to determine the maximum tolerated dose and recommended Phase 2 clinical dose of CTX-009 monotherapy in patients with metastatic or advanced solid tumors in whom standard therapy had failed (NOV150101-101, NCT03292783) is complete. CTX-009 was administered in 9 dose levels, at doses of 0.3, 1, 2.5, 5, 7.5, 10, 12.5, 15, and 17.5 mg/kg given intravenous (IV) biweekly, using a standard 3+3 design. After performing the dose-escalation, dose-expansion cohorts were added to the 7.5, 10.0, 12.5, and 15.0 mg/kg cohorts to explore safety, efficacy, and pharmacokinetic and pharmacodynamic characteristics. Dose-limiting toxicities (DLTs) were assessed for 21 days after the first administration of CTX-009. Subsequently, CTX-009 was administered every two weeks in cycles of 28 days. A total of 45 patients with solid tumors received CTX-009, and

tumor evaluation was performed in 39 patients (including 18 patients with gastric cancer, 14 patients with colorectal cancer, and 7 patients with other malignancies).

Of the 45 patients participating in the Phase 1 monotherapy study, 40 patients experienced one or more AEs. The most frequent treatment emergent adverse events (TEAEs) occurring in 3 or more patients were hypertension (37.8%), headache (22.2%), asthenia (13.3%), anemia (13.3%), fatigue (11.1%), abdominal pain (8.9%), nausea (8.9%), proteinuria (8.9%), pulmonary hypertension (8.9%), abdominal pain upper (6.7%), alanine aminotransferase increased (6.7%), constipation (6.7%), dyspnea (6.7%), hypoalbuminemia (6.7%), insomnia (6.7%), pruritus (6.7%), pyrexia (6.7 %), and weight decreased (6.7%). The most common Grade 3 TEAE was hypertension, occurring in 7 patients (15.6%).

Thirty-nine of the 45 patients enrolled in the study were evaluable for response to treatment. There were 4 partial responses (PRs), three of which were confirmed by RECIST. There were two confirmed PRs in patients with colorectal cancer treated at the 10.0 mg/kg dose level. These two patients had three and four prior lines of therapy, respectively. There were also two PRs in patients with gastric cancer treated at the 12.5 and 15.0 mg/kg dose levels. The PR in the patient treated at 12.5 mg/kg was confirmed by RECIST. There was a suggestion of a dose-response, with all confirmed responses seen at the 10.0 and 12.5 mg/kg dose levels. The waterfall for all patients treated in the Phase 1 study appears in Figure 5.

Figure 5: Phase 1 Waterfall Plot



1.2.2.2 Phase 1b Combination Study with Chemotherapy and Phase 2

The Phase 1b clinical trial to assess the safety, tolerability, pharmacokinetics and anti-tumor activity of CTX-009 in combination with irinotecan 150 mg/m^2 or paclitaxel 80 mg/m^2 for patients with metastatic or advanced solid cancer who are refractory to the existing standard therapy or have progression of the disease and do not have other treatment options (CTX-009-001, NCT04492033) has been completed. A total of 17 patients received CTX-009 and irinotecan or paclitaxel in Phase 1b, of which 9 were enrolled in the paclitaxel arm and 8 were enrolled in the irinotecan arm. Based on two deep and durable PRs in patients with cholangiocarcinoma who were treated with CTX-009 at 10 mg/kg with paclitaxel, a Phase 2 Simon 2-stage arm was added to the study and enrolled patients with biliary tract cancers. A total

of 24 patients with biliary tract cancers have been enrolled and received CTX-009 and paclitaxel in Phase 2.

Phase 1b

Of the 17 patients participating in Phase 1b of the CTX-009 combination trial, all patients in the irinotecan group and the paclitaxel group experienced one or more adverse events. The most frequent TEAE in 3 or more patients was nausea (87.5%), diarrhea (62.5%), decreased appetite (37.5%), fatigue (37.5%), pyrexia (37.5%), pulmonary hypertension (37.5%), and hypertension (37.5%) in the Irinotecan group; and neutrophil count decreased (88.9%), diarrhea (62.5%), hypertension (55.6%), anemia (44.4%), aspartate aminotransferase increased (44.4%), blood bilirubin increased (44.4%), dyspnea (44.4%), constipation (33.3%), platelet count decreased (33.3%), abdominal pain (33.3%), diarrhea (33.3%), pyrexia (33.3%), and fatigue (33.3%) in the Paclitaxel group.

Five of 8 patients in the irinotecan group (62.5.%) and 7 of 9 patients in the paclitaxel group (77.8%) of the CTX-009 combination trial experienced at least one Grade 3 or higher TEAE. In the Irinotecan group, a single case of anemia, asthenia, blood bilirubin increased, fatigue, neutropenia, nausea, and platelet count decreased occurred in the combination with CTX-009 10 mg/kg. Two cases of hypertension occurred in the CTX-009 10 mg group and 1 case in the CTX-009 12.5 mg/kg group. One case of neutrophil count decrease occurred in the 12.5 mg irinotecan group.

Two cases each of neutrophil count decreased, blood bilirubin increased, anemia, and hypertension were reported in the paclitaxel group. All other TEAEs reported were single cases.

No deaths occurred in the CTX-009 combination therapy Phase 1b trial.

Tumor response evaluation of 17 patients who received CTX-009 combination therapy, 3 patients (2 patients in the 10 mg/kg paclitaxel combination and 1 patient in the 12.5 mg paclitaxel combination) had confirmed PRs for an ORR of 33.3%including a confirmed PR in a patient with pancreatic cancer. There was one unconfirmed PR in a patient with non-small cell lung cancer. Nine (52.9%) patients were evaluated as SD (5 patients in the irinotecan combination [3 patients in 10 mg/kg and 2 patients in 12.5 mg/kg] and 4 patients in the paclitaxel combination [1 patient in 10 mg/kg and 3 patients in 12.5 mg/kg]), and the DCR was 70.6% (12/17 patients).

Phase 2

In the Phase 2, patients receive 10 mg/kg of CTX-009 biweekly plus paclitaxel 80 mg/m^2 weekly 3 of 4 weeks. 24 subjects have been enrolled: 10 (42%) with intrahepatic cholangiocarcinoma, 3 (13%) with extrahepatic cholangiocarcinoma, 6 (25%) with gallbladder cancer, and 5 (21%) with ampullary carcinoma.

Of the 24 patients participating in Phase 2 Stage 1 of the CTX-009 combination trial, all patients experienced one or more adverse events. The most frequent TEAE (>10% or 3/24 patients) in all patients was neutrophil count decreased (91.7%), hypertension (50.0%), haemoptysis or haemorrhage (41.7%), platelet count decreased (37.5%), anemia (20.5%), ascites (16.7%), decreased appetite (16.7%), and pulmonary hypertension (16.7%).

Twenty-two of 24 patients in the CTX-009 combination trial experienced at least one Grade 3 or higher TEAE. The most common TEAE occurring in 3 or more patients was neutrophil count

decreased (83.3%), anemia (12.5%), and hypertension (12.5%). Interim efficacy data are currently available. There are 9 PRs confirmed by response evaluation criteria in solid tumors (RECIST). This represents a 37.5% ORR in patients treated in the second-line and third-line settings.

1.2.3 Rationale of the Clinical Study

Presently, there is no uniform consensus post-second-line therapies for patients with CRC in whom first- and second-line therapies have failed. In the Phase 1 study of CTX-009, there were 6 patients with CRC treated in the 10.0 and 12.5 mg/kg cohorts, and 2 of these 6 patients (both received CTX-009 at 10mg/kg) had confirmed PRs with declines of greater than 40% in their linear tumor burden from the baseline. Both patients had multiple prior therapies. The median PFS for the 6 patients with CRC treated at 10.0 and 12.5 mg/kg in the Phase 1 Study was 6.7 months. These patients had received a median of 3 prior systemic therapies, including fluoropyrimidine-, oxaliplatin-, irinotecan-, and bevacizumab-containing regimes. While the patient numbers are small; however, a 33% ORR (2 confirmed PRs among 6 patients treated) in the fourth line setting is encouraging and warrants further exploration. This study will assess the efficacy of CTX-009 in patients with CRC who have received either two or three prior systemic chemotherapy regimens for advanced or metastatic disease.

1.3 Study Overview

This study is designed as an open-label, adaptive Simon Two Stage study to evaluate the efficacy of CTX-009 in patients with metastatic CRC.

1.3.1 Selection of Patient Populations

This study will enroll patients with metastatic CRC who have progression or relapse of the disease after receiving two or three prior systemic therapies for metastatic disease. Prior therapy must have included regimens that contained a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF therapy such as bevacizumab, and an anti-EGFR therapy in those patients whose tumors are RAS wild type.

2. OBJECTIVES

2.1 Primary Objective

- To assess the efficacy of CTX-009 in patients with CRC who have received two or three systemic therapies for metastatic disease, as measured by overall response rate (ORR)

2.2 Secondary Objectives

- To assess the efficacy of CTX-009 in patients with CRC as measured by Disease Control Rate (DCR)
- To assess the efficacy of CTX-009 in patients with CRC as measured by Duration of Response (DOR)
- To assess the efficacy of CTX-009 in patients with CRC as measured by Progression Free Survival (PFS)
- To assess the efficacy of CTX-009 in patients with CRC as measured by Overall Survival (OS)
- To evaluate the safety profile of CTX-009, including immunogenicity of CTX-009 in treated patients.

2.3 Pharmacokinetic Objectives

- To characterize the pharmacokinetics of CTX-009 and explore exposure response by sparse population PK sampling

2.4 Exploratory Objective

- To evaluate Health Related Quality of Life in patients treated with CTX-009.

3. ENDPOINTS

3.1 Primary Endpoints

- Percentage of patients whose Best Overall Response (BOR) is assessed as Complete Response (CR) or Partial Response (PR) as assessed by RECIST v1.1

3.2 Secondary Endpoints

- Percentage of patients whose BOR is assessed as CR, PR, or Stable Disease (SD)
- The number of days between the date of the radiological evaluation that first confirmed CR or PR and the date of the radiological evaluation that first confirmed Progressive Disease (PD) or the date of censoring
- The number of days from C1D1 until the date of objective PD (as assessed by an Independent Central Radiology (ICR) review and defined by RECIST v1.1) or the date of death (by any cause in the absence of disease progression) or the date of censoring
- The number of days from C1D1 until the date of death by any cause. Patients who are still alive at the time of the analysis, or who have become lost to follow-up or withdrawn consent will be censored at their last date known to be alive
- Incidence of TEAEs and changes in clinical abnormalities for all patients who received at least one dose of CTX-009

3.3 Pharmacokinetic Endpoints

- Serum concentrations of CTX-009 at specified timepoints

3.4 Exploratory Endpoint

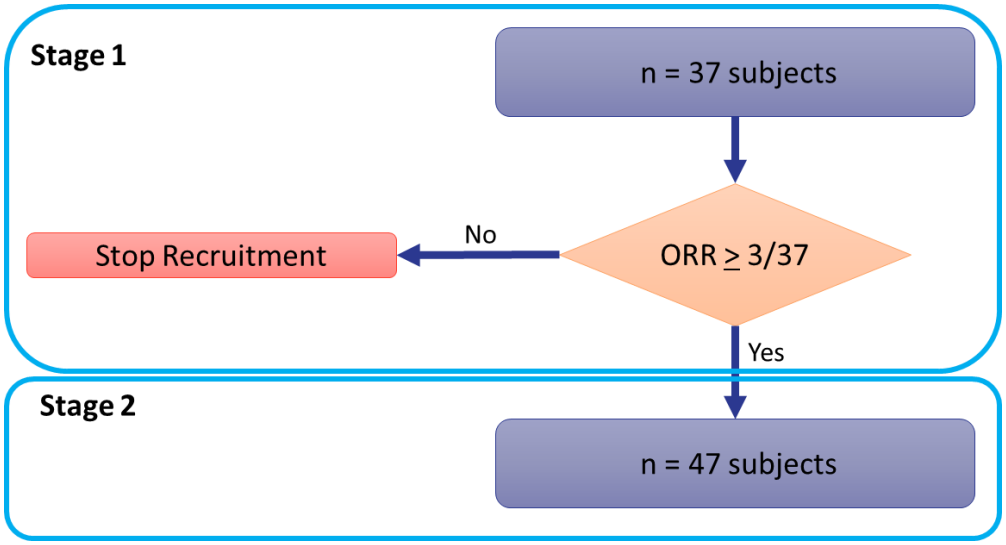
- Changes in QoL scores from baseline

4. STUDY DESIGN

This study is designed as an open-label, adaptive Simon Two stage study to evaluate the efficacy of CTX-009 in patients with metastatic CRC.

The study design is presented in Figure 6. A Simon 2-stage adaptive design will enroll approximately 37 patients into Stage 1, and if criteria are met to move to Stage 2, an additional 47 patients will be enrolled.

Figure 6: Study Design



5. STUDY POPULATION

All patients must meet the following inclusion/exclusion criteria, and no exceptions will be granted by the Sponsor.

5.1 Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. 18 years of age or older
2. Histologically or cytologically confirmed colorectal cancer that is metastatic or recurrent
3. The primary tumor must have been resected > 3 months prior to planned C1D1.
4. Patients who experienced progressive disease or relapse after receiving two or three prior lines of systemic therapy in the metastatic setting. Prior lines of systemic treatment must have included at least one fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab containing chemotherapy regimen (in any combination and may have been administered in the neoadjuvant or adjuvant setting).
    a. Patients whose tumor is not rightsided and RAS wild type must also have received an anti-EGFR therapy.
    b. Patients with tumors harboring mutations or other alterations for which there are available targeted therapies (e.g., BRAF V600E, HER2-positive, MSI-H/dMMR, etc.) must have also received the relevant approved targeted therapies.
    c. If patient received peri-operative treatment (neoadjuvant and/or adjuvant), please consult the Sponsor Medical Monitor for review of prior treatment lines.
5. At least one lesion measurable as defined by RECIST v1.1
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
7. Predicted life expectancy of at least 12 weeks
8. Adequate hepatic and renal function within 14 days of C1D1 as described below:
    a. Total bilirubin ≤ 1.5 X upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) ≤ 3.0 X ULN (≤ 5 x ULN in case of hepatic metastasis)
    c. Estimated creatinine clearance ≥ 30 mL/min based on the Cockcroft-Gault calculation of estimated creatinine clearance
    d. Urine protein ≤ 1+ by spot urinalysis or, if >1+ then 24 hr urine protein <1.0 g/24hr)
9. Female patients who are women of childbearing potential (WCBP) must have a negative pregnancy test (serum- human chorionic gonadotropin [hCG] or urine-hCG) at Screening within 14 days of C1D1.
10. Female patients must be surgically sterile (or have a monogamous partner who is surgically sterile) or be at least 2 years postmenopausal or commit to use 2 acceptable forms of birth control (defined as the use of an intrauterine device (IUD), a barrier

method with spermicide, condoms, any form of hormonal contraceptives, or abstinence) for the duration of the study and for 4 months following the last dose of study treatment. Male patients must be sterile (biologically or surgically) or commit to the use of a reliable method of birth control (condoms with spermicide) for the duration of the study and for 4 months following the last dose of study treatment.

11. Signed and dated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) before any protocol-directed screening procedures are performed.

5.2 Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. From the time point of signed informed consent,
    a. Less than 4 weeks have elapsed since patients had a surgery or major procedure
    b. Less than 2 weeks have elapsed from the last treatment date since patients had any radiation therapy
2. Prior to the planned C1D1,
    a. Less than 4 weeks have elapsed since patients had chemotherapy or targeted therapy for colorectal cancer
    b. Less than 4 weeks have elapsed since patients had anticancer immunotherapy or investigational drug treatment
3. A history of the following cardiovascular diseases may be exclusionary, as determined by the Sponsor Medical Monitor:
    a. Congestive heart failure that corresponds to Class II or a higher class) under New York Heart Association (NYHA) classification or less than 50% of left ventricular ejection fraction (LVEF)
    b. Uncontrolled hypertension (systolic blood pressure [SBP]/diastolic blood pressure [DBP] > 140/90 mmHg) (e.g., patient with SBP/DBP > 140/90 mmHg despite the best care including anti-hypertensive medications)
    c. Patients with a history of hypertensive crisis or pre-existing hypertensive encephalopathy
    d. Pulmonary hypertension
    e. Myocardial infarction
    f. Uncontrolled arrhythmia
    g. Unstable angina
    h. Patients with any significant vascular diseases (e.g., aortic aneurysm requiring surgery or recent peripheral artery thrombosis) within 6 months prior to the initial treatment of the investigational product
4. Symptomatic or uncontrolled central nervous system (CNS) metastasis

(However, patients with asymptomatic CNS metastasis can participate provided that systemic corticosteroid treatment was discontinued at least 4 weeks prior to screening and that the patient is radiologically and neurologically stable or improving.)

5. A history of the following hemorrhage-related or gastroenterological disease:
    a. Active hemorrhage, hemorrhagic diathesis, coagulopathy or tumor invasion into great arteries
    b. History of clinically significant and active (within 6 months) gastroenterological disease, such as peptic ulcer, gastrointestinal (GI) bleeding, GI or non-GI fistula, perforation, abdominal abscess, clinical symptoms and signs of GI obstruction, need for parenteral hydration or nutrition, or inflammatory bowel disease.
6. Patients who received antiplatelet drugs (aspirin, clopidogrel, etc.) or anticoagulant drugs (warfarin, heparin, direct thrombin inhibitors, etc.) within 2 weeks prior to C1D1, or are expected to need those drugs during the clinical study.
7. Patients requiring continuous treatment with systemic non-steroidal anti-inflammatory drugs (NSAIDs) or systemic corticosteroids (the following cases are permitted):
    a. NSAIDs: Up to 3 consecutive days' use is permitted.
    b. Corticosteroids: Topical use of corticosteroid, such as topical intra-articular injection, intranasal administration, eye drops, inhaler, etc., or temporary systemic corticosteroid use for treatment and prevention of patient's contrast media allergy, or adverse event, is permitted.
8. Severe infection requiring systemic antibiotics, antivirus drugs, etc., or other uncontrolled acute active infectious diseases
9. Patients with evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Inactive hepatitis B carriers who tested HBsAg positive may enroll provided that the patient's liver function values are normal. Also, patients with chronic HBV infection which has been controlled by the site's treatment guideline may enroll. HCV patients showing sustained viral response or patients with immunity to HBV infection may enroll.
10. Patients with other severe diseases or uncontrolled illnesses that warrant the exclusion from the study (permitted only if medically controlled) including but not limited to:
    a. Pre-existing hemoptysis (≥ ½ teaspoon of bright red blood per episode) within 28 days prior to screening
    b. Major, unhealed injury, active ulcer or untreated fracture
    c. History of cerebrovascular incident (ischemic or hemorrhagic stroke), transient ischemic attack or subarachnoid hemorrhage within 6 months prior to screening 1.
    d. Moderate to severe ascites and/or pleural effusion
11. Clinically significant abnormal electrocardiography (ECG) findings or history determined as clinically significant by the Investigator
12. QT interval (Fridericia's formula) (QTcF) interval > 450 msec at the time of screening

6. STUDY PROCEDURES AND ASSESSMENTS

6.1 Study Procedures and Assessments

Time points for assessments to be collected throughout the study can be found in Table 1: Schedule of Assessments. A brief description of each assessment can be found below.

6.1.1 Informed Consent

An 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 14 days from C1D1.

6.1.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively) will be reviewed for each potential patient. Eligibility will be documented in the electronic case report form (eCRF).

6.1.3 Medical History, Demographics, and Cancer History

Complete medical history will be obtained, including demographics, current medical conditions, surgery, chemotherapy, and radiation therapy within 4 weeks of screening, cardiovascular disease within the past 5 years, cancer history, and prior anticancer treatment history.

6.1.4 Concomitant Medications and Procedures

At Screening, concomitant medications will be recorded. Assessment of any change in concomitant medications or procedures since the last visit will occur at all further patient visits through end of treatment.

6.1.5 Physical Exam and Vital Signs

A full physical examination (PE) including vital signs will be conducted at Screening and end of treatment (EOT). Symptom-directed PE will be performed at other study visits specified in Table 1: Schedule of Assessments. Physical exams will also be conducted as clinically indicated.

The PE will include an assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory, abdomen, height (screening only), and weight.

Vital signs should be collected prior to CTX-009 infusion. Vital signs will include temperature, blood pressure (after sitting for 5 minutes), pulse rate, pulse oximetry, and respiratory rate. If vital signs need to be repeated during a single visit, assessments should be conducted approximately 5 minutes apart.

Any new clinically significant abnormality from baseline should be recorded as an adverse event (AE) according to Section 8.

6.1.6 Echocardiography

Echocardiogram will be performed at the time points specified in Table 1: Schedule of Assessments. Echocardiogram should be done at screening and every 3 months (±7 days) thereafter; however if brain natriuretic peptide (BNP) is elevated beyond the upper limit of normal range, then an echocardiogram must be performed. Additional echocardiography may be performed at the Investigator's discretion. In the event of any clinically significant abnormal result, only 1 re-test may be performed.

In the event of symptoms signaling pulmonary hypertension (dyspnea, fatigue, chest pain, etc.), the Investigator must conduct an echocardiogram, with a cardiology or pulmonary medicine consult at the Investigator's discretion. When pulmonary hypertension is diagnosed, an adequate medication should be prescribed by a cardiologist or pulmonologist according to the center's treatment guideline (ex. Sidenafil, Bosental, etc.). A decision to continue CTX-009 treatment should be made by monitoring the symptoms of pulmonary hypertension and in collaboration with the Sponsor.

6.1.7 Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be performed according to Appendix 1.

6.1.8 Electrocardiogram

At Screening, a standard 12-lead ECG will be conducted in all patients and will be interpreted by the Investigator to confirm eligibility. ECGs will be conducted following an approximate 10-minute rest period in supine position and obtained within approximately a 5-minute time period. In the event of any clinically significant abnormal result, only 1 re-test may be performed.

On C1D1, the electrocardiogram should be taken within approximately 2 hours after the completion of the CTX-009 infusion.

6.1.9 Clinical Laboratory Tests

The following laboratory parameters will be measured and will be analyzed locally:

- Serum or urine pregnancy test for all WCBP
- Hematology laboratory parameters include white blood cells (WBC), red blood cell (RBC), hemoglobin, hematocrit, platelet, WBC differential count (neutrophil, lymphocyte, monocyte, eosinophil, basophil), absolute neutrophil count (segmented neutrophils + bands)
- Blood chemistry laboratory parameters include glucose, AST, ALT, total bilirubin, alkaline phosphatase, lactate dehydrogenase, total protein, albumin, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, calcium, magnesium, phosphorus, total CO_2, amylase, lipase
- Cardiac assessments: cardiac troponin, BNP

- Coagulation laboratory parameters include prothrombin time, partial thromboplastin time, and international normalized ratio
- Complete urinalysis: pH, specific gravity, protein (albumin), glucose, bilirubin, urobilinogen, ketone, RBC, WBC
- Hepatitis serologies (Screening only)
  - Anti-hepatitis C antibody (anti-HCV); hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb)

Unscheduled assessments should be performed as clinically indicated.

Abnormal laboratory findings at Screening should be recorded as medical history or AE only if considered clinically significant. In the event of any clinically significant abnormal result, only 1 re-test may be performed.

Clinical laboratory assessments should be performed prior to CTX-009 infusion. At C1D1 only, clinical laboratories collected for Screening within 7 days of C1D1 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 8.1.1 for definition of an AE).

6.1.10 Tumor Evaluation and Response Assessment

Disease assessment by computed tomography (CT)/magnetic resonance imaging (MRI) as applicable for disease type and anatomic involvement (at minimum chest, abdomen, and pelvis), will be performed. Tumor evaluation performed as standard of care can be used for screening purposes to confirm eligibility, however, the baseline study scan must occur within 14 days prior to Cycle 1 Day 1 (C1D1). Unscheduled imaging is permitted if clinically indicated. Ongoing tumor evaluations will be performed every 8 weeks (±7 days) 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. Assessment of response will follow RECIST v1.1 (Appendix 3).

Of note, for patients who achieve a complete response/remission (CR) or partial response/remission (PR), a follow-up response assessment (including CT or MRI) should be performed after 4 weeks to confirm the response. Patients will be expected to continue to follow the response assessment schedule as outlined in Table 1: Schedule of Assessments.

6.1.11 Independent Central Radiology (ICR)

An ICR may be used for the primary and secondary efficacy assessments of tumor response if determined necessary. All imaging will be sent to the ICR for evaluation per RECIST v1.1. These independent interpretations will not be used to make treatment decisions. A detailed charter for the ICR will be created before the first ICR assessment.

6.1.12 Archival Tumor Tissue (Optional)

Archival tumor tissue samples should be submitted if the patient consents to provide this optional assessment. Archival tumor tissue samples may be sent any time post C1D1 until EOT. Tissue may come from the primary tumor or metastatic sites. See the CTX-009-003 Laboratory Manual for tumor tissue handling instructions.

6.1.13 Evaluation of Health-Related Quality of Life

Patients will complete the European Organization for Research and Treatment of Cancer, Quality of Life questionnaires (EORTC QLQ-C30).

EORTC QLQ-C30 consist of general questions to evaluate cancer patients' health-related quality of life.

6.1.14 Study Drug Administration

Detailed instructions on the administration of CTX-009 can be found in Section 7.

6.1.15 Immunogenicity Sampling and Assessments

Blood samples for immunogenicity assessments will be collected from all patients at multiple time points for analysis of anti-drug antibodies (ADA).

Refer to the CTX-009-003 Laboratory Manual for immunogenicity sample handling instructions.

6.1.16 Pharmacodynamic/Exploratory Biomarker Sampling and Assessments

Samples will be collected for exploratory biomarker analysis focused on evaluating target engagement, biological effects, and predictive biomarkers for CTX-009.

Samples collected during the study may be banked for up to 15 years. Any material left over may be used to conduct research related to either CTX-009 and DLL4/VEGF pathways or to cancer biology in general.

Refer to the CTX-009-003 Laboratory Manual for biomarker sample handling procedures.

6.1.17 Pharmacokinetic Sampling and Assessments

Serum samples for PK will be collected from all patients at pre- and post-dose of Day 1 of Cycles 1, 2, and 3, pre- and post-dose of Cycle 1 Day 15, and End of Treatment. Pre-dose samples should be taken as close to treatment administration, but at least within 60 minutes of start of infusion. Post-dose samples should be taken 1-2 hours following completion of the scheduled infusion.

Samples collected during the study may be banked for up to 15 years.

6.1.18 Refer to the CTX-009-003 Laboratory Manual for pharmacokinetic sample handling procedures. Monitoring of Adverse Events

Patients will be monitored continuously for toxicity while on CTX-009. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher (Appendix 2).

AEs should be captured on the eCRF from the time of signing of ICF through 30 days after last dose. AEs considered at least possibly related to CTX-009 should be followed until resolution, return to baseline, or deemed chronic or stable. Dose modifications for AEs at least possibly related to CTX-009 according to severity are described in Section 8.2.

All serious adverse events (SAEs) will be immediately (within 24 hours) reported to the Sponsor from the time of signing the ICF through 30-days after last dose or until the patient has been deemed to be a screen failure.

See Section 8.2 for a full description of the collection and reporting of AEs during this study.

6.2 End of Treatment (Treatment Discontinuation)

In the event of any conditions described below, the treatment should be permanently discontinued:

1) When PD is confirmed according to RECIST v1.1 or when the Investigator finds clinical evidence of progressive disease (Investigators should make a reasonable and clinically appropriate attempt to confirm an assessment of clinical progression with a radiographic assessment)
    a. Note: Patients may continue on study treatment beyond disease progression if, based on the opinion of the Investigator, they are deriving clinical benefit after discussion with the study monitor and the Sponsor. In order 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 be discontinued from treatment with CTX-009.
2) Intercurrent illness (adverse events unrelated to study treatment) preventing continuation of treatment with the investigational drug
3) Adverse events related to study treatment preventing continuation of treatment (see Section 7.1.2.1 for AEs requiring permanent discontinuation)
4) When the Investigator determines that discontinuation of the clinical study treatment is for the patient's best interest
5) When a patient withdraws consent to participate in the clinical study
6) Pregnancy of the patient
7) When patient becomes lost to follow up
8) When CTX-009 treatment is delayed by more than 12 weeks from the last treatment with CTX-009 for any reason

6.3 Safety Follow-Up Visit

All patients will have a Safety Follow-Up Visit 60 days after the end of treatment visit, unless the patient withdraws from the study prematurely (Section 6.5). Ongoing AEs considered at least possibly related to CTX-009 treatment should be followed until resolution, return to baseline or they are considered stable or chronic. This visit is to occur prior to initiation of additional anticancer therapy. If a patient plans to start new anticancer therapy prior to the Safety Follow-Up Visit, this visit should occur as soon as possible prior to the initiation of any new anticancer therapies. If the Safety Follow-Up visit is completed in person, all assessments should be performed. If the visit is done by phone, only AEs and concomitant medications will be collected.

6.4 Survival Follow-Up

Survival Follow-Up assessments following EOT will be collected at the timepoints specified in Table 1: Schedule of Assessments until patient's death, withdrawal of consent or the end of the clinical study (whichever occurs 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.

6.5 End of Study

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 by patient
- Termination of the study by Sponsor

If possible, prior to withdrawal by the patient, an EOT Visit should occur after the last dose of CTX-009. If the patient withdraws consent from the overall 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 TREATMENT

7.1 CTX-009 Treatment

CTX-009 is an investigational study drug and will be provided by the Sponsor. CTX-009 is supplied as a clear colorless to pale yellow injectable solution in a 20 mL single-use glass vial containing 10 mL of extractable volume.

Additional information is provided in the CTX-009 Investigator's Brochure and the CTX-009-003 Pharmacy Manual.

7.1.1 Dosage, Administration, and Storage

CTX-009 10 mg/kg is administered as an IV infusion once every 2 weeks in a 28 day cycle (2 infusions per cycle) until meeting Treatment Discontinuation criteria, found in Section 6.2. CTX-009 may be stored between 2°C to 8°C or -10˚C to -30˚C, according to the label, and protected from light in a secure, temperature-monitored refrigerator.

CTX-009 infusion should be administered using a calibrated infusion pump over 1 hour (± 5 minutes) under the supervision of a physician, or other medically qualified study personnel, experienced in the use of IV agents. CTX-009 will be diluted with a 250 mL NaCl injection solution. The final concentration of CTX-009 administered should not exceed 10 mg/mL and the IV drip rate should not exceed 5 mL per minute, however, it may be slowed when necessary, at the Investigator's discretion.

See Section 7.1.2 for dose modification guidance for the management of AEs. See Section 7.1.2.2 for detailed guidance regarding infusion administration interruptions due to infusion reactions.

Please refer to the CTX-009-003 Pharmacy Manual for detailed administration instructions.

7.1.2 CTX-009 Dose Modification

Dose reduction levels of CTX-009 are specified in Table 2. The starting dose of CTX-009 is 10 mg/kg and it is possible to reduce it by one step to 7.5 mg/kg. The dose may be reduced within the treatment cycle or at the start of the next treatment cycle. After a dose reduction, dose escalation is not permitted. A second dose reduction for recurrent toxicity is not permitted.

Table 2: CTX-009 Dose Reduction

Drug	Initial Dose	Dose Reduction 1	Dose Reduction 2
CTX-009 Administer on D1 and D15 of each treatment cycle	10.0 mg/kg	7.5 mg/kg	Not Applicable

The adverse events requiring dose reductions for CTX-009 are hypertension, pulmonary hypertension, proteinuria, heart failure, wound healing and others, based on the grade of the adverse event.

The criteria for dose modification of CTX-009 are specified in Table 3. When reducing the dose of CTX-009, the AE grade (per CTCAE v5.0) should be followed regardless of the relationship

with CTX-009. When considering dose reductions, also refer to Section 7.1.2.1 for the full list of AEs requiring treatment discontinuation.

For AEs not specified in Table 3, Investigator discretion may be used for dose modifications.

Table 3: CTX-009 Dose Modification

CTCAE v5.0	Grade*	CTX-009 Dose Modification
Hypertension	1	None
	2	Withhold treatment until BP is <150/100mmHG, resume at same dose
	3**	Withhold treatment until AE is decreased to Grade 1 or 2 and resume at the lower dose Dose reduction**
	4	Treatment discontinuation
Pulmonary Hypertension	1	May be reduced at the Investigator's discretion
	2-4	Treatment discontinuation
Thrombocytopenia	3, with bleeding	If bleeding is clinically significant, withhold treatment until AE is decreased to Grade 1 or 2 before resuming treatment at the lower dose
Proteinuria	1	None
	2	Dose reduction
	3	Withhold treatment, confirm Grade 3 proteinuria by 24 hour urine, then based on results resume are lower dose (if ≤Grade 2) or discontinue treatment (if confirmed Grade 3)
Heart failure	1***	Withhold treatment until AE is resolved and resume at the lower dose***
	2	Withhold treatment until AE is resolved and resume at the lower dose
	3-4	Treatment discontinuation
Wound healing****	1-2	Withhold treatment until AE is resolved and resume at the lower dose
	3-4	Treatment discontinuation
Others	1-2*	None
	3*****	Withhold treatment until AE has decreased to Grade 1 or less and resume at the lower dose
	4*****	Treatment discontinued*****

*If Grade 1 or Grade 2 AEs occur continuously or recurrently, the dose may be reduced per Investigator's discretion.

**Treatment with CTX-009 must be withheld until the Grade 3 hypertension has resolved to Grade 1. The dose must then be reduced. If hypertension is determined by the Investigator to be related to a suboptimal antihypertensive medication regimen, CTX-009 treatment may be held until BP returns to baseline with appropriate optimization of the concomitant antihypertensive medication regimen, and CTX-009 may be resumed at the same dose.
***Grade 1 heart failure excludes asymptomatic elevations of troponin or BNP. Refer to Table 4 in this instance.
****Includes AEs of wound complication, wound dehiscence, and soft tissue necrosis.
*****Excluding anemia, thrombocytopenia, neutropenia, and isolated asymptomatic electrolyte abnormalities

7.1.2.1 Adverse Events Requiring Permanent Discontinuation

The following AEs will require permanent discontinuation from CTX-009 treatment:

- Gastrointestinal perforations: regardless of grade
- Hemoptysis
- Tracheoesophageal fistula: regardless of grade
- Grade 4 fistula
- Fistula formation involving any organ: regardless of grade
- Necrotizing fasciitis
- Grade 3 or 4 wound healing AEs
- Grade 3 or Grade 4 hemorrhage
- Grade 3 or Grade 4 arterial thromboembolism
- Grade 4 venous thromboembolism
- Grade 4 Hypertension
- Hypertensive encephalopathy
- Posterior reversible encephalopathy syndrome
- Nephrotic syndrome
- Congestive heart failure: Grade 3 or 4 heart failure, or more than one event of Grade 2 heart failure
- Grade 3 or 4 left ventricular systolic dysfunction
- Grade 2, 3 or 4 pulmonary hypertension
- Grade 3 or 4 proteinuria
- Grade 3 or Grade 4 infusion related reactions
- Grade 4 anemia

- Any other Grade 4 toxicity, excluding asymptomatic isolated lab abnormalities, to be discussed with the Sponsor Medical Monitor

7.1.2.2 Criteria for Starting the Next CTX-009 Treatment

. The date of the next administration of CTX-009 should not exceed 12 weeks from the date of the last administration and should be at least 2 weeks (±3 days) from the immediately preceding administration date.

If CTX-009 is held due to an AE, the criteria for restarting the next treatment cycle should follow Table 4. To restart CTX-009, AEs including wound complication, wound dehiscence, hemoptysis, hypertension, and proteinuria will be investigated and the treatment of CTX-009 must be withheld until the restart criteria are met.

Table 4: Criteria for Restarting Next CTX-009 Treatment

AE (per CTCAE v5.0)	CTX-009 Criteria on D1
Wound complication Wound dehiscence	Full recovery of the wound (complication or dehiscence)
Hypertension	Controlled hypertension, defined as AE Grade ≤ 1
Asymptomatic cardiac enzyme elevation	Restart treatment once cardiac enzymes retuned to within normal limits.
Thrombocytopenia	Platelet count defined as AE Grade ≤2, with bleeding resolved
Proteinuria*	Dipstick ≤1+ or less than 1g/24hr
Others**	Grade 1 or baseline
*In case of proteinuria, if the urine protein result performed with dipstick on urinalysis is 2 positive (+) or higher, the total amount of protein must be confirmed through a 24-hour urine test. **In the case of Grade 2 AE not related to CTX-009, including lab abnormalities not otherwise specified, administration of CTX-009 may be considered by the Investigator's discretion.	

7.2 Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of CTX-009 received and comparing it with the accompanying drug order form. After full drug accountability and reconciliation, the Investigator will dispose of any CTX-009 at the clinical trial site per site procedures, or if necessary, all CTX-009 will be returned to the Sponsor or its designee. Disposition of all CTX-009 should be documented, including any CTX-009 that is lost or damaged.

7.3 Permitted Concomitant Treatment

Concomitant drugs permitted are shown below. Additional concomitant drugs may be administered at the Investigator's discretion.

a. Drugs for prevention and treatment of diarrhea, nausea and vomiting

- Atropine, loperamide

- Neurokinin-1 (NK_1) receptor inhibitors such as aprepitant, etc., serotonin ($5\text{-}HT_3$) receptor inhibitors such as ondansetron, granisetron, etc. and antiemetics including metoclopramide, etc.
- Dexamethasone administered to augment the antiemetic effect of serotonin ($5\text{-}HT_3$) receptor inhibitors

b. Pre-treatment to prevent and treatment for hypersensitivity

c. Antibiotics, antifungal drugs and antivirus drugs

- Prophylactic antibiotics for prevention and management of dermal toxicity (e.g., minocycline) are permitted.
- Antibiotics, antifungal drugs or antivirus drugs are permitted in the event of febrile neutropenia or after an evaluation of adverse event of infection.

d. Antihypertensive drugs

e. Localized palliative radiotherapy is allowed for symptom control (e.g., for painful bone metastases) while on study.

7.4 Prohibited Treatment

The drugs and treatments listed below are prohibited throughout the clinical study duration (from screening to the end-of-treatment visit):

a. Anticancer drugs other than the investigational product (e.g.: Chemotherapy, molecular-target therapy, immunotherapy including topical treatment)

b. Immunosuppressors and corticosteroid (topical use of corticosteroid such as intra-articular injection, intranasal administration, eye drops, inhaler, etc.; or temporary systemic corticosteroid use for treatment and prevention of patient's contrast media allergy or adverse event, is permitted.)

c. Non-steroidal anti-inflammatory drugs (NSAIDs) (However, permitted only up to 3 consecutive days.)

d. Antiplatelet drugs (aspirin, clopidogrel, etc.) and anticoagulant drugs (warfarin, heparin, direct thrombin antagonists, etc.) (However, the use of heparin for flushing of vascular access devices and catheters is allowed)

e. Radiation therapy (Use of radiopharmaceuticals intended for testing or diagnosis is permitted.)

f. Transplantation or cell therapy (CAR-T cell, etc.)

g. Other investigational products of clinical studies

8. SUPPORTIVE CARE GUIDELINES, SAFETY DATA COLLECTION, RECORDING, AND REPORTING

8.1 Adverse Events

8.1.1 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 it is considered to be related to study treatment.

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

Note that death is not an AE, but is an outcome of an AE. If a subject dies on study, every attempt should be made to record an underlying cause of death as the AE.

8.1.2 Definition of Treatment Emergent Adverse Event

A TEAE is defined as an AE that started or worsened in severity on or after the date the CTX-009 was first administered. TEAE information will be collected from the time of the patient's first dose of CTX-009 until 30 days after the last dose.

8.1.3 Definition of Adverse Events of Special Interest

Because CTX-009 has limited safety data, the following adverse events commonly seen in the same class of drugs are defined as "adverse event of special interest" (AESI): All adverse events listed below must be reported promptly to the Sponsor within 24 hours of detection in accordance with SAE reporting procedures (see Section 8.2.2).

- Gastrointestinal or tumor perforation
- Pulmonary hypertension
- Hemoptysis and bleeding
- Surgery and wound healing complication

8.1.4 Definition of Serious Adverse Event

A Serious Adverse Event (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.

Hospitalizations or prolongation of an existing hospitalization for one the following reasons is not considered a serious adverse event:

- Admission or prolongation of admission in a hospice facility, nursing or rehabilitation
- Admission or prolongation of admission for scheduled treatment of a pre-existing condition at baseline
- Less than 24-hour stay in an emergency room
- Admission or prolongation of admission that had been scheduled before signing of the patient's consent form
- Admission or a prolongation of admission that had been scheduled previously for routine testing, etc.
- Admission or prolongation of admission for routine maintenance (e.g., battery replacement) of a device placed before participating in the study
- Admission for the investigational product treatment

8.2 Procedures for Recording and Reporting Adverse Events

8.2.1 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 reported in the eCRF from the time of signing the ICF through 30 days after the last dose of CTX-009. Ongoing AEs considered at least possibly related to CTX-009 treatment should be followed until resolution, return to baseline or until they are considered stable or chronic. All SAEs occurring from the signing of ICF through 30 days after the last dose of CTX-009 or date of screen failure will be processed as outlined in Section 8.2.2.

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 non-serious.

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 CTX-009
- Action taken with CTX-009 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). If the frequency or severity of an adverse event changes during the study, a new adverse event should be reported.

8.2.1.1 Relationship to Study Drug

The Investigator must assess whether the AE may be related to CTX-009 or study mandated procedure, when applicable. The relationship is defined below:

Relationship assessments that indicate the event is "Not Drug Related":

- None: The event is related to an etiology other than the study product administration (the alternative etiology must be documented in the study patient's medical record).
- Remote: The event is unlikely to be related to the study product and likely to be related to factors other than study product.

Relationship assessments that indicate the event is "Drug Related":

- Possible: There is an association between the event and the administration of CTX-009 and there is a plausible mechanism for the event to be related to the study product; but there may also be alternative etiology, such as characteristics of the patient's clinical status or underlying disease.
- Probable: There is an association between the event and the administration of CTX-009 and there is a plausible mechanism for the event to be related to the study product, and the event could not be reasonably explained by known characteristics of the patient's clinical status or an alternative etiology is not apparent.
- Definite: There is an association between the event and the administration of CTX-009, there is a plausible mechanism for the event to be related to the study product and causes

other than CTX-009 have been ruled out and/or the event re-appeared on re-exposure to CTX-009.

8.2.1.2 Adverse Event Severity

The Investigator will assess the Grade of the AE per the NCI-CTCAE version 5.0 or higher (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 8.1 above.

8.2.1.3 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 CTX-009
- Requires treatment or adjustment to concomitant medications
- Is considered to be an AE by the Investigator

8.2.1.4 Medication Errors, Misuse, and Abuse of CTX-009

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

- Overdose: refers to the administration of a quantity of CTX-009 given per administration or cumulative, which is above the maximum dose according to the protocol.
- Medication error: refers to an unintentional error in dispensing or administration of CTX-009 not in accordance with the protocol
- Off-label use: relates to situations where CTX-009 are intentionally used for medical purpose not in accordance with the protocol

- Misuse: refers to situations where CTX-009 are intentionally and inappropriately used not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of CTX-009, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to CTX-009 because of one's professional or non-professional 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.

8.2.2 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 CTX-009 from the time of signing ICF through 30 days after the last dose of CTX-009.

The initial SAE eCRF must be as complete as possible, including details of the current illness and SAE, an assessment of the relationship between the event and CTX-009. 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.

8.2.2.1 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 will notify the appropriate IRB/IEC 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.

8.2.3 Pregnancy and In Utero Drug Exposure

CTX-009 has not been evaluated in pregnant or nursing women. Thus, pregnant women or WCBP who are not using effective contraception are excluded from this study (see Section 5.1 and Section 6.1.9 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 30 days after the last dose of CTX-009. If a pregnancy occurs in a patient, CTX-009 must be discontinued immediately. The pregnant woman should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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 (.e.g., 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 (e.g., 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 CTX-009 should also be reported to the Sponsor or designee.

9. STATISTICAL METHODS

The statistical analysis plan (SAP) will be completed and approved prior to database lock or any planned data analysis. However, the following is a summary of the planned statistical analyses for the key endpoints.

9.1 Sample Size

A sample size of 84 total patients (37 in Stage 1 and 47 additional in Stage 2) will have approximately 90% power on a two-sided alpha of 0.05 based on a Simon 2 Stage optimal design with a lower response rate bound of 5% and an upper bound of 15%.

9.2 Analysis Sets

- **Enrolled**: includes all patients who have signed the consent form, met inclusion and exclusion criteria, and obtained a subject identification number. This analysis set will be used for disposition analysis and used as the basis for subject data listings, unless otherwise specified.
- **All Treated:** includes all patients who received at least 1 dose of CTX-009. All efficacy data and safety data will be analyzed based on All Treated unless otherwise specified.
- **Response-Evaluable**: includes all patients who received CTX-009 and had baseline and at least 1 post-baseline response assessment or discontinued treatment due to disease progression (including death caused by disease progression) within 8 weeks (± 5 days window) of the first dose of study treatment. This analysis set, if differs from All Treated, will be used for the sensitivity analysis of selected efficacy endpoints, unless otherwise specified.

9.3 Statistical Analysis

9.3.1 General Considerations

In general, all available efficacy and safety data will be included in data listings and relevant analysis results will be presented via tabulations or figures. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as 2-sided 95% confidence intervals (CIs), unless stated otherwise. For continuous variables, the number of patients, mean, median, standard deviation, minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% CIs, as well as number and percentage of censored observations.

In general, missing data will be treated as missing and no data imputation will be applied, unless otherwise specified.

Other details of the statistical analyses will be specified in the SAP.

9.3.2 Background Characteristics

9.3.2.1 Patient Disposition

The number and percentage of enrolled 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.

The All-Treated set will be used as the basis for percentages, as appropriate.

9.3.2.2 Demographics and Baseline Disease Characteristics

The following demographics and baseline characteristics will be summarized for All Treated: sex, race, ethnicity, age, type of colorectal cancer (colon vs. rectum), tumor stage (tumor-node-metastases) at diagnosis, ECOG performance status, and prior anti-cancer therapies. Additional parameters may be provided in the SAP.

All patients' demographics data and baseline disease characteristics data will be listed in respective by-patient data listing.

9.3.3 Efficacy Analyses

Tumor response will be evaluated according to RECIST v1.1 (Appendix 3).

The overall response rate (ORR, the proportion of patients with CR or PR) will be summarized and presented. Best overall response will be summarized and tabulated based on response category (CR, PR, SD or PD). Additionally, patients' timepoint response will be similarly analyzed.

For each patient, the best overall response is the best response across all efficacy assessments.

Disease control rate (defined as the percentage of patients with best overall response of CR, PR or SD) will be summarized and presented.

Duration of Response will be defined as the time from when the criteria for CR or PR were first met until the earlier date of either disease progression or death.

Progression Free Survival is defined as the number of days from the date of C1D1 to the date of disease progression, documented death, or the date of censoring. PFS will be analyzed via KM methods.

Overall survival (OS) is defined as the number of days from the date of C1D1to the date of documented death, or the date of censoring. OS data will be analyzed similarly as PFS data.

KM plots will be generated as appropriate for the relevant endpoints.

The relevant details for censoring for each endpoint will be described in the SAP.

All efficacy analyses will be based on the All-Treated population unless otherwise specified. Sensitivity analysis of the primary endpoint (ORR) will also be performed using the Response-Evaluable analysis set.

Other details of efficacy analysis will be specified in SAP.

9.3.4 Safety Analyses

Safety data will be analyzed based on All Treated.

9.3.4.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher and will be graded according to the NCI-CTCAE version 5.0 or higher (Appendix 2).

All AEs occurring during the study will be included in by-patient data listings and the incidence of TEAEs will be tabulated by medical dictionary for regulatory activities (MedDRA) System Organ Class and Preferred Term, and, in selected cases, by High Level Group Term and High Level Term. A TEAE is an AE that emerges or worsens in the period from the first dose of CTX-009 to 30 days after the last dose of study drug.

TEAEs will be summarized for overall, by relationship to CTX-009, and by severity (CTCAE Grade). AEs leading to death; SAEs; and TEAEs resulting in treatment discontinuation, interruption, and/or dose modification will be listed, and tabulated.

Other details of adverse event analyses will be specified in SAP.

9.3.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using International System units.

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. The evaluation of laboratory abnormality will include all scheduled and unscheduled relevant laboratory assessments.

A listing of individual patient hematology, serum chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

9.3.5 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 at any timepoint will be provided. 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 tabulated. Once binding ADA binding has been identified, neutralizing antibodies will also be tested and presented by dose. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

9.4 Pharmacodynamic/Exploratory Biomarker Analyses

Pharmacodynamic 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 a sufficient number of patients are collected. Additional details on the pharmacodynamic analyses will be provided in a separate analysis plan.

10. STUDY ADMINISTRATION

10.1 Good Clinical Practice Statement

This study is to be performed in accordance with the protocol, Investigator's Brochure and ICFs approved by the IRB and the FDA, or local regulatory authority. All institutions must conduct this study in compliance with the Declaration of Helsinki, the International Conference on Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP), and all applicable local regulatory requirements.

The procedures defined in the protocol were established to ensure that performance and evaluation of the study and recording of the outcomes by the sponsor and the investigator comply with the ethical regulations based on the Declaration of Helsinki, FDA, and relevant bylaws.

All investigators and staff members in charge of the study must have a full understanding of the protocol and perform the clinical study in compliance with the protocol. The principal investigator should ensure pre-study measures, such as sufficient education and training of staff members in charge of the study, etc., as well as prompt actions and necessary reporting of adverse events. Any changes to the protocol, unless necessary to protect the safety and wellbeing of the subject, should not be implemented without prior approval.

It is the investigative site's responsibility to ensure compliance with local IRB/IEC or site standard operating procedures.

10.2 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/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 is responsible for appropriately obtaining 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, the 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 Sponsor allows the use of translators in obtaining informed consent. Investigative sites should follow applicable local policies and are responsible for procuring a translator if one is needed. If a subject is unable to read, then informed consent may be obtained by having the consent form read and explained to the subject. This process must be thoroughly documented and follow local site procedure.

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 which 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.

10.3 Patient Confidentiality and Inclusivity

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 and will not identify the patient by name or other personal characteristics that can be used to reveal their identity.

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.

Patients must not be excluded from participation for reasons such as race, national or ethnic origin, color, religion, sexual orientation, sex/gender, or disability (unless said disability would affect the safety and wellbeing of the patient in this study).

10.4 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 clinical trial 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.

10.5 Case Report Forms and Source Documentation

eCRFs 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.

10.6 Sponsor Monitoring

Before the first patient signs consent to participate in the study, a representative of the Sponsor will meet with the study site in-person or remotely to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities with regard to 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 clinical trial site, and have regular visits to the clinical trial 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

10.7 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 in order to discuss findings and issues.

10.8 Study or Clinical Site Termination

The Sponsor, or designee, reserves the right to terminate the study or a clinical trial 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 clinical trial 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.

10.9 Duration of the Study, Expected Duration of Patient Participation, and End of Study

Patients assigned to receive CTX-009 will continue treatment until documented disease progression, and/or unacceptable toxicity, until patient's withdrawal of consent or decision to discontinue the clinical study's treatment, etc.

10.10 Records Retention

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, eCRFs, treatment 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 CTX-009, or until 2 years after shipment and delivery of the CTX-009 for investigational use is discontinued or as long as 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.

10.11 Publications

Publication by the clinical trial site(s) of any data from this study must be carried out in accordance with the Clinical Trial Agreement. Authorship of any publications will be objective and fair and will follow guidelines set forth by the International Committee of Medical Journal Editors.

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12. 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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited 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)

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 LLT (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 selfcare 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 five options for Grade selection. Grade 5 Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

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

**Selfcare ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Appendix 3. RECIST v1.1 Response Criteria

Response criteria were adapted from: Response Evaluation Criteria in Solid Tumors (RECIST) Criteria; Version 1.1, 2009.[21]

1.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess overall response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where overall tumor response is an endpoint. Measurable disease is defined by the presence of at least one measurable lesion.

A measurable tumor lesion is defined as one that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- **1.0 cm by CT scan (CT scan slice thickness no greater than 0.5 cm).**
- **1.0 cm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).**
- **2.0 cm by chest X-ray.**

A measurable malignant and pathological lymph node is defined as one that can be accurately measured ≥ 1.5 cm in short axis when assessed by CT scan (CT scan slice thickness no greater than 0.5 cm).

Non-measurable lesions are defined as all other lesions, including small lesions (longest diameter <1.0 cm or pathological lymph nodes with ≥1.0 to <1.5 cm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

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 considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

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 patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

1.2 Baseline Documentation of Target and Non-Target Lesions

Baseline documentation of tumor sites should include imaging assessment of disease as applicable for disease type and anatomic involvement (at minimum chest, abdomen, and pelvis). A baseline imaging study of the brain is not required unless there is a prior history of brain metastasis or the patient has clinical symptoms of brain metastasis. All baseline tumor measurements must be documented within 4 weeks prior to start of therapy.

1.2.1 Target Lesions

All measurable lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of 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 which can be measured reproducibly should be selected. 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.

1.2.2 Non-Target Lesions

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

1.3 Tumor Response Criteria

1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <1.0 cm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum 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 0.5 cm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<1 cm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

1.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. In non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

DETERMINATION OF TUMOR RESPONSE			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Response Assessment**
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	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

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.

Conditions that may define "early progression, early death, and inevaluability" are study-specific and should be clearly defined in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy), before confirming the complete response status.

1.5 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of treatment.

Note: Tumor lesions in a previously irradiated area are not optimally considered measurable disease. If the Investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions will only be considered measurable when they are superficial and 1 cm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

For **Chest lesions**, Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Cross Sectional Imaging: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 0.5 cm or less. When CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

1.6 Duration of Response

1.6.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

1.6.2 Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

1.6.3 Time to Disease Progression

Defined as the time from the date of first day of enrollment to progression as assessed by the conventional response criteria, death, or the start of further antitumor therapy. Patients lost to follow-up will be censored at their last known alive date.

Appendix 4. Quality Of Life Questionnaire

European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire (EORTC QLQ-C30)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent