# STUDY PROTOCOL

# CTX-471-001

**A Phase 1, Open-Label, Multiple-Ascending Dose Study of the Safety and Tolerability of CTX-471 Administered Either as a Monotherapy or in Combination with Pembrolizumab in Patients with Inadequate Responses to PD-1/PD-L1 Checkpoint Inhibitors in Metastatic or Locally Advanced Malignancies**

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|---|---|
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| **Phase:** | 1 |
| **Date of Protocol:** | 09Nov2023 |
| **Version:** | 8.0 |
| **IND:** | 139423 |
| **Sponsor:** | Compass Therapeutics, Inc.<br>80 Guest Street, Suite 601<br>Brighton, MA 02135 |

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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

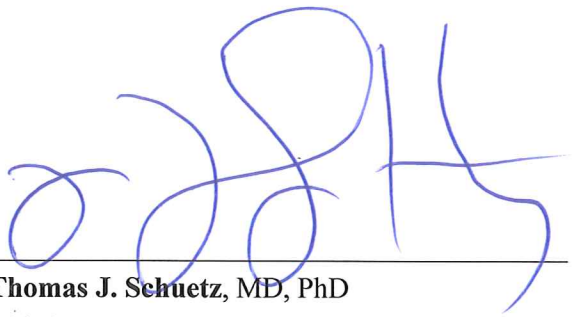
Print Name: _____

Signature: _____

Date (dd/mm/yyyy): _____

## SPONSOR PROTOCOL APPROVAL

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



November 21, 2023

**Thomas J. Schuetz**, MD, PhD
Chief Executive Officer
Compass Therapeutics, Inc.

Date

# CONTACT INFORMATION

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# PROTOCOL SYNOPSIS

**Study Title:**

A Phase 1, Open-Label, Multiple-Ascending Dose Study of the Safety and Tolerability of CTX-471 Administered Either as a Monotherapy or in Combination with Pembrolizumab in Patients with Inadequate Responses to PD-1/PD-L1Checkpoint Inhibitors in Metastatic or Locally Advanced Malignancies

**Protocol Number:**

CTX-471-001

**Phase:**

1

**CTX-471 and Study Rationale:**

This study is divided into 2 arms; Monotherapy Arm 1 will investigate CTX-471 as a monotherapy; Combination Arm 2 will investigate CTX-471 in combination with pembrolizumab (Keytruda®). Each Arm will have two Parts: a dose escalation cohort and a dose expansion cohort, referred to as Part 1 and Part 2, respectively, for each of the two Arms.

CTX-471 Rationale:

Immune checkpoint inhibition with programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) blockade has transformed cancer therapy and resulted in long-term disease-free survival in several advanced malignancies. However, most of the patients treated with these agents will still experience disease progression and eventually die of their underlying disease. Deep and durable immune response is an important goal for improved long-term prognosis.

Cluster of differentiation 137 (CD137) (4-1BB, TNFRSF9), a member of the tumor necrosis factor receptor superfamily, is a key costimulatory factor for T cells and natural killer (NK) cells activation through the nuclear factor-κB signaling pathway. Agonists of CD137 enhance the function of cytotoxic T cells, promote cell proliferation and survival, and augment the host immune response. Two lead CD137 agonists, utomilumab (PF-05082566) and urelumab (BMS-663513) have been tested in Phase 1 and 2 clinical trials (Segal 2017; Segal 2018). Early urelumab studies with higher doses were associated with hepatic toxicity. Subsequent studies with both compounds have shown clinical efficacy and acceptable safety profiles. The recently solved crystal structures of the CD137/CD137 ligand (CD137L) complex along with utomilumab and urelumab clearly illustrated that agonistic antibodies that engage different epitopes on a costimulatory receptor can have distinct pharmacology (Chin 2018).

CTX-471 is a fully human immunoglobulin G4 (IgG4) anti-CD137 antibody that binds to a distinct epitope on CD137 and agonizes the receptor. Extensive preclinical studies in a variety of murine tumor models have demonstrated that CTX-471 (and its mouse affinity-matched variant, CTX 471 AF) as a monotherapy or as combination therapy has potent antitumor

activity. Four-week repeat dose Good Laboratory Practice (GLP) compliant toxicology studies in cynomolgus monkeys and mice have been completed. The overall findings support further investigation of CTX-471 in clinical trials.

CTX-471 combined with pembrolizumab (Combination Arm 2):

While checkpoint inhibitors have been transformational therapies, a significant proportion of patients either do not respond to these agents or progress following initial stable disease or a response.

Combination of CTX-471 with a checkpoint blockade, such as pembrolizumab, may have some synergy in syngeneic animal models. In the absence of checkpoint blockade, there is little T-cell infiltration into the tumor. Treatment with pembrolizumab increases the T-cell infiltration in the tumor, which can then be activated by CD137 agonism with CTX-471 (Azpilikueta 2016; Chen 2014).

Preclinical studies of CTX-471 combined with pembrolizumab in PD-1/PD-L1 transgenic C57/BL6 mice inoculated with MC38-hPD-L1 cells showed superior efficacy in tumor growth inhibition over monotherapy of either agent.

With this potential synergistic effect, CTX-471 in combination with pembrolizumab may have the potential to further enhance immune responses and may help patients in whom PD-1/PD-L1 therapy has failed, and the combination could overcome immune escape to improve clinical outcomes.

**Objectives and Endpoints:**

***Monotherapy Arm 1 (CTX-471 alone)***

***Part 1 – Dose Escalation***

| Primary Objectives | Primary Endpoints |
|---|---|
| Evaluate the safety and tolerability of escalating doses of CTX-471 | - Incidence of DLTs, incidence of TEAEs, changes in clinical laboratory abnormalities |
| Determine the dose(s) of CTX-471 to be examined in Part 2 and the recommended Phase 2 dose(s) | |

***Part 2 – Dose Expansion***

| Primary Objective | Primary Endpoints |
|---|---|
| Evaluate the safety and tolerability of the CTX-471 dose(s) selected from Part 1 | - Incidence of TEAEs and clinical laboratory abnormalities |

***Combination Arm 2 (CTX-471+Pembrolizumab):***

***Part 1 – Dose Escalation***

| Primary Objectives | Primary Endpoints |
|---|---|
| Evaluate the safety and tolerability of escalating doses of CTX-471in combination with pembrolizumab | - Incidence of DLTs, incidence of TEAEs, changes in clinical laboratory abnormalities |
| Determine the dose(s) of CTX-471 in combination with pembrolizumab to be examined in Part 2 and the recommended Phase 2 dose(s). | |

***Part 2 – Dose Expansion***

| Primary Objective | Primary Endpoints |
|---|---|
| Evaluate the safety and tolerability of the CTX-471 dose(s) selected from Part 1 in combination with pembrolizumab | - Incidence of TEAEs and clinical laboratory abnormalities |

***Monotherapy Arm 1: Parts 1 and 2***

| Secondary Objectives | Secondary Endpoints |
|---|---|
| Evaluate the PK of CTX-471 | - Serum concentrations of CTX-471, including $C_{max}$, AUC, and $t_{1/2}$ |
| Evaluate the immunogenicity of CTX-471 | - Development of ADAs and/or neutralizing antibodies of CTX-471 |
| Evaluate the clinical activity of CTX-471 | - ORR, DOR, PFS per RECIST 1.1, and OS |
| **Exploratory Objective** | **Exploratory Endpoints** |
| Characterize pharmacodynamic markers related to CTX-471 exposure | - Peripheral blood mononuclear cell subpopulations (eg, T cell subsets)<br>- Serum cytokines<br>- Tumor tissue cell subpopulations, biomarkers, and gene expression when appropriate biopsy samples are available (Monotherapy Arm 1 Only) |

Abbreviations: ADAs = antidrug antibodies; AUC = area under the plasma drug concentration-time curve; $C_{max}$ = maximum concentration in plasma; DLT = dose-limiting toxicity; DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PK = pharmacokinetics; RECIST = Response evaluation criteria in solid tumors; $t_{1/2}$ = half-life; TEAE = treatment-emergent adverse event

***Combination Arm 2, Parts 1 and 2:***

| Secondary Objectives | Secondary Endpoints |
|---|---|
| Evaluate the PK of CTX-471 in combination with pembrolizumab | - Serum concentrations of CTX-471, including $C_{max}$, AUC, and $t_{1/2}$ |
| Evaluate the immunogenicity of CTX-471 in combination with pembrolizumab | - Development of ADAs and/or neutralizing antibodies to CTX-471 |
| Evaluate the clinical activity of CTX-471 in combination with pembrolizumab | - ORR, DOR, PFS per RECIST 1.1, and OS |

**CTX-471 Administration:**

**Monotherapy Arm 1:**

*Part 1 – Dose Escalation*

Patients will receive CTX-471 as an intravenous (IV) infusion at the assigned dose level once every 2 weeks.

Part 1 Dose levels of CTX-471

| Dose Level | Dose [a] |
|---|---|
| 1 | 0.1 mg/kg |
| 2 | 0.3 mg/kg |
| 3 | 0.6 mg/kg |
| 4 | 1.2 mg/kg |
| 5 | 2.5 mg/kg |
| 6 | 5.0 mg/kg |

[a] Intermediate or additional dose levels may be tested if recommended by the Safety Monitoring Committee (SMC) based upon review of emerging safety, PK, or pharmacodynamic data

The starting dose of 0.1 mg/kg once every 2 weeks was calculated based on modeling a level of intratumoral mononuclear cell CD137 receptor occupancy (mean 10%) that was considered to be biologically active but safe, ie, a minimum anticipated biological effective level (MABEL). Further, a reasonable margin of safety is expected with this starting dose because it

is 10-fold lower than the highest non-severely toxic dose (HNSTD) in the mouse, which is the most sensitive toxicology species. Comparisons of the dose derived from the modeling data to the nonclinical and published clinical data for other CD137 agonists (Niu 2007; Ye 2014; Saber 2016; Segal 2017; Segal 2018) supported the safety of the proposed clinical starting dose of 0.1 mg/kg once every 2 weeks.

*Part 2 – Dose Expansion*

Part 1 Dose Escalation established a maximum tolerated dose (MTD) of 0.6 mg/kg. Part 2 Dose Expansion patients will receive CTX-471 as an IV infusion at one of two expanded dose levels: 0.3 mg/kg or 0.6 mg/kg.

**Combination Arm 2 (CTX-471+Pembrolizumab):**

*Part 1 – Dose Escalation*

Patients will receive CTX-471 as an intravenous (IV) infusion at the assigned dose level once every 2 weeks.

Patients will receive pembrolizumab as an intravenous (IV) infusion at 400 mg every 6 weeks. Patients will be dosed with pembrolizumab first followed by CTX-471.

Part 1 Dose Levels of CTX-471

| Dose Level | CTX-471 Dose (q2wks) | Pembrolizumab Dose (q6wks) |
|---|---|---|
| 1 | 0.1 mg/kg | 400 mg |
| 2 | 0.3 mg/kg | |
| 3 | 0.6 mg/kg | |

*Part 2 Dose Expansion*

Part 2 Dose Expansion will further evaluate CTX-471 + pembrolizumab in two CTX-471 dose level cohorts (0.3 mg/kg and 0.6 mg/kg) and three tumor type subgroups (NSCLC, SCLC, and melanoma). Approximately 60 patients will be enrolled (30 per cohort) with approximately 10 response evaluable patients per tumor type subgroup.

**Cohort 1 - CTX-471 Dose 0.3 mg/kg**
Group 1A - NSCLC (n=10)
Group 1B - SCLC (n=10)
Group 1C - Melanoma (n=10)

**Cohort 2 - CTX-471 Dose 0.6 mg/kg**
Group 2A - NSCLC (n=10)
Group 2B - SCLC (n=10)
Group 2C - Melanoma (n=10)

**Number of Patients:**

Monotherapy Arm 1 (CTX-471 alone):

Part 1 Dose Escalation: approximately 36*

Part 2 Dose Expansion: approximately 60

*A total of 19 patients were treated in Part 1 Dose Escalation, defining the NTD of 1.2 mg/kg and MTD of 0.6 mg/kg.

Combination Arm 2 (CTX-471+pembrolizumab):

Part 1 Dose Escalation: approximately 10*

Part 2 Dose Expansion: approximately 60

*A total of 10 patients were treated in Part 1 Dose Escalation. No DLTs were observed.

**Study Population:**

This study will enroll patients with metastatic or locally advanced malignancies that have progressed after at least 12 weeks and a minimum of 2 doses of treatment with a PD-1 or PD-L1 inhibitor per the approved prescriber's information. Patients will be informed of available treatment options and, in consultation with the study Investigator, will decide whether participation in the CTX-471-001 clinical trial offers the best available option for treatment.

**Study Duration:**

The study will consist of a Screening Period (up to 28 days), a Treatment Period (continuous treatment until disease progression, unacceptable toxicity, death, or withdrawal of consent), and a Follow-up Period.

Patients may continue therapy beyond disease progression based upon Investigator judgement of potential benefit. Please see Section 10.9 for the specific requirements that need to be met in order for patients to receive treatment beyond disease progression.

**Study Centers:**

Enrollment is anticipated at approximately 5 to 10 clinical sites.

**Study Design:**

This is a Phase 1, open-label, first-in-human study of CTX-471 administered as a monotherapy or in combination with pembrolizumab in patients with metastatic or locally advanced malignancies that have progressed while receiving an approved PD-1 or PD-L1 inhibitor. The study will be conducted in 2 treatment arms (Monotherapy Arm 1 and Combination Arm 2). Each Arm will have two Parts: a dose escalation cohort and a dose expansion cohort, referred to as Part 1 and Part 2, respectively, for each of the two Arms.

**Monotherapy Arm 1:**

*Part 1 – Dose Escalation*

The starting dose of CTX-471 will be 0.1 mg/kg, based on the MABEL and findings from the GLP toxicology studies.

Part 1 will use a 3+3 design to evaluate escalating doses of CTX-471 monotherapy. Approximately 36 patients are anticipated for enrollment.

At any dose level, if no DLT occurs among the first 3 patients enrolled at the dose level, then escalation to the next dose level may proceed if approved by the SMC. If 1 DLT occurs in the first 1 to 3 patients, the dose level will expand to a maximum of 6 patients. If no DLT occurs among the 3 additional patients enrolled at that dose level, then escalation to the next dose level may proceed if approved by the SMC. The non-tolerated dose (NTD) is the dose level at which 2 or more patients experience a DLT during the DLT evaluation period. The maximum tolerated dose (MTD) will be defined as the dose level immediately below the NTD. At least 6 patients will be treated at the MTD before expansion in Part 2. Of note, dose escalation may not identify an NTD or MTD. If NTD/MTD is not identified, the SMC may recommend the dose(s) for expansion based upon cumulative safety, pharmacokinetic (PK), and pharmacodynamic data. Dose escalation will continue until one of the following occurs:

- Identification of an NTD/MTD
- Recommendation by the SMC to halt dose escalation based on comprehensive review of all applicable data

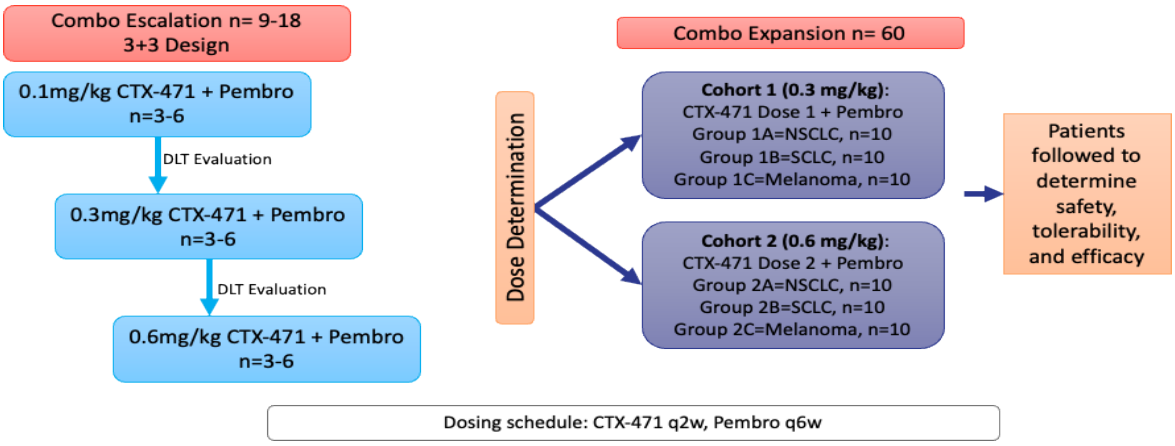
*Part 2 – Dose Expansion*

During Dose Expansion, the safety, tolerability, and preliminary efficacy of CTX-471 will be evaluated in two dose levels: 0.3 mg/kg and 0.6 mg/kg.

Approximately 30 patients will be enrolled in each dose group for a total of 60 patients.

**Combination- Arm 2:**

*Study Schema*




*Part 1 – Dose Escalation*

The starting dose of CTX-471 in Arm 2 will be 0.1 mg/kg, based on the findings from monotherapy Arm 1 of the study.

Part 1 will use a 3+3 design to evaluate escalating doses of CTX-471 in combination with pembrolizumab. Approximately 9-18 patients are anticipated for enrollment.

At any dose level, if no DLT occurs among the first 3 patients enrolled at the dose level, then escalation to the next dose level may proceed if approved by the SMC. If 1 DLT occurs in the first 1 to 3 patients, the dose level will expand to a maximum of 6 patients. If no DLT occurs among the 3 additional patients enrolled at that dose level, then escalation to the next dose level may proceed if approved by the SMC.

Dose escalation will continue until one of the following occurs:

- Confirmation that the CTX-471 doses used in the Monotherapy Arm 1 Part 2 do not result in a DLT in the Combination Arm
- Recommendation by the SMC to halt dose escalation based on comprehensive review of all applicable data

*Part 2 – Dose Expansion*

During Dose Expansion, the safety, tolerability, and preliminary efficacy of CTX-471 in combination with pembrolizumab will be further evaluated in two CTX-471 dose level cohorts (0.3 mg/kg and 0.6 mg/kg) and in three tumor type subgroups (NSCLC, SCLC, and melanoma). Approximately 60 patients will be enrolled (30 per cohort) with approximately 10 response evaluable patients per tumor type subgroup.

Both CTX-471 dose levels will enroll simultaneously, and dose level assignments will be alternating based on each tumor type group.

**Assessment of Safety:**

Safety will be assessed in both Arms through the monitoring of adverse events (AEs) (including DLTs) and clinical laboratory evaluations.

Patients will be monitored continuously for toxicity while on treatment until the Safety Follow-Up Visit. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher. Dose modifications will be applied for AEs at least possibly related to CTX-471 and of particular severity according to the guidelines set forth in the study protocol.

**DLT Definition and Evaluation Period:**

DLTs will be evaluated during Part 1 Dose Escalation of both Arms. The DLT evaluation period will include the first 2 doses of CTX-471 and 1 dose of pembrolizumab (Combination Arm 2 only) and will run for approximately 4 weeks (Monotherapy Arm 1) or 6 weeks (Combination Arm 2), beginning on W1/D1 and ending on W5/D1 (Monotherapy) or W7/D1 (Combination Arm 2) before the administration of the third dose of CTX-471 (Monotherapy Arm 1) or the fourth dose of CTX-471 and second dose of pembrolizumab (Combination Arm 2) (W = study week, D = study day). Patients who do not receive all CTX-471 doses during the DLT evaluation period and do not experience a DLT will be replaced. No patient with a DLT will be replaced. DLTs are any of the toxicities listed below occurring during the DLT evaluation period, except those attributable solely to disease progression, intercurrent illness, or concomitant medications. Other than the laboratory abnormalities listed below, Grade 3 or 4 laboratory abnormalities that occur without clinical sequelae, do not require hospitalization, last < 72 hours and resolve spontaneously or to conventional medical interventions, will not be considered DLTs.

Any AEs that meet DLT criteria but occur after the DLT evaluation period may be considered by the SMC in the evaluation for Part 2 dose selection. DLTs will be graded using the NCI-CTCAE version 5.0 or higher.

Specific DLT criteria for each arm can be found in Section 4.8.1 for Monotherapy Arm 1 and Section 4.8.2 for Combination Arm 2.

CTX-471 DLTs are defined as the following:

| **Hematologic Toxicities** | |
|---|---|
| Neutropenia | Grade 4 neutropenia (absolute neutrophil count [ANC] < $0.5 \times 10^9$/L) persisting for ≥ 7 days, and/or complicated by infection |
| Febrile neutropenia | ANC < 1000/$mm^3$ with a temperature of ≥ 38.3 °C |
| Thrombocytopenia | Grade 4 thrombocytopenia (platelets < $25 \times 10^9$/L)<br>Grade 3 thrombocytopenia with clinically significant bleeding |
| **Non-hematological Toxicities** | |

| | |
|---|---|
| Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations | ≥ Grade 3 |
| Hy's Law | ALT or AST elevation > 3 × upper limit of normal (ULN), total bilirubin elevation > 2 × ULN, absence of initial findings of cholestasis (ie, absence of elevation of alkaline phosphatase > 2 × ULN), and no other explanation of the combination of increased ALT/AST and total bilirubin |
| Any other ≥ Grade 3 non-hematological AE with the following exceptions:<br>• Fatigue<br>• Diarrhea or vomiting that recovers to ≤ Grade 1 with supportive treatment (per clinical site practice) within 72 hours<br>• Cytokine Release Syndrome that recovers to ≤ Grade 1 with supportive treatment (per clinical site practice, Appendix 2) within 72 hours<br>• Immune-related AEs [a] that recover to ≤ Grade 1 within 7 days with treatment (per clinical site practice) | |

**Abbreviations:** AE = adverse event; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; CRS = cytokine release syndrome; ULN = upper limit of normal

[a] Potential immune-related AEs include pneumonitis, colitis, hepatitis, vitiligo, hypophysitis, thyroiditis, nephritis/renal dysfunction, diabetes, and myocarditis.

AEs such as chills, rigors, fever, nausea/vomiting, flu-like symptoms and/or hypotension associated with CTX-471 infusion that are ≤ Grade 3 and resolve to ≤ Grade 1 within 24 hours with standard supportive care will **not** be considered DLTs.

An AE believed by the Investigator to be caused by tumor flare should **not** be considered a DLT. Any such cases that would otherwise meet DLT criteria must be discussed immediately with the Medical Monitor. If the Investigator, Medical Monitor, and Sponsor agree that tumor flare is a likely explanation for the AE, treatment with CTX-471 and/or pembrolizumab may continue so long as the patient is closely monitored by the Investigator or study staff.

Patients who experience a DLT will have CTX-471 and/or pembrolizumab dosing withheld until the toxicity has returned to ≤ Grade 1. If the Investigator determines that continued treatment with CTX--471 is in the patient's best interest, treatment may resume at a reduced dose, one dose level lower than the patient's current dose after consultation with the Medical Monitor. All dose modifications and modifications for pembrolizumab must follow Section 7.2.4.

Dose holds for CTX-471 lasting longer than 1 week past a scheduled dosing date will result in a "missed dose." If an AE results in a missed CTX-471 dose, the timing of the next CTX-471 administration will remain on the schedule determined by the patient's first dose of CTX-471.

*Safety Monitoring Committee*

This study will utilize an SMC that will meet regularly during Part 1 Dose Escalation for both study arms to review all accumulated safety and tolerability data. Other supporting data, including PK, pharmacodynamic, and efficacy, will be reviewed as available. The SMC will be comprised at minimum of all Principal Investigators (PIs) who have enrolled at least 1 patient in the cohort and the Medical Monitor as voting members. Additional Investigators from active sites may also participate as voting members. Non-voting representatives of the SMC will include a medical representative from the Sponsor, other relevant study staff, and site staff. The SMC will recommend all dose escalation decisions, and/or any changes to the dosing paradigm based on review of the received data. The SMC will also make all recommendations about the dose(s) selected for Part 2 Dose Expansion for each arm. During Part 2, the SMC will continue to meet periodically to review study data and provide recommendations about the conduct of the study, as needed.

**Assessment of PK, Immunogenicity, Clinical, and Pharmacodynamic Activity:**

Imaging by computed tomography/magnetic resonance imaging as appropriate to anatomical regions of disease involvement will be conducted using a consistent modality to enable response assessment according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Adjunctive imaging by positron emission tomography is permitted. Tumor biopsies will be collected to characterize potential pharmacodynamic markers, and blood samples will be collected to assess PK, immunogenicity, tumor biomarkers, and molecular profiling.

**Inclusion Criteria**

All patients must meet the following criteria for inclusion:

1. Age 18 years or older
2. Histologically confirmed diagnosis of
    a. Monotherapy Arm 1 (Part 1 and 2): metastatic or locally advanced malignancies
    b. Combination Arm 2 Part 1 Dose Escalation: metastatic or locally advanced non-small cell lung, small cell lung cancer, mesothelioma, melanoma, or head and neck cancer
    c. Combination Arm 2 Part 2 Dose Expansion: metastatic or locally advanced non-small cell lung, small cell lung cancer, or melanoma.
3. Measurable disease per RECIST 1.1
4. Disease progression after at least 12 weeks and at least 2 doses of a commercially available PD-1 or PD-L1 inhibitor per approved prescriber's information, whether monotherapy or in combination therapy, with no other intervening systemic anticancer therapy prior to enrollment
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
6. Life expectancy > 12 weeks

7. Adequate bone marrow function defined by ANC of ≥ $1.5\times10^9$/L, platelet count of ≥$100.0\times10^9$/L, and hemoglobin of ≥ 9.0 g/dL (with or without transfusion)
    a. For Combination Arm 2, these criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Patients can be on a stable dose of erythropoietin (≥ approximately 3 months).
8. Adequate hepatic function defined as serum total bilirubin < 1.5 ULN, AST/ALT ≤ 2.5 × ULN (or ≤ 5 × ULN in patients with liver metastases)
9. Adequate renal function defined as creatinine clearance > 30 mL/min as determined by the Cockcroft-Gault equation
10. Female patients must be surgically sterile (or have a monogamous partner who is surgically sterile) or be least 2 years postmenopausal or commits to use 2 acceptable forms of birth control (defined as the use of an intrauterine device, 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. Female patients who are women of childbearing potential (WCBP) must have a negative serum pregnancy test at Screening within 7 days of dosing with CTX-471 for Monotherapy Arm 1, and within 72 hours of dosing with CTX-471 and pembrolizumab for Combination Arm 2.
12. For Monotherapy Arm 1 Only: Last dose of previous PD-1 or PD-L1 therapy ≥ 28 days, other anticancer therapy > 21 days (or 2 half-lives for proteins, whichever is longer), radiotherapy > 21 days (concurrent localized palliative radiotherapy is allowed during CTX-471 treatment), or surgical intervention >21 days prior to the first dose of CTX-471
13. Resolution of all prior anti-cancer therapy toxicities ≤ Grade 1. Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤ Grade 2 neuropathy may be eligible. Patients with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible
14. Willingness to provide pre- and post-treatment fresh tumor biopsies (Monotherapy Arm 1 only)
15. Capable of understanding and complying with protocol requirements
16. Signed and dated institutional review board/independent ethics committee-approved informed consent form 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. Developed clinically significant adverse reaction to PD-1 or PD-L1 therapy, including immune related adverse reactions, which led to discontinuation of treatment
2. Prior treatment with other investigational immune-oncology therapies
3. Systemic therapy with immunosuppressive agents within 7 days before the start of CTX-471 treatment. Topical, intranasal, intraocular, or inhaled corticosteroids and physiologic replacement for patients with adrenal insufficiency are allowed
4. Patient is a pregnant or lactating WCBP
5. Prior solid organ transplantation
6. Active hepatitis B virus, hepatitis C virus, or human immunodeficiency virus infection or a positive serological test at Screening within 28 days of dosing with CTX-471
    a. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization.

       Note: Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

    b. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

       Note: Participants must have completed curative anti-viral therapy at least 4 weeks prior to randomization.

    c. HIV infected participants must be on anti-retroviral therapy (ART) and have a well-controlled HIV infection/disease defined as:

       - Participants on ART must have a CD4+ T-cell count >350 cells/mm3 at time of screening
       - Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening
       - Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1)
7. Active autoimmune disease or medical conditions requiring chronic steroid (ie, > 10 mg/day prednisone or equivalent) or immunosuppressive therapy. Patients with a prior history of autoimmune disease may be eligible following discussion with the Medical Monitor

8. History of central nervous system metastases (Monotherapy Arm 1 only)
9. History of seizure disorders
10. Congestive heart failure (> New York Heart Association Class II), active coronary artery disease, unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or clinically significant cardiac arrhythmias
11. Other systemic conditions or organ abnormalities that in the opinion of the Investigator may interfere with the conduct and/or interpretation of the current study

For Combination Arm 2, the following additional criteria will exclude participation:

12. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (could consider shorter interval for kinase inhibitors or other short half-life drugs) prior to treatment. Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

    Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
13. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis.

    Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
14. Has had an allogeneic tissue transplant.
15. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccines are allowed.
16. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of bladder, that have undergone potentially curative therapy are not excluded.
17. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
18. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
19. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.

20. Has an active infection requiring systemic therapy.
21. Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
22. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
23. Has received radiation therapy to the lung that is > 30Gy within 6 months of the first dose of trial treatment.

**Statistical Methodology**

Statistical methods will be primarily descriptive in nature. No hypothesis will be formally tested. Categorical variables will be summarized using numbers and percentages. Continuous variables will be summarized by total number (n), mean, standard deviation, median, and range (minimum and maximum).

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

*Sample Size Determination*

No formal hypothesis testing is planned. The number of patients in each part of the study is based on safety and tolerability.

The anticipated enrollment for the study is approximately 96 patients in Monotherapy Arm 1, 78 patients in Combination Arm 2, for a total of approximately 174 patients.

Monotherapy Arm 1:

Part 1 (Dose Escalation) will enroll approximately 36 patients using a 3+3 dose escalation design without intra-patient dose escalation. Part 2 (Dose Expansion) will enroll approximately 60 patients to be apportioned equally across two CTX-471 dose levels (0.3 mg/kg and 0.6 mg/kg). Assuming 2 different dose cohorts are enrolled in Part 2, with 30 patients in each cohort, if the true incidence rate for an AE/lab abnormality of interest is 20% or less, the probability of observing 8 or less such AEs is 87%.

Combination Arm 2

Part 1 (Dose Escalation) will enroll approximately 9-18 patients using a 3+3 dose escalation design without intra-patient dose escalation. Part 2 (Dose Expansion) will enroll approximately 60 patients to be apportioned equally across two CTX-471 dose level cohorts (0.3 mg/kg and 0.6 mg/kg) in combination with pembrolizumab and across three tumor type subgroups. Assuming 2 different dose cohorts are enrolled in Part 2, with 30 patients in each Cohort, if the true incidence rate for an AE/lab abnormality of interest is 20% or less, the probability of observing 8 or less such AEs is 87%.

*Analysis Sets*

The **DLT-Evaluable Analysis Set** is defined as all patients in Part 1 (Dose Escalation) who received at least 1 dose of CTX-471 and 1 dose of pembrolizumab (Combination Arm 2 Only) and either completed the DLT evaluation period or experienced a DLT during this period. This

analysis set will be used to assess the tolerability of CTX-471 in the dose-escalation phase. Over the entire dose escalation phase, patients will be grouped based on the highest dose level each patient received.

The **All-Treated Analysis Set** is defined as all patients who received any amount of CTX-471 or pembrolizumab (Combination Arm 2 Only) with treatment group based on the highest dose level received. This analysis set will be the primary analysis set for all safety endpoints, excluding DLT evaluation. This analysis set will also be used for analysis of efficacy endpoints for Combination Arm 2.

The **Response-Evaluable Analysis Set** is defined as all patients with measurable disease at Baseline who received any amount of CTX-471 or pembrolizumab (Combination Arm 2 Only) and had 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. For Combination Arm 2, this will also include patients who discontinue treatment due to toxicity before having a post-baseline response assessment. This analysis set will be the primary analysis set for efficacy endpoints for Monotherapy Arm 1.

The **PK Analysis Set** will include all enrolled patients who received at least one dose of CTX-471 or pembrolizumab (Combination Arm 2 Only) and have at least one post dose measurement of one analyte without protocol deviations or events affecting the validity of the PK results. This analysis set will be used for the analysis of PK parameters as further defined in the protocol. Pharmacokinetic-response correlations may be performed. The PK exposure-response analysis will include patients who have both valid PK and valid response data.

The **Pharmacodynamic Analysis Set** (Monotherapy Arm 1 Only) will include all enrolled patients who received at least one dose of CTX-471 and have at least one post dose pharmacodynamic or biomarker measurement. This analysis set will be used for the analysis of pharmacodynamic endpoints as further defined in the protocol.

*Statistical Analysis*

For Part 1 of each arm, the number and type of DLTs experienced by patients will be summarized for each dose level, accompanied by a by-patient listing of DLT events. The listing will include the description, severity, and relationship of the events to CTX-471 and pembrolizumab (Combination Arm 2 only).

For Part 1 and Part 2 of each arm, safety data, including vital signs, electrocardiograms (ECGs), laboratory test results, physical examinations, and AEs, will be summarized by dose and assessment time points, as appropriate. Change from Baseline will be included in summary tables for laboratory, ECG, and vital sign parameters. Shifts in grade from Baseline to maximum post-Baseline grade will be summarized for each dose level, as appropriate, for applicable laboratory data. Summaries of patients with AE of Grade 3 or higher or laboratory values ≥ Grade 3 in severity will be tabulated by dose level, as appropriate.

ORR will be assessed according to RECIST 1.1 and will be reported with category (complete response/remission, partial response/remission, stable disease, or progressive disease) counts by dose, percentage, and 95% confidence interval. The number and percentage of patients in each response category will be summarized by efficacy assessment visit.

PK, immunogenicity, pharmacodynamic endpoints, including PK parameters, anti-drug antibodies, changes in peripheral blood mononuclear cell subpopulations, serum cytokines, and tumor tissue cellular subpopulations and biomarker expression, will be summarized and tabulated.

## Table 1: Schedule of Assessments Monotherapy Arm 1

| | Screening [a] | On-Treatment DLT Evaluation Period [b] | | | | On Treatment | | | | | | | | Following Treatment Discontinuation (disc) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W2 | W3 | W4 | W5 | W6 [t] | W7 | W8 [t] | W9 | W10 [t] | W11 | W13+ q2wks | EOT [c] | Safety Follow-up [d] | Survival Follow-up [e] |
| | D-28 to D-1 | D1 | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | ≤7 d from disc. | 60 (±5) d from last dose | q3mos ± 1 week |
| **Study Drug Administration** | | | | | | | | | | | | | | | | |
| Dose number | | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | 7+ | | | |
| Administration of CTX-471 [f] | | X | | X | | X | | X | | X | | X | X | | | |
| Post-infusion observation [g] | | X | | X | | X | | X | | X | | X | X | | | |
| **Screening/History** | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Medical history & demographics | X | | | | | | | | | | | | | | | |
| Cancer history | X | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Inclusion / Exclusion | X | X [h] | | | | | | | | | | | | | | |
| ECOG performance status | X | X [h] | | X | | X | | X | | X | | X | X | X | X | |
| Con. Medications & Procedures | X | X [h] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| AE Assessment [i] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital Signs [j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| ECG (12-lead) [k] | X | X | X | X | | X | | | | X | | | q4wks | X | X | |
| Physical Examination [l] | X | X | | X | | X | | X | | X | | X | X | X | X | |
| Ophthalmologic examination (with dilation) [l] | X | | | | | | | | | | | | | | | |
| **Clinical Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Hepatitis B and C serology [m] | X | | | | | | | | | | | | | | | |
| TSH testing | X | | | | | | | | X | | | | | X | X | |
| HIV testing | X | | | | | | | | | | | | | | | |
| Pregnancy [n] | X | X | | | | X | | | | X | | | q4wks | X | X | |
| Urinalysis | | X | | X | | X | | X | | X | | X | X | X | X | |
| Blood chemistry / hematology [o] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation [o] | X | X | | | | X | | | | X | | | q4wks | X | X | |
| Immunogenicity blood serum sampling [o] | X | X | | | | X | | | | X | | | q4wks | X | X | |
| PD/Biomarker blood serum sampling [o, p, u] | X | X | | | | X | | | | q8wks[u] | | | | X | X | |
| PD/Biomarker blood cells sampling [o, p, u] | X | X | | | | X | | | | q8wks[u] | | | | X | X | |
| **Response Assessments** | | | | | | | | | | | | | | | | |
| Tumor evaluation [q] | X | | | | | | | | | X | | | q8wks | X | X [r] | |
| Fresh tumor biopsy [s, u] | X | | | | | | | | | X [s, u] | | | | X [s, u] | | |
| Survival Status (phone screen) [e] | | | | | | | | | | | | | | | | X |

**Abbreviations:** AE = adverse event; CT = computed tomography; D = study day; d = days; disc=discontinuation; DLT = dose limiting toxicity; EOT = End of Treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; q2wks = every 2 weeks; q3mos = every 3 months; q4wks = every 4 weeks; q8wks = every 8 weeks; SAE = serious AE; TSH = thyroid stimulating hormone; W = study week; WCBP = women of childbearing potential

## Table 1: Schedule of Assessments, continued

a. Screening assessments to be performed ≤28 days from the first dose (W1D1). See Section 6 for details on each study assessment.
b. All assessments indicated apply to patients enrolled in Part 1 or Part 2. For Part 1, W1D1 to pre-dose W5D1 (approximately 4 weeks) will represent the DLT evaluation period.
c. Individual assessments performed within the previous 2 weeks or tumor evaluation within the previous 30 days do not need to be repeated. Documentation regarding continued study participation for survival follow-up and retention status of biologic specimens should be obtained at this visit.
d. This visit is to occur prior to initiation of any new anticancer therapy. If the patient plans to start new anticancer therapy prior to the 60-day Safety Follow Up Visit, this visit should occur as soon as possible. If the visit is completed in person, then all assessments should be performed. If the follow-up visit is done by phone, only AEs and concomitant medications will be collected.
e. Survival follow-up assessments will be collected for a total duration of 24 months after the first dose of CTX-471. These assessments may be conducted by telephone. Information on 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.
f. CTX-471 to be infused over 1 hour (± 5 minutes); see Section 7.1 for CTX-471 administration instructions and Section 7.1.6 for dose modification instructions.
g. During DLT evaluation period patients to be observed for 6 hours post end of infusion. After DLT evaluation period patients to be observed for 1 hour post end of infusion.
h. To be performed pre-dose on W1D1.
i. For all patients, AEs should be monitored from signing of the ICF through completion of the Safety Follow-Up Visit or until the patient is determined to be a screen failure. After completion of the initial screening assessments, any new clinically significant findings for enrolled patients will be captured as an AE on the electronic case report form. SAEs for all patients will be reported from the time of the signing of the ICF until completion of the Safety Follow-Up Visit. At any time after completion of the AE reporting period, if an Investigator becomes aware of an SAE suspected to be related to any CTX-471, the event must be reported.
j. Vital signs (temperature, pulse rate, respiratory rate, diastolic and systolic blood pressure, O2 pulse oximetry). On days of infusion, to be measured prior to CTX-471, every 15 min. (± 3 min.) during infusion, then hourly (± 10 min.) during the post-infusion observation period.
k. 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 W1D1, ECGs performed prior to CTX-471 administration and following completion of CTX-471 infusion (1-6 hours post completion). On all subsequent CTX-471 infusion days, ECG performed prior to CTX-471 administration. At W13D1+, assessments to be performed pre-dose every 4 weeks.
l. 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. A complete ophthalmologic exam will be conducted at Screening but may be optional during the COVID-19 pandemic. Additional ophthalmologic exams are permitted if clinically indicated per Investigator discretion.
m. All patients will be tested for anti-hepatitis C antibody (anti-HCV Ab), hepatitis B surface antigen (HbsAg), and hepatitis B core antibody (HbcAb) at Screening. Patients with abnormal testing will be excluded.
n. For WCBP only, a screening serum pregnancy test must be performed within 7 days prior to the first CTX-471 dose to confirm eligibility. For WCBP, urine pregnancy tests will be done approximately monthly while on study.
o. Clinical laboratory assessments should be collected prior to CTX-471 infusion when applicable. At W1D1 only, clinical laboratories collected for Screening within 7 days of first CTX-471 dose of CTX-471 may be used as W1D1 laboratory values. Results from all clinical laboratory assessments (including blood chemistries and hematology) must be obtained and reviewed prior to administration of the CTX-471 infusion.
p. At W9D1+, assessments to be performed or samples to be collected pre-dose every 8 weeks.
q. Tumor evaluation via CT/MRI as applicable for disease type and anatomic involvement (at minimum, chest, abdomen, and pelvis) to occur within 4 weeks prior to first CTX-471 dose. Ongoing tumor evaluations will be performed every 8 weeks from W1D1 (± 5d) 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.
r. Perform tumor evaluation only if > 4 weeks since last tumor evaluation.
s. Fresh tumor biopsy to occur within 7 days prior to first CTX-471 dose and either W9D1 or EOT (± 5d), whichever is sooner, but may be optional during the COVID-19 pandemic.
t. For non-dosing visits W6D1, W8D1, and W10D1, assessments, including Vital Signs, AE collection, con. Medications & procedures, TSH testing, and blood chemistry/hematology, may be conducted at patient's home via a visiting nurse and over the telephone during the COVID-19 pandemic.
u. Biomarker and biopsy collection will no longer be collected as of protocol Amendment 7.

## Table 2: Schedule of Assessments Combination Arm 2

| | Screening [a] | Cycle 1 (DLT Evaluation Period) [b] | | | | | | Cycle 2 and Beyond | | | | Following Treatment Discontinuation (disc) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | W1 | W2 | W3 | W4 | W5 | W6 | W7+ | W9+ | W11+ | W13+ q2wks | EOT [c] | Safety Follow-up [d] | Survival Follow-up [e] |
| | D-28 to D-1 | D1 | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | D1±2d | ≤7 d from disc. | 60 (±5) d from last dose | q3mos ± 1 week |
| **Study Drug Administration** | | | | | | | | | | | | | | |
| Administration of CTX-471 [f] | | X | | X | | X | | X | X | X | X | | | |
| Administration of pembrolizumab [f] | | X | | | | | | X | | | q6wks | | | |
| Post-infusion observation [g] | | X | | X | | X | | X | X | X | X | | | |
| **Screening/History** | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | |
| Medical history & demographics | X | | | | | | | | | | | | | |
| Cancer history | X | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | |
| Inclusion / Exclusion | X | X [h] | | | | | | | | | | | | |
| ECOG performance status | X | X [h] | | X | | X | | X | X | X | X | X | X | |
| Con. Medications & Procedures | X | X [h] | X | X | X | X | X | X | X | X | X | X | X | |
| AE Assessment [i] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital Signs [j] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| ECG (12-lead) [k] | X | X | X | X | | X | | | X | | q6wks | X | X | |
| Physical Examination [l] | X | X | | X | | X | | X | X | X | X | X | X | |
| Ophthalmologic examination (with dilation) [l] | X | | | | | | | | | | | | | |
| **Clinical Laboratory Assessments** | | | | | | | | | | | | | | |
| Hepatitis B and C serology [m] | X | | | | | | | | | | | | | |
| Thyroid function testing [n] | X | | | | | | | X | | | q6wks | X | X | |
| HIV testing | X | | | | | | | | | | | | | |
| Pregnancy [o] | X | X | | | | | | X | | | q6wks | X | X | |
| Urinalysis | | X | | X | | X | | X | X | X | X | X | X | |
| Blood chemistry / hematology [p] | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Coagulation [p] | X | X | | | | X | | | X | | q6wks | X | X | |
| Immunogenicity blood serum sampling [p] | X | X | | | | X | | | X | | q6wks | X | X | |
| PK sampling Part 1 [q] | | X | X | X | | | | | | | X | | | |
| PK sampling Part 2 [r] | | X | | | | | | X | | | X | | | |
| **Response Assessments** | | | | | | | | | | | | | | |
| Tumor evaluation [s] | X | | | | | | | | X | | q8wks | X | X [t] | |
| Survival Status (phone screen) [e] | | | | | | | | | | | | | | X |

**Abbreviations:** AE = adverse event; CT = computed tomography; D = study day; d = days; disc=discontinuation; DLT = dose limiting toxicity; EOT = End of Treatment; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; q2wks = every 2 weeks; q3mos = every 3 months; q6wks = every 6 weeks; q8wks = every 8 weeks; q12wks = every 12 weeks SAE = serious AE; TSH = thyroid stimulating hormone; W = study week; WCBP = women of childbearing potential

## Table 2: Schedule of Assessments, continued

a. Screening assessments to be performed ≤28 days from the first dose (W1D1). See Section 6 for details on each study assessment.
b. All assessments indicated apply to patients enrolled in Part 1 or Part 2. For Part 1, W1D1 to pre-dose W7D1 (approximately 6 weeks) will represent the DLT evaluation period.
c. Individual assessments performed within the previous 2 weeks or tumor evaluation within the previous 30 days do not need to be repeated. Documentation regarding continued study participation for survival follow-up and retention status of biologic specimens should be obtained at this visit.
d. This visit is to occur prior to initiation of any new anticancer therapy. If the patient plans to start new anticancer therapy prior to the 60-day Safety Follow Up Visit, this visit should occur as soon as possible. If the visit is completed in person, then all assessments should be performed. If the follow-up visit is done by phone, only AEs and concomitant medications will be collected.
e. These assessments may be conducted by telephone. Information on 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.
f. CTX-471 to be infused over 1 hour (± 5 minutes); see Section 7.1 for CTX-471 administration instructions and Section 7.1.6 for dose modification instructions. Pembrolizumab to be infused over 30 minutes (-5/+10 minutes) followed by CTX-471 infusion; see Section 7.2 for administration instructions and Section 7.2.4 for dose modification instructions. CTX-471 infusion is given every 2 weeks, pembrolizumab infusion is given every 6 weeks.
g. Patients to be observed for approximately 1 hour post end of infusion(s).
h. To be performed pre-dose on W1D1.
i. For all patients, AEs should be monitored from signing of the ICF through completion of the Safety Follow-Up Visit and at least 90 days after the last dose of pembrolizumab, or until the patient is determined to be a screen failure. After completion of the initial screening assessments, any new clinically significant findings for enrolled patients will be captured as an AE on the electronic case report form. SAEs for all patients will be reported from the time of the signing of the ICF until completion of the Safety Follow-Up Visit, or 90 days after the last dose of pembrolizumab. At any time after completion of the AE reporting period, if an Investigator becomes aware of an SAE suspected to be related to any CTX-471, the event must be reported.
j. Vital signs (temperature, pulse rate, respiratory rate, diastolic and systolic blood pressure, O2 pulse oximetry). On days of infusion, to be measured prior to CTX-471/pembrolizumab, and monitored every 15 min. (± 3 min.) during infusion, then once at 60 min (± 10 min.) post-infusion.
k. 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 W1D1, ECGs performed prior to pembrolizumab administration and following completion of CTX-471 infusion (1-6 hours post completion). On all subsequent CTX-471/pembrolizumab infusion days, ECG performed prior to pembrolizumab/CTX-471 administration. At W13D1+, assessments to be performed pre-dose every 6 weeks.
l. 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. A complete ophthalmologic exam will be conducted at Screening. Additional ophthalmologic exams are permitted if clinically indicated per Investigator discretion.
m. All patients will be tested for anti-hepatitis C antibody (anti-HCV Ab), hepatitis B surface antigen (HbsAg), and hepatitis B core antibody (HbcAb) at Screening. Patients with abnormal testing will be excluded.
n. Thyroid panel to include Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4), and Thyroid stimulating hormone (TSH).
o. For WCBP only, a screening serum pregnancy test must be performed within 72 hours prior to the first CTX-471 and pembrolizumab dose to confirm eligibility. For WCBP, urine pregnancy tests will be done approximately once per cycle while on study.
p. Clinical laboratory assessments should be collected prior to CTX-471/pembrolizumab infusion when applicable. At W1D1 only, clinical laboratories collected for Screening within 7 days of first CTX-471 dose may be used as W1D1 laboratory values. Results from all clinical laboratory assessments (including blood chemistries and hematology) must be obtained and reviewed prior to administration of the CTX-471/pembrolizumab infusion.
q. Collection required in Part 1 only. Collection timepoints include Cycle 1 Week 1: pre-dose, 1, 6, and 24 (day 2) hour post CTX-471 infusion start, Week 2 Day 1, Week 3 Day 1 pre-dose, and Cycle 3 Week 13: Day 1 pre-dose.
r. Collection required in Part 2 only. Collection timepoints include Cycle 1 Week 1: predose and 1 hour post CTX-471 infusion start and predose on Cycle 2: Week 7 Day 1 and Cycle 3 Week 13: Day 1.
s. Tumor evaluation via CT/MRI as applicable for disease type and anatomic involvement (at minimum, chest, abdomen, and pelvis) to occur within 4 weeks prior to first CTX-471 dose. Ongoing tumor evaluations will be performed every 8 weeks from W1D1 (± 5d) 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.
t. Perform tumor evaluation only if > 4 weeks since last tumor evaluation.

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | antidrug antibody |
| ADL | activities of daily living |
| AE | adverse event |
| ALT/SGPT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST/SGOT | aspartate aminotransferase |
| AUC | area under the curve |
| CD | cluster of differentiation |
| CNS | central nervous system |
| COPD | chronic obstructive pulmonary disease |
| CR | complete response/remission |
| CT | computed tomography |
| CTLA-4 | cytotoxic T-lymphocyte antigen 4 |
| DILI | drug induced liver injury |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| DRESS | Drug Rash with Eosinophilia and Systemic Symptom |
| ECG | Electrocardiogram |
| ECI | Events of Clinical Interest |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOT | End of Treatment |
| E-R | exposure response |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| HbcAb | hepatitis B core antibody |
| HbsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HNSTD | highest non-severely toxic dose |
| ICF | informed consent form |

| Abbreviation | Definition |
|---|---|
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| IgG | immunoglobulin |
| IO | Immuno-oncology |
| IP | investigational product |
| IR | immune related |
| irAEs | immune related adverse events |
| IRB | institutional review board |
| IUD | intrauterine device |
| IV | Intravenous |
| LEC | Local Ethics Committee |
| mAb | monoclonal antibody |
| MABEL | minimum anticipated biological effective level |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| M&S | modeling and simulation |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NK | natural killer |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| NSCLC | non-small cell lung cancer |
| NTD | non-tolerated dose |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed cell death 1 |
| PD-L1 | programmed cell death ligand 1 |
| PD-L2 | programmed cell death ligand 2 |
| PE | physical examination |
| PFS | progression-free survival |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PKCθ | protein kinase C-theta |
| PR | partial response/remission |

| Abbreviation | Definition |
|---|---|
| PT | preferred term |
| QTcF | QT interval corrected with Fridericia's method |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RO | receptor occupancy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| SJS | Stevens-Johnson Syndrome |
| SMC | Safety Monitoring Committee |
| TEAE | treatment-emergent adverse event |
| TEN | Toxic Epidermal Necrolysis |
| T1DM | Type 1 diabetes mellitus |
| ULN | upper limit of normal |
| WCBP | women of childbearing potential |
| ZAP | zeta-chain-associated protein kinase |

# 1. BACKGROUND

Inhibition of immune checkpoints with blocking antibodies against programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) has transformed cancer therapy and resulted in long-term disease-free survival in several advanced malignancies. Despite these advancements, most patients treated with these agents will still experience disease progression and eventually die of their underlying disease. Achieving deep and durable immune responses is an important goal for improving long-term prognosis and, to achieve this end, novel therapies that stimulate anti-tumor immunity through different mechanisms are critically needed.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

## 1.1. Unmet Needs after PD-1/PD-L1 Inhibitors

Tumor cells can evade immune surveillance by engaging PD-1 with its ligand PD-L1 to down regulate T cell effector function and limit tumor killing (Gong 2018). Blocking the PD-1/PD-L1 ligation can mitigate tumor immune suppression and improve survival. Since the first approval of pembrolizumab for the treatment of advanced melanoma, several PD-1/PD-L1 blocking antibodies (nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, etc.) have been approved for the treatment of multiple advanced malignancies (Gong 2018). Recent data also led to regulatory approvals of PD-1/PD-L1 regimens as part of first- or second-line therapies (Gong 2018).

Unmet needs in patients with disease progression following PD-1/PD-L1 treatment remain high. In the KEYNOTE-407 study, patients with untreated metastatic, squamous non-small cell lung cancer (NSCLC) were randomized to pembrolizumab or placebo in combination with carboplatin and paclitaxel. Over 50% of patients experienced disease progression at 6 months. Long term follow-up of this study is not available; nonetheless, over half of the patients died during the reported period at 18 months (Paz-Ares 2018). Similar observations have been made for other cancer types including renal cell carcinoma and urothelial carcinoma (Gong 2018).

A successful immune response to PD-1/PD-L1 blockade requires reactivation and clonal proliferation of antigen-experienced T cells present in the tumor microenvironment (Jenkins 2018). Failure of PD-1/PD-L1 inhibitors may be due to insufficient generation of anti-tumor T cells, exclusion of T cells from tumors, inadequate function of tumor specific T cells, and/or impaired formation of T cell memory. Immuno-oncology therapies that target different immune mechanisms, such as activation of costimulatory receptors, have the potential to further

enhance immune response and may help patients who failed PD-1/PD-L1 therapy overcome immune escape to improve their clinical outcome.

## 1.2. CD137: A Promising Immunostimulatory Target

Cluster of differentiation 137 (CD137) (also known as 4-1BB and TNFRSF9), a member of the tumor necrosis factor receptor superfamily, is a surface glycoprotein that is expressed on activated T-cells, natural killer (NK) cells, regulatory T-cells, monocytes, and dendritic cells (Makkouk 2016). CD137 enhances the cytotoxic effector function of T cells and NK cells and has long been considered a promising target for cancer immunotherapy. Preclinical studies demonstrated that antibodies capable of crosslinking and agonizing CD137 had potent antitumor activity in a variety of immunocompetent mouse tumor models (Melero 1997). Therapeutic efficacy was shown to be T-cell-dependent; however, CD137 agonists have also been shown to modulate the function of NK cells, regulatory T cells, and macrophages (Makkouk 2016; Takeda 2010). The signaling domain of CD137 is a key component for the efficacy of some chimeric antigen receptor T cells, including tisagenlecleucel, approved in 2017 (Makkouk 2016).

The first anti-CD137 antibody to enter the clinic was urelumab (Segal 2017), a fully human, hinge-stabilized immunoglobulin G4 (IgG4) antibody. However, when administered at doses >1 mg/kg, urelumab caused severe (Grade ¾) elevations of liver aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) (Segal 2017). The second anti-CD137 antibody tested in humans, utomilumab (Pfizer), is a fully human IgG2 antibody that had no dose-limiting toxicities (DLTs) at doses up to 10 mg/kg (Segal 2018). Both antibodies have shown limited clinical activity (Chester 2018), and no registrational trials have been conducted to date. Given that urelumab and utomilumab bind to CD137 with similar affinities (~10 nM) (Jure-Kunkel 2007; Ahrens 2012), their contrasting clinical safety profiles are likely related to the different epitopes of CD137 to which they bind, with the different human IgG isotypes used as another potential contributing factor. The recently solved crystal structures of the CD137/CD137 ligand (CD137L) complex along with utomilumab and urelumab clearly illustrated that agonistic antibodies that engage different epitopes on a costimulatory receptor can have distinct pharmacology (Chin 2018).

## 1.3. CTX-471: A Differentiated Agonistic Antibody Against CD137

Compass Therapeutics, the Sponsor, has developed CTX-471, a fully human IgG4 antibody that functionally agonizes CD137 and is cross-reactive with human, mouse, and cynomolgus monkey isoforms. It is non-ligand blocking and binds to a unique CD137 epitope within CRD3-4 that is completely distinct from the epitopes recognized by urelumab and utomilumab. CTX-471 had a similar affinity for human and cynomolgus CD137 (50-70 nM and 30-100 nM, respectively). A human semi-mechanistic pharmacokinetic (SM-PK)/pharmacodynamic model was developed based on mouse and cynomolgus data and estimated the human terminal half-life of approximately 47 days.

Extensive preclinical studies in a variety of murine tumor models have demonstrated that CTX-471 (and its mouse affinity-matched variant, CTX-471-AF) as a monotherapy or as combination therapy has potent antitumor activity. As monotherapies, both CTX-471 and CTX-471-AF have shown high rates of tumor eradication in established models of CT26 colon carcinoma, EMT-6 breast carcinoma, and A20 B cell lymphoma at very low dose levels. All

mice that rejected their tumors following CTX-471 or CTX-471-AF treatment showed complete protection when subjected to tumor rechallenge, demonstrating the establishment of durable anti-tumor immune memory. Importantly, CTX-471-AF showed a unique ability to eliminate very large CT26 tumors (~450 $mm^3$) in mice when compared against a panel of well-characterized immune-oncology antibodies.

In the GLP mouse toxicology study of CTX-471, dose-dependent treatment-related mononuclear infiltrates were observed in the meninges of the brain, spinal cord, and the optic nerve. In a few animals, the infiltrates extended into the neuropil. CTX-471 was well tolerated at 1 mg/kg and this dose was identified as the highest non-severely toxic dose (HNSTD). Therefore, the first-in-human dose is 10-fold lower than the HNSTD in the mouse, which is the most sensitive toxicology species. In the GLP monkey study, no adverse effects were identified in any tissue up to 100 mg/kg with weekly dosing for 4 weeks. Neither the monkey nor the mouse showed the hepatic toxicity associated with other CD137 agonist antibodies. Finally, no treatment-related cytokine release was observed in a valid and appropriately controlled in vitro assay using human PBMCs.

For more information on the preclinical findings, please see the CTX-471 Investigator's Brochure.

Based on the preclinical findings with CTX-471, Compass has initiated this first-in-human study in patients with advanced malignancies to characterize the safety, tolerability, PK, pharmacodynamic profile, and anti-tumor activity of CTX-471.

In this current study, a total of 31 patients have received at least one dose of CTX-471. Of the 31 patients enrolled, 29 (93.5%) patients have experienced at least 1 treatment-emergent AE (TEAE), and 13 (41.9%) patients have experienced Grade 3 or higher TEAEs.

The most commonly occurring TEAEs (occurring in ≥ 2 patients) for all grades include fatigue (10 patients; 32.3%); constipation (9 patients; 29.0%); nausea (8 patients; 25.8%); anaemia (7 patients; 22.6%); cough and headache (6 patients, 19.4% each event); vomiting, pyrexia, and dyspnoea (5 patients; 16.1% each event); abdominal pain, diarrhea, peripheral oedema, weight decreased, and appetite decreased (4 patients; 12.9% each event); alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, hypoxia, urinary tract infection, arthralgia, myalgia, and hypotension (3 patients, 9.7% each event); and dry mouth, dysphagia, gastrooesophageal reflux disease, non-cardiac chest pain, amylase increased, lipase increased, platelet count decreased, upper airway cough syndrome, dizziness, dehydration, hypomagnesaemia, hyponatraemia, hypophosphataemia, muscle spasms, muscular weakness, pain in extremity, insomnia, rash, hot flush, and hypothyroidism (2 patients; 6.5% each event).

## 1.4. Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can

be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley 2005; Hunder 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald 2005; Okazaki 2001].

The structure of murine PD-1 has been resolved [Zhang 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki 2001; Chemnitz 2004; Sheppard et al., 2004; and Riley 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry 2005; Francisco 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in combination with CTX-471.

### 1.4.1. Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [Hirano 2005; Blank 2004; Weber 2010; Strome 2003; Spranger 2014; Curran 2010; Pilon 2010]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [Strome 2003; Curran 2010; Pilon 2010; Nomi 2007; Zhang 2004]. In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [Curran 2010]. Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

## 1.5. Study Overview

This is a Phase 1, open-label, first-in-human study of CTX-471 monotherapy in patients with metastatic or locally advanced malignancies that have progressed while receiving an approved PD-1 or PD-L1 inhibitor. The study will be conducted in 2 parts: Part 1 Dose Escalation and

Part 2 Dose Expansion. The objectives of this study are to evaluate the safety and tolerability of CTX-471 and determine the dose(s) of CTX-471 to be further examined. During Part 2, the safety and tolerability of CTX-471 will be evaluated in two dose levels: 0.3 mg/kg and 0.6 mg/kg. Combination Arm 2 will explore the same objectives for CTX-471 in combination with pembrolizumab. The preliminary clinical PK and immunogenicity of CTX-471, along with clinical activity, will be characterized. The study will examine the effect of CTX-471 on peripheral blood immune cell subsets and gene expression, tumor biopsy cell subsets, and serum biomarkers.

### 1.5.1. Selection of Patient Populations

This study will enroll patients with metastatic or locally advanced malignancies that have progressed after at least 12 weeks and a minimum of 2 doses of treatment with a PD-1/PD-L1 inhibitor per the approved prescriber's information. These patients represent a population with high unmet needs. Patients will be informed of available treatment options and, in consultation with the study Investigator, will decide whether participation in the CTX-471-001 clinical trial offers the best available option for treatment.

### 1.5.2. Determination of Starting Doses and Regimen for CTX-471

The starting dose of CTX-471 0.1 mg/kg once every 2 weeks was determined based on the minimum anticipated biological effective level (MABEL) by modeling a level of intratumoral mononuclear cell CD137 receptor occupancy (mean 10%) that was considered to be biologically active but safe.

In the model, the simulated maximum receptor occupancy (RO) at this dose and frequency was 24.3% during the first 2-week dosing period (Weeks 0-2) and was 31.5% during the last dosing period (Weeks 14-16). The simulated RO levels align with RO levels of 20%-80% in cancer patients treated with other immune activators and that are associated with acceptable toxicities (Saber 2016). Furthermore, the proposed starting dose of 0.1 mg/kg is within the range of clinical starting doses of other CD137 agonists (eg, 0.3 mg/kg urelumab q3wks and 0.06 mg/kg utomilumab q4wks) that have higher affinities for CD137 and different toxicity profiles than CTX-471 (Segal 2017; Segal 2018). Finally, the 0.1 mg/kg dose is equivalent to 10% of the highest non-severely toxic dose in the mouse, which in this case is considered the most sensitive species based on the observation of dose-dependent mononuclear cell meningeal infiltrates. Unlike previous reports in mice with CD137 agonist antibodies (Niu 2007), infiltrates in other tissues such as liver and treatment-related increases in transaminases were not observed with CTX-471. Further, except from mild immunophenotyping changes consistent with CD137 agonism, no treatment-related effects of any kind were observed in cynomolgus monkeys receiving CTX-471 over 4 weeks at doses up to 100 mg/kg every week. No evidence of cytokine release syndrome (CRS) was observed in appropriately controlled and valid in vitro assays using human peripheral blood mononuclear cells, regardless of assay format, at concentrations of antibody up to 100 nM (compared to the free CTX-471 concentration needed in tumor to achieve 10% mean RO which was estimated to be 0.156 nM). These findings were consistent with prior observations that CD137 expression is low on peripheral blood mononuclear cells (Ye 2014), but upregulated on tumor-infiltrating lymphocytes, and support the safety of higher peripheral concentrations of CTX-471 prior to intratumoral equilibration. The projected intratumoral concentration is also well below the $EC_{50}$ value for functional activity (IFNγ release) in activated

human T cells in vitro.

Overall, the proposed dose escalation paradigm (Table 3) is based on the anticipated average RO across the dose range, derived from semi-mechanistic PK/PD modeling and simulation. The first dose escalation from level 1 (0.1 mg/kg) to level 2 (0.3 mg/kg) employs a half-log increment increase. At 0.1 mg/kg, the anticipated RO from the first dosing interval (0-2 weeks) to steady state was 10.6% to 18.2%, and for 0.3 mg/kg was 33.4% to 67.5% from the first dosing interval to steady state. Subsequent dose increases employ a more conservative 2-fold increase up to the highest proposed dose of 5.0 mg/kg, at which point RO saturation is predicted. The predicted average RO across this dose range is anticipated to be efficacious.

For more information on the preclinical findings, please see the CTX-471 Investigator's Brochure.

### 1.5.3. Justification for Dose of Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg every 6 weeks (Q6W).

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate [Lala 2020]. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- Pharmacokinetic (PK) simulations demonstrating that in terms of pembrolizumab exposures
    - Average concentration over the dosing interval ($C_{avg}$) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
    - Trough concentrations ($C_{min}$) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
    - Peak concentrations ($C_{max}$) at 400 mg Q6W are well below the $C_{max}$ for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
    - Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and non-small cell lung cancer (NSCLC) demonstrate that efficacyat 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.

### 1.5.4. Benefit-Risk Assessment

CTX-471 is a fully human IgG4 antibody that binds a unique CD137 epitope, stimulates the host immune response, and has demonstrated potent anti-tumor effects in several well-established mouse models. The first-in-human dose is 0.1 mg/kg, anticipated to achieve the minimal biologic effect based on 10% intra-tumoral CD137 RO from simulated models. A reasonable margin of safety is expected because the first-in-human dose is 10-fold lower than the HNSTD in the mouse, which is the most sensitive toxicology species. No adverse effects were identified in the monkey GLP study.

Since animal toxicology studies do not always predict the consequences of immunologic activation in humans, the potential for immune mediated toxicities associated with other immune-oncology therapies cannot be excluded. These risks are partially mitigated by aligning the initial dose with RO rather than animal toxicology data. Additionally, CTX-471 did not induce cytokine release in a controlled and valid in vitro assay using human peripheral blood mononuclear cells.

Although this Phase 1 trial is primarily designed to assess the safety and tolerability of CTX-471, the study patient population includes those with advanced malignancies that have progressed following PD-1/PD-L1 inhibitor therapy. These patients have limited treatment options outside of conventional chemotherapy, which is cytotoxic and has not demonstrated meaningful clinical benefit in this setting. Thus, CTX-471 represents a promising alternative for these patients who are in need of effective therapies. To mitigate the potential risks with CTX-471, the study design includes close monitoring of patient safety by study investigators. A Safety Monitoring Committee (SMC) will review all available data at regular intervals to ensure the benefit/risk ratio continues to support the study of CTX-471 in patients.

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# 2. OBJECTIVES

## 2.1. Monotherapy Arm 1 (CTX-471)

### 2.1.1. Primary Objectives (Part 1)

- Evaluate the safety and tolerability of escalating doses of CTX-471
- Determine the dose(s) of CTX-471 to be examined in Part 2 and the recommended Phase 2 dose(s)

### 2.1.2. Primary Objectives (Part 2)

- Evaluate the safety and tolerability of the CTX-471 dose(s) selected from Part 1

### 2.1.3. Secondary Objectives (All Parts)

- Evaluate the PK of CTX-471
- Evaluate the immunogenicity of CTX-471
- Evaluate the clinical activity of CTX-471

### 2.1.4. Exploratory Objectives (All Parts)

- Characterize pharmacodynamic markers related to CTX-471 exposure

## 2.2. Combination Arm 2 (CTX-471+Pembrolizumab)

### 2.2.1. Primary Objectives (Part 1)

- Evaluate the safety and tolerability of escalating doses of CTX-471 in combination with pembrolizumab
- Determine the dose(s) of CTX-471 in combination with pembrolizumab to be examined in Part 2 and the recommended Phase 2 dose(s)

### 2.2.2. Primary Objectives (Part 2)

- Evaluate the safety and tolerability of the CTX-471 dose(s) selected from Part 1 in combination with pembrolizumab

### 2.2.3. Secondary Objectives

- Evaluate the PK of CTX-471 in combination with pembrolizumab
- Evaluate the immunogenicity of CTX-471 in combination with pembrolizumab
- Evaluate the clinical activity of CTX-471 in combination with pembrolizumab

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# 3. ENDPOINTS

The primary endpoints described below will be used for both Monotherapy Arm 1 and Combination Arm 2 of the study. Monotherapy Arm 1 will assess these in monotherapy with CTX-471 and Combination Arm 2 will assess these in combination therapy of CTX-471 and pembrolizumab.

## 3.1. Primary Endpoints (Part 1)

- Incidence of DLTs, incidence of treatment-emergent adverse events (TEAEs), and changes in clinical laboratory abnormalities

## 3.2. Primary Endpoints (Part 2)

- Incidence of TEAEs and clinical laboratory abnormalities

## 3.3. Secondary Endpoints (All Parts)

- Serum concentrations of CTX-471, including $C_{max,}$ area under the curve (AUC), and $t_{1/2}$
- Development of anti-drug antibodies (ADAs) and/or neutralizing antibodies of CTX-471
- Overall response rate (ORR), duration of response (DOR), PFS per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Appendix 4), and OS

## 3.4. Exploratory Endpoints (All Parts)

- Peripheral blood mononuclear cell subpopulations (eg, T cell subsets)
- Serum cytokines
- Tumor tissue cell subpopulations, biomarkers, and gene expression when appropriate biopsy samples are available (Monotherapy Arm 1 Only)

# 4. STUDY DESIGN

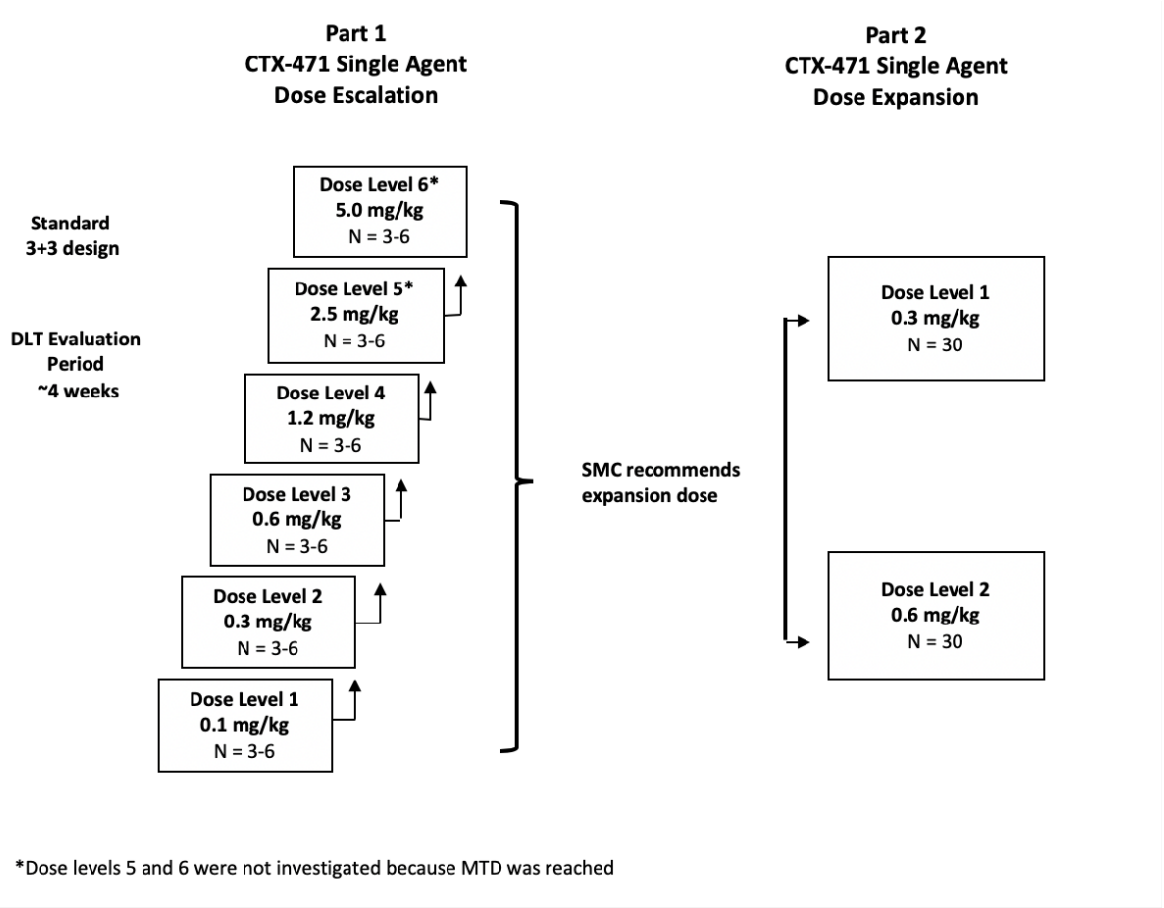
This study is divided into 2 arms; Monotherapy Arm 1 will investigate CTX-471 as monotherapy, Combination Arm 2 will investigate CTX-471 in combination with pembrolizumab (Keytruda®). Each Arm will have two Parts: a dose escalation cohort and a dose expansion cohort, referred to as Part 1 and Part 2, respectively, for each of the two Arms.

## 4.1. Monotherapy Arm 1 Schema

This is a Phase 1, open-label, first-in-human study of CTX-471 monotherapy in patients with metastatic or locally advanced malignancies that have progressed while receiving an approved PD-1 or PD-L1 inhibitor. The study will be conducted in 2 parts: Part 1 Dose Escalation and Part 2 Dose Expansion. Enrollment is anticipated at 5 to 10 clinical sites.

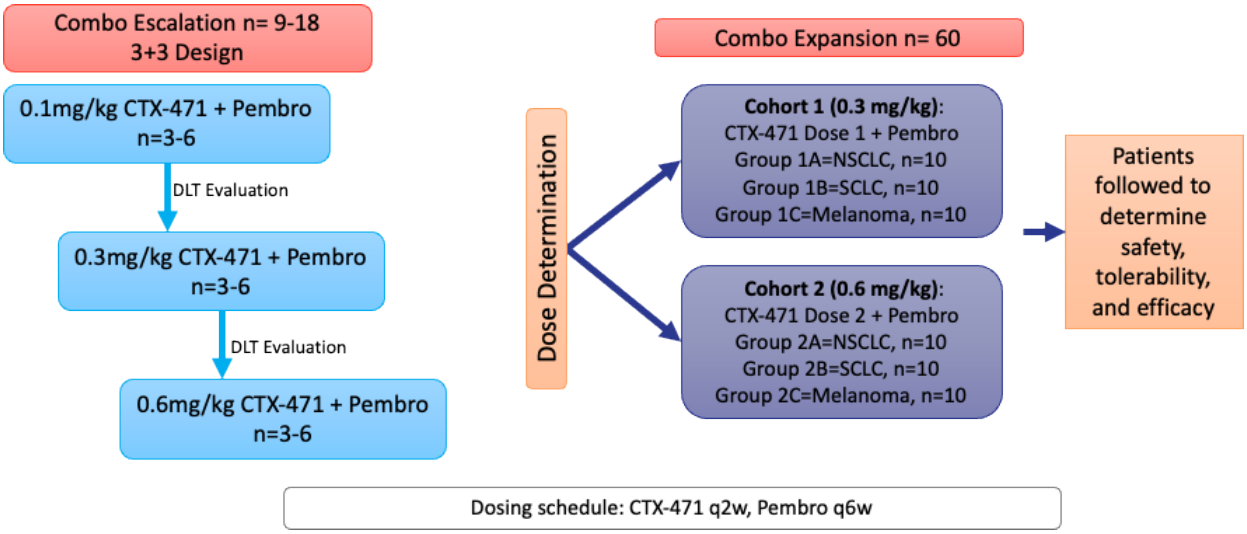
The study design is presented in Figure 1.

**Figure 1: Monotherapy Arm 1 Study Design**



## 4.2. Combination Arm 2 Schema

**Figure 2: Combination Arm 2 Study Design**




## 4.3. Monotherapy Arm 1, Part 1 (Dose-Escalation)

The starting dose of CTX-471 will be 0.1 mg/kg, based on the MABEL and findings from the GLP toxicology studies as described in Section 1.5.2.

Part 1 will use a 3+3 design to evaluate escalating doses of CTX-471 monotherapy. Up to 36 patients are anticipated for enrollment.

The following doses will be examined in Part 1:

**Table 3: Dose Levels Monotherapy Arm 1, Part 1**

| Dose Level | Dose [a] |
|---|---|
| 1 | 0.1 mg/kg |
| 2 | 0.3 mg/kg |
| 3 | 0.6 mg/kg |
| 4 | 1.2 mg/kg |
| 5 | 2.5 mg/kg |
| 6 | 5.0 mg/kg |

[a] Intermediate or additional dose levels may be tested if recommended by the SMC based upon review of emerging safety, PK, or pharmacodynamic data.

At any dose level, if no DLT occurs among the first 3 patients enrolled at the dose level, then escalation to the next dose level may proceed if approved by the SMC. If 1 DLT occurs in the first 1 to 3 patients, the dose level will expand to a maximum of 6 patients. If no DLT occurs among the 3 additional patients enrolled at that dose level, then escalation to the next dose level may proceed if approved by the SMC. The non-tolerated dose (NTD) is the dose level at which 2 or more patients experience a DLT during the DLT evaluation period. The maximum tolerated dose (MTD) will be defined as the dose level immediately below the NTD. At least 6 patients will be treated at the MTD before expansion in Part 2. Of note, dose escalation may not identify an NTD or MTD. If NTD/MTD is not identified, the SMC may recommend the dose(s) for expansion based upon cumulative safety, PK, and pharmacodynamic data. Dose escalation will continue until one of the following occurs:

- Identification of an NTD/MTD
- Recommendation by the SMC to halt dose escalation based on comprehensive review of all applicable data

A total of 19 patients were treated in Part 1 Dose Escalation, defining the NTD of 1.2 mg/kg and MTD of 0.6 mg/kg.

## 4.4. Monotherapy Arm 1, Part 2 (Dose Expansion)

During Dose Expansion, the safety, tolerability, and preliminary efficacy of CTX-471 will be evaluated in two dose levels: 0.3 mg/kg and 0.6 mg/kg. Approximately 30 patients will be enrolled in each CTX-471 dose group for a total of 60 patients in Part 2 Expansion.

During Part 2 of the study, the SMC will continue to meet periodically to review study data and provide recommendations about the conduct of the study, as needed.

## 4.5. Combination Arm 2, Part 1 (Dose-Escalation)

Combination Arm 2, Part 1 will use a 3+3 design to evaluate escalating doses of CTX-471 in combination with pembrolizumab. The starting dose will be 0.1 mg/kg, which follows the same starting dose from the Monotherapy Arm 1, Part 1 of the study, since this is the first time CTX-471 and pembrolizumab will be administered in combination in patients. Up to 18 patients are anticipated for enrollment.

The following doses will be examined in Part 1:

**Table 4: Dose Levels Combination, Part 1**

| Dose Level | CTX-471 Dose (q2wks) | Pembrolizumab Dose (q6wks) |
|---|---|---|
| 1 | 0.1 mg/kg | 400 mg |
| 2 | 0.3 mg/kg | |
| 3 | 0.6 mg/kg | |

At any dose level, if no DLT occurs among the first 3 patients enrolled at the dose level, then

escalation to the next dose level may proceed if approved by the SMC. If 1 DLT occurs in the first 1 to 3 patients, the dose level will expand to a maximum of 6 patients. If no DLT occurs among the 3 additional patients enrolled at that dose level, then escalation to the next dose level may proceed if approved by the SMC.

Dose escalation will continue until one of the following occurs:

- Confirmation that the CTX-471 doses used in the Monotherapy Arm 1 Part 2 do not result in a DLT in the Combination Arm
- Recommendation by the SMC to halt dose escalation based on comprehensive review of all applicable data

A total of 10 patients were treated in Part 1 Dose Escalation. No DLTs were observed.

## 4.6. Combination Arm 2, Part 2 (Dose Expansion)

During Dose Expansion, the safety, tolerability, and preliminary efficacy of CTX-471 in combination with pembrolizumab will be further evaluated in two CTX-471 dose level cohorts (0.3 mg/kg and 0.6 mg/kg) and in three tumor type subgroups (NSCLC, SCLC, and melanoma). Approximately 60 patients will be enrolled (30 per cohort) with approximately 10 response evaluable patients per tumor type subgroup.

**Cohort 1 - CTX-471 Dose 0.3 mg/kg**
Group 1A - NSCLC (n=10)
Group 1B - SCLC (n=10)
Group 1C - Melanoma (n=10)

**Cohort 2 - CTX-471 Dose 0.6 mg/kg**
Group 2A - NSCLC (n=10)
Group 2B - SCLC (n=10)
Group 2C - Melanoma (n=10)

**Table 5: Dose Levels Combination, Part 2**

| Cohort Dose Level | CTX-471 Dose (q2wks) | Pembrolizumab Dose (q6wks) |
|---|---|---|
| Cohort 1 NSCLC/SCLC/melanoma (N=10/10/10) | 0.3 mg/kg | 400 mg |
| Cohort 2 NSCLC/SCLC/melanoma (N=10/10/10) | 0.6 mg/kg | |

Both CTX-471 dose levels will enroll simultaneously, and dose level assignments will be alternating based on each tumor type group.

During Part 2 of the study, the SMC will continue to meet periodically to review study data and provide recommendations about the conduct of the study, as needed.

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## 4.7. Dosing Frequency

Patients will receive CTX-471 as an intravenous (IV) infusion at the assigned dose level once every 2 weeks and pembrolizumab as an IV infusion of 400mg once every 6 weeks (Combination Arm 2 only) until disease progression, unacceptable toxicity, or withdrawal of consent. Patients may continue study therapy beyond disease progression. Please see Section 10.9 for the specific requirements that need to be met in order for patients to receive treatment beyond disease progression.

## 4.8. Monitoring of Adverse Events

Patients will be monitored continuously for toxicity while on CTX-471. AE severity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 or higher (Appendix 3). Dose modifications for AEs at least possibly related to CTX-471and according to severity are described in Section 7.1.6.

### 4.8.1. Part 1 Monotherapy Dose -Limiting Toxicities

DLTs will be evaluated during Part 1 Dose Escalation. For Monotherapy Arm 1, the DLT evaluation period will include the first 2 doses of CTX-471 and will run for approximately 4 weeks, beginning on W1/D1 and ending on W5/D1 before the administration of the third dose of CTX-471 (W = study week, D = study day). Patients who do not receive both doses during the DLT evaluation period and do not experience a DLT will be replaced.

No patient with a DLT will be replaced. DLTs are any of the following toxicities outlined in Table 6 occurring during the DLT evaluation period, except those attributable solely to disease progression, intercurrent illness, or concomitant medications. Other than the laboratory abnormalities listed in Table 6, Grade 3 or 4 laboratory abnormalities that occur without clinical sequelae, do not require hospitalization, last < 72 hours and resolve spontaneously or to conventional medical interventions, will not be considered DLTs.

Any AEs that meet DLT criteria but occur after the DLT evaluation period may be considered by the SMC in the evaluation for Part 2 dose selection. DLTs will be graded using NCI-CTCAE version 5.0 or higher (Appendix 3).

**Table 6: Dose-Limiting Toxicities (Part 1)**

| ***Hematologic Toxicities*** | |
|---|---|
| Neutropenia | Grade 4 neutropenia (absolute neutrophil count [ANC] < $0.5 \times 10^9$/L) persisting for ≥ 7 days, and/or complicated by infection |
| Febrile neutropenia | ANC < $1000/mm^3$ with a temperature of ≥ 38.3°C |
| Thrombocytopenia | Grade 4 thrombocytopenia (platelets < $25 \times 10^9$/L)<br>Grade 3 thrombocytopenia with clinically significant bleeding |

**Table 6: Dose-Limiting Toxicities (Part 1)**

| ***Non-Hematological Toxicities*** | |
|---|---|
| AST and ALT elevations | ≥ Grade 3 |
| Hy's Law | ALT or AST elevation > 3 × upper limit of normal (ULN), total bilirubin elevation > 2 × ULN, absence of initial findings of cholestasis (ie, absence of elevation of alkaline phosphatase > 2 × ULN), and no other explanation of the combination of increased ALT/AST and total bilirubin |
| Any other ≥ Grade 3 non-hematological AE with the following exceptions:<br>• Fatigue<br>• Diarrhea or vomiting that recovers to ≤ Grade 1 with supportive treatment (per clinical site practice) within 72 hours<br>• CRS that recovers to ≤ Grade 1 with supportive treatment (per clinical site practice, Appendix 2) within 72 hours<br>• Immune-related AEs [a] that recover to ≤ Grade 1 within 7 days with treatment (per clinical site practice) | |

**Abbreviations:** AE = adverse event; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; CRS = cytokine release syndrome; ULN = upper limit of normal

[a] Potential immune-related AEs include pneumonitis, colitis, hepatitis, vitiligo, hypophysitis, thyroiditis nephritis/renal dysfunction, diabetes, and myocarditis.

AEs such as chills, rigors, fever, nausea/vomiting, flu-like symptoms and/or hypotension associated with CTX-471 infusion that are ≤ Grade 3 and resolve to ≤ Grade 1 within 24 hours with standard supportive care will **not** be considered DLTs.

An AE believed by the Investigator to be caused by tumor flare should **not** be considered a DLT. Any such cases that would otherwise meet DLT criteria must be discussed immediately with the Medical Monitor. If the Investigator, Medical Monitor, and Sponsor agree that tumor flare is a likely explanation for the AE, treatment with CTX-471 may continue so long as the patient is closely monitored by the Investigator or study staff.

Patients who experience a DLT will have CTX-471 dosing withheld until the toxicity has returned to ≤ Grade 1. If the Investigator determines that continued treatment with CTX-471 is in the patient's best interest, treatment may resume at a reduced dose, 1 dose level lower than the patient's current dose after consultation with the Medical Monitor.

CTX-471 dose holds lasting longer than 1 week past a scheduled dosing date will result in a "missed dose." If an AE results in a missed CTX-471 dose, the timing of the next CTX-471 administration will remain on the schedule determined by the patient's first dose of CTX-471. Refer to Section 7.1.6 for additional information about dose holds and modification.

### 4.8.2. Part 1 Combination Dose -Limiting Toxicities

For the Combination Arm 2 Part 1, the DLT evaluation period will include the first 3 doses of CTX-471 and the first dose of pembrolizumab, and will run for approximately 6 weeks, beginning on W1/D1 and ending on W7/D1 before the administration of the fourth dose of CTX-471 and second dose of pembrolizumab. Patients who do not receive these doses during the DLT evaluation period and do not experience a DLT will be replaced.

All toxicities will be graded using NCI-CTCAE Version 5.0 based on the investigator assessment.

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study treatment administration.

1. Grade 4 nonhematologic toxicity (not laboratory).
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with clinically significant bleeding
3. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Clinically significant medical intervention is required to treat the participant or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for >1 week.
   - The abnormality results in a Drug-induced Liver Injury (DILI)
   - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
5. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as ANC <1000/$mm^3$ with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour
   - Grade 4 is defined as ANC <1000/$mm^3$ with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
7. Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1.
8. Missing >25% of CTX-471 doses as a result of drug-related AE(s) during the first cycle.

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9. Grade 5 toxicity.

### 4.8.3. Safety Monitoring Committee

This study will utilize a SMC that will meet regularly during Part 1 Dose Escalation of both study arms to review all accumulated safety and tolerability data. Other supporting data, including PK, pharmacodynamics, and efficacy, will be reviewed as available. The SMC will be comprised at minimum of all Principal Investigators (PIs) who have enrolled at least 1 patient in the cohort and the Medical Monitor as voting members. Additional Investigators from active sites may also participate as voting members. Non-voting members will include a medical representative from the Sponsor and other relevant study and site staff. The SMC will recommend all dose escalation decisions, and/or any changes to the dosing paradigm based on review of the received data. The SMC will also make all recommendations about the dose(s) selected for Part 2 Dose Expansion. During Part 2, the SMC will continue to meet periodically to review study data and provide recommendations about the conduct of the study, as needed.

## 4.9. Treatment Discontinuation

Patients will be discontinued from treatment for any of the following reasons:

- An AE that requires permanent discontinuation of study treatment*
- Disease progression as measured by the appropriate response criteria**
- Noncompliance to the protocol
- Investigator decision
- Patient becomes pregnant
- Patient death
- Patient lost to follow-up
- Termination of the study by the Sponsor
- Voluntary withdrawal of consent by patient
- For Combination Arm 2: pembrolizumab must be discontinued following completion of 18 administrations (approximately 2 years).

* *AEs leading to the discontinuation of CTX-471 and/or pembrolizumab will be followed until resolution, resolution to baseline or until the event is considered stable or chronic.*

** *Patients may continue therapy beyond disease progression. Please see Section 10.9 for the specific requirements that need to be met in order for patients to receive treatment beyond disease progression.*

The reason for treatment discontinuation should be documented.

Following treatment discontinuation, an End of Treatment (EOT) Visit should occur within 7 days after the last dose of CTX-471 and/or pembrolizumab. Each EOT assessment need not be

performed if the patient has had the identical assessment within the previous 2 weeks or previous 30 days for disease response assessments.

All patients will have a Safety Follow-Up Visit approximately 60 (± 5) days after the last dose of CTX-471 and/or pembrolizumab, unless the patient withdraws from the study prematurely (Section 4.10). If a patient plans to start new anticancer therapy prior to the 60-day Safety Follow-Up Visit, this visit should occur as soon as possible. If the visit is completed in person, then all assessments should be performed. If follow-up by phone, only AEs and concomitant medications will be collected.

All patients who discontinue study treatment should enter Survival Follow-Up (see Section 6.3).

## 4.10. Study Withdrawal

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

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

- Patient death
- Patient lost to follow-up
- Voluntary withdrawal by patient
- Investigator's opinion
- Termination of the study by Sponsor

If possible, prior to withdrawal, an EOT Visit should occur within 7 days after the last dose of CTX-471 and/or pembrolizumab. 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.

# 5. STUDY POPULATION

## 5.1. Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. Age 18 years or older
2. Histologically confirmed diagnosis of
   a. Monotherapy Arm 1 (Part 1 and 2): metastatic or locally advanced malignancies
   b. Combination Arm 2 Part 1 Dose Escalation: metastatic or locally advanced non-small cell lung, small cell lung cancer, mesothelioma, melanoma, or head and neck cancer
   c. Combination Arm 2 Part 2 Dose Expansion: metastatic or locally advanced non-small cell lung, small cell lung cancer, or melanoma.
3. Measurable disease per RECIST 1.1 (Appendix 4)
4. Disease progression after at least 12 weeks and at least 2 doses of a commercially available PD-1 or PD-L1 inhibitor per the approved prescriber's information, whether monotherapy or in combination therapy, with no other intervening systemic anticancer therapy prior to enrollment.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
6. Life expectancy > 12 weeks
7. Adequate bone marrow function defined by ANC of $\geq 1.5\times10^9$/L, platelet count of $\geq 100.0\times10^9$/L, and hemoglobin of $\geq 9.0$ g/dL (with or without transfusion)
   a. For Combination Arm 2, these criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Patients can be on a stable dose of erythropoietin (≥ approximately 3 months).
8. Adequate hepatic function defined as serum total bilirubin < 1.5 ULN, AST/ALT ≤ 2.5 × upper limit of normal (ULN) (or ≤ 5 × ULN in patients with liver metastases)
9. Adequate renal function defined as creatinine clearance > 30 mL/min as determined by the Cockcroft-Gault equation.
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. Female patients who are women of childbearing potential (WCBP) must have a negative serum pregnancy test at Screening within 7 days of dosing with CTX-471 for Monotherapy Arm 1, and within 72 hours of dosing with CTX-471 and pembrolizumab for Combination Arm 2.
12. For Monotherapy Arm 1 Only: Last dose of previous PD-1 or PD-L1 therapy ≥ 28 days, other anticancer therapy > 21 days (or 2 half-lives for proteins, whichever is longer), radiotherapy > 21 days (concurrent localized palliative radiotherapy is allowed during CTX-471 treatment), or surgical intervention > 21 days prior to the first dose of CTX-471
13. Resolution of all prior anti-cancer therapy toxicities ≤ Grade 1. Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤Grade 2 neuropathy may be eligible. Patients with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible
14. Willingness to provide pre- and post-treatment fresh tumor biopsies (Monotherapy Arm 1 Only)
15. Capable of understanding and complying with protocol requirements
16. 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. Developed clinically significant adverse reaction to PD-1 or PD-L1 therapy, including immune-related adverse reactions, that led to discontinuation of treatment
2. Prior treatment with other investigational immune-oncology therapies
3. Systemic therapy with immunosuppressive agents within 7 days before the start of CTX-471 treatment. Topical, intranasal, intraocular, or inhaled corticosteroids and physiologic replacement for patients with adrenal insufficiency are allowed.
4. Patient is a pregnant or lactating WCBP
5. Prior solid organ transplantation
6. Active hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection or a positive serological test at Screening within 28 days of dosing with CTX-471
    a. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization.

       Note: Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

b. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

   Note: Participants must have completed curative anti-viral therapy at least 4 weeks prior to randomization.

c. HIV infected participants must be on anti-retroviral therapy (ART) and have a well-controlled HIV infection/disease defined as:

   - Participants on ART must have a CD4+ T-cell count >350 cells/mm3 at time of screening
   - Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 copies/mL or the lower limit of qualification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening
   - Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks prior to study entry (Day 1)

7. Active autoimmune disease or medical conditions requiring chronic steroid (ie, > 10 mg/day prednisone or equivalent) or immunosuppressive therapy. Patients with a prior history of autoimmune disease may be eligible following discussion with the Medical Monitor.
8. History of central nervous system metastases (Monotherapy Arm 1 Only)
9. History of seizure disorders
10. Congestive heart failure (> New York Heart Association Class II), active coronary artery disease, unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or clinically significant cardiac arrhythmias
11. Other systemic conditions or organ abnormalities that in the opinion of the Investigator may interfere with the conduct and/or interpretation of the current study

For Combination Arm 2, the following additional criteria will exclude participation:

12. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (could consider shorter interval for kinase inhibitors or other short half-life drugs) prior to treatment. Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy may be eligible. Participants with endocrine-related AEs Grade ≤ 2 requiring treatment or hormone replacement may be eligible.

    Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.

13. Has received prior radiotherapy within 2 weeks of start of study treatment or have had a history of radiation pneumonitis.

Note: Participants must have recovered from all radiation-related toxicities and not require corticosteroids. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

14. Has had an allogeneic tissue transplant.
15. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccines are allowed.
16. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of bladder, that have undergone potentially curative therapy are not excluded.

17. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
18. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
19. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
20. Has an active infection requiring systemic therapy.
21. Has a history or current evidence of any condition, therapy, or laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
22. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
23. Has received radiation therapy to the lung that is > 30Gy within 6 months of the first dose of trial treatment.

# 6. STUDY PROCEDURES AND ASSESSMENTS

Time points for assessments to be collected throughout the study can be found in the Schedule of Assessments (Table 1 or Table 2). A brief description of each assessment can be found below.

## 6.1. Screening and Treatment Procedures and Assessments

### 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 the Screening period.

### 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, cancer history, and prior anticancer treatment history, including prior treatment with PD-1 and/or PD-L1 inhibitors.

### 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 safety follow-up. For Combination Arm 2, all concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study intervention should be recorded.

### 6.1.5. Physical Exam and Vital Signs

A full physical examination (PE), symptom-directed PE, and vital signs check will be performed at the time points specified in the Schedule of Assessments (Table 1 or Table 2). 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, and weight. Vital signs will include temperature, blood pressure (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.

While the patient is on study treatment, PE will be symptom-directed and will include vital signs. Any new clinically significant abnormality from baseline should be recorded as an AE.

### 6.1.6. Ophthalmologic Exam

A standard ophthalmologic exam (Rupp 2018) will be performed at Screening and will include visual acuity, refraction, pupil function, extraocular motility and alignment, intraocular pressure, visual fields, external examination, slit-lamp examination, and fundoscopic examination.

While the patient is on study treatment, ophthalmologic exams may be performed as clinically indicated.

### 6.1.7. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be performed at the time points specified in the Schedule of Assessments (Table 1 or Table 2). Refer to Appendix 1 for a sample of the ECOG assessment.

### 6.1.8. Electrocardiogram

At Screening, a standard 12-lead electrocardiogram (ECG) will be conducted following an approximate 10-minute rest period in all patients and will be interpreted by the Investigator to confirm eligibility.

ECGs will be conducted following an approximate 10-minute rest period and obtained within approximately a 5-minute time period at the time points as outlined in Table 1 or Table 2.

### 6.1.9. Clinical Laboratory Tests

The following laboratory parameters will be measured at Screening and at the time points specified in the Schedule of Assessments (Table 1 or Table 2) and will be analyzed locally:

- A negative serum pregnancy test at Screening within 7 days of dosing with CTX-471 for Monotherapy Arm 1, and within 72 hours of dosing with CTX-471 and pembrolizumab for Combination Arm 2.
- Urine pregnancy testing for all WCBP approximately every 4 weeks (Monotherapy Arm 1) or 6 weeks (Combination Arm 2) during treatment
- Thyroid stimulating hormone (TSH) testing
- Hematology laboratory parameters include red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count, mean corpuscular volume (MCV) and white blood cell differential
- Blood chemistry laboratory parameters include blood urea nitrogen, creatinine, C-reactive protein, glucose, AST, ALT, alkaline phosphatase, bilirubin (total and direct), electrolytes (sodium, chloride, bicarbonate, potassium), amylase, lipase, albumin, magnesium, calcium, and phosphorus
- Coagulation laboratory parameters include prothrombin time, partial thromboplastin time, and international normalized ratio
- Complete urinalysis (during treatment, not at Screening)
- HIV assessment (Screening only)
  *Note: Patients with active HIV are not eligible for study participation and positive testing will meet exclusion criteria.*
- Hepatitis serologies (Screening only)
  - Anti-hepatitis C antibody (anti-HCV); hepatitis B surface antigen (HbsAg) and hepatitis B core antibody (HbcAb)

*Note: Patients with active HBV or HCV are not eligible for study participation and positive testing will meet exclusion criteria.*

Unscheduled assessments should be performed as clinically indicated.

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

Clinical laboratory assessments should be performed prior to CTX-471/pembrolizumab infusion when applicable. At W1D1 only, clinical laboratories collected for Screening within 7 days of first CTX-471/pembrolizumab dose may be used as W1D1 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 at Screening (within 4 weeks prior to first dose) and during the study as outlined in Table 1 or Table 2 and Appendix 4. Unscheduled imaging is permitted if clinically indicated. Ongoing tumor evaluations will be performed every 8 weeks from W1D1 (± 5d) until disease progression or the start of subsequent new anticancer therapy including in patients who discontinue treatment for reasons other than disease progression. Historical disease assessment scans (i.e. scans performed prior to screening) from up to 6 months prior to Screening may be requested, if available, for informational purposes.

Positron emission tomography (PET) imaging may be performed as adjunctive imaging.

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

Prior to treatment initiation, for all parts of the study, target and non-target lesions will be identified by the Investigator per RECIST 1.1 criteria (Appendix 4). During the course of the study, disease response and progression will be determined by Investigator assessment per RECIST 1.1 response criteria at the time points indicated in Table 1 or Table 2 and Appendix 4.

Of note, for patients who achieve a complete response/remission (CR) or partial response/remission (PR), at the discretion of the Investigator, 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 the schedule of events.

Disease assessment and response determination will be performed until disease progression, initiation of subsequent anti-cancer therapy, or study discontinuation.

Table 7, Table 8, and Appendix 4 show the criteria employed for lesion response assessment.

**Table 7: RECIST 1.1 Lesion Response Criteria**

| | |
|---|---|
| **Evaluation of Target Lesions** | |
| Complete Response (CR) | Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis |
| Partial Response (PR) | At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters |
| Progressive Disease (PD) | At least a 20% increase from the smallest value on study (including baseline, if that is the smallest). The sum of diameters must also demonstrate an absolute increase of at least 5 mm |
| Stable Disease (SD) | Neither sufficient shrinkage (compared to Baseline) to qualify for PR nor sufficient increase (taking as a reference the smallest sum of diameters while on study) to qualify for PD |
| **Evaluation of Non-Target Lesions** | |
| Complete Response (CR) | Disappearance of all extranodal non-target lesions, all lymph nodes must be non-pathological in size (< 10 mm in short axis), and normalization of tumor marker level |
| Non-CR/Non-PD | Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits |
| Progressive Disease (PD) | Unequivocal progression of existing non-target lesions |

Evaluation for target, non-target, and new lesions is to be considered together to assess an overall response status at a time point as detailed in Table 8. For CR or PR, confirmation of the response status at a subsequent time point at least 4 weeks apart from the initial observation is recommended. An independent evaluation may be performed at the Sponsor's discretion.

**Table 8: Evaluation of Overall Response by RECIST 1.1**

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/Non-PD | No | PR |
| CR | NE | No | PR |
| PR | Non-PD or NE | No | PR |
| SD | Non-PD or NE | 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/remission; NE = not evaluable; PD = progression of disease; PR = partial response/remission, SD = stable disease

### 6.1.11. Tumor Biopsy (Monotherapy Arm 1 Only)

A fresh tumor biopsy should be obtained during Screening (within 7 days prior to the first CTX-471 dose) and during the study as outlined in Table 1, unless a biopsy is not medically feasible per the discretion of the Investigator. See the CTX-471-001 Laboratory Manual for specific instructions on fixation and processing of tumor tissue. Tumor biopsies should be at least two passes of core, incisional, or excisional biopsies, not fine needle aspirates.

Collection of samples will cease as of protocol Amendment 7.

### 6.1.12. CTX-471 and Pembrolizumab Administration

Detailed instructions on the administration of CTX-471 can be found in Section 7.

### 6.1.13. Pharmacokinetic Sampling

PK sample collection will be performed in Part 1 of both treatment arms. Days of collection are shown in Table 1 or Table 2. Time of collection is shown in Table 9.

**Table 9: PK Time Points**

| Cycle | Week | Day | Timepoint |
|---|---|---|---|
| 1 | 1 | 1 | Predose |
| | | | 1-hour post-infusion |
| | | | 6 hours post-infusion |
| | | 2 | 24 hours post-infusion |
| | 2 | 1 | ~168 hours post-infusion C1D1 infusion |
| | 3 | 1 | Predose |
| 3 | 13 | 1 | Predose |

The date and time of each sample collection and the date and time of the prior CTX-471 and/or pembrolizumab dose must be recorded for all collected samples.

An additional PK sample, beyond those listed in Table 1 or Table 2 and Table 9 may be requested (when feasible) at the time of any unusual safety event (i.e., an AE different in type and severity from that expected in the setting of CTX-471 use).

For Combination Arm 2, Part 2, sparse PK will be collected. Collection timepoints

| Cycle | Week | Day | Timepoint |
|---|---|---|---|
| 1 | 1 | 1 | Predose |
| | | | 1-hour post-infusion |
| 2 | 7 | 1 | Predose |
| 3 | 13 | 1 | Predose |

Refer to the CTX-471-001 Laboratory Manual for details on processing, storage, and shipment of PK samples.

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### 6.1.14. Immunogenicity Sampling and Assessments

As shown in Table 1 or Table 2, blood samples for immunogenicity assessments will be collected from all patients at multiple time points for analysis of ADA.

Refer to the CTX-471-001 Laboratory Manual for immunogenicity sample handling procedures and shipping requirements.

### 6.1.15. Pharmacodynamic/Biomarker Sampling and Assessments (Monotherapy Arm 1 Only)

Samples will be collected for biomarker analysis focused on evaluating target engagement, biological effects, and predictive biomarkers for CTX-471. Collection of these assessments is outlined in Table 1.

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-471 and CD137 pathways or to cancer biology in general. Collection of samples will cease as of protocol Amendment 7.

Refer to the CTX-471-001 Laboratory Manual for biomarker sample handling procedures.

### 6.1.16. Adverse Events

Non-serious AEs should be captured on the eCRF from the time of signing of ICF through the Safety Follow-Up Visit. AEs considered at least possibly related to CTX-471 and/or pembrolizumab should be followed until resolution, return to baseline, or deemed chronic or stable.

All serious adverse events (SAEs) will be immediately reported to the Sponsor from the time of signing the ICF through the Safety Follow-Up Visit or until the patient has been deemed to be a screen failure. After completion of the AE reporting period (ie, Safety Follow-Up Visit), only SAEs attributed to CTX-471 must be reported to the Sponsor.

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

## 6.2. Safety Follow-Up Visit

All patients will have a Safety Follow-Up Visit at 60 (± 5) days after discontinuation of study treatment, unless the patient withdraws from the study prematurely (Section 4.10). Ongoing AEs considered at least possibly related to CTX-471 and/or pembrolizumab treatment should be followed until resolution, return to baseline or 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 60-day 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, then all assessments should be performed. If the visit is done by phone, only AEs and concomitant medications will be collected.

## 6.3. Survival Follow-Up

Survival Follow-Up assessments following EOT (last dose of CTX-471) will be collected every 3 months (± 1 week). These assessments may be conducted by telephone interview. Information on the initiation of other anticancer therapy (including start date, therapy type/name, and

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response on treatment) may be collected. Additional Survival Follow-Up calls may occur periodically if needed for data analysis.

## 6.4. Concomitant Medications

### 6.4.1. Prohibited: Other Anticancer Therapy or Investigational Agents

During the study treatment period, any additional anticancer therapy or other investigational agents are prohibited, including chemotherapy, radiation, targeted therapy, cell-based therapy, and immunotherapy. Localized palliative radiotherapy **is allowed** while on study. Corticosteroids used as an anticancer therapy are not permitted. However, topical, intranasal, or inhaled corticosteroids and physiologic replacement for patients with adrenal insufficiency (ie, > 10 mg/day prednisone or equivalent) or used to treat AEs are allowed.

### 6.4.2. Other Concomitant Therapies

Any other medication that is considered necessary for the patient's welfare, including antimicrobial prophylaxis, biologically derived therapies (eg, insulin), and supportive care (eg, antiemetics, analgesics, megestrol acetate for anorexia), and that is not expected to interfere with the evaluation of CTX-471 and/or pembrolizumab may be given at the discretion of the Investigator. Immune suppression agents, such as anti-TNFα and anti-interleukin-6, are prohibited. In cases involving concomitant therapies whose predicted interference with CTX-471 and/or pembrolizumab is unknown to the Investigator, the Sponsor should be contacted for discussion.

### 6.4.3. Concomitant Therapy for Combination Arm 2

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study intervention or vaccination may be required. The investigator is to discuss prohibited medication/vaccination with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live or live attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Note: Killed vaccines are allowed.

Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat COPD exacerbations (only short-term oral or IV use in doses >10mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
  - Other glucocorticoid use except when used for the following purposes:
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

Note: Inhaled steroids are allowed for management of asthma.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study treatment of CTX-471 and/or pembrolizumab must be discontinued.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs are to be recorded. SAEs are defined in Section 8.1.2.

#### 6.4.3.1. Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.1.6 and 7.2.4.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 11 for guidelines regarding dose modification and supportive care.

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

### 6.4.4. Contraception and Pregnancy

The effects of CTX-471 on conception, pregnancy, and lactation are unknown. CTX-471 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

At Screening, all female patients who are not surgically sterile or postmenopausal must agree to use at least 2 medically acceptable methods of birth control (defined as the use of an IUD, a barrier method with spermicide, condoms, any form of hormonal contraceptives, or abstinence) for the duration of the study and for 4 months after the last dose of CTX-471 and/or pembrolizumab.

At Screening, all male patients who are not sterile (biologically or surgically) must commit to the use of a reliable method of birth control (condoms with spermicide) for the duration of the study and for 4 months after the last dose of CTX-471 and/or pembrolizumab. Male patients should not donate sperm for 4 months following the last dose of CTX-471 and/or pembrolizumab.

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# 7. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

## 7.1. CTX-471

### 7.1.1. Description of CTX-471

CTX-471 is supplied as a clear and colorless to pale yellow, occasionally containing visible particles, sterile, aqueous solution in a 5 mL single-use glass vial containing 4.4 mL of 10 mg/mL solution (4 mL extractable volume). In addition to CTX-471, the solution contains 20 mM L-Histidine, 100 mM sodium chloride, 10% sucrose, 0.03% polysorbate 80, and has a pH of 6.0.

Additional information is provided in the CTX-471-001 Pharmacy Manual.

### 7.1.2. Dosage and Administration of CTX-471

CTX-471 is diluted in 500 mL of normal saline and administered as an IV infusion supplied by the Sponsor at the dose specified per dose escalation level for Part 1 (Table 3) or as 0.3 mg/kg or 0.6 mg/kg for Part 2. Patients participating in Part 1 when Part 2 of the study initiates may be allowed to dose adjust to the dose selected for Part 2, as applicable.

See Section 7.1.6 for dose modification guidance for the management of AEs.

CTX-471 infusion should be administered over 1 hour (± 5 minutes) under the supervision of a physician, or other medically qualified study personnel, experienced in the use of IV agents. In cases where a temporary interruption is required, the total infusion should be completed within 24 hours of thawing the drug product. See Section 7.1.6.1 for detailed guidance regarding infusion administration interruptions due to infusion reactions. Please refer to the CTX-471-001 Pharmacy Manual for detailed administration instructions.

For patients receiving both CTX-471 and pembrolizumab, pembrolizumab will be administered first.

During the DLT evaluation period, patients will be observed for 6 hours (Monotherapy Arm 1) or 1 hour (Combination Arm 2) post completion of CTX-471 and/or pembrolizumab infusion. After the DLT evaluation period, patients will be observed for 1 hour post completion of CTX-471 and/or pembrolizumab infusion. For the Monotherapy Arm 1, patients may be admitted to the study center overnight on W1D1 and W9D1 at the discretion of the Investigator to facilitate 24-hour assessments on W1D2 and W9D2. For the Combination Arm 2, patients may be admitted to the study center overnight on W1D1 at the discretion of the Investigator to facilitate 24-hour assessments on W1D2.

### 7.1.3. Pre-Infusion Medications

The following pre-medications may be administered approximately 1 hour prior to CTX-471 infusion at the discretion of the Investigator:

- Antipyretics (oral acetaminophen 650 to 1000 mg)
- Antihistamine (oral or IV diphenhydramine 25 to 50 mg or equivalent).

### 7.1.4. Post-Infusion Medications

No specific post-infusion medications are required for CTX-471 but may be administered at the discretion of the Investigator.

### 7.1.5. Storage

CTX-471 is supplied in vials for single use. CTX-471 is to be stored at -20°C and protected from light in a temperature-monitored, locked freezer.

### 7.1.6. CTX-471 Dose Holds and Modifications

Patients will be monitored continuously for AEs while on study treatment. AE severity will be assessed using the NCI-CTCAE version 5.0 or higher (Appendix 3). Guidance regarding CTX-471 dose holds and reductions for AEs related to CTX-471 (ie, assessed as unrelated to disease, intercurrent illness, or concomitant medications) is described in Table 10.

**Table 10: Dose Modifications**

| CTX-471 Toxicities [a, b] | Dose Interruption/Hold/Modification/Recommendation |
|---|---|
| **Gr 1 or 2 (except Gr 2 immune-related AEs)** | No dose modification |
| **Nonhematologic:**<br>Gr 2 or higher immune-related AE [c]<br>*Or*<br>Gr 3 other non-hematologic AE | **First occurrence:**<br>Withhold until return to ≤ Gr 1 or baseline level; re-challenge therapy at original dose level<br><br>**Second occurrence of the same AE:**<br>Withhold until return to ≤ Gr 1 or baseline level; reinitiate therapy at 1 dose level lower from current dose [d]<br><br>**Third occurrence of the same AE:**<br>Discontinue patient from CTX-471 |
| **Hematologic:**<br>Gr 3 or higher febrile neutropenia<br>*Or*<br>Gr 3 or higher thrombocytopenia with Gr 2 or higher hemorrhage<br>*Or*<br>Gr 4 hematologic AE | |
| **Gr 3 pneumonitis and transaminitis or**<br>**Gr 4 non-hematologic AEs [e]** | |

AE = adverse event; Gr = CTCAE Grade

[a] CTX-471-related toxicity = possible, probable, or definite relationship to CTX-471

[b] Toxicity grades are defined per CTCAE Version 5.0 (Appendix 3).

[c] Potential immune-related AEs include pneumonitis, colitis, hepatitis, transaminitis, endocrinopathies, vitiligo, hypophysitis, thyroiditis and nephritis/renal dysfunction. For any suspected immune-related AEs, ensure adequate evaluation to confirm etiology or exclude other causes. For endocrinopathies, administer replacement therapy. For other immune-related events administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent); upon improvement to ≤ Gr 1, initiate corticosteroid taper.

[d] Refer to Table 3 for CTX-471 dose levels.

[e] Includes all Grade 4 AEs, both immune-related and non-immune related.

Patients requiring treatment interruption should be re-evaluated at least weekly until the toxicity improves to ≤ Grade 1 or returns to Baseline level.

For Part 1, dose reductions to previously evaluated dose levels are permitted.

Dose holds lasting longer than 1 week past a scheduled dosing date will result in a "missed dose". If an AE results in a missed CTX-471 dose, the timing of the next CTX-471 administration will remain on the schedule determined by the patient's first dose of CTX-471 on W1D1.

CTX-471 may be withheld for up to 28 days for toxicity. Doses withheld for > 28 days due to treatment-related toxicity will result in permanent study treatment discontinuation unless reinitiating CTX-471 is approved by the Medical Monitor after discussion with the Investigator. Any patient who requires a dose reduction below 0.1 mg/kg due to treatment-related toxicities will be permanently discontinued from study treatment.

#### 7.1.6.1. Infusion-Related Reactions

In the event that an infusion reaction occurs during CTX-471 administration, the following treatment recommendations are provided and may be modified based on local treatment standards and guidelines as appropriate.

- Grade 1 (mild): Infusion rate modification not indicated. Administer symptomatic treatment (e.g., antihistamines, antipyretics, antiemetics) as needed. Closely monitor patient until resolution. Prophylaxis with diphenhydramine 25 to 50 mg (or equivalent) and/or acetaminophen 650 to 1000 mg is recommended approximately 1 hour prior to future CTX-471 infusions.
- Grade 2 (moderate): Slow infusion to 50% of the original infusion rate and treat symptoms with appropriate medical therapy, including, but is not limited to, antihistamines, antipyretics, and analgesics. Increase monitoring of vital signs as medically indicated until patient is deemed stable. Prophylaxis with diphenhydramine 25 to 50 mg (or equivalent) and/or acetaminophen 650 to 1000 mg is recommended approximately 1 hour prior to future CTX-471 infusions.
- Grade 3 (severe): Stop infusion and institute appropriate symptom-directed therapy, including, but not limited to, antihistamines, antipyretics, corticosteroids, bronchodilators, and oxygen. Increase monitoring of vital signs as medically indicated until patient is deemed stable. The remainder of the infusion should not be administered, resulting in a reduced dose. Prophylaxis with diphenhydramine 25 to 50 mg (or equivalent) and/or acetaminophen 650 to 1000 mg is required approximately 1 hour prior to future CTX-471 infusions. The next infusion should initiate at a rate of 2 hours per dose (± 5 minutes), or 50% of the rate at which the reaction occurred. If no infusion-related reactions are observed within the first 30 minutes, the infusion rate may increase to the original 1 hour per dose rate as outlined in Section 7.1.2. Permanently discontinue CTX-471 upon a second occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Stop infusion and immediately institute appropriate symptom-directed therapy and supportive measures as necessary, including, but not limited to, corticosteroids, bronchodilators, oxygen/respiratory support, and vasopressors.

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Hospitalization and/or ICU admission may be indicated. Permanently discontinue treatment.

## 7.2. Pembrolizumab

### 7.2.1. Description of Pembrolizumab

Pembrolizumab is supplied as a clear to slightly opalescent, colorless to slightly yellow solution in a single use vial. The Sponsor will be responsible for all costs associated with pembrolizumab infusions, including the drug itself.

Additional information is provided in the CTX-471-001 Pharmacy Manual.

### 7.2.2. Dosage and Administration of Pembrolizumab

Pembrolizumab to be administered prior to CTX-471.

Pembrolizumab will be administered as a dose of 400 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

See Section 7.2.4 for dose modification guidance for the management of AEs.

### 7.2.3. Storage

Pembrolizumab is to be stored in refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.

#### 7.2.3.1. Storage of Diluted Pembrolizumab Solution

The product does not contain a preservative. Store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

### 7.2.4. Pembrolizumab Dose Holds and Modifications

AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds may represent an immune-related response. These immune related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce

complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 11.

*Attribution of Toxicity:*

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to CTX-471 alone, or to pembrolizumab alone, for adverse events listed in Table 11, both interventions must be held according to the criteria in [Table 11 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with pembrolizumab].

*Holding Study Interventions:*

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

*Restarting Study Interventions:*

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 11.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

If the toxicities do resolve and conditions are aligned with what is defined in Table 11, CTX-471 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to CTX-471 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

**Table 11 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

| **irAEs** | Toxicity grade (CTCAE V5.0) | Action with pembrolizumab | Corticosteroid and/or other therapies | Monitoring and follow-up |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper<br>Add prophylactic antibiotics for opportunistic infections | Monitor participants for signs and symptoms of pneumonitis<br>Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment |
| | Recurrent Grade 2, Grade 3 or 4 | Permanently discontinue | | |
| Diarrhea / Colitis | Grade 2 or 3 | Withhold | Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie. Peritoneal signs and ileus)<br>Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis<br>Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | |

| | | | | |
|---|---|---|---|---|
| AST or ALT elevation or Increased Bilirubin | Grade 2 [a] | Withhold | Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper | Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable) |
| | Grade 3 [b] or 4 [c] | Permanently discontinue | Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | |
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | New onset T1DM<br>or<br>Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold [d] | Initiate insulin replacement therapy for participants with T1DM<br>Administer antihyperglycemic in participants with hyperglycemia | Monitor participants for hyperglycemia or other signs and symptoms of diabetes |
| Hypophysitis | Grade 2 | Withhold | Administer corticosteroids and initiate hormonal replacements as clinically indicated | Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hyperthyroidism | Grade 2 | Continue | Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate | Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hypothyroidism | Grade 2 | Continue | Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care | Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold until clinically stable or permanently discontinue | | |

| | | | | |
|---|---|---|---|---|
| Nephritis: grading according to increased creatinine or acute kidney injury | Grade 2 | Withhold | Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper | Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Neurological Toxicities | Grade 2 | Withhold | Based on severity of AE administer corticosteroids | Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1) | Withhold | Based on severity of AE administer corticosteroids | Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 2, 3 or 4 | Permanently discontinue | | |
| Exfoliative Dermatologic Conditions | Suspected SJS, TEN, or DRESS | Withhold | Based on severity of AE administer corticosteroids | Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue | | |
| All Other irAEs | Persistent Grade 2 | Withhold | Based on severity of AE administer corticosteroids | Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the event [e] | | |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | |

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=73mmune-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

**Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.**

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. Vasculitis and sclerosing cholangitis).

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#### 7.2.4.1. Infusion-Related Reactions Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 12.

**Table 12: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines**

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction; infusion interruption not indicated; intervention not indicated | • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. | None |
| **Grade 2**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs. | • **Stop Infusion.**<br>• Additional appropriate medical therapy may include but is not limited to:<br>• IV fluids<br>• Antihistamines<br>• NSAIDs<br>• Acetaminophen<br>• Narcotics<br>• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment** | Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |

| | | |
|---|---|---|
| **Grades 3 or 4**<br><br>**Grade 3:**<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br>**Grade 4:**<br>Life-threatening; pressor or ventilator support indicated | • **Stop Infusion.**<br>• Additional appropriate medical therapy may include but is not limited to:<br>• Epinephrine**<br>• IV fluids<br>• Antihistamines<br>• NSAIDs<br>• Acetaminophen<br>• Narcotics<br>• Oxygen<br>• Pressors<br>• Corticosteroids<br>• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>• Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>Participant is permanently discontinued from further study drug treatment. | No subsequent dosing |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov. | | |

#### 7.2.4.2. Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 6 weeks or 42 days of the originally scheduled dose and within 84 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the patient's study record.

## 7.3. Drug Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of Investigational Product (IP, CTX-471 and/or pembrolizumab) received and comparing it with the accompanying drug order form. All unused IP will be retained at the site. After full drug accountability and reconciliation, the Investigator will dispose of any IP at the clinical trial site per site procedures, or if necessary, all IP will be returned to the Sponsor or its designee. Disposition of all IP should be documented, including any IP that is lost or damaged.

## 7.4. Assignment to Treatment

All patients will receive IP at a dose and regimen based on the study design (see Section 4). Once enrolled, each patient will be assigned a unique subject identification number. This number will be recorded on the patient's eCRF pages and used to identify the patient throughout the study. Once a subject number is assigned, it cannot be reassigned to any other patient. Patients will be assigned to a CTX-471 dose level based on the next available spot in the cohort(s)

currently being enrolled. In the Combination Arm 2, all patients will also receive pembrolizumab at no cost to the patient. Patients will be allocated to the different treatment doses in each arm in an alternating manner.

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# 8. 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 consider 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 considered related to the medicinal product.

AEs include worsening of a pre-existing medical condition as well as clinically significant changes from baseline laboratory values/conditions. Worsening of the 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.

### 8.1.2. Definition of Serious Adverse Event

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

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

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### 8.1.3. Combination Arm 2 Events of Clinical Interest (ECI)

For Combination Arm 2, selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor within 24 hours of awareness.

Events of clinical interest for this trial include:

1. An overdose of Sponsor's product, as defined in Section 8.2.1.4, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3 x the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2 x the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2 x the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

## 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 recorded in the eCRF from the time of signing the ICF through the Safety Follow-Up Visit after the last dose of CTX-471 and 90 days after the last dose of pembrolizumab (if applicable). An AE will be followed until it is either resolved, has returned to baseline, or is determined to be a stable or chronic condition. All SAEs occurring from the signing of ICF through the Safety Follow-Up Visit after the last dose of CTX-471 and/or pembrolizumab 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-471 and/or pembrolizumab
- Action taken with each CTX-471 and/or pembrolizumab 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).

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

#### 8.2.1.1. Relationship to CTX-471 and/or Pembrolizumab

The Investigator must assess whether the AE may be related to each CTX-471, pembrolizumab and/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-471 and/or pembrolizumab, 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-471 and/or pembrolizumab, 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-471 and/or pembrolizumab, there is a plausible mechanism for the event to be related to the study product and causes other than CTX-471 and/or pembrolizumab have been ruled out and/or the event re-appeared on re-exposure to CTX-471 and/or pembrolizumab.

#### 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 3). 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 8.1.2 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-471 and/or pembrolizumab
- 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-471 or Pembrolizumab

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

- Overdose: refers to the administration of a quantity of CTX-471 given per administration or cumulative, which is above the maximum dose according to the protocol.
  - For Combination Arm 2 of this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

    No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
- Medication error: refers to an unintentional error in dispensing or administration of CTX-471 or pembrolizumab not in accordance with the protocol
- Off-label use: relates to situations where CTX-471 or pembrolizumab is intentionally used for medical purpose not in accordance with the protocol
- Misuse: refers to situations where CTX-471 or pembrolizumab is intentionally and inappropriately used not in accordance with the protocol
- Abuse: corresponds to the persistent or sporadic, intentional excessive use of CTX-471 or pembrolizumab, which is accompanied by harmful physical or psychological effects
- Occupational exposure: refers to the exposure to CTX-471 or pembrolizumab 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-471 and/or pembrolizumab, from the time of signing ICF through the Safety Follow-Up Visit after the last dose of CTX-471 and/or pembrolizumab.

SAEs for Combination Arm 2 must be followed for 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier. All pregnancies and exposure during breastfeeding in Combination Arm 2 will be followed from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy

The initial SAE eCRF must be as complete as possible, including details of the current illness and SAE, and an assessment of the relationship between the event and CTX-471 and/or pembrolizumab 1. Additional information relating to a previously reported SAE must also be reported within 24 hours of the Investigator's first knowledge of information. The Investigator may also be asked, by the Sponsor or designee, to provide clarifications or additional information.

If the Investigator becomes aware of an SAE considered related to CTX-471 and/or pembrolizumab, occurring more than 60 (± 5) days after the last dose of CTX-471 and/or, the SAE must be reported as described above.

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

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

### 8.2.3. Pregnancy and In Utero Drug Exposure

CTX-471 has not been evaluated in pregnant or nursing women. Pembrolizumab may have adverse effects on a fetus in utero. Thus, pregnant women or WCBP who are not using effective

contraception are excluded from this study (see Section 6.4.4 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 the Safety Follow-Up Visit after the patient's last dose of CTX-471 and/or pembrolizumab. If a pregnancy occurs in a patient, CTX-471 and/or pembrolizumab 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 (ie, 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 (ie, 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-471 and/or pembrolizumab should also be reported to the Sponsor or designee.

For Combination Arm 2, all pregnancies and exposure during breastfeeding should be reported, from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy.

# 9. STATISTICAL METHODS

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

## 9.1. Sample Size

No formal hypothesis testing is planned. The number of patients in each part/cohort is based on safety and tolerability.

The anticipated enrollment for the study is approximately 96 patients in Monotherapy Arm 1, 78 patients in Combination Arm 2, for a total of approximately 174 patients.

Monotherapy Arm 1

Part 1 (Dose Escalation) will enroll approximately 36 patients using a 3+3 escalation without intra-patient dose escalation. Part 2 (Dose Expansion) will enroll approximately 60 patients to be apportioned equally across two dose levels: 0.3 mg/kg and 0.6 mg/kg. Assuming 2 different dose cohorts are enrolled in Part 2, with 30 patients in each cohort, if the true incidence rate for an AE/laboratory abnormality of interest is 20% or less, the probability of observing 8 or less such AEs is 87%.

Combination Arm 2

Part 1 (Dose Escalation) will enroll approximately 9-18 patients using a 3+3 dose escalation design without intra-patient dose escalation. Part 2 (Dose Expansion) will enroll approximately 60 patients to be apportioned equally across two CTX-471 dose levels cohorts (0.3 mg/kg and 0.6 mg/kg) in combination with pembrolizumab and across three tumor type subgroups. Assuming 2 different dose cohorts are enrolled in Part 2, with 30 patients in each Cohort, if the true incidence rate for an AE/lab abnormality of interest is 20% or less, the probability of observing 8 or less such AEs is 87%.

## 9.2. Analysis Sets

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

- **DLT-Evaluable Analysis Set:** all patients in Part 1 (Dose Escalation) who received at least 1 dose of CTX-471 and 1 dose of pembrolizumab (Combination Arm 2 Only) and either completed the DLT evaluation period or experienced a DLT during this period. This analysis set will be used to assess the tolerability of CTX-471 and pembrolizumab in the dose-escalation phase. Over the entire dose escalation phase, patients will be grouped based on the highest dose level each patient received.
- **All-Treated Analysis Set:** all patients who received any amount of CTX-471 and pembrolizumab (Combination Arm 2 Only) with treatment group based on the highest dose level received. This analysis set will be the primary analysis set for all safety endpoints, excluding DLT evaluation. This analysis set will also be used for analysis of efficacy endpoints for Combination Arm 2.

- **Response-Evaluable Analysis Set:** all patients with measurable disease at Baseline who received any amount of CTX-471 and pembrolizumab (Combination Arm 2 Only) and had 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. For Combination Arm 2, this will also include patients who discontinue treatment due to toxicity before having a post-baseline response assessment. This analysis set will be the primary analysis set for efficacy endpoints for Monotherapy Arm 1.
- **PK Analysis Set:** all enrolled patients who received at least 1 dose of CTX-471 and pembrolizumab (Combination Arm 1 Only) and have at least 1 post dose measurement of 1 analyte without protocol deviations or events affecting the validity of the PK results. This analysis set will be used for the analysis of PK parameters as further defined in the protocol. Pharmacokinetic-response correlations may be performed. The PK exposure-response analysis will include patients who have both valid PK and valid response data.
- **Pharmacodynamic Analysis Set:** all enrolled patients who received at least 1 dose of CTX-471 and pembrolizumab (Combination Arm 2 Only) and have at least 1 post dose pharmacodynamic or biomarker measurement. This analysis set will be used for the analysis of pharmacodynamic endpoints as further defined in the protocol.

## 9.3. Background Characteristics

### 9.3.1. Patient Disposition

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

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

### 9.3.2. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized by treatment group and cohort for the All-Treated Analysis Set: sex, race, age, type of cancer, tumor stage (tumor-node-metastases) at diagnosis and study entry, World Health Organization performance status, time elapsed since cancer diagnosis, and prior anti-cancer therapies. Additional parameters may be provided in the SAP.

## 9.4. Exposure and Compliance

The summary statistics of exposure will be tabulated by part, by cohort or by dose level, as appropriate. In the summary, the following will be included:

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

All variables are predefined:

- The cumulative number of days of exposure for each patient equals to the date of the last day of exposure minus the date of the first day of exposure plus 1.
- For the number of doses completed, if a patient has any record of starting administration number "X," the patient will be counted as completed administration X-1.
- The relative dose intensity is defined as the percentage of the planned treatments completed. It is the ratio of the cumulative actual dose (mg) and cumulative planned dose (mg) times 100. In this definition,
  - the cumulative actual dose (mg) is the sum of the actual doses (mg) that the patient receives during the study
  - the cumulative planned dose (mg) is the cumulative number of days of exposure times the planned dose level (mg)

All analyses within this section will be based on the All-Treated Set unless otherwise specified.

## 9.5. Efficacy Analyses

Response will be assessed according to RECIST 1.1 (Appendix 4) and will be reported with response category (CR, PR, SD or PD) counts.

For each scheduled efficacy assessment visit, the number and percentage of response will be tabulated by category for each dose level and cohort.

For each patient, the ORR is defined via the best overall response across all efficacy assessments. For each dose level and each cohort, the ORR will be summarized by response category determined by the Investigator. The Clopper-Pearson 95% confidence interval will also be included in the summaries for cohorts (and dose levels) in the dose expansion phase.

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

- DOR will be calculated for those patients with a CR, or PR from the time of first response (of CR or PR) to PD (or censoring).
- PFS will be assessed from time of first treatment to PD (or censoring) as determined by the Investigator, or death.
- OS will be assessed from time of first CTX-471 and/or pembrolizumab treatment to end of study (or censoring)

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

All efficacy analyses will be based on the Response Evaluation Analysis Set for Monotherapy Arm 1 unless otherwise specified. Efficacy analysis for Combination Arm 2 will be based on All-Treated Analysis Set.

## 9.6. Safety Analyses

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

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For Part 1 the number and type of DLTs experienced by patients will be summarized for each dose level, accompanied by a by-patient listing of DLT events. The listing will include the description, severity, and relationship of the events to CTX-471 and/or pembrolizumab (Combination Arm 2 only).

For Part 1 and Part 2, safety data, including vital signs, ECGs, laboratory test results, PEs, and AEs will be summarized by dose and assessment time points, as appropriate. Cumulative data from both parts will be separated by study arm, unless otherwise noted.

### 9.6.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher and will be graded according to the NCI-CTCAE version 5.0 or higher (Appendix 3).

Summaries of AEs will include TEAEs. A TEAE is an AE that emerges or worsens in the period from the first dose of study treatment to the Safety Follow-Up Visit after the last dose of CTX-471 and/or pembrolizumab.

For Part 1 and Part 2, AEs will be summarized by cohort and by dose within cohort if applicable.

TEAEs will be summarized by the frequency within MedDRA system organ class and PT. Separate tabulations will also be provided for TEAEs related to CTX-471 and/or pembrolizumab, TEAEs that led to treatment discontinuation, TEAEs that led to death, and TEAEs ≥ Grade 3 in severity. Treatment-emergent SAEs and SAEs related to CTX-471 and/or pembrolizumab will also be tabulated.

Detailed information of AEs will be included in a listing.

### 9.6.2. Clinical Laboratory Assessments

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

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

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

### 9.6.3. Immunogenicity

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those patients with at least 1 positive ADA at any timepoint will be provided by dose regimen. The frequency of subjects with at least 1 positive ADA assessment, and frequency of patients who develop ADA after a negative baseline assessment will be provided by dose. Once binding ADA binding has been identified, neutralizing antibodies will also be tested and presented by dose. To examine the potential relationship between

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immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

## 9.7. Pharmacokinetic Analyses

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

| | |
|---|---|
| $C_{max}$ | Maximum observed serum concentration |
| $t_{max}$ | Time of maximum observed serum concentration |
| $AUC_{0\text{-last}}$ | Area under the serum concentration-time curve from time zero to the last quantifiable time point |
| $AUC_{0\text{-INF}}$ | Area under the serum concentration-time curve from time zero extrapolated to infinity |
| $AUC_{0\text{-tau}}$ | Area under the serum concentration-time curve from time zero to the end of the dosing interval |
| $t_{1/2}$ | Terminal elimination half-life |

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

## 9.8. Pharmacodynamic 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 the PK/pharmacodynamic analysis plan.

# 10. STUDY ADMINISTRATION

## 10.1. Good Clinical Practice Statement

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

## 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 will obtain written, informed consent. The patient will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Following the discussion regarding the study, a patient will be asked if they are willing to sign and personally date a statement of informed consent. Only if the patient voluntarily agrees to sign the informed consent statement and has done so, may he/she enter the study. A copy of the signed and dated ICF will be provided to the patient. The signed ICF is to remain in the Investigator's file, per local requirements.

The ICF and any other written information provided to the patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or if there is an amendment to the protocol 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

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

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

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

## 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 visit the study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) (and other personnel involved with the study) their responsibilities 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 will continue to receive treatment until documented disease progression, unacceptable toxicity, withdrawal of consent, or other reasons as specified in Section 4.9. Patients may continue on study treatment beyond disease progression if they are deriving clinical benefit. 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 not receive additional treatment. Patients who continue treatment beyond disease progression will need to re-sign the ICF.

## 10.10. Records Retention

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, eCRFs, IP 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-471, or until 2 years after shipment and delivery of the IP 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.

Confidential



## 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.

Confidential



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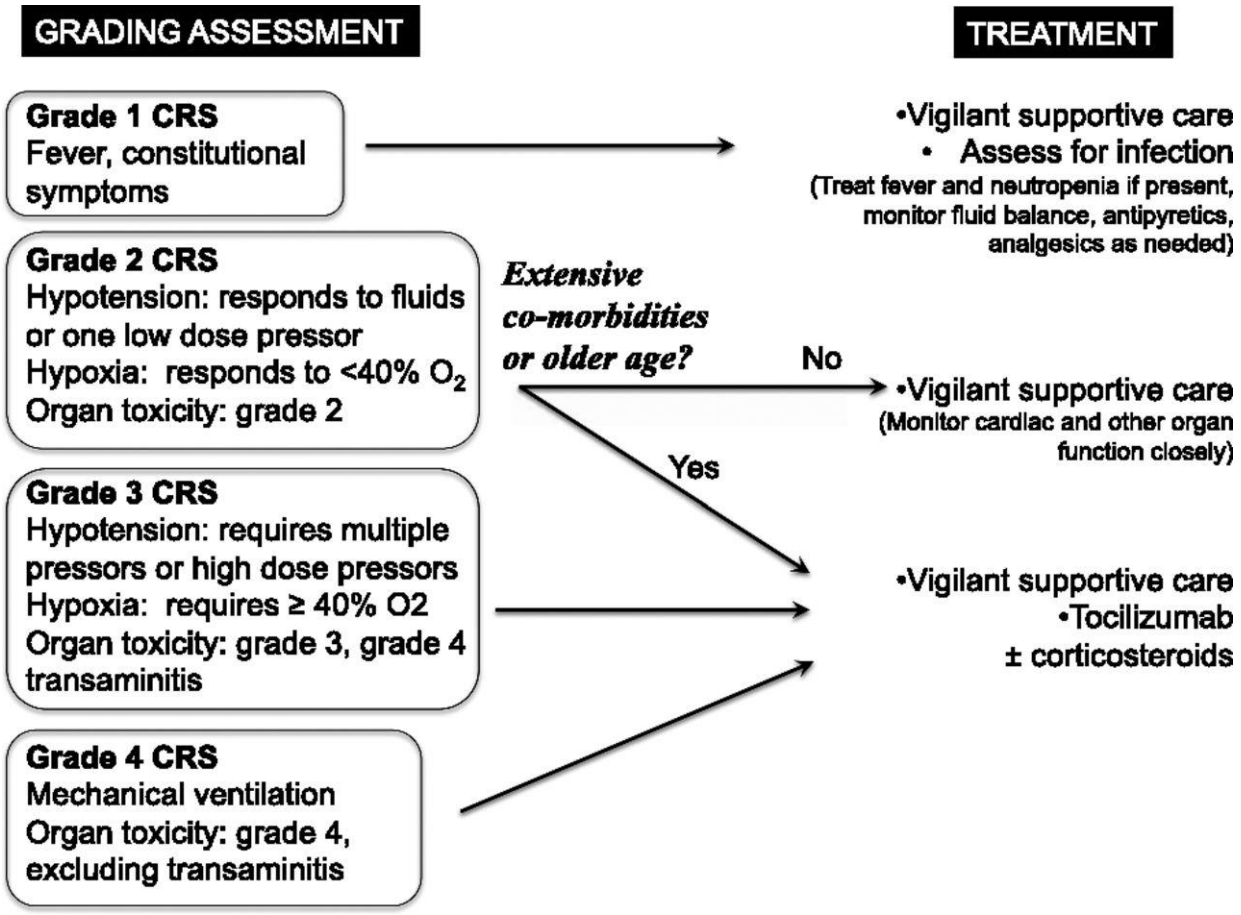
# 12. APPENDICES

# 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. TREATMENT ALGORITHM FOR CYTOKINE RELEASE SYNDROME




(Lee 2014)

# APPENDIX 3. 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 4. RECIST 1.1 RESPONSE CRITERIA

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

## 1.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective 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 objective 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 subjected 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 (i.e. ‘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 (i.e., 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 (i.e., 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.

Confidential



## 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.