A PHASE 1/2, FIRST-IN-HUMAN, TWO-PART, OPEN-LABEL CLINICAL TRIAL OF INTRAVENOUS ADMINISTRATION OF CTL-002 GIVEN AS MONOTHERAPY AND/OR IN COMBINATION WITH AN ANTI-PD-1 CHECKPOINT INHIBITOR IN SUBJECTS WITH ADVANCED-STAGE, RELAPSED/REFRACTORY SOLID TUMORS

Version 6.0 Global dated 21Dec2022

Protocol Number	CTL-002-001
Investigational Medicinal Product	CTL-002 (Visugromab)
EudraCT Number	2020-002103-19
Phase	1/2
Sponsor	CatalYm GmbH Am Klopferspitz 19 D-82152 Planegg-Martinsried Germany
Sponsor Contact	[redacted]
Medical Monitor/Study Physician	[redacted]

DOCUMENT APPROVAL

By signing this document, I attest that I have read and approve the Clinical Protocol **CTL-002-001** for **CTL-002**. This document has been prepared in accordance with the principles of Good Clinical Practice, as outlined by the International Council for Harmonisation and applicable regional regulations.

		Date / Signature:
[redacted]		

INTERNATIONAL COORDINATING INVESTIGATOR SIGNATURE PAGE

COORDINATING INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR'S AGREEMENT

- I have read the protocol **CTL-002-001** and agree to conduct the study as outlined. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Council for Harmonisation Guideline for Good Clinical Practice (GCP) E6 (R2) and the ethical principles that have their origins in the Declaration of Helsinki.
- I agree to assume responsibility for the proper conduct of the study at this site and I will ensure that all persons assisting in the study under my supervision are adequately informed about the protocol/amendments, the investigational product and their study related duties and functions as described in the protocol.
- I will not implement any deviation from, or changes to the protocol without agreement from the Sponsor and prior submission to and written approval from (where required) the responsible regulatory authorities and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) of an amendment, except when necessary to eliminate an immediate hazard to the study subjects.
- I understand that the study may be terminated, or enrolment may be suspended at any time by the Sponsor, with or without cause, or by myself if it becomes necessary to protect the best interest of the study subjects.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

SYNOPSIS

Name of Sponsor/Company: CatalYm GmbH

Name of Investigational Product: CTL-002 (Visugromab)

Title of Study:

A Phase 1/2, first-in-human, two-part, open-label clinical trial of intravenous administration of CTL-002 given as monotherapy and/or in combination with an anti-PD-1 checkpoint inhibitor in subjects with advanced-stage, relapsed/refractory solid tumors

Short Title of Study:

Phase 1/2 FIH clinical trial of CTL-002 in subjects with advanced-stage, relapsed/refractory solid tumors

Trial Sites:

Part A (Phase 1) of the study will be conducted in up to 7 trial sites in Europe (2-3 sites in Spain, 2-3 sites in Germany, and 1 site in Switzerland).

For Part B (Phase 2a) of the study, additional countries and/or sites will be added to achieve up to 22 trial sites (in Europe: 6-7 sites in Spain, 2-3 sites in Germany, 3 sites in Switzerland, 4-5 sites in Italy, 1-2 sites in UK; in the USA: 1-2 sites).

PART A (Phase 1; dose escalation):

OBJECTIVES:

Primary Objective:

- To determine the safety and tolerability of intravenous (IV) administration of CTL-002 as monotherapy and in combination with an anti-programmed death 1 (PD-1) checkpoint inhibitor in subjects with advanced-stage solid tumors that relapsed post or were refractory to a prior anti-PD-1/programmed death ligand 1 (PD-L1) therapy.

Secondary Objectives:

- To explore the pharmacokinetics (PK) of CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor.
- To explore the pharmacodynamics of CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor.
- To determine the recommended dose(s) for the expansion cohorts (Part B [expansion]) of CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor.
- To explore the preliminary anti-tumor activity of CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor.
- To explore the effect of CTL-002 on prevention of anorexia and muscle wasting (cachexia).

Exploratory Objective:

- To explore additional pharmacodynamics in peripheral blood and tumor tissue (e.g., growth differentiation factor 15 [GDF-15] levels, immune cell phenotypes, and activation status), with CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor.

ENDPOINTS:

Primary Endpoints:

- Evaluation of the number of subjects with adverse events (AEs), including serious adverse events (SAEs), clinical laboratory data, vital signs, electrocardiograms (ECGs), physical examination (including neurological assessment) and Eastern Cooperative Oncology Group (ECOG) performance status.
- Determination of dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) in Part A of the study using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Secondary Endpoints:

- Evaluation of PK parameters of CTL-002 (e.g., maximum concentration [C_{max}], area under the curve [AUC], and half-life [$t_{1/2}$]).
- Evaluation of treatment-emergent cytokine and chemokine profiles in peripheral blood.
- Evaluation of treatment-induced anti-drug antibodies (ADA).
- Evaluation of the clinical efficacy according to Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 of CTL-002 as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor by assessment of:
    - The proportion of subjects with tumor shrinkage, a confirmed partial response (PR) and/or complete response (CR), and overall response rate (ORR).
    - The interval between the date of first CTL-002 administration and first documented evidence of a PR or CR (time to response [TTR]).
    - The interval between the date of first documented evidence of PR or CR, until first documented evidence of disease progression or death, due to any cause (duration of response [DOR]).
    - The interval between the date of first CTL-002 administration and the earliest date of disease progression or death (progression free survival [PFS]).
    - The interval between the date of first CTL-002 administration and date of death due to any cause (overall survival [OS]).
- To assess appetite, body mass index (BMI), and muscle mass (e.g., L3 skeletal muscle index [L3SMI]).

Exploratory Endpoints:

- Evaluation of GDF-15 serum levels and their correlation with pharmacodynamic and clinical response.
- Immune cell phenotyping including activation status and immune cell infiltration pattern in tumor tissue.
- Molecular profiling (e.g., transcriptional profiling, mutational status, mutational burden of tumor tissue).
- To assess anti-tumor efficacy (PR, CR, DOR, PFS, and OS) of CTL-002 in combination with an anti-PD-1 checkpoint inhibitor using modified RECIST for immune-based therapeutics (iRECIST; (Seymour et al., 2017) criteria in solid tumors in subjects with advanced-stage solid tumors that relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy.

PART B (Phase 2a; expansion):

OBJECTIVES:

Primary Objectives:

- To explore the preliminary anti-tumor activity of CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor in subjects with advanced-stage relapsed/refractory solid tumors in non-curable state as per current clinical knowledge that have either

(1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound, or

(2) colorectal cancer (micro-satellite stable [MSS]/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy, or

(3) biomarker cohort with mixed solid tumors ("basket" cohort) that are relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound that have exhausted existing treatment options or are not eligible for them anymore.

- To confirm the safety and tolerability of CTL-002 administered as an IV infusion, in combination with an anti-PD-1 checkpoint inhibitor.

Secondary Objectives:

- To confirm and further explore the PK/pharmacodynamics of CTL-002 given in combination with an anti-PD-1 checkpoint inhibitor.
- To confirm the recommended Phase 2 dose (RP2D) of CTL-002.

Exploratory Objectives:

- To assess the antitumoral activity of CTL-002 in combination with cemiplimab (checkpoint inhibitor) using World Health Organization (WHO) bidimensional measurements in subjects with advanced-stage cutaneous squamous cell carcinoma that relapsed on or were primary refractory to a prior anti-PD-1/PD-L1 therapy.
- To explore the preliminary anti-tumor activity of CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor in patients with stable disease after receiving stereotactic radiotherapy.
- To explore additional pharmacodynamics in peripheral blood and tumor tissue (e.g., GDF-15 level, immune cell phenotypes, and activation status), with CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor in patients with stable disease after receiving stereotactic radiotherapy.

ENDPOINTS:

Primary Endpoints:

- Evaluation of the clinical efficacy according to RECIST V1.1 of CTL-002 in combination with an anti-PD-1 checkpoint inhibitor by assessment of:
  - The proportion of subjects with tumor shrinkage, a confirmed PR and/or CR, and ORR.
  - The interval between the date of first CTL-002 administration and first documented evidence of a PR or CR (TTR).
  - The interval between the date of first documented evidence of PR or CR, until first documented evidence of disease progression or death, due to any cause (DOR).
  - The interval between the date of first CTL-002 administration and the earliest date of disease progression or death (PFS).
  - The interval between the date of first CTL-002 administration and date of death due to any cause (OS).
- Evaluation of the number of subjects with AEs, including SAEs, clinical laboratory data, vital signs, ECGs, physical examination (including neurological assessment), and ECOG performance status.

Note: Protocol amendment post Clinical trial directive harmonization will adjust DoR definition to definition provided as in Am J Canc Res 2021;11(4)1121-31.

Secondary Endpoints:

- Evaluation of PK parameters of CTL-002 (e.g., C_{max}, AUC, and $t_{1/2}$).
- Evaluation of treatment-emergent cytokine and chemokine profiles in peripheral blood.
- Evaluation of treatment-induced ADA.
- Evaluation of GDF-15 serum levels and their correlation with pharmacodynamics and clinical response.

Exploratory Endpoints:

- In subjects that undergo tumor biopsy: Immune cell phenotyping including activation status and immune cell infiltration pattern in tumor tissue.
- In subjects that undergo tumor biopsy: Molecular profiling, (e.g., transcriptional profiling, sequencing of genes of interest, mutational status, mutational burden of tumor tissue) and evaluation of GDF-15 levels.
- To assess anti-tumor efficacy (PR, CR, DOR, PFS, and OS) of CTL-002 in combination with an anti-PD-1 checkpoint inhibitor using iRECIST criteria (Seymour et al., 2017), in solid tumors that relapsed on or were primary refractory to a prior anti-PD-1/PD-L1 therapy.
- To assess in subjects with advanced-stage cutaneous squamous cell carcinoma that relapsed on or were primary refractory to a prior anti-PD-1/PD-L1 therapy: the anti-tumor efficacy (PR, CR, DOR, PFS, and OS) of CTL-002 in combination with cemiplimab checkpoint inhibitor using WHO bidimensional measurements.
- The proportion of subjects with tumor shrinkage, a confirmed partial PR and/or CR, and ORR after receiving stereotactic radiotherapy according to RECIST V1.1 (ORR-2).
- The interval between application of stereotactic radiotherapy and first documented evidence of a PR or CR according to RECIST V1.1 (TTR-2).
- The interval between the date of first documented evidence of PR or CR after having received stereotactic radiotherapy, until first documented evidence of disease progression or death, due to any cause according to RECIST V1.1 (DOR-2).

INTRODUCTION

In recent years increasing evidence has emerged that GDF-15 does play a critical immuno-regulatory role in cancer, acting most likely mainly as “T cell repellant” and also local immuno-suppressant. A wealth of publications has emerged indicating that high GDF-15 serum levels in various cancer types correlate with shorter overall survival and that GDF-15 is an independent factor for subject survival within various tumor types (Wischhusen et al, 2020). Furthermore, GDF-15 has been linked to non-response to checkpoint inhibitors such as pembrolizumab and nivolumab. Preclinical and translational data by the sponsor and others do support these findings and have demonstrated induction of potent antitumoral response by checkpoint inhibitors if GDF-15 is suppressed (Haake et al. AACR2020; Abstract #5597; Hurt et al. ASCO 2021; Abstr. #1828; Wang et al. J Imm Canc 2021).

Therefore, clinical development of CTL-002 was initiated in Dec 2020 in combination with an anti-PD- 1 antibody. This Phase 1 study (CTL-002-001) demonstrated the safety and preliminary efficacy of CTL-002 in combination with nivolumab in subjects with last-line tumor disease (on average 4.4 prior lines of systemic treatment) and fully anti-PD-1/PD-L1 relapsed/refractory disease (Melero et al., 2022). At the higher dose levels a remarkable tumor regression rate of 23% (Dose Level [DL] 3-5 [3.0 – 20.0 mg/kg]) to 25% (DL4-5 [10.0 – 20.0 mg/kg]) was observed in this population. Several lasting, deep, confirmed partial remissions occurred. One additional subject showed progression in liver lesions and following stereotactic radiotherapy of one lesion showed a deep partial response with abscopal antitumor effects. Importantly, the safety profile observed for the combination was excellent, with no dose limiting toxicity (DLT) or Grade 4 or 5 treatment emergent adverse event observed throughout the complete observation period in Phase 1, making the combination of nivolumab and CTL-002 a very safe treatment combination. In addition, various biomarker analyses were conducted and indicated that (1) in last-line

disease PD-L1 expression by tumor cells and elevated tumor inflammation score could be predictive markers for treatment benefit by CTL-002 in combination with a checkpoint inhibitor and (2) that immunologically „cold“ tumors can be turned „hot“ by CTL-002 + nivolumab.

Therefore, Phase 2 development of CTL-002 in combination with checkpoint inhibitors has been initiated and is currently ongoing, evaluating various tumor types of interest (identified by a proprietary translational research program of the sponsor) and investigating if „cold“ tumors can be turned „hot“ and may respond then to treatment and if certain markers are predictive at baseline for treatment outcome.

For further information on the observed safety and antitumoral activity of visugromab please refer to the current Investigator's Brochure.

METHODOLOGY:

Overall Study Design:

This is a Phase 1/2a, multi-center, first-in-human (FIH), open-label study consisting of Part A (Phase 1; dose escalation) followed by Part B (Phase 2a; expansion).

Part A (Phase 1; dose escalation):

At least 24 subjects will receive, in "3+3" cohorts, escalating doses of CTL-002 IV given as monotherapy or in combination with an anti-PD-1 checkpoint inhibitor in subjects with advanced-stage solid tumors that relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy.

Note: Enrollment of subjects in Part A (Phase 1; dose escalation phase) of the study has been completed. No further patients will be treated in this part.

Part B (Phase 2a; expansion):

In Part B of the study, various cohorts with defined tumor indications as provided below will be enrolled.

Up to 249 subjects in different expansion cohorts will receive CTL-002 IV in combination with an anti-PD-1 checkpoint inhibitor. In the initial set of expansion cohorts, subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge and with the following indications will receive treatment with CTL-002 and the defined checkpoint inhibitor:

(1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma, or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound, or

(2) colorectal cancer (MSS/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy, or

(3) biomarker cohort with mixed solid tumors ("basket" cohort) that are relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound and that have exhausted existing treatment options or are not eligible for them anymore.

- For the **first group,** for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, N = 14 response-evaluable subjects will be initially recruited per each tumor indication. This shall allow to detect 2 responses in a cohort with 80% probability if the true response rate is 20% or more, and at least 1 response in the cohort with 77% probability if the true response rate is 10% or more. For cutaneous squamous-cell carcinoma, N = 12 response-evaluable subjects will be recruited initially. This should result in 2 responses or more with 80% probability if the true response rate is 25% or higher.

  For cutaneous squamous-cell carcinoma: Subjects must have locally advanced disease or metastatic disease. Subjects with cutaneous squamous-cell carcinoma with locally advanced disease must not be candidates for surgery for one or both of the following reasons: disease

recurrence after two or more surgical procedures and as per treating physician curative resection is unlikely or surgery would result in substantial complications or deformity.

- For the **second group** (colorectal cancer [MSS/mismatch-repair competent, a currently non-approved anti-PD-1/PD-L1 indication]), N = 10 response-evaluable subjects will be recruited. This shall allow to detect 1 response with 89% probability (if the true response rate is 20% or more), and 1 response with 80% probability if the true response rate is 15% or more.
- The **third group** (biomarker cohort with mixed solid tumors, "basket" cohort) investigated are subjects with anti-PD-1/PD-L1 relapsed/refractory mixed advanced solid tumors that have exhausted existing treatment options or are no longer eligible for them). Initial biomarker analyses by the sponsor for Part A (dose escalation) suggest that Tumor Proportion Score (TPS) PD-L1 might be a biomarker allowing to enrich for responders. In addition, it was shown that 60% of non-melanoma solid tumor patients with PD-L1 TPS ≤ 1 could be transformed from immunologically "cold" tumor status to immunologically "warm/hot". This cohort is enrolled to further evaluate these preliminary findings and will investigate biomarker and response findings in both groups. In Phase 1, PD-L1 TPS > 1 patient constituted 1/3 of all last-line treated patients. Therefore, up to N = 75 subjects are planned to be enrolled to have at least N = 25 response-evaluable subjects with TPS PD-L1 > 1 status and ideally up to N = 50 response-evaluable subjects with PD-L1 TPS ≤ 1. For the TPS PD-L1 > 1 group this would ideally confirm a response rate of ≥ 30% (with 81% probability resulting in a minimum of 6 or more responders in the cohort). For subjects with TPS ≤ 1, a response rate > 20% would be seen as clinically of interest and beneficial, and this would result in a minimum of 8 (10) responders with a probability of 81% (56%), respectively. If recruitment of 25 response-evaluable subjects with TPS PD-L1 > 1 is achieved, recruitment into the third group will be stopped and the TPS ≤ 1 cohort will be evaluated with given patient number in descriptive way.

For **all groups** the following additional requirements and restrictions apply:

(a) **All subjects** generally **must have received** a **currently for their tumor type approved anti-PD-1/PD-L1 compound;** non-approved, experimental anti-PD-1/PD-L1 treatments are not permissive for enrolment into this group unless condition (e) applies. (Group 2 with MSS-CRC is exempted from this regulation)

(b) **Baseline tumor biopsies** are **mandatory for all subjects** to further evaluate for predictive biomarkers of response as detected in Phase 1 and to further deepen the understanding of "cold-to-hot" tumor transitions for response under treatment.

(c) For **melanoma**, **cutaneous squamous-cell carcinoma** and the **biomarker cohort with mixed solid tumors** ("basket" cohort), an additional **follow-up, on-treatment biopsy** is mandatory to assess for immunologic changes in the tumor. **Important note**: All biopsies are only taken if considered **safe** and **feasible** by the treating physician/Investigator.

(d) All subjects that **achieve/maintain stable disease by week 24** but do not show tumor shrinkage beyond -10% as per RECIST criteria can undergo if desired by the treating physician and agreed by the patient stereotactic radiotherapy of one or more tumor lesions to increase neoantigen exposure and potential for response improvement (as was seen in two Phase 1 patients). This should always be pre-discussed with the medical representative of the sponsor and the radiotherapy area should not include all lesions that are used for RECIST response assessment to allow for abscopal antitumor effect assessment. **Note:** In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, if seen as safe and medically feasible by the treating physician.

For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) the following additional requirements and restrictions apply:

(e) Up to **5 subjects** (but no more) in the PD-L1 TPS > 1 group with **tumor indications that are currently not yet approved at all for anti-PD-1/PD-L1 treatment** may be enrolled if treated with a currently approved anti-PD-1/PD-L1 (for other indication(s)), if also all other criteria for the group apply. For the PD-L1 TPS ≤ 1 group this may be up to 10 patients.

(f) No subjects with melanoma (cutaneous, mucosal or uveal) can be enrolled in this cohort.

For all cohorts, response is defined as a subject presenting with a partial or complete response to treatment according to RECIST criteria.

If responses are seen and considered to be of interest by number and depth of response, the Safety Review Committee (SRC) may decide in agreement with the Sponsor to expand individual cohorts **following a Simon-2-stage design** to confirm a certain response rate with the following assumptions:

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, a minimum of 1 responder each is required to allow for continuation. Treating an additional N = 13 subjects shall generate a total of ≥ 4 responders to assume the overall response rate to be 20% or higher. For cutaneous squamous-cell carcinoma, a minimum of 2 responders is required to allow for continuation. Treating an additional N = 24 subjects shall result in a total of ≥ 6 responders to assume the overall response rate to be 25% or higher.
- For the **second group**, for colorectal cancer with N = 10 fixed for the first stage, if at least 1 responder was observed in the first stage, an additional N = 19 subjects may be added to a cohort. In a total of N = 29 subjects at least ≥ 4 responders are expected to assume the true response rate could be at 20% or higher.
- For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) with up to N = 75 subjects no such further expansion is considered. Instead, depending on response rate, - depth and - duration observed a potential registration size trial design will be considered and reviewed with the competent authorities (separate protocol). For the PD-L1 TPS > 1 group ("hot" tumors), a response rate of ≥ 30% is seen as clinically of significance, for the PD-L1 TPS ≤1 ("cold" tumors) a response rate > 20%.

In case of progressive disease (PD), treatment beyond progression might be applied as per Investigator assessment in agreement with the patient.

Proposed indications were selected based upon an **extensive translational research program** by the Sponsor, indicating a negative impact of GDF-15 on the immune response in the tumor microenvironment in the proposed indications, resulting in lack of immune cell infiltration, activation and in some indications proven resistance to checkpoint inhibitor treatment. In all subjects of all cohorts a baseline biopsy is mandatory to evaluate for potential predictive biomarker. In selected cohorts (i.e., melanoma, cutaneous squamous-cell carcinoma and in the biomarker cohort with mixed solid tumors ["basket" cohort]) sequential, dual tumor biopsies will be taken in subjects with accessible lesions. Enrolment into all cohorts may occur in parallel.

Due to the excellent tolerability of the combination of CTL-002 and nivolumab, the defined checkpoint inhibitor in Part A (Phase 1) of the trial and as per request of Investigators study treatment is made accessible to all subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge, and the prior, additional requirement to have no therapeutic alternative is removed. For the first and third group in Phase 2a, the requirement of failure or progression on prior anti-PD-1/-PD-L1 treatment is maintained.

For the cutaneous squamous cell carcinoma cohort, combination treatment will be done with cemiplimab (not nivolumab), as the approved checkpoint inhibitor for cutaneous squamous-cell carcinoma treatment. Subjects interested in participation in the trial are in each case informed about all treatments available for their disease situation. The potential advantages and disadvantages of participating in this

experimental trial will be discussed in relationship to available alternative treatment options, among them any remaining approved treatment opportunities. Participating subjects that have still existing alternative treatment options must have understood that these options are available to them, and that trial participation encompasses an experimental treatment. As stated above, subjects enrolling must have completed and failed prior anti-PD-1/PD-L1 in all cases and must be in non-curative state.

Note: Additional cohorts may be added at a later stage to Part B (Phase 2a) of the study but only upon approval of a substantial amendment(s) defining detailed target populations, combination exploration, dose/schedule of CTL-002 for the expansion phase and detailed enrolment criteria of the respective selected target populations. In such an amendment a separate monotherapy cohort may be added to explore the single agent safety profile in detail.

Treatment cycles are as follows:

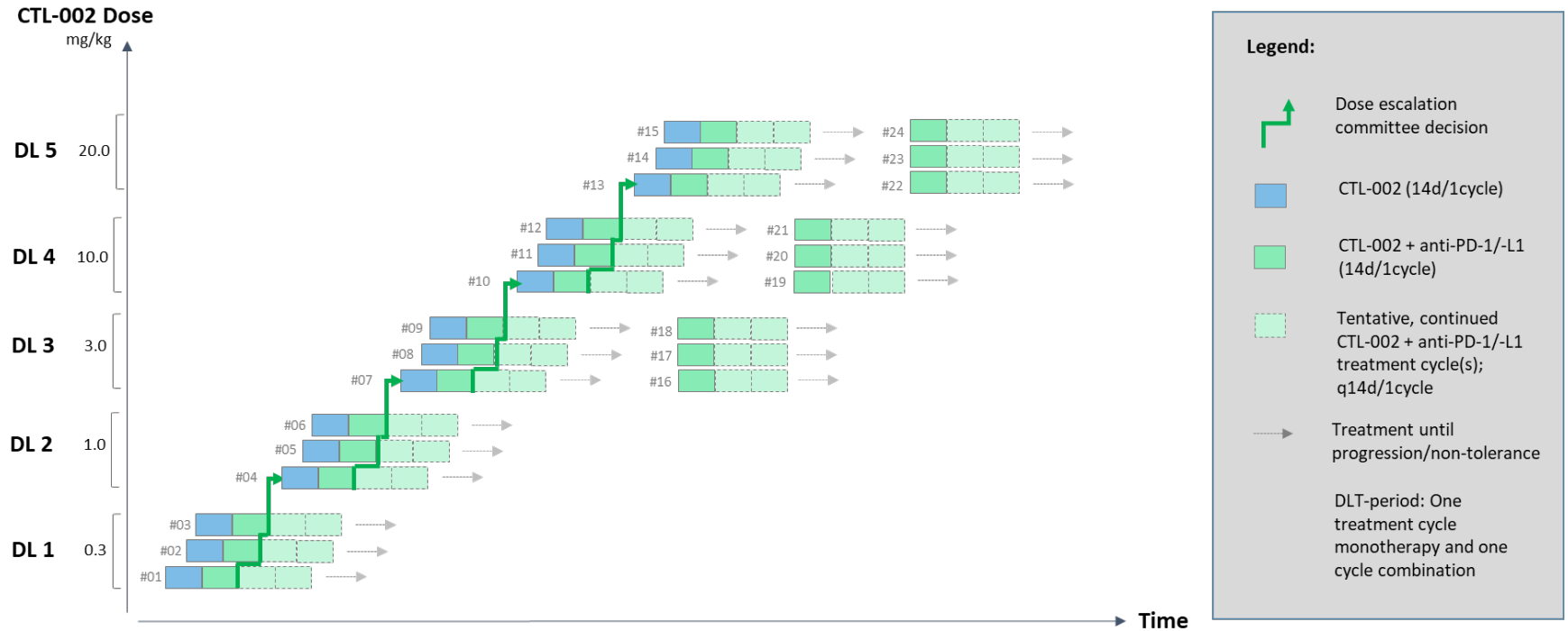
- Q2wk for bladder cancer, hepatocellular cancer, non-small cell lung cancer, melanoma, colorectal cancer and biomarker cohort with mixed solid tumors ("basket" cohort)
    - 10 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q2wk
    - 240 mg nivolumab as an IV infusion over approximately 30 minutes, Q2wk
- Q3wk for the cutaneous squamous-cell carcinoma cohort
    - 20 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q3wk
    - 350 mg cemiplimab as an IV infusion over approximately 30 minutes, Q3wk

Pharmaco-modelling and obtained PK/pharmacodynamic data from Part A (Phase 1) indicate complete GDF-15 neutralization at the dose of 10 mg/kg and the dosing interval of 2 weeks (Q2wk) or the dose of 20 mg/kg and the dosing interval of 3 or 4 weeks (Q3wk or Q4wk), respectively in serum and tumor vasculature (tumor microenvironment) in subjects with a wide range of baseline GDF-15 serum levels. In the current development phase (Phase 2a) the dosing interval follows for subject convenience the dosing interval of the checkpoint inhibitor. No safety events of concern and no DLT have been observed at any dose in Phase 1, including the doses of 10 mg/kg and 20 mg/kg. In addition, the for this initial Phase 2 exploration selected dose of 10 mg/kg and 20 mg/kg (with dosing interval of Q2wk and Q3wk, respectively) provide exposure that is still below the no-observed adverse effect level (NOAEL) in non-human primate (NHP).

Depending on further PK/pharmacodynamics data observed and safety and efficacy data, the SRC may modify these Phase 2 doses if seen as recommended or if a second dose is decided to be explored (all via substantial amendment).

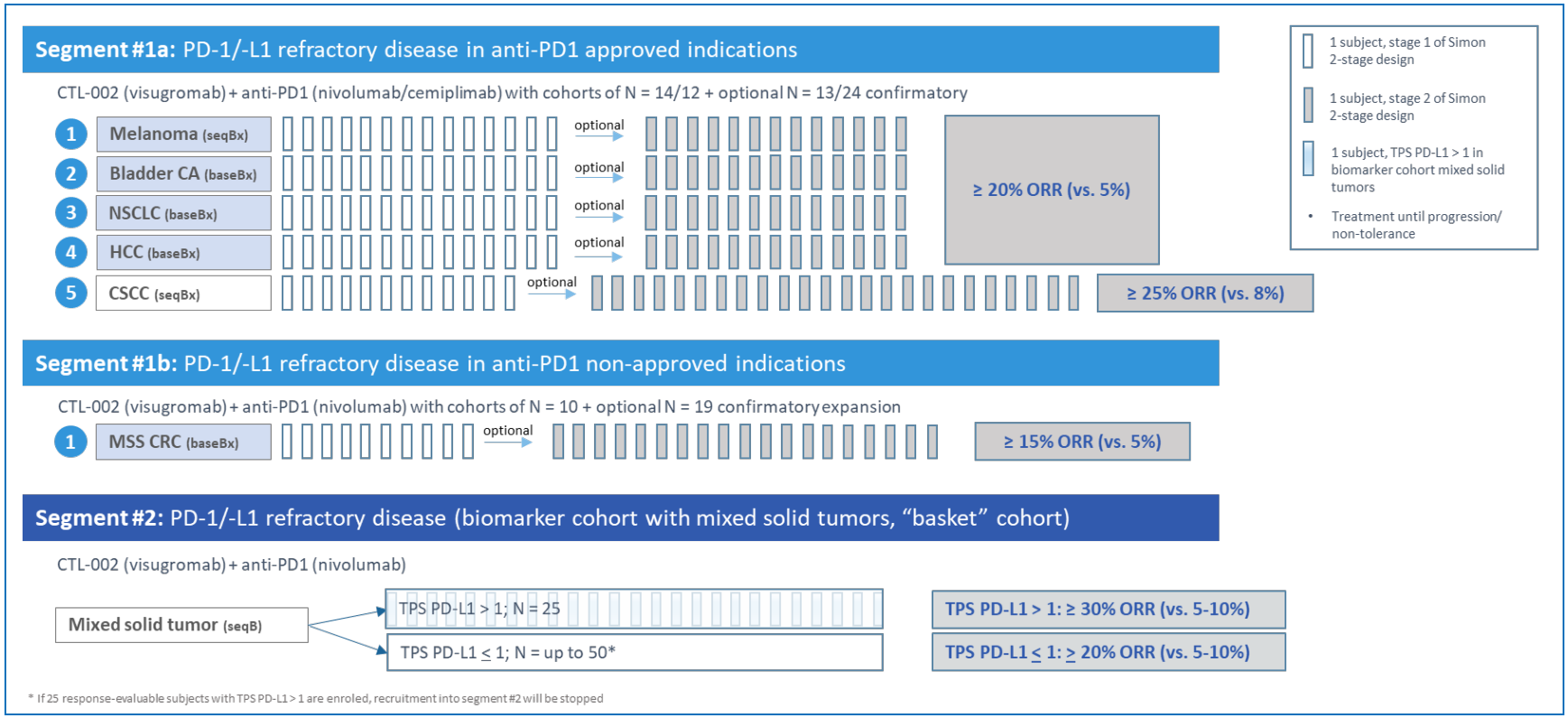
Part A (Phase 1; dose escalation)

Note: Enrollment has been completed. No further subjects will be enrolled.



Abbreviations: d = day; DL = dose level; DLT = dose-limiting toxicity; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; q14d = once every 14 days

Part B (Phase 2a; expansion):



Abbreviations: baseBx = baseline biopsy; CA = cancer; CRC = colon adenocarcinoma, rectum adenocarcinoma; CSCC = Cutaneous Squamous Cell Carcinoma, HCC = Hepatocellular Cancer; MSS= microsatellite stability, NSCLC = Non-small cell lung cancer; ORR = overall response rate; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; seqBx = sequential biopsy; TPS= Tumor Proportion Score.

Pre-Screening

For Part A (Phase 1, dose escalation) of the study, subjects with advanced-stage, relapsed and/or refractory solid tumors (subjects must have received an anti-PD-1/PD-L1 treatment [alone or in combination] and progressed on or relapsed after completion of anti-PD-1/PD-L1 treatment) with no available approved therapeutic alternative will sign a Pre-screening Informed Consent form (ICF) allowing the site/Sponsor to evaluate serum GDF-15 levels prior to entering the screening period.

1. Screening

For Part A (Phase 1; dose escalation) only, based on pre-screening GDF-15 serum levels, the Sponsor will approve pre-screened subjects for consent on the main study. Ideally 50% of enrolled subjects per dose level should show increased serum GDF-15 levels at pre-screening (> 1.5 ng/ml).

Subjects considered to be eligible to participate in the study will sign an ICF allowing the site/Sponsor to perform the screening procedures to confirm eligibility for the study (therefore, Screening is defined as the day of informed consent, and "Screening" is used throughout the synopsis and protocol to refer to this visit). The Screening Period is up to 21 days (for Part A) and up to 28 days (for Part B).

2. Treatment Period

Part A (Phase 1; dose escalation)

This study will employ a standard "3+3" dose escalation design for which 3 to 6 subjects will be enrolled at each assigned dose level, per cohort, depending on the occurrence of DLTs. The planned doses of CTL-002 to be tested are outlined below:

- Cohort 1: 0.3 mg/kg
- Cohort 2: 1.0 mg/kg
- Cohort 3: 3.0 mg/kg
- Cohort 4: 10 mg/kg
- Cohort 5: 20 mg/kg

The start dose of 0.3 mg/kg for Cohort 1 is fixed. Doses explored in Cohorts 2-5 (as outlined above) may be modified by the SRC established for the study based on emerging data (i.e., available safety, PK/pharmacodynamic, other biomarker data).

The DLT Observation Period will be the first 2 treatment cycles (i.e., first 4 weeks) for each dosing cohort. All treatment cycles are defined as 2 weeks in duration. CTL-002 will be administered Q2wk as an IV infusion over 60 minutes. Subjects will first receive 1 dose of CTL-002 given as monotherapy for 1 cycle, followed by a combination of CTL-002 given together with the defined anti-PD-1 checkpoint inhibitor for 1 cycle, where the defined checkpoint inhibitor will be administered at a dose of 240 mg IV Q2wk infused over approximately 30 minutes.

For the combination, CTL-002 and the defined checkpoint inhibitor will be given on the same day concomitantly, where CTL-002 will always be administered first and for the first combination infusion, there will be a 30-minute observation period to assess safety, which will then be followed by the defined checkpoint inhibitor infusion administered per Summary of Product Characteristics (SmPC) and local guidelines. The period of observation may be modified (i.e., shortened or lengthened) based on emerging safety data.

The first 2 treatment cycles (i.e., first 4 weeks) represent the DLT Observation Period. Thereafter, subjects will continue with the combination treatment, until progression or until withdrawal from the study for any other reasons (e.g., toxicity or subject withdraws consent).

Additional intermediate dose cohorts may be explored based on emerging data and upon SRC request. The maximum dose of CTL-002 to be tested in this study will not exceed 20 mg/kg.

All subjects will be hospitalized overnight after receiving the first dose of CTL-002 and also after receiving the first combination dose of CTL-002 and the defined checkpoint inhibitor, for the purposes of safety observation and to enable logistical collection of sampling time-points (e.g., PK).

Dose Escalation Rules

Initially, 3 subjects will be enrolled in any given dose cohort.

- If 0/3 subjects experience a DLT, then proceed to next dose
- If 1/3 subjects experience a DLT, then an additional 3 subjects will be tested at the same dose level
- If ≥ 2/3 subjects experience a DLT, this is considered the limiting dose and then an additional 3 subjects will be tested at the previous dose level to ensure a total of 6 subjects treated safely at that dose. In the situation where there is no lower dose level (i.e., if limiting dose is confirmed in Cohort 1), the Sponsor/SRC will make a recommendation about study continuation
- If 1/6 subjects experience a DLT, then proceed to the next dose level
- If ≥ 2/6 subjects experience a DLT, this would be defined as the limiting dose and dose escalation will stop. The previous lower dose would be considered the MTD. At least 6 subjects evaluable for safety must be enrolled at this dose level before it may be confirmed as the MTD
- Intermediate dose levels may be explored based on emerging data (safety, PK/pharmacodynamic) and if explored, will be discussed and agreed by the SRC and such decisions will be documented in writing.

Note: Moving from 1 dose cohort to the next requires subjects eligible for evaluation. Evaluable subjects must have received 2 weeks of CTL-002 monotherapy and 2 weeks of the combination (i.e., a subject must complete the 4-week DLT Observation Period). Subjects who have confirmed disease progression during the 4-week DLT Period or those subjects who discontinue for any reason, other than a DLT, may be replaced in the applicable dosing cohort. Subjects who experience a DLT will not be replaced.

In each dose cohort, the first subject will be dosed and observed for 6 calendar days to allow for initial assessment of safety before any other subjects may be dosed. Upon confirmation that the first subject has tolerated CTL-002 monotherapy and there are no significant toxicities that preclude further dosing, the second subject may be dosed and will be observed for safety for 2 days. Upon confirmation that the second subject has tolerated CTL-002 monotherapy and there are no significant toxicities within the first 2 days that preclude further dosing, the third subject may be dosed. In the case a DLT is observed in the first 3 subjects, there will be a 2-day stagger between the enrolment of the 3 additional subjects.

The first subject in the next higher dose cohort will not receive treatment with CTL-002 until the previous dose cohort has met the criteria for dose escalation and agreement from the SRC has been obtained and the decision documented in writing.

Intra-Patient Dose Escalation in Extended Treatment

If any Cohort 1 subjects are still on 0.3 mg/kg treatment when Cohort 2 has been completed and reviewed by the SRC, the subjects can be increased to the Cohort 2 dose of 1.0 mg/kg. If any Cohort 1 or 2 subjects are still on 1.0 mg/kg treatment when Cohort 3 has been completed and reviewed by the SRC, the subjects can be increased to the Cohort 3 dose of 3.0 mg/kg.

Note: Any subjects still on 0.3 mg/kg treatment must be treated at 1.0 mg/kg prior to advancing to 3.0 mg/kg in agreement with the Sponsor Medical Monitor. The maximum a subject dose can be increased to, through intra-dose escalation, will be 3.0 mg/kg.

Available safety, PK/pharmacodynamic data, as well as preliminary efficacy data will inform the MTD/dose(s) to be further explored in Part B of the study.

The MTD is defined as the highest dose level of CTL-002 at which no more than 1 out of 6 subjects experienced a DLT during the first 2 treatment cycles (i.e., the first 4 weeks, where CTL-002 is given as

monotherapy [Weeks 1 and 2] and in combination with the defined checkpoint inhibitor [Weeks 3 and 4]).

In addition, for Cohorts 3-5, in the absence of any DLT, an additional 3 subjects can be recruited into each of these cohorts (up to a total of 6 subjects per cohort), to increase the understanding of the PK and pharmacodynamic data. This occurs while dose escalation continues. These additional "backfill" subjects will receive the combination treatment of CTL-002 and the defined checkpoint inhibitor Q2wk from Cycle 1 Day 1 onwards, with CTL-002 always administered first and the defined checkpoint inhibitor given thereafter as outlined above.

For Part A subjects (except backfill subjects), 3 sequential tumor biopsies are mandated; one at baseline, the second prior to the initiation of the combination therapy (after 2 weeks), and the third after the first cycle of combination therapy (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3).

For backfill subjects, only 2 biopsies are mandated; one at baseline, and the second after 4 weeks of combination treatment (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3). These biopsies are mandatory in order to assess immune cell infiltration in the tumor. If a biopsy cannot be taken for safety reasons, this must be discussed with the Medical Monitor.

Dose-Limiting Toxicity Criteria:

The DLT Observation Period is the first 2 treatment cycles (i.e., 4 weeks). The SRC will review all DLTs as per the SRC charter. A DLT is defined as any of the following AEs graded using the NCI-CTCAE Version 5.0.

Hematologic Toxicity:

- Any Grade 4 hematologic toxicity

Non-Hematologic Toxicity:

- Any Grade 4 non-hematologic toxicity
- Any other ≥ Grade 3 non-hematologic toxicity lasting more than 96 hours despite appropriate supportive therapy
- Any ≥ Grade 3 pneumonitis, adrenal insufficiency, myocarditis, hepatitis (immune-related ≥ Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin elevation)
- Occurrence of Stevens-Johnson syndrome (SJS)

General Toxicity:

- Any Grade 5 toxicity
- Any other toxicity that is not captured with above regulations but is considered by the Investigator and the SRC as qualifying for a dose-limiting event/toxicity (e.g., any permanent discontinuation criteria of the defined anti-PD-1 checkpoint inhibitor)

Note: Transfusions of blood products or use of growth factors are NOT permitted during the Screening Period or during the 4-week DLT Observation Period (with the exception of a requirement to treat a DLT/SAE).

Part B (Phase 2a; expansion)

In Part B of the study, various cohorts with defined tumor indications as provided above will be enrolled.

The treatment dose for CTL-002 in Part B is set at 10 mg/kg Q2wk or 20 mg/kg Q3wk.

Pharmaco-modelling and obtained PK/pharmacodynamic data from Part A (Phase 1) indicate complete GDF-15 neutralization at the dose of 10 mg/kg and the dosing interval of 2 weeks (Q2wk) or the dose

of 20 mg/kg and the dosing interval of 3 or 4 weeks (Q3wk or Q4wk), respectively in serum and tumor vasculature (tumor microenvironment) in subjects with a wide range of baseline GDF-15 serum levels. In the current development phase (Phase 2a) the dosing interval follows for subject convenience the dosing interval of the checkpoint inhibitor. No safety events of concern and no DLT have been observed at any dose in Phase 1, including the doses of 10 mg/kg and 20 mg/kg. In addition, the for this initial Phase 2 exploration selected dose of 10 mg/kg and 20 mg/kg (with dosing interval of Q2wk and Q3wk, respectively) provide exposure that is still below the no-observed adverse effect level (NOAEL) in non-human primates (NHP).

Depending on further PK/pharmacodynamics data observed and safety and efficacy data, the SRC may modify these Phase 2 doses if seen as recommended or if a second dose is decided to be explored (all via substantial amendment).

In the expansion cohorts, subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state that have either of the following indications will receive treatment with a combination of CTL-002 and the defined checkpoint inhibitor:

(1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma, or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound, or

(2) colorectal cancer (MSS/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy, or

(3) biomarker cohort with mixed solid tumors ("basket" cohort) that are relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound and that have exhausted existing treatment options or are not eligible for them anymore.

- For the **first group** (currently approved anti-PD-1/PD-L1 indications), N = 14 response-evaluable subjects each will be recruited for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, for cutaneous squamous-cell carcinoma N = 12.
- For the **second group** (currently non-approved anti-PD-1/PD-L1 indication) N = 10 response-evaluable subjects will be recruited for colorectal cancer (MSS/mismatch-repair competent).
- The **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) investigated, are subjects with anti-PD-1/PD-L1 relapsed/refractory mixed advanced solid tumors that have exhausted existing treatment options or are no longer eligible for them. Up to N = 75 subjects are planned to be enrolled to have at least N = 25 response-evaluable subjects with TPS PD-L1 > 1 status and ideally up to N = 50 response-evaluable subjects with PD-L1 TPS ≤ 1. If recruitment of 25 response-evaluable subjects with TPS PD-L1 > 1 is achieved, recruitment into the third group will be stopped and the TPS ≤1 cohort will be evaluated with given patient number in descriptive way.

For **<u>all groups</u>** the following additional requirements and restrictions apply:

a) **All subjects** generally **must have received** a **currently for their tumor type approved anti-PD-1/PD-L1 compound;** non-approved, experimental anti-PD-1/PD-L1 treatments are not permissive for enrolment into this group (does not apply for other cohorts) <u>unless</u> condition (e) applies. (Group 2 is exempted from this regulation)
b) **Baseline tumor biopsies are mandatory for all subjects to further evaluate for predictive biomarkers of response as detected in Phase 1 and to further deepen the understanding of "cold-to-hot" tumor transitions for response under treatment**
c) **Baseline tumor biopsies** are **mandatory for all subjects** to further evaluate for predictive biomarkers of response as detected in Phase 1 and to further deepen the understanding of "cold-to-hot" tumor transitions for response under treatment.

d) For **melanoma**, **cutaneous squamous-cell carcinoma** and the **biomarker-cohort with mixed solid tumors** ("basket" cohort), an additional **follow-up, on-treatment biopsy** is mandatory to assess for immunologic changes in the tumor. **Important note**: All biopsies are only taken if considered **safe** and **feasible** by the treating physician/Investigator.

e) All subjects that **achieve/maintain stable disease by week 24** but do not show tumor shrinkage beyond – 10% as per RECIST criteria can undergo if desired by the treating physician and agreed by the patient stereotactic radiotherapy of one or more tumor lesions to increase neoantigen exposure and potential for response improvement (as was seen in two Phase 1 patients). This should always be pre-discussed with the medical representative of the sponsor and the radiotherapy area should not include all lesions that are used for RECIST response assessment to allow for abscopal antitumor effect assessment.

Note: In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, if seen as safe and medically feasible by the treating physician.

For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) the following additional requirements and restrictions apply:

f) Up to **5 subjects** (but no more) in the PD-L1 TPS > 1 group with **tumor indications that are currently not yet approved at all for anti-PD-1/PD-L1 treatment** may be enrolled if treated with a currently approved anti-PD-1/PD-L1 (for other indication(s)), if also all other criteria for the group apply. For the PD-L1 TPS ≤ 1 group this may be up to 10 patients.

g) No subjects with melanoma (cutaneous, mucosal or uveal) can be enrolled into this cohort.

Treatment cycles are as follows:

- Q2wk for bladder cancer, hepatocellular cancer, non-small cell lung cancer, melanoma, colorectal cancer and biomarker cohort with mixed solid tumors ("basket" cohort)
  - 10 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q2wk
  - 240 mg nivolumab as an IV infusion over approximately 30 minutes, Q2wk
- Q3wk for the cutaneous squamous-cell carcinoma cohort
  - 20 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q3wk
  - 350 mg cemiplimab as an IV infusion over approximately 30 minutes, Q3wk

In all subjects of all cohorts a baseline biopsy is mandatory to evaluate for potential predictive biomarkers (either fresh biopsy or archived biopsy taken within 120 days prior to treatment start). For melanoma, cutaneous squamous-cell carcinoma and the biomarker cohort with mixed solid tumors ("basket" cohort), an additional on-treatment biopsy is mandatory. If there is a safety risk at the discretion of the investigator to perform an on-treatment biopsy, this must be discussed with the Medical Monitor. An optional third biopsy can be taken at the next medically feasible timepoint during ongoing treatment in case the first biopsy is evaluable, but the second biopsy is non-evaluable, to assure assessable histology data.

In cutaneous squamous-cell carcinoma, multiple punch biopsies will be taken at a single timepoint (as per clinical possibility, ideally 3-5) , as extensive molecular analyses are pursued (messenger ribonucleic acid [mRNA] expression analyses, such as T cell clonality analyses, RNAseq, nanostring analyses or genome sequencing etc.).

Enrolment into the Phase 2a cohorts may occur in parallel. Subjects that do not reach the first response assessment for reasons other than disease progression will be replaced to assure a full set of response assessable subjects. All subjects will be treated until progression under observation of RECIST criteria.

For the purposes of safety observation and to enable logistical collection of sampling time points (i.e., PK sampling), all subjects will be hospitalized overnight after receiving the first dose of CTL-002 (in case

of future monotherapy cohort) or after receiving the first combination dose with CTL-002 and the defined checkpoint inhibitor (combination therapy cohort), respectively.

As part of Phase 2a, a dedicated CTL-002 monotherapy cohort may be conducted within a defined tumor indication to explore the safety profile of CTL-002 given as monotherapy (e.g., in subjects with advanced-stage melanoma) at a later timepoint, introduced per substantial amendment.

3. Follow-up

Following the Safety Follow-up Visit / End of Core Study Visit, subjects will be followed up with an Efficacy and Survival follow-up for response duration and survival every 3 months for 12 months (in Part A) and every 3 months for 24 months (in Part B). The follow-up will be performed by telephone contact or (e)mail.

NUMBER OF SUBJECTS (PLANNED):

For Part A of the study (Phase1; dose escalation), it is anticipated that a minimum of 24 subjects will be enrolled. For Part B of the study (Phase 2a; expansion), up to 249 subjects will be enrolled in different expansion cohorts (79 response evaluable subjects in the first cohorts, with expansion option of 4×13, 1×24 and 1x19 subjects = 95 subjects, and 75 subjects in the biomarker cohort with mixed solid tumors ("basket" cohort). Therefore, a total of approximately 274 subjects might be enrolled (Part A: n = 25 / Part B: n = 79 + 95 + 75 = 249). Additional cohorts may be added via substantial amendment, only.

ELIGIBILITY CRITERIA:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Provide signed and dated informed consent. For Part A only: signed pre-screening consent for subjects that undergo pre-screening procedures or collection of historical data prior to informed consent procedure.
2. Male or female aged ≥ 18 years.
3. Subjects with histologically or cytologically confirmed/documented diagnosis of advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge.
4. For Part A (Phase 1), subjects must have received during their prior treatment at least one anti-PD-1/PD-L1 treatment (alone or in combination) and progressed on or relapsed after completion of the anti-PD-1/PD-L1 treatment (with a minimum of 12 weeks of anti-PD1/PD-L1 exposure).

   For Part B (Phase 2a), subjects must either have

   (1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma, or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound (with a minimum of 12 weeks of anti-PD-1/PD-L1 exposure).

   For cutaneous squamous-cell carcinoma, subjects have to have locally advanced disease or metastatic disease. Cutaneous squamous-cell carcinoma subjects with locally advanced disease must not be candidates for surgery for one or both of the following reasons: disease recurrence after two or more surgical procedures and as per treating physician curative resection is unlikely or surgery would result in substantial complications or deformity.

   (2) colorectal cancer (MSS/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy

   (3) biomarker cohort with mixed solid tumors ("basket" cohort;) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound and that have exhausted available approved therapies for their disease or

do not qualify for them anymore.

Note: All Subjects in cohorts (1) and (3) must have received an approved anti-PD-1/PD-L1 compound with a minimum of 12 weeks of anti-PD1/PD L1 exposure. Non-approved, experimental anti-PD-1/PD-L1 treatments are not permissive for enrolment into this group (does not apply for other cohorts).

5. Ability to understand the purpose of the study, provide signed and dated informed consent prior to performing any protocol-related procedures (including Screening evaluations), and able to comply with the study procedures and any locally required authorization.
6. For Part A, ideally ~50% of subjects enrolled per dose level should have increased GDF-15 serum levels (based on pre-screening result or historic serum GDF-15 data [up to 2 months prior to the start of treatment with CTL-002 where available]).
7. All subjects must have biopsy-accessible tumor lesions and be willing to undergo tumor biopsy: triple-sequential biopsies (Part A) or dual-sequential biopsies (Part A backfill); in Part B, baseline biopsy (new or archived if obtained within 120 days prior to treatment start) from all subjects. For melanoma, cutaneous squamous-cell carcinoma and the biomarker cohort with mixed solid tumors ("basket" cohort), an additional on-treatment biopsy is mandatory. All biopsies are mandatory unless not seen as safe and feasible by the treating physician or another specific reason that precludes a biopsy sample being taken and which should be discussed with the Medical Monitor prior to Screening or if applying to the sequential biopsy, prior to that biopsy. All other study eligibility criteria must be met before the baseline biopsy sample is obtained.
8. For Part B, presence of radiologically measurable disease at baseline – with at least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter with computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for accurate, repeated measurements as per RECIST V1.1/iRECIST is required. This shall not be the lesion that is going to be biopsied.
9. ECOG performance status 0-1.
10. Life expectancy > 3 months as assessed by the Investigator.
11. Adequate organ function:
    a. Bone marrow function: hemoglobin ≥ 9.0 g/dL (equal to 5.59 mmol/L); platelet count ≥ 100×10^9/L; leukocyte count ≥ 2.5×10^9/L.
    b. Hepatic function: AST and ALT ≤ 2 × upper limit of normal (ULN) (3 × ULN in the case of liver metastases); bilirubin ≤ 1.5 × ULN (2 × ULN in case of liver metastases/subjects with Gilbert's disease).
    c. Renal function: serum creatinine < 1.5 × ULN and/or creatinine clearance ≥ 50 ml/min (Cockcroft-Gault equation).
    d. Coagulation: no evidence for clinically relevant hypo- or hypercoagulability or presence of thrombosis/thrombotic event as per D-Dimer, antithrombin III (ATIII), prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT) analysis and treating physician's assessment.
12. All toxicities related to prior radiotherapy, chemotherapy, and any type of immunotherapy or other anti-cancer therapy, or surgical procedure must have recovered to Grade ≤ 1 based on NCI-CTCAE v5.0, except alopecia (any grade), and Grade 2 peripheral sensory neuropathy, and AEs that are clinically not considered as significant in this context and/or are stable on supportive therapy.
13. If subject has type II diabetes and receives metformin, metformin has to be replaced with other antidiabetic(s) prior to start of study treatment (at minimum 7 days prior to study baseline GDF-15 measurement) and for the whole study treatment duration.

14. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to CTL-002 treatment. If a pregnancy test is not performed within 7 days of dosing with CTL-002, a repeat test must be performed prior to Day 1 dosing.

    Women of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

15. All subjects, male and female, who are not surgically sterilized or postmenopausal as defined above, and subjects' partners of childbearing potential must agree to use "highly effective methods of contraception" during the study and for at least 5 months (5 times the predicted halflife of CTL-002 in humans) after the last dose of CTL-002.

    "Highly effective methods of contraception" are combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence.

    The double-barrier method (synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel), periodic abstinence (such as calendar, symptothermal, or post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method and spermicide only are NOT acceptable as "highly effective methods of contraception."

Exclusion Criteria:

Subjects meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Pregnant or breastfeeding.
2. Has received any tumor-directed therapy within 21 days before start of study treatment.
3. Treatment with any investigational agent within 21 days before start of study treatment.
4. Radiotherapy within 14 days before the start of the study treatment; however, subjects may receive palliative radiotherapy upon discussion and approval from the Medical Monitor if needed on non-target lesions.
5. Any acute or chronic major tissue injury that may require maintained GDF-15 function for tissue protection as per Investigator assessment (diagnosed with liver, kidney, myocardial infarction, or other major organ failure, all within < 6 months prior to Screening).
6. Pre-existing arrhythmia (unless considered clinically not relevant), uncontrolled angina pectoris, diagnosed with heart failure New York Heart Association (NYHA) Grade IV, any myocardial infarction/coronary event as well as any central nervous system (CNS)-ischemic event and any thromboembolic event at any time < 6 months prior to Screening or presence of uncontrolled heart failure NYHA Grade III or higher.
7. Left ventricular ejection fraction (LVEF) < 50% as measured by an echocardiogram (ECHO) or multigated acquisition (MUGA) scan if ECHO cannot be performed at site for any reason.
8. QT interval corrected for heart rate using Fridericia's formula (QTcF) interval > 450 ms for men or > 470 ms for women.
9. Any active autoimmune disease that requires systemic immunosuppressive treatments, for which (re-)activation may present a medical threat to the subject as per Investigator's assessment.
10. Any history of non-infectious pneumonitis < 6 months prior to Screening.
11. Any active inflammatory bowel disease such as Crohn's disease or ulcerative colitis which are generally excluded or active autoimmunthyroiditis present < 6 months prior to Screening.
12. Type I diabetes.

13. History of CNS disease such as stroke, seizure, encephalitis, or multiple sclerosis (< 6 months prior to Screening).
14. Any history of motor neuron disorder or disease that affects motor neuron function.
15. Ongoing immune-related AEs (irAEs) and/or AEs ≥ Grade 2 not resolved from previous therapies except vitiligo, stable peripheral sensory neuropathy up to Grade 2, hair loss, and stable endocrinopathies with substitutive hormone therapy.
16. Active allergy requiring systemic treatment (with the exception of histamine H1 receptor blocker treatment) or active infections requiring systemic anti-infectious therapy.
17. History of or clinical evidence of CNS primary tumors or metastases including leptomeningeal metastases, unless they have been previously treated, demonstrated no progression at least for 3 months before Screening, are asymptomatic and have had no requirement for steroids or enzyme inducing anticonvulsants in the last 14 days before Screening – subjects with suspected brain metastases at Screening should undergo a CT/MRI of the brain prior to study entry.
18. Systemic steroids at a daily dose of > 10 mg of prednisolone, > 2 mg of dexamethasone or equivalent, except non-systemic (inhaled, topical, nasal), for the last 28 days and ongoing.
19. Subjects with rapidly progressing disease (as per Investigator assessment), which may predispose to inability to tolerate treatment and/or study procedure.
20. Major surgery within last 4 weeks prior to Screening.
21. Known/expected hypersensitivity against CTL-002 and/or anti-PD-1/PD-L1 agents or their ingredients or previously had a severe hypersensitivity (≥ Grade 3) reaction to treatment with monoclonal antibodies (including pembrolizumab, nivolumab, cemiplimab etc.) and/or any of their excipients.
22. Evidence for active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as per adequate testing performed.
23. Dementia or altered mental status that would prohibit informed consent.
24. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory abnormality giving reasonable suspicion of a disease or condition that in the opinion of the Investigator would contraindicate the use of an investigational drug.
25. Receipt of any organ transplantation, including hematopoietic cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant).
26. Paraneoplastic syndrome (PNS) of autoimmune nature, requiring systemic treatment (systemic steroids or immunosuppressive agents) or a clinical symptomatology suggesting worsening of PNS.
27. Vaccine administration within 4 weeks of investigational drug administration (exception: coronavirus disease 2019 [COVID-19] vaccination). Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines like inactivated influenza vaccines or RNA vaccines is allowed, including COVID-19.
28. Known active drug or alcohol abuse.

INVESTIGATIONAL PRODUCT, DOSAGE AND MODE OF ADMINISTRATION:

CTL-002 is a humanized, hinge-stabilized immunoglobulin (Ig) G4 monoclonal antibody targeting GDF-15 with high-affinity, for IV infusion, to be administered over approximately 60 minutes, Q2wk (Phase 1 and Phase 2a, except for cutaneous squamous-cell carcinoma cohort) or Q3wk (cutaneous squamous-cell carcinoma cohort only).

DURATION OF TREATMENT:

The Screening Period will be up to 21 days (Part A) and up to 28 days (Part B), with a core Treatment Period for Part A (Phase 1; dose escalation) of 4 weeks (first 4 weeks will be the DLT Observation Period) and for Part B (Phase 2a; expansion) of 8 weeks or 9 weeks. Thereafter, subjects will continue with the combination treatment, until progression or until withdrawal from the study for any other reasons (e.g., toxicity or subject withdraws consent). An End of Treatment Visit will occur 2 weeks after the last CTL-002 dose and a Safety Follow-up Visit will occur 30 days (±2 days) after the last CTL-002 dose. Following the Safety Follow-up Visit / End of Core Study Visit, subjects will be followed up with an Efficacy and Survival follow-up for response duration and survival every 3 months for up to 12 months (in Part A) and every 3 months for up to 24 months (in Part B).

END OF STUDY:

The end of the Core study is defined as the time point when the last subject has completed the last Safety Follow-up Visit (End of Core Study Visit) 30 days from the last dose.

The end of study is defined as the time point when the last subject has completed the last Efficacy and Survival follow-up. This is 12 months after end of the core study for Part A and 24 months after end of the core study for Part B.

SAFETY REVIEW COMMITTEE:

A SRC will be established consisting of the Sponsor, the Sponsor's Medical Expert(s), and the Investigators. The SRC will review and evaluate the available safety and efficacy data (i.e., AEs including DLTs, other available clinical data and PK/pharmacodynamic data) collected during the study. Additional internal or external experts may be consulted by the SRC as necessary.

For Part A of the study (Phase 1; dose escalation), the SRC will meet upon the completion of each dose escalation cohort or upon member-request ad-hoc and review all available, cumulative safety data that are reported in a rolling fashion to the SRC. For dose escalation decisions all safety data for the DLT Period must be available to the SRC.

The SRC can recommend at any dose level that more subjects should be enrolled for DLT evaluation, to dose escalate/de-escalate or to stop enrolment. When Part A has been completed, the SRC will receive a cumulative safety report for review. Any subsequent exploration of CTL-002 can only start, if the SRC agrees with commencement of Part B of the study.

During Part B of the study (Phase 2a; expansion), the SRC will meet regularly or upon member-request ad-hoc. All safety data will again be reported in rolling fashion at these time-points to the SRC.

For Part B (Phase 2a; expansion), the SRC will decide together with the Sponsor which cohorts may undergo Simon-2-stage expansion. An expansion only takes place with SRC and Sponsor agreement, both based upon observed antitumor activity and safety warranting further cohort expansion.

A respective SRC Charter will describe the composition, activities, as well as the way recommendations for further treatments are made.

EVALUATION PROCEDURES:

Safety:

The safety and tolerability of IV infusions of CTL-002 monotherapy and CTL-002 in combination with the defined checkpoint inhibitor will be evaluated by the incidence of AEs (all AEs will be evaluated according to NCI-CTCAE v5.0), SAEs, DLTs, and use of concomitant medications. Safety assessments will include: ECGs, physical examinations including neurological examination to exclude motor neuropathy, ECOG performance status, vital signs and clinical laboratory samples (hematology, clinical chemistry, coagulation, thyroid function (thyroid stimulating hormone [TSH] and free T3), cytokines,

assessment of hemoglobin A1c [HbA1c], N-terminal B-type natriuretic peptide [NT-proBNP], and urinalysis).

Subjects are assessed for safety at Screening as well as during the Treatment Period until the Safety Follow-up Visit. Thereafter safety related to the study is further captured during the follow-up of up to 12 months (in Part A) or up to 24 months (in Part B) post-treatment.

As part of the safety oversight for this study, in addition to the staggering of subject dosing with CTL-002 in Part A (Phase 1; dose escalation), subjects will only be enrolled and treated with CTL-002 at carefully selected investigational sites who have experience in FIH studies and immunotherapy, handling of related AEs, access to intensive care units (ICU) and immediate and appropriate resuscitation measures at all times during hospitalization.

Medical measures have been implemented which ensures a quick diagnosis of events and the implementation of quick actions (e.g., central venous access, hospitalization, close subject monitoring for vital signs, cardiac monitoring).

In addition, subjects will be provided with immune-oncology wallet cards that may help health care providers who are not involved with the subject's cancer treatment, to identify that subjects have received immune-oncology therapy as well as to recognize rare or subtle symptoms of immune-oncology toxicity. Pregnancy must be reported from the time of the signing of the ICF until 5 months after last dosing with CTL-002 and the defined checkpoint inhibitor.

Tumor Biopsy:

Timing of biopsies are as follows:

- Part A (all subjects except backfill subjects): 3 sequential tumor biopsies are mandated; one biopsy at baseline, the second biopsy prior to the initiation of the combination therapy (after 2 weeks) and the third biopsy after the first cycle of combination treatment (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3). These biopsies are mandatory in order to assess immune cell infiltration in the tumor.

  Part A (backfill subjects): 2 serial tumor biopsies are mandated; one biopsy at baseline and a second biopsy after 4 weeks of combination treatment (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3)

  <u>For all Part A subjects:</u> in case a tumor biopsy is non-evaluable, an optional biopsy can be collected at the next medically feasible timepoint during ongoing treatment and as per treating physician's decision to assure assessable histology data.

- Part B: Baseline biopsies are mandatory in all subjects; for melanoma, cutaneous squamous-cell carcinoma and the biomarker cohort with mixed solid tumors ("basket" cohort), an additional on-treatment biopsy after the first 8 weeks (for cutaneous squamous-cell carcinoma: 9 weeks) of treatment (dependent on dosing scheme i.e., combination with nivolumab after 4 cycles [8 weeks] and with cemiplimab after 3 cycles [9 weeks]) is mandatory. In case the second biopsy is non-evaluable, an optional third biopsy can be collected if seen as safe and feasible at the next possible timepoint during ongoing treatment and as per treating physician's decision.

  <u>Note</u>: In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, again only if seen as safe and medically feasible by the treating physician, as in all biopsy cases.

  - For subjects enrolled under this version of the protocol and previous protocols v4.0 and v5.0: an optional retrospective analysis of PD-L1 and other relevant biomarkers might be conducted on archival tumor tissue any time after Screening provided the available material is < 120 days old and that the subject agrees in writing to this testing.
  - For cutaneous squamous-cell carcinoma subjects: multiple punch biopsies will be taken at a single timepoint (as per clinical possibility, ideally 3-5), as extensive molecular

analyses are pursued (messenger ribonucleic acid [mRNA] expression analyses, such as T cell clonality analyses, RNAseq, nanostring analyses or genome sequencing etc.).

There has to be a lesion that is amenable to sequential biopsy, if possible, or a lesion in close proximity, but this lesion should ideally not be the only target lesion that will be radiologically assessed during the course of the study. If a sequential biopsy cannot be taken for safety reasons, this must be discussed with the Medical Monitor.

If stereotactic radiotherapy is initiated, another follow-up biopsy after 4 wks of the initiation of radiotherapy should be performed. Note: All biopsies are to be performed only if seen as safe and feasible from treating physician's discretion.

Biomarkers may be analyzed from biopsy tumor tissue samples. Additional immune cell markers and/or tumor markers specific to any of the tumor type may be included.

Anti-tumor activity:

Tumor response will be assessed radiologically using RECIST V1.1 and iRECIST criteria. To explore the anti-tumor activity of CTL-002 in monotherapy and/or in combination with the defined checkpoint inhibitor, tumor lesions will be evaluated by tumor assessments, imaging, and tumor biopsies to evaluate immune cell infiltration. A central reading of images by a reading center will be performed post-hoc in addition to local reading by the Investigator during the trial.

PK and ADA (Immunogenicity):

The PK of CTL-002 given as monotherapy and/or in combination with the defined checkpoint inhibitor will be measured from blood samples collected at the start of treatment and at various subsequent time points (Part A, Phase 1). Additional PK data may be evaluated in the expansion cohorts (Part B; Phase 2a).

Blood samples will be taken at the start of treatment and at various subsequent time points to determine, if antibodies directed against CTL-002 may have developed.

Pharmacodynamics:

The pharmacodynamics of CTL-002 administered as monotherapy and/or in combination with the defined checkpoint inhibitor will be determined from peripheral blood, urine and tumor biopsies as available. Urine GDF-15, serum total GDF-15, intratumoral GDF-15, and tumor immune cell infiltration will be determined.

Exploratory Assessments:

Various molecular and immunohistochemical biomarkers and immune parameters (e.g., including but not limited to molecular profiling, mutation status, mutational burden or other markers of interest relating to immune activation or disease may be explored) will be assessed in peripheral blood, serum, urine and tumor tissue.

Statistical Methods:

The sample size for Part A (Phase 1; dose escalation) of the study is not based on any statistical assumptions; rather, it follows the classic '3+3 rule", a well-established methodology in the design of dose-finding clinical trials in oncology.

The study plans for up to 5 dose escalation cohorts in Part A, with each cohort comprising a minimum of 3 subjects to be treated with CTL-002 in combination with the defined checkpoint inhibitor at each dose escalating level and with typical DLT driven expansions up to 6 subjects per cohort and at the MTD.

In Part B (Phase 2a; expansion), cohorts with several defined tumor indications will be treated to detect efficacy signals, in a screening effort to identify tumor indications where CTL-002 has clinically relevant antitumor activity. All indications have been selected based upon translational research results by the

sponsor and other scientific groups that indicate an immunosuppressive role of GDF-15 in these tumor indications.

To achieve this and based upon a **conditional probability calculation** the following subject numbers are recruited:

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, N=14 response-evaluable subjects will be initially recruited per each tumor indication. This shall allow to detect 2 responses in a cohort with 80% probability if the true response rate is 20% or more, and at least 1 response in the cohort with 77% probability if the true response rate is 10% or more. For cutaneous squamous-cell carcinoma, N = 12 response-evaluable subjects will be recruited initially. This should result in 2 responses or more with 80% probability if the true response rate is 25% or higher.
- For the **second group** (colorectal cancer [MSS/mismatch-repair competent, a currently non-approved anti-PD-1/PD-L1 indication]), N=10 response-evaluable subject will be recruited. This shall allow to detect 1 response with 89% probability (if the true response rate is 20% or more), and 1 response with 80% probability if the true response rate is 15% or more.
- For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort), N = 75 subjects are planned to be enrolled to have at least N = 25 response-evaluable subjects with TPS PD-L1 > 1 status and ideally up to N = 50 response-evaluable subjects with PD-L1 TPS ≤ 1. For the TPS PD-L1 > 1 group this would ideally confirm a response rate of ≥ 30% (with 81% probability resulting in a minimum of 6 or more responders in the cohort), resulting in a lower limit of the 95% confidence interval of 0.15 (15% lower end response rate), allowing to well rule out background response rates at 5-10% level. For subjects with TPS ≤ 1, a response rate > 20% would be seen as clinically of interest and beneficial, and this would result in a minimum of 8 (10) responders with a probability of 81% (56%), respectively, if the true response rate is 20% or above. If recruitment of 25 response-evaluable subjects with TPS PD-L1 > 1 is achieved, recruitment into the third group will be stopped and the TPS ≤ 1 cohort will be evaluated with given patient number in descriptive way.

Response is defined as a subject presenting with a partial or complete response to treatment according to RECIST criteria.

If responses are seen and considered to be of interest by number and depth of response, the SRC may decide in agreement with the Sponsor to expand individual cohorts **following a Simon-2-stage design** to confirm a certain response rate with the following assumptions:

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and with N = 14 fixed for the first stage, an additional N = 13 subjects may be added to a cohort to achieve at least 4/27 responders and confirm a true response rate of 20% with 80% power. For cutaneous squamous-cell carcinoma, N = 12 fixed for the first stage, an additional N = 24 subjects may be added to a cohort to achieve at least 6/36 responders and confirm a true response rate of 25% with 80% power.
- For the **second group**, for colorectal cancer with N = 10 fixed for the first stage, an additional N = 19 subjects may be added to a cohort to achieve at least 4/29 responders and confirm a true response rate of 20% with 80% power.
- For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort), with up to N = 75 subjects no such further expansion is considered. Instead, depending on response rate, - depth and - duration observed a potential registration size trial design will be considered and reviewed with the competent authorities (separate protocol). For the PD-L1 TPS > 1 group ("hot" tumors), a response rate of ≥ 30% is seen as clinically of significance, for the PD-L1 TPS ≤ 1 ("cold" tumors) a response rate > 20%.

Descriptive and inferential statistics will be used to summarize the data. Continuous variables will be summarized by number, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized by subject counts and related percentages.

The Efficacy Evaluable Analysis Set as per statistical definition will consist of all subjects who complete at least 2 cycles of treatment (e.g., 1 cycle monotherapy followed by 1 cycle combination therapy for Part A or 2 cycles combination therapy for Part A backfill subjects and Part B subjects), and have baseline and at least one valid post-baseline tumor assessment demonstrating progression or were declared to be clinically progressing or terminated treatment due to a treatment-related AE.

Efficacy analyses will include summaries of confirmed PR/CR, ORR, DOR, PFS, TTR, and OS by dose level (Part A) or cohort (Part B). Tumor response will be evaluated according to institutional standards using RECIST (version 1.1) for solid tumors, as well as iRECIST criteria.

For DOR, PFS, TTR and OS, Kaplan-Meier curves and estimates including medians and 95% confidence intervals (CIs) will be provided. For analysis of the ORR, summary tables will be generated, presenting the number and proportion of responders in each dose group and 2-sided 95% Pearson-Clopper CIs. Logistic regression analyses may be used to test potential predictive factors for overall response.

The Safety Analysis Set will consist of all subjects who received at least one dose of CTL-002.

Safety will be assessed on the basis of AE summaries, clinical laboratory data, vital signs, ECG, physical examinations (including neurological examination) and ECOG performance status. All safety summaries will be presented by dose level (Part A) or cohort (Part B) and visit. The number of subjects experiencing each AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, NCI-CTCAE grade, and relationship to study treatment. Serious and related Adverse Events and AEs leading to discontinuation will be summarized separately.

Vital signs, physical examination findings, ECG parameters and clinical laboratory tests (i.e., clinical chemistry, hematology, cytokines & chemokines, pharmacodynamic biomarkers, ADA, and urinalysis) will be summarized. For laboratory data, abnormal values will be flagged in the data listings. All safety data will be included in the subject data listings.

The PK Analysis Set will consist of all subjects who received at least one dose of study medication and have at least one measurable concentration of CTL-002.

Plasma concentrations of CTL-002 will be summarized by dose level (Part A) and cohort (Part B) using descriptive statistics (number of subjects [n], mean, standard deviation, coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum by nominal time point). Summary statistics will also be provided for PK parameters by cycle, including but not limited to AUC, Cmax, and $t_{1/2}$.

For Part A (Phase 1; dose escalation), L3SMI results and the 5 Mini Cachexia Score [MCASCO] components and the 3 cachexia classification groups will be summarized by dose level and visit using descriptive statistics.

Pharmacodynamic effects will be based on appropriate summaries of cytokines, chemokines, and other circulating biomarkers. Correlations of GDF-15 serum levels with certain PD results may be included graphically.

Exploratory endpoints will be based on summaries of immune cell phenotyping, molecular profiling, RECIST V1.1, and iRECIST parameters.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug Antibodies
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARE	Adverse Radiation Effect
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATIII	Antithrombin III
AUC	Area Under the Curve
AUC_{inf}	Area Under the Curve from 0 to Infinity
β-HCG	β-human Chorionic Gonadotropin
BLCA	Bladder Urothelial Carcinoma
BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood Pressure
BRCA	Breast Invasive Carcinoma
CAR-T	Chimeric Antigen Receptor Therapy
CD	Cluster of Differentiation
CDC	Complement-dependent Cytotoxicity
CESC	Cervical Squamous Cell Carcinoma and Endocervical Adenocarcinoma
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Concentration
CMS	Consensus Molecular Subtype
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CPMP	Committee for Proprietary Medicinal Products
CR	Complete Response
CRC	Colorectal Cancer (Colon Adenocarcinoma, Rectum Adenocarcinoma)
CRP	C-reactive protein

Abbreviation	Definition
CSCC	Cutaneous Squamous-Cell Carcinoma
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DRF	Dose Range Finding
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	Formalin-fixed Paraffin-embedded
FIH	First-in-human
GCP	Good Clinical Practice
GDF-15	Growth Differentiation Factor 15
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hGDF-15	Human Growth Differentiation Factor 15
HIV	Human Immunodeficiency Virus
HNSC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
Hr(s)	Hour(s)
IATA	International Airline Transportation Association
ICAM-1	Intracellular Adhesion Molecule-l
ICF	Informed Consent form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit

Abbreviation	Definition
IEC	Independent Ethics Committee
IFN	Interferon
IgG4	Immunoglobulin G4
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
irAE	Immune Related Adverse Event
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors for Immune-based Therapeutics
IRR	Infusion-related Reaction
iUPD	Immune Unconfirmed Progressive Disease
IV	Intravenous(ly)
KIRC	Kidney Renal Clear Cell Carcinoma
L3SMI	L3 skeletal muscle index
LFA-1	Lymphocyte Function-associated Antigen 1
LDH	Lactate Dehydrogenase
LUAD	Lung Adenocarcinoma
LVEF	Left Ventricular Ejection Fraction
MCASCO	Mini Cachexia Score
MedDRA	Medical Dictionary for Regulatory Activities
MIG	Monokine Induced by Gamma
Min	Minute(s)
MMR	Mismatch-repair
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSI	Microsatellite Instability
MSS	Micro-satellite Stable
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHP	Non-Human Primate

Abbreviation	Definition
NOAEL	No-observed Adverse Effect Level
NOEL	No-observed Effect Level
NSAID	Non-steroidal Anti-inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
NT-proBNP	N-terminal B-type natriuretic peptide
NYHA	New York Heart Association
OAE	Other Adverse Event
ORR	Overall Response Rate
OS	Overall Survival
PAAD	Pancreatic Adenocarcinoma
PD	Progressive Disease
PD-1	Programmed Death 1
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death Ligand 2
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PNS	Paraneoplastic Syndrome
PR	Partial Response
PT	Prothrombin Time
Q2wk	Every second week
Q3wk	Every third week
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RNAseq	Ribonucleic Acid Sequencing
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Stable Disease

Abbreviation	Definition
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SoA	Schedule of Assessments
SRC	Safety Review Committee
STAD	Stomach Adenocarcinoma
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half-life
TB	Tuberculosis
TCGA	The Cancer Genome Atlas
TEAE	Treatment Emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
TGCT	Testicular Germ Cell Tumors
TGF-β	Transforming Growth Factor-Beta
TMB	Tumor Mutational Burden
TMTB	Total Measured Tumor Burden
TNF	Tumor Necrosis Factor
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
ULN	Upper Limit of Normal
WKS	Weeks
WHO	World Health Organization

1. INTRODUCTION

1.1. Summary of CTL-002 (Visugromab)

CTL-002 is a humanized, hinge-stabilized immunoglobulin (Ig) G4-kappa monoclonal antibody targeting growth differentiation factor 15 (GDF-15). GDF-15 is a cytokine of the transforming growth factor-beta (TGF-ß) superfamily, which is involved in immune-exclusion in cancer. High tumor/serum levels correlate with recurrence, short progression-free survival (PFS) and overall survival (OS) in various cancer indications.

CTL-002 binds GDF-15 and thus neutralizes its function. This interferes with the immunosuppressive capabilities of the tumor and should render it susceptible to immune clearance. Development of CTL-002 in combination with programmed death-1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors is foreseen as a rational initial development step.

1.2. Summary of Non-Clinical Data

GDF-15 is a remote member of the TGF-ß superfamily and is expressed in healthy tissue at low levels, only. Its biologic role appears to be prevention of overshooting immune cell invasion into tissues under (patho-) physiologic stress. In this context, GDF-15 is highly expressed in the placenta which appears to protect the fetus from the mothers' immune system. Tumors are suspected to hijack this mechanism and have been shown to overexpress GDF-15 substantially. Successful immune cell infiltration is a key prerequisite for most immunotherapeutic strategies in cancer, such as checkpoint inhibitors and chimeric antigen receptor therapy (CAR-T) cells. Therefore, neutralization of GDF-15 is expected to mediate immune cell infiltration to tumor tissues for subsequent successful immunotherapy.

GDF-15 inhibits successful adhesion of leukocytes to endothelial cells by inhibiting or destabilizing the high-affine conformation of lymphocyte function-associated antigen 1 (LFA-1) on leukocytes necessary for tight interaction with intracellular adhesion molecule-l (ICAM-1) on endothelial cells. Based on flow-adhesion assays and super-resolution microscopy techniques it could be shown that neutralization of GDF-15 by CTL-002 restores the ability of T-cells to adhere to activated endothelium and form stable LFA-1-ICAM-1 interactions. GDF-15 still bound on the surface of cells can also be bound by CTL-002 which abrogates its cleavage and subsequent release and therefore is also neutralized efficiently.

To study GDF-15 in vivo a human growth differentiation factor 15 (hGDF-15) overexpressing MC38 cell line was generated. MC38 is a murine colorectal adenocarcinoma cell line that is syngeneic with C57BL6. Experiments show that after implantation GDF-15 overexpressing tumors grow faster than non-GDF-15 expressing control tumors. Furthermore, GDF-15 overexpression negatively impacts response to anti-PD-1 therapy: in GDF-15 low MC38 100% of the animals survive with anti-PD-1 therapy whilst only 10% survive with GDF-15 high MC38 and therapy. This is most likely due to limitation of immune cell infiltration necessary for successful immunotherapy. When CTL-002 is co-administered with anti-PD-1 therapy in GDF-15 high MC38 tumor bearing mice, 50% of mice do survive, which was confirmed in a syngeneic orthotopic Panc02 model which naturally expresses high levels of GDF-15. This supports the notion that CTL-002 may reestablish immune cell infiltration, required for efficacious therapy with anti-PD-1/PD-L1 compounds. CTL-002 inhibits the function of GDF-15 but does not elicit

complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Overall, the available pharmacology data provide a thorough characterization of the mode of action of CTL-002 as well as a well-supported rationale for its clinical evaluation in patients with cancer and GDF-15 elevation in the tumor microenvironment. Pharmacokinetic and pharmacodynamic (GDF-15 inhibition in serum) data of CTL-002 were generated in non-human primates and used to predict pharmacokinetics as well as pharmacokinetics (PK)/pharmacodynamics in humans. Data from the PK/pharmacodynamic model also provided important information for the estimation of a safe starting dose in the first-in-human (FIH) study of CTL-002. CTL-002 is being developed for the treatment of patients with advanced, refractory cancer, either as stand-alone treatment and/or in combination with PD-1/PD-L1 inhibitors or other immunotherapeutic combination therapies. Therefore, both International Council for Harmonisation (ICH) S6 and ICH S9 have been considered in the design of the non-clinical development program.

The cynomolgus monkey was identified as the most relevant species for toxicity testing. The binding affinity of CTL-002 to human and cynomolgus GDF-15 is 38.3 and 108 pM, respectively. Therefore, pivotal toxicology was only assessed in the Cynomolgus monkey in a 4-week study with once weekly IV administration of CTL-002. No toxicity was observed up to the highest tested dose of 100 mg/kg, despite full target inhibition across the dosing interval. A Good Laboratory Practice (GLP)-compliant tissue cross-reactivity study was conducted using human and Cynomolgus monkey tissues. Staining with CTL-002 in the tissue panels examined was limited to the cytoplasm of trophoblasts in the human and monkey placenta, which was consistent with the reported expression of its target protein, GDF-15, in the placenta. No unanticipated cross-reactivity was observed as it is expected for a soluble cytokine. In conclusion, sufficient non-clinical data have been generated to allow an adequate risk assessment. There were no findings that would preclude the clinical development of CTL-002 in patients with advanced, refractory cancer.

Refer to the Investigator's Brochure for more detailed information.

1.3. Core Development Rationale

CTL-002 is a humanized, hinge-stabilized IgG4 monoclonal antibody targeting GDF-15, a remote member of the transforming growth factor β superfamily of cytokines, that is associated with poor outcome and reduced overall survival in a multitude of cancer types and has been linked to immunosuppression in the tumor microenvironment. Based on the by CatalYm identified mode-of-action, suppression of tumor-derived GDF-15 by CTL-002 should reverse the T-cell and immune cell repellent effect of tumor-secreted GDF-15 and allow for effective T cell/immune cell transgression from the intravascular space into the tumor microenvironment. This would allow to turn so-called "cold tumors" into "hot tumors" (Bonaventura et al., 2019), removing a well-recognized major obstacle for effective checkpoint-inhibitor therapy. In this context, it has been shown that tumor regression after therapeutic PD-1 blockade requires presence of already resident cluster of differentiation (CD)8+ T cells in the tumor microenvironment (Tumeh et al, 2014). Despite the huge advances in immunotherapy by checkpoint-inhibitors their efficacy often remains quite limited due to restricted infiltration of immune cells in the tumor microenvironment (Galon et al, 2019; Bonaventura et al, 2019). When GDF-15 levels were measured in melanoma patients treated with anti-PD-1, a strong inverse correlation of GDF-15 serum levels with response to anti-PD-1 was observed. The purported role of GDF-15 in feto-maternal tolerance and

immunosuppression during tissue injury and preclinical data generated by CatalYm supports the concept that tumor-derived GDF-15 prevents immune cell infiltration into the tumor and neutralizing it with CTL-002 could exert significant benefit. In recent years increasing evidence has emerged that GDF-15 does play a critical immune-regulatory role in cancer, acting most likely mainly as "T cell repellant" and also local immuno-suppressant. A wealth of publications has emerged indicating that high GDF 15 serum levels in various cancer types correlate with shorter overall survival and that GDF-15 is an independent factor for subject survival within various tumor types (Wischhusen et al, 2020). Furthermore, GDF-15 has been linked to non-response to checkpoint inhibitors such as pembrolizumab and nivolumab. Preclinical and translational data by the sponsor and others do support these findings and have demonstrated induction of potent antitumoral response by checkpoint inhibitors if GDF-15 is suppressed [Haake et al.. AACR2020; Abstract #5597; Hurt et al. ASCO 2021; Abstr. #1828; Wang et al.J Imm Canc 2021]. CTL-002 is developed as a targeted therapy to allow for effective T cell/immune cell shuttling into the tumor, making it e.g., a most natural combination partner for established checkpoint-inhibitor therapies.

Consequently, the initial clinical development strategy for CTL-002 has been focused on a combination with checkpoint inhibitors and potentially T cell-based therapies as another option. Early Phase 1 development has been aimed to establish safety of the combination of an approved checkpoint inhibitor with CTL-002, to explore the ability to reverse GDF-15-mediated resistance to checkpoint inhibitors. Phase 2 development of CTL-002 in combination with checkpoint inhibitors has been initiated and is currently ongoing, evaluating various tumor types of interest (identified by a proprietary translational research program of the sponsor) and investigating if „cold" tumors can be turned „hot" and may respond then to treatment and if certain markers are predictive at baseline for treatment outcome.

Stereotactic radiotherapy of tumor lesion(s) has been reported as a promising modality to enhance efficacy of immunotherapy and first observations of the so called "abscopal" effect were published in the 1950s (Mole et al., 1953, Formenti et al., 2009). This phenomenon describes shrinkage of non-irradiated tumor lesions, and it is shown that radiotherapy may trigger the release of tumor-associated antigens and subsequently may improve the anti-tumor immune response (Dagoglu et al., 2019, Barsoumian et al., 2020, Zhang et al., 2022). Therefore, the application of non-ablative, stereotactic radiotherapy should be considered as an option to optimize immunotherapy and for any combination treatment with a checkpoint inhibitor particularly.

1.4. The Target and its Role in Cancer

In cancer, GDF-15 had so far been mainly associated with cachexia, mediated via a brainstem selective receptor (GFRAL; Emmerson et al, 2017). Recent research indicated in this context, that its main role in cachexia relates to induction of anorexia, while muscle wasting may rather be linked to another GDF-family member (GDF-11; George et al, 2016, Hammers et al, 2017).

In recent years though increasing evidence has emerged that GDF-15 may play a critical immuno-regulatory role in physiology, pathophysiology and in cancer, Physiologically GDF-15 has a prominent role in the generation of feto-maternal immune tolerance and protect the semi-allogenic fetus from maternal immune attack (Carbillon et al., 2004). Expressed by the trophoblasts, GDF-15 inhibits infiltration into the placenta thus acting most likely mainly as "T cell repellant". For cancer cells it would naturally be highly attractive to utilize and "hijack" such an immune-cell repellant mechanism, blocking immune-cell entry into the tumor

microenvironment, and consequently preventing the immune system from removing cancer cells. In line with this, in recent years a wealth of publications has emerged indicating that high GDF-15 serum levels in various cancer types correlate with shorter overall survival and that GDF-15 is an independent factor for patient survival within various tumor types (Wischhusen et al, 2020). Serum levels are elevated in e.g., skin, colorectal, ovarian, head & neck, gastric, prostate, esophageal cancer and glioblastoma (see Table 1).

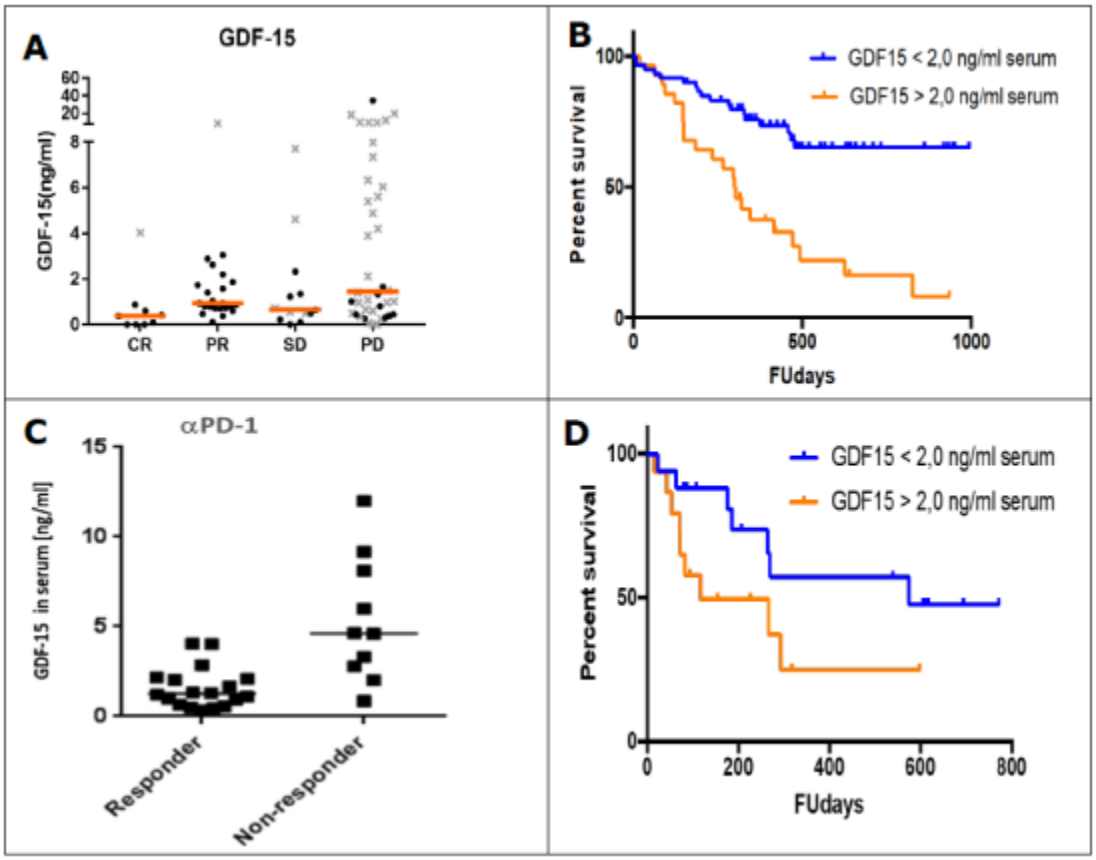
Table 1 Scientific Publications Analyzing Serum GDF-15 Levels in Various Tumor Types and Correlation with Outcome and Overall Survival

Indication	GDF-15 and survival	Reference
Colorectal cancer	GDF-15 correlates with shorter OS	Mehta et al, 2015 Li et al, 2016 Vocka et al, 2018
Gastric cancer	GDF-15 level correlates with differentiation stage	Baek et al., 2009
Ovarian Cancer	GDF-15 level correlates with PFS and platinum- refractory disease	Zhao et al., 2018
NSCLC	GDF-15 correlates with shorter OS	Liu et al, 2016
Multiple myeloma	GDF-15 correlates with shorter OS and b2- microglobulin level and disease stage	Corre et al, 2012
HNSCC	GDF-15 correlates with shorter OS and tumor load	Schiegnitz et al, 2012
Melanoma / Uveal melanoma	GDF level correlates with shorter OS/ GDF-15 high in patients with clinically detectable metastasis	Weide et al, 2016 Suesskind et al, 2009
Prostate cancer	GDF-15 correlates with shorter OS	Brown et al, 2009
Esophageal cancer	GDF-15 correlates with shorter OS	Wang et al., 2014
Pancreatic cancer	GDF-15 shows trend for shorter OS	Ratnam et al, 2017
Glioblastoma	High CSF-GDF-15 levels correlates with shorter OS	Shnaper et al, 2009

Abbreviations: CSR = colony-stimulating factor; GDF-15 = growth differentiation factor-15; HNSCC = head and neck squamous-cell carcinoma; NSCLC = Non-small cell lung carcinoma; OS = overall survival; PFS = progression-free survival

Two proprietary analyses by the Sponsor indicated in addition that GDF-15 levels also seem to correlate with non-response to PD-1 antagonists. This again is in line with the concept that GDF-15 acts as immune- and T cell repellant and keeps CD8+/CD4+ T cells out of the tumor, preventing PD-1 antagonism-based activity (Figure 1).

Figure 1: Baseline GDF-15 Serum Level Correlates with Response to Anti-PD-1/PD-L1 Treatment



Abbreviations: CR = complete response; FU = Follow-up; GDF-15 = growth differentiation factor-15; PD = progressive disease; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PR = partial response; SD = stable disease

In vitro data by CatalYm have demonstrated that blockade of GDF-15 with CTL-002 results in increased adhesion and transgression of immune cells and in vivo experiments confirmed that blocking GDF-15 results in significantly increased T cell numbers in the tumor tissue and leads to reversal of anti-PD-1 refractoriness.

1.5. Translational Data Suggesting GDF-15 Dependency of Specific Indications

Bioinformatic processing and statistical analysis of The Cancer Genome Atlas (TCGA) data was performed in collaboration with the Institute of Bioinformatics, Medizinische Universität Innsbruck by the group of Prof Dr. Trajanoski (data unpublished). The aim of this work was to delineate the impact of GDF-15 messenger ribonucleic acid (mRNA) expression on the tumor microenvironment and its immune cell landscape in order to elucidate the role of GDF-15 for T cell exclusion from the tumor. The overall objective was to perform pan-cancer immunogenomic and integrative analyses of high throughput and clinical data from the public domain. For this purpose, GDF-15 gene expression patterns from The Cancer Genome Atlas of 33 cancer types and more than 11,000 patients were used to study the distribution in tumor and normal tissue and to specifically correlate with:

- expression patterns and hallmarks of the tumor and its microenvironment
- estimation of the immune phenotype/contexture
- immune related expression, signatures or scores
- clinical parameter and outcome, as well as
- molecular subgroups and genotypes

As a result, in most indications GDF-15 mRNA is higher expressed in tumor tissue compared to adjacent normal tissue or healthy individual normal tissue, supported by findings from single cell ribonucleic acid (RNA) sequencing (RNAseq) analyses. A larger group of major cancer indications showed a consistent negative association between GDF-15 mRNA level and immune related scores and estimations of CD8+ T cells or cytotoxic T-lymphocytes (testicular germ cell tumors [TGCT], cervical squamous cell carcinoma and endocervical adenocarcinoma [CESC], pancreatic adenocarcinoma [PAAD], colorectal carcinoma [CRC], lung adenocarcinoma [LUAD], breast invasive carcinoma [BRCA], bladder urothelial carcinoma [BLCA]), including indications that are or in part are checkpoint blocker indications (CRC and LUAD). Further analyses investigating potential correlations for molecular subtypes in different indications revealed higher GDF-15 mRNA expression in luminal subtypes (BRCA, BLCA) in contrast to basal subtypes with lower GDF15 expression. Whereas in microsatellite instability (MSI) high samples versus MSI low and microsatellite stable samples no significant differences of GDF15 mRNA expression were observed, analyses of the consensus molecular subtypes (CMS) in CRC demonstrated that GDF-15 mRNA expression was significantly higher in CMS2 and CMS3 compared to CMS1 and CMS4. This is in contrast to high GDF15 mRNA expression in MSI, Eppstein-Barr virus (EBV)+, or human papillomavirus (HPV)+ related subtypes in head and neck squamous cell carcinoma (HNSC) and stomach adenocarcinoma (STAD), respectively.

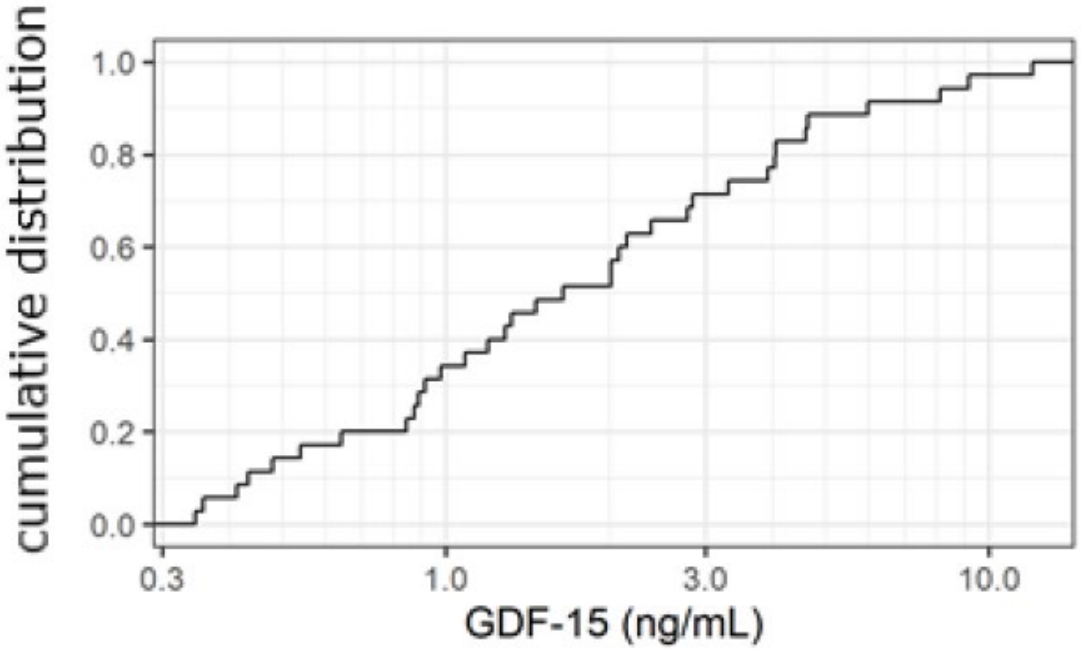
In summary, for CRC, BLCA, BRCA, PAAD, LUAD, kidney renal clear cell carcinoma (KIRC), CESC, and TGCT in at least 10 of 13 selected immune related analyses an inverse relation to GDF-15 mRNA expression was observed, which is consistent with the GDF-15 related T-cell exclusion mechanism.

1.6. Starting Dose Rationale

In setting an acceptable starting dose for clinical testing it is important to consider the potential pharmacological activity as well as published clinical experience with similar molecules. Analysis of available non-clinical and clinical safety data for immuno-oncology drugs shows that FIH doses based on either 20 to 80% target occupancy and/or 20 to 80% in vitro functional activity had acceptable clinical toxicity. Furthermore, FIH systemic exposure above target saturation was also acceptable for antibodies with either normal or silenced ADCC activity (Saber et al., 2016). CTL-002 is an IgG4 antibody targeting the soluble cytokine GDF-15, a member of the TGF-ß superfamily. GDF-15 has its primary function in feto-maternal tolerance and anorexia. CTL-002 neutralizes the function of GDF-15 but cannot induce ADCC or CDC. Therefore, the intrinsic risk of inhibiting GDF-15 is considered relatively low. This is further evidenced by the lack of any findings in the GLP-toxicity study in monkeys, in which complete target inhibition was sustained across the dosing period at all dose levels tested, as well as the largely unremarkable phenotype of GDF-15 knock-out mice. In contrast, elevated GDF-15 levels are frequently reported in cancer patients, where they elicit immune evasion in the tumor microenvironment. This is related to the

primary mode of action of GDF-15, which inhibits the leukocyte integrin activation and thereby prevents leukocyte infiltration into tissues. GDF-15 serum levels observed in a cohort of 34 patients with advanced melanoma are depicted in Figure 2 (Unpublished data, Prof. R. Dummer, University of Zurich). While the normal serum level of GDF-15 in healthy subjects has a mean of about 0.5 ng/ml (Verhamme et al, 2017, Wollert et al, 2018), the mean in this cohort was approximately 2.0 ng/ml and maximum levels above 10 ng/ml were observed, considered to be generated by tumor tissue.

Figure 2: Cumulative Distribution of GDF-15 Levels in a Cohort of 34 Patients with Advanced Melanoma Refractory to Anti-PD-1/PD-L1 Treatment

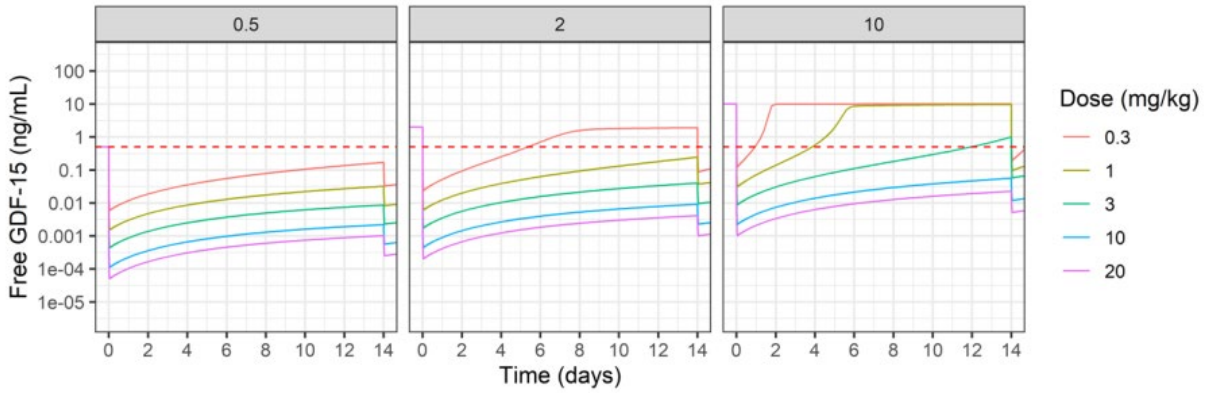


Abbreviations: GDF-15 = growth differentiation factor-15; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1

Of note, intratumoral levels of GDF-15 in such GDF-15-expressing cancers are expected to be significantly higher than those which can be measured in the systemic circulation. This is due to the localized production of GDF-15 by the tumor. Using PK/pharmacodynamic modeling, GDF-15 levels within the tumor have been predicted to be more than 10-fold higher than in the systemic circulation (see the Investigator's Brochure for details).

Based on all the information summarized above and using PK and GDF-15 data obtained in the GLP toxicity study and the dose range finding (DRF) study in Cynomolgus monkeys, a PK/pharmacodynamic model was built and used to predict the PK/pharmacodynamic characteristics of CTL-002 in humans. As the extent and duration of GDF-15 suppression by CTL-002 is expected to depend on the baseline level of GDF-15, simulations were run for baseline levels of either 2.0 ng/ml GDF-15, (approximately the mean observed in the patient cohort described above), as well as 10 ng/ml (the 95th percentile), and 0.5 ng/ml, (the 15th percentile and the mean level observed in healthy individuals). Details of the model are provided in the Investigator's Brochure and a summary is shown in Figure 3.

Figure 3: Predicted Inhibition of Serum GDF-15 at Planned Clinical Doses and for a Range of Baseline Levels



Abbreviation: GDF-15 = growth differentiation factor-15

The proposed starting dose derived from this PK/pharmacodynamic model is 0.3 mg/kg.

As indicated in Figure 3 above on the right, at the high end of the range of GDF-15 baseline levels observed in advanced melanoma patients (10 ng/ml), the proposed starting dose of 0.3 mg/kg CTL-002 will only lower serum GDF-15 slightly below normal levels (0.5 ng/ml) at maximum concentration (C_{max}), so that its endogenous functions should not be compromised. Only in patients with lower GDF-15 levels, transient reductions below 0.5 ng/ml are expected. However, as explained above, transient and even long-lasting neutralization of GDF-15 has not been associated with any adverse effects in monkeys nor serious findings in knock-out mice. Therefore, the risk of lowering GDF-15 below 'healthy' baseline in a fraction of patients for limited time is considered very low. Furthermore, based on the higher GDF-15 concentration in the tumor microenvironment, target inhibition at the site of intended action will initially likely be subtherapeutic and further dose escalation required to achieve anti-tumor efficacy, especially in the population with high GDF-15 baseline levels. Therefore, the proposed starting dose of 0.3 mg/kg, administered every other week, is primarily based on safety considerations for the fraction of the population with relatively low baseline levels of the target.

In addition to the PK/pharmacodynamic model described above, C_{max} and area under the curve (AUC) from 0 to infinity (AUC_{inf}) after the first dose at the no-observed effect level (NOEL) of 100 mg/kg observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys were compared with the predicted exposure in humans for each dose in the proposed dose escalation regimen. The proposed 0.3 mg/kg starting dose is anticipated to give a 683-fold lower C_{max} and a 487-fold lower AUC_{inf} than the NOEL in non-human primate (NHP) and this reduces to a 6-fold lower C_{max} and 5-fold lower AUC at the end of the currently planned dose escalation phase in human (20 mg/kg). Furthermore, the PK and Pharmacodynamic behavior of CTL-002 in human will be confirmed during dose escalation, enabling any dose adjustments to be made. Thus, the proposed starting dose and dose range are well covered by the available toxicology data in monkeys. Of note, in line with the mechanism of action of CTL-002, no cytokine release was observed in the monkeys at any of the tested dose levels.

For completeness, standard extrapolation as described in Food and Drug Administration's (FDA's) guidance on the selection of a safe starting dose for FIH trials leads to a safety margin of 333-fold

between the proposed starting dose and the NOEL in monkeys, which increases to 666-fold for the AUC, if the once- versus twice-weekly dosing regimen in monkeys and humans, respectively, is taken in to account (FDA, 2005). While the results are similar, margins derived from PK modeling are considered more reliable.

Overall, these data and analyses support 0.3 mg/kg/Q2wk as a safe and reasonable starting dose and regimen that balances well between cautious safety considerations, desire to start with an at least theoretically clinically beneficial dose and the ultimate goal to have the ability to reach within reasonable time frame therapeutic doses that provide permanent target suppression in immediate tumor proximity even in patients with very high baseline GDF-15 serum values (e.g., 10 ng/ml and above).

Importantly, current data and modelling also confirms that doses of 3 mg/kg and above may achieve sustained target neutralization in the direct vascular proximity of the tumor, even in patients with high serum concentrations of GDF-15, supporting the validity of the concept to develop CTL-002 as potentially highly effective immunomodulatory compound neutralizing the T-cell repellent GDF-15 and facilitating T cell entry into the tumor microenvironment to empower T cell activating agents such as anti-PD-1/PD-L1 to eliminate tumor cells.

In summary, the proposed starting dose of 0.3 mg/kg/Q2wk IV CTL-002 has been selected based upon a state-of-the-art integrated analysis of all pharmacologic and toxicologic data and subsequent PK/pharmacodynamic-modeling of degree of target neutralization. No data or observations were made during the analysis being suggestive of a need for an even lower starting dose.

Consequently, 0.3 mg/kg/Q2wk IV CTL-002 is seen as safe and reasonable starting dose for the initial exploration of CTL-002 as anticancer treatment in combination with anti-PD-1/PD-L1 agents in patients suffering from advanced-stage, refractory cancer disease.

1.7. Clinical Experience with Visugromab (CTL-002)

1.7.1. Phase 1 Study CTL-002-001

This first-in-human study of CTL-002, CTL-002-001, consists of Part A (Phase 1; dose escalation) followed by Part B (Phase 2a; expansion). Enrolment into Part A has been completed, Part B has been started in Feb2022 in Europe and is still ongoing. As of 27 Oct 2022, a cumulative total of 80 subjects have been treated with CTL-002 and Nivolumab as an IV infusion.

In the Phase 1 part of study CTL-002-001, a total of 25 subjects received in “3+3” cohorts escalating doses of CTL-002 with doses ranging from 0.3 to 20 mg/kg, given every 2 weeks, as intravenous (IV) infusion over approximately 1 hour in combination with the anti-PD-1 antibody nivolumab at a dose of 240 mg given every 2 weeks as IV infusion over approximately 30 minutes. All subjects were treated in a last-line, heavily pretreated setting (on average 4.4 prior lines of therapy) and relapsed/refractory to prior anti-PD-1/PD-L1 treatment with a minimum of 12 weeks continued exposure to anti-PD-1/-L1. The combination of CTL-002 and nivolumab was very well tolerated, with no DLT occurring and no Grade 4 or 5 AE being linked to study drug.

For 6 subjects in this heavily pre-treated last-line tumor population clinical benefit was observed, with three achieved confirmed partial responses of currently up to 17 months duration (one CUP tumor, one hepatocellular carcinoma, one mesothelioma) and three additional subjects

experiencing long-term disease stabilization (2 x beyond 6 months, 1 x 5.5 months followed by non-target lesion local irradiation and partial response with continued CTL-002/nivolumab treatment).

In the Phase 2 part, a total of 55 subjects have been treated with CTL-002 at 10.0 mg/kg and Nivolumab as an IV infusion. Phase 2 exploration of the combination of CTL-002 and checkpoint inhibitors is ongoing in various tumor types and settings.

The initial clinical experience is reflective of a very benign safety profile and significant clinical antitumoral activity in last-line tumor subjects.

The combination of CTL-002 and nivolumab has so far been well tolerated; and no DLT did occur in any subject throughout the full observation period and no safety event of major concern was reported for Phase 1. Confirmatory signs for lasting and complete GDF-15 neutralization and consistent signs of a multi-fold tumor-selective T cell influx in the majority of subjects have been observed with CTl-002 in sequential tumor biopsies.

Refer also to the Investigator's Brochure.

1.8. Benefit/Risk and Ethical Assessment

CTL-002-001 is the first study conducted in humans with CTL-002. Consequently, only limited experiences in humans exist.

In the Phase 1 part of CTL-002-001, the combination of CTL-002 and nivolumab has so far been very well tolerated. No CTCAE Grade 4 or 5 treatment emergent adverse event (TEAE) and no DLT did occur in any subject throughout the entire dosing/observation period and no safety event of major clinical concern was reported. All subjects included had advanced-stage/metastatic disease with all available, approved treatment options being exhausted, including at least one prior anti-PD-1/PD-L1 treatment of minimum 12 weeks duration and being relapsed/refractory to it. Of 24 evaluable subjects six experienced significant, meaningful clinical benefit by either achieving lasting and confirmed partial remissions (N = 3, one patient beyond 17 months duration and ongoing, or long-term disease stabilization (N = 3) with 2 lasting beyond 6 months duration with CTL-002/nivolumab combination treatment. In addition, various biomarker analyses were conducted and indicated that (1) in last-line disease PD-L1 expression by tumor cells and elevated tumor inflammation score could be predictive markers for treatment benefit by CTL-002 in combination with a checkpoint inhibitor and (2) that immunologically „cold" tumors can be turned „hot" by CTL-002 + nivolumab.

The guidance provided for the Investigator is based upon (1) known biology of GDF-15, (2) identified mode-of-action of CTL-002 and (3) all available non-clinical data, including data from GDF-15 knock-out mouse models and (4) all available clinical data from the study CTL-002-001.

Cancer tissues, normal organ tissues in distress and placenta are known to overexpress GDF-15, most likely in all cases to prevent excessive immune cell infiltration to the respective tissue. As per available in vitro and in vivo research data, GDF-15 produced by above tissues does substantially reduce vascular T cell adhesion and endothelial transmigration, preventing T cell entry into the respective tissue or its immediate proximity.

In cancer, neutralizing GDF-15 with CTL-002 in the tumor proximity should block this T cell repelling mechanism and facilitate entry of predominantly CD8+ T cells into the tumor microenvironment. This should potentiate activity of T cell activating agents such as anti-PD-1/PD-L1 compounds and/or reverse GDF-15 mediated resistance to anti-PD-1/PD-L1 compounds.

To date, CTL-002 has shown a benign and well acceptable safety profile in animals at all doses tested. No non-clinical mortality or toxicity of any significance has been observed. Neutralizing GDF-15 with CTL-002 has induced potent antitumoral activity in in vivo mouse models by reversing GDF-15 mediated resistance to anti-PD-1/PD-L1 agents. These findings warrant clinical exploration of CTL-002 in subjects with advanced cancer.

Yet, this mode-of-action naturally carries various potential risks that are illustrated and evaluated in detail below. One potential area of concern is the expected potentiation of effects initiated by anti-PD-1/PD-L1 compounds when combining them with CTL-002. Apart from anti-PD-1/PD-L1 mediated efficacy, toxicities of these compounds may also be enhanced. A second potential area of concern is the physiologic role of GDF-15 in organ protection for organs in distress. If GDF-15 is suppressed during treatment with CTL-002 and organ distress occurs (e.g., myocardial infarction, infection, toxic organ damage) excessive organ infiltration by immune cells and unwelcome tissue disturbance/destruction may occur. A third potential area of concern are rare findings made in individual mouse knock-out models for GDF-15.

Based on nonclinical toxicology findings and clinical experience to date with CTL-002 or similar drugs, potential risks of exposure to CTL-002 have been identified as summarized in the following sections.

1.8.1. Possible Potentiation of Adverse Events of Anti-PD-1/PD-L1 Compounds

Apart from anti-PD-1/PD-L1 mediated efficacy also toxicities may be enhanced. This enhancement may result in:

- Earlier occurrence of a particular anti-PD-1/PD-L1 related toxicity
- More rapid evolution of a particular anti-PD-1/PD-L1 related toxicity
- Higher overall toxicity grade reached for any so far described anti-PD-1/PD-L1 toxicity such as pruritus, rash, diarrhea, pneumonitis, colitis, hepatitis, and hypothyroidism among many others
- Also new autoimmune-related phenomena may be triggered, affecting organs and organ systems so far not known to be affected by anti-PD-1/PD-L1 toxicity

1.8.2. Organ Distress During CTL-002 Treatment Leading to Excessive Immune Cell Infiltration

GDF-15 is regarded as stress-response cytokine that during organ damage and inflammation may play an important immunoregulatory role. Knock-out model experiments point towards critical functions in preventing an overshooting immune cell infiltration into tissues that underwent significant hypoxic, toxic, infectious/inflammatory or metabolic damage. Yet, also some contradictory reports exist, claiming that GDF-15 elevation may contribute e.g., to smoking induced lung tissue damage (Verhamme et al, 2017), where reduction in GDF-15 would be beneficial.

GDF-15 levels are significantly increased in critically ill patients with beginning or established organ failure or major infection/inflammation (e.g., myocardial infarction, heart failure, lung failure, toxic liver failure, kidney failure, infection/inflammation and septic events). High GDF-15 levels have been identified for several of these conditions as disease severity marker and being prognostic of short and long-term mortality risk (Buendgens et al, 2017, George et al, 2016). Although the functional role of GDF-15 has not been fully elucidated in any of these conditions it can be assumed that GDF-15 levels may be elevated in general as stress-response and to limit a potentially overshooting immune cell reaction that may add to tissue disturbance or even induce tissue destruction in these affected tissues, although also isolated contradicting reports exist.

Consequently, suppression of GDF-15 by CTL-002 may lead to increased immune cell infiltration and potentially increased tissue disturbance or destruction in any subject that experiences or suffers from:

- Myocardial infarction or other hypoxic events
- Existing heart failure or progression of existing heart failure
- Central nervous system (CNS) hypoxic events
- Pneumonia, sepsis, any severe organ infection
- Liver failure of any type
- Kidney failure of any type
- Pancreatitis, pneumonitis, thyroiditis, hepatitis, colitis or any other "-itis" due to immune cell dysreactivity with healthy tissue
- Any other major hypoxic, toxic, metabolic or immunologic event with significant organ stress or damage.

This may lead in any such event to adverse events (AEs) related to the respective organ or disease situation. Such AEs may encompass functional disturbance of an organ or tissue down to organ or tissue destruction in severe cases.

1.8.3. Potentially Relevant Findings from GDF-15 Knock-out Models

As GDF-15 knock-out mice are reflective of total GDF-15 neutralization in an organism, they represent the most extreme model for potential AEs that may be induced by potent and complete GDF-15 suppression. Naturally, it needs to be kept in mind that the mouse immune system composition has a distinctly different phenotype compared to the human one and findings may not be transferable at all. Notably, GDF-15 knock-out mice show no obvious aberrant phenotype per se. They do not develop any autoimmune phenotype. However, a few findings, described mostly in individual knock-out strains, only, still need to be considered for patient monitoring and expected potential AE profile:

- Accelerated thrombus formation following injury, and decreased bleeding times (Rossaint et al, 2013).
- Progressive postnatal loss of motoneurons (spinal, facial, trigeminal), and dorsal-root sensory neurons, beginning at month 3 and culminating at month 6 affecting rotarod capabilities (Strelau et al, 2009).

- Dopaminergic neurons in the substantia nigra appeared GDF-15 supported, but no findings of concern were made in this region in any knock-outs (Strelau et al, 2000).
- Task-dependent increase in locomotion and reduced anxiety-related behavior (Low et al, 2017).

For guidance on the management for each risk, refer to Guidelines provided in Section 5. Detailed information about the known and expected benefits and risks can be found in the Investigator's Brochure for CTL-002, and details of supportive care guidelines for each expected AE are provided in Section 5 of the protocol.

Based on the SmPC (Summary of Product Characteristics; Opdivo SMPC, 2020) or Product Label (Opdivo Product Label, 2021) for nivolumab, the defined checkpoint inhibitor for all cohorts (except the cutaneous squamous-cell carcinoma cohort), the following are identified as potential risks of exposure to nivolumab:

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis and hepatotoxicity, immune-mediated endocrinopathies, immune-mediated dermatological adverse reactions and immune-mediated nephritis and renal dysfunction
- Fatigue
- Infusion-related reactions
- Pancreatitis
- Cardiovascular toxicity
- Hematologic toxicity
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
- Embryo-fetal toxicity

Detailed information about the known and expected benefits and risks can be found in the nivolumab SmPC or Product Label, and details of supportive care guidelines for each expected AE are provided in Section 5 of the protocol.

Based on the SmPC (Summary of Product Characteristics; Libtayo, SmPC, 2022) or Product Label (Libtayo, Product Label, 2021) for cemiplimab, the defined checkpoint inhibitor for the cutaneous squamous-cell carcinoma cohort, the following are identified as potential risks of exposure to cemiplimab:

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, and immune-mediated dermatologic adverse reactions, and solid organ transplant rejection
- Infusion-Related Reactions
- Solid organ transplant rejection
- Complications of Allogeneic HSCT
- Embryo-fetal toxicity

Detailed information about the known and expected benefits and risks can be found in the cemiplimab SmPC or Product Label, and details of supportive care guidelines for each expected AE are provided in Section 5 of this protocol.

1.8.4. Possible Potentiation of Adverse Events after Radiotherapy

All subjects that achieve/maintain stable disease by week 24 but do not show tumor shrinkage beyond – 10% as per RECIST criteria can undergo if desired by the treating physician and agreed by the patient stereotactic radiotherapy of one or more tumor lesions to increase neoantigen exposure and potential for response improvement (as was seen in one Phase 1 patient). The rationale behind is to utilize the well-described mechanism of radiotherapy to release tumor-associated antigens and to enhance the anti-tumor immune response.

Any additional immune activation after application of radiotherapy might lead to a potentiation of adverse events, particularly of immune-related type. However, multiple studies have investigated different schedules of radiotherapy in combination with immunotherapy (including checkpoint inhibitor) in solid tumor patients and such combinations have been generally reported with an acceptable safety profile (Luke et al., 2018, Bang et al., 2019).

1.8.5. Conclusion

The benefit-risk for CTL-002 administration as monotherapy and/or in combination with nivolumab/cemiplimab has been carefully reviewed in the planning of this study and is considered positive in light of preclinical safety and current clinical safety profile. The adverse event profile for CTL-002 in combination with nivolumab and cemiplimab is expected to be similar, as both are anti-PD-1 agents with identical mode of action and have a similar AE profile reported.

A total of 25 subjects have been treated in the Phase 1 (dose escalation) of this study, with some individuals receiving up to 12 months of treatment. The initial safety profile of CTL-002 in monotherapy as well as in combination with nivolumab has demonstrated excellent tolerability with no DLT and no Grade 4 or 5 TEAE in any subject throughout the entire dosing period and no clinical finding of significant concern. Of 24 evaluable subjects six experienced significant, meaningful clinical benefit by either achieving lasting and confirmed partial remissions (N = 2) currently in one patient beyond 17 months duration and ongoing, or long-term disease stabilization (N = 3) with 2 lasting beyond 6 months duration with CTL-002/nivolumab combination treatment. Pharmacodynamic data indicate a tumor-selective influx of CD8+ and CD4+ T cells indicative for an anti-tumor immune response in the majority of subjects.

Based upon the excellent safety profile observed in Phase 1 (dose escalation) of the study and the signs for preliminary efficacy (specifically potent antitumoral activity observed in several subjects with lasting partial remissions in anti-PD-1/PD-L1 relapsed/refractory subjects), Phase 2a exploration has been initiated in the first EU countries in subjects with advanced-stage, relapsed or refractory solid tumors and is planned to be opened in Italy, UK and the US. In addition, various biomarker analyses were conducted and indicated that (1) in last-line disease PD-L1 expression by tumor cells and elevated tumor inflammation score could be predictive markers for treatment benefit by CTL-002 in combination with a checkpoint inhibitor and (2) that immunologically „cold“ tumors can be turned „hot“ by CTL- 002 + nivolumab/cemiplimab.

Numerous reports are published describing the immune-modulating capabilities of stereotactic radiotherapy in combination with immunotherapy (Luke et al., 2018). Additionally, the experience

of one subject in Part A who showed progression in liver lesions and following stereotactic radiotherapy, a deep partial response could be observed – not only affecting the radiated lesion but also demonstrating an "abscopal" effect, supports introduction of the option to apply stereotactic radiotherapy and might offer an additional chance to achieve a clinically relevant benefit and might guide such combination towards further development.

The study is conducted with a design to minimize potential risks for subjects.

Thus, the benefit-risk assessment for this first in human Phase 1/2a study is considered positive for subjects with advanced stage, relapsed and refractory solid tumors.

1.9. Trial Objectives

1.9.1. Primary Objective

Part A (Phase 1; dose escalation):

- To determine the safety and tolerability of IV administration of CTL-002 as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor in subjects with advanced-stage solid tumors that relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy.

Part B (Phase 2a; expansion):

- To explore the preliminary anti-tumor activity of CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor in subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge that have either:

  (1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound, or

  (2) colorectal cancer (micro-satellite stable [MSS]/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy, or

  (3) biomarker cohort with mixed solid tumors ("basket" cohort) that are relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound.
- To confirm the safety and tolerability of CTL-002 administered as an IV infusion, in combination with an anti-PD-1 checkpoint inhibitor

1.9.2. Secondary Objectives

Part A (Phase 1; dose escalation):

- To explore the PK of CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor
- To explore the pharmacodynamics of CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor

- To determine the recommended dose(s) for the expansion cohorts (Part B [expansion]) of CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor
- To explore the preliminary anti-tumor activity of CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor
- To explore the effect of CTL-002 on prevention of anorexia and muscle wasting (cachexia)

Part B (Phase 2a; expansion):

- To confirm and further explore the PK/pharmacodynamics of CTL-002 given in combination with an anti-PD-1 checkpoint inhibitor
- To confirm the recommended Phase 2 dose (RP2D) of CTL-002

1.9.3. Exploratory Objectives

Part A (Phase 1; dose escalation):

- To explore additional pharmacodynamics in peripheral blood and tumor tissue (e.g., GDF-15 levels, immune cell phenotypes and activation status), with CTL-002 administered as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor

Part B (Phase 2a; expansion):

- To assess the antitumoral activity of CTL-002 in combination with cemiplimab (checkpoint inhibitor) using World Health Organization (WHO) bidimensional measurements in subjects with advanced-stage cutaneous squamous-cell carcinoma that relapsed on or were primary refractory to a prior anti-PD-1/PD-L1 therapy
- To explore the preliminary anti-tumor activity of CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor in patients with stable disease after receiving stereotactic radiotherapy
- To explore additional pharmacodynamics in peripheral blood and tumor tissue (e.g., GDF-15 level, immune cell phenotypes, and activation status), with CTL-002 administered in combination with an anti-PD-1 checkpoint inhibitor in patients with stable disease after receiving stereotactic radiotherapy.

1.10. Trial Endpoints

1.10.1. Primary Endpoints

Part A (Phase 1; dose escalation):

- Evaluation of the number of subjects with AEs, including serious adverse events (SAEs), clinical laboratory data, vital signs, electrocardiograms (ECGs), physical examination (including neurological assessment) and Eastern Cooperative Oncology Group (ECOG) performance status

Determination of DLTs and maximum tolerated dose (MTD) in Part A of the study using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0**Part B (Phase 2a; expansion):**

- Evaluation of the clinical efficacy according to Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 of CTL-002 in combination with an anti-PD-1 checkpoint inhibitor by assessment of:
    - The proportion of subjects with tumor shrinkage, a confirmed partial response (PR) and/or complete response (CR), and overall response rate (ORR)
    - The interval between the date of first CTL-002 administration and first documented evidence of a PR or CR (time to response [TTR])
    - The interval between the date of first documented evidence of PR or CR, until first documented evidence of disease progression or death, due to any cause (duration of response [DOR])
    - The interval between the date of first CTL-002 administration and the earliest date of disease progression or death (progression free survival [PFS])
    - The interval between the date of first CTL-002 administration and date of death due to any cause (overall survival [OS])
- Evaluation of the number of subjects with AEs, including SAEs, clinical laboratory data, vital signs, ECGs, physical examination (including neurological assessment), and ECOG performance status

1.10.2. Secondary Endpoints

Part A (Phase 1; dose escalation):

- Evaluation of PK parameters of CTL-002 (e.g., C_{max}, AUC, and $t_{1/2}$)
- Evaluation of treatment-emergent cytokine and chemokine profiles in peripheral blood
- Evaluation of treatment-induced anti-drug antibodies (ADA)
- Evaluation of the clinical efficacy according to RECIST V1.1 of CTL-002 as monotherapy and in combination with an anti-PD-1 checkpoint inhibitor by assessment of:
    - The proportion of subjects with tumor shrinkage, a confirmed PR and/or CR, and ORR
    - The interval between the date of first CTL-002 administration and first documented evidence of a PR or CR (TTR)
    - The interval between the date of first documented evidence of PR or CR, until first documented evidence of disease progression or death, due to any cause (DOR)
    - The interval between the date of first CTL-002 administration and the earliest date of disease progression or death (PFS)
    - The interval between the date of first CTL-002 administration and date of death due to any cause (OS)
- To assess appetite, body mass index (BMI, and muscle mass (e.g., L3 skeletal muscle index [L3SMI])

Part B (Phase 2a; expansion):

- Evaluation of PK parameters of CTL-002 (e.g., maximum concentration [C_{max}], area under the curve [AUC], and half-life [$t_{1/2}$])
- Evaluation of treatment-emergent cytokine and chemokine profiles in peripheral blood
- Evaluation of treatment-induced ADA
- Evaluation of GDF-15 serum levels and their correlation with pharmacodynamics and clinical response

1.10.3. Exploratory Endpoints

Part A (Phase 1; dose escalation):

- Evaluation of GDF-15 serum levels and their correlation with pharmacodynamic and clinical response
- Immune cell phenotyping including activation status and immune cell infiltration pattern in tumor tissue
- Molecular profiling (e.g., transcriptional profiling, mutational status, mutational burden of tumor tissue)
- To assess anti-tumor efficacy (PR, CR, DOR, PFS, and OS) of CTL-002 in combination with an anti-PD-1 checkpoint inhibitor using iRECIST (Seymour et al., 2017), criteria in solid tumors in subjects with advanced-stage solid tumors that relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy

Part B (Phase 2a; expansion):

- In subjects that undergo tumor biopsy: Immune cell phenotyping including activation status and immune cell infiltration pattern in tumor tissue
- In subjects that undergo tumor biopsy: Molecular profiling (e.g., transcriptional profiling, sequencing of genes of interest, mutational status, mutational burden of tumor tissue) and evaluation of GDF-15 levels
- To assess anti-tumor efficacy (PR, CR, DOR, PFS, and OS) of CTL-002 in combination with an anti-PD-1 checkpoint inhibitor using iRECIST criteria (Seymour et al., 2017), in solid tumors that relapsed on or were primary refractory to a prior anti-PD-1/PD-L1 therapy
- To assess in subjects with advanced-stage cutaneous squamous-cell carcinoma that relapsed on or were primary refractory to a prior anti-PD-1/PD-L1 therapy: the anti-tumor efficacy (PR, CR, DOR, PFS, and OS) of CTL-002 in combination with cemiplimab checkpoint inhibitor using WHO bidimensional measurements
- The proportion of subjects with tumor shrinkage, a confirmed partial PR and/or CR, and ORR after receiving stereotactic radiotherapy according to RECIST V1.1 (ORR-2)
- The interval between application of stereotactic radiotherapy and first documented evidence of a PR or CR according to RECIST V1.1 (TTR-2)
- The interval between the date of first documented evidence of PR or CR after having received stereotactic radiotherapy, until first documented evidence of disease progression or death, due to any cause according to RECIST V1.1 (DOR-2)

2. INVESTIGATIONAL PLAN

2.1. Overall Study Design

This is a Phase 1/2a, multi-center, FIH, open-label study consisting of Part A (Phase 1; dose escalation; Figure 4) followed by Part B (Phase 2a; expansion; Figure 5).

Part A (Phase 1; dose escalation): At least 24 subjects will receive in "3+3" cohorts escalating doses of CTL-002 IV given as monotherapy or in combination with an anti-PD-1 checkpoint inhibitor in subjects with advanced-stage solid tumors that relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy.

Note: Enrollment of subjects in Part A (Phase 1; dose escalation phase) of the study has been completed. No further patients will be treated in this part.

Part B (Phase 2a; expansion):

In Part B of the study, various cohorts with defined tumor indications as provided below will be enrolled.

Up to 249 subjects in different expansion cohorts will receive CTL-002 IV in combination with an anti-PD-1 checkpoint inhibitor. In the initial set of expansion cohorts, subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge and with the following indications will receive treatment with CTL-002 and the defined checkpoint inhibitor:

(1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma, or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound, or

(2) colorectal cancer (MSS/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy, or

(3) biomarker cohort with mixed solid tumors ("basket" cohort) that are relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound and that have exhausted existing treatment options or are not eligible for them anymore.

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer and melanoma), N = 14 response-evaluable subjects will be initially recruited per each tumor indication. This shall allow to detect 2 responses in a cohort with 80% probability if the true response rate is 20% or more, and at least 1 response in the cohort with 77% probability if the true response rate is 10% or more. For cutaneous squamous-cell carcinoma, N = 12 response-evaluable subjects will be recruited initially. This should result in 2 responses or more with 80% probability if the true response rate is 25% or higher.

  For cutaneous squamous-cell carcinoma: Subjects must have locally advanced disease or metastatic disease. Subjects with cutaneous squamous-cell carcinoma with locally advanced disease must not be candidates for surgery for one or both of the following reasons: disease recurrence after two or more surgical procedures and as per treating physician curative resection is unlikely or surgery would result in substantial complications or deformity.

- For the **second group** (colorectal cancer [MSS/mismatch-repair competent], a currently non-approved anti-PD-1/PD-L1 indication), N = 10 response-evaluable subjects will be recruited. This shall allow to detect 1 response with 89% probability (if the true response rate is 20% or more), and 1 response with 80% probability if the true response rate is 15% or more.
- The **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) investigated are subjects with anti-PD-1/PD-L1 relapsed/refractory mixed advanced solid tumors. Initial biomarker analyses by the sponsor for Part A (dose escalation) suggest that Tumor Proportion Score (TPS) PD-L1 might be a biomarker allowing to enrich for responders. In addition, it was shown that 60% of non-melanoma solid tumor patients with PD-L1 TPS ≤ 1 could be transformed from immunologically "cold" tumor status to immunologically "warm/hot". This cohort is enrolled to further evaluate these preliminary findings and will investigate biomarker and response findings in both groups. In Phase 1, PD-L1 TPS > 1 patient constituted 1/3 of all last-line treated patients. Therefore, up to N = 75 subjects are planned to be enrolled to have at least N = 25 response-evaluable subjects with TPS PD-L1 > 1 status and ideally up to N = 50 response-evaluable subjects with PD-L1 TPS ≤ 1. For the TPS PD-L1 > 1 group this would ideally confirm a response rate of ≥ 30% (with 81% probability resulting in a minimum of 6 or more responders in the cohort). For subjects with TPS ≤ 1, a response rate > 20% would be seen as clinically of interest and beneficial, and this would result in a minimum of 8 (10) responders with a probability of 81% (56%), respectively. If recruitment of 25 response-evaluable subjects with TPS PD-L1 > 1 is achieved, recruitment into the third group will be stopped and the TPS ≤ 1 cohort will be evaluated with given patient number in descriptive way.

For **all groups** the following additional requirements and restrictions apply:

(a) **All subjects** generally **must have received** a **currently for their tumor type approved anti-PD-1/PD-L1 compound;** non-approved, experimental anti-PD-1/PD-L1 treatments are not permissive for enrolment into this group unless condition (e) applies. (Group 2 with MSS-CRC is exempted from this regulation)

(b) **Baseline tumor biopsies** are **mandatory for all subjects** to further evaluate for predictive biomarkers of response as detected in Phase 1 and to further deepen the understanding of "cold-to-hot" tumor transitions for response under treatment.

(c) For **melanoma**, **cutaneous squamous-cell carcinoma** and the **biomarker cohort with mixed solid tumors** ("basket" cohort), an additional **follow-up, on-treatment biopsy** is mandatory to assess for immunologic changes in the tumor. **Important note**: All biopsies are only taken if considered **safe** and **feasible** by the treating physician/Investigator.

(d) All subjects that **achieve/maintain stable disease by week 24** but do not show tumor shrinkage beyond – 10% as per RECIST criteria can undergo if desired by the treating physician and agreed by the patient stereotactic radiotherapy of one or more tumor lesions to increase neoantigen exposure and potential for response improvement (as was seen in two Phase 1 patients). This should always be pre-discussed with the medical representative of the sponsor and the radiotherapy area should not include all lesions that are used for RECIST response assessment to allow for abscopal antitumor effect assessment.

Note: In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, if seen as safe and medically feasible by the treating physician.

For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) the following additional requirements and restrictions apply:

(e) Up to **5 subjects** (but no more) in the PD-L1 TPS > 1 group with **tumor indications that are currently not yet approved at all for anti-PD-1/PD-L1 treatment** may be enrolled if treated with a currently approved anti-PD-1/PD-L1 (for other indication(s)), if also all other criteria for the group apply. For the PD-L1 TPS ≤ 1 group this may be up to 10 patients.

(f) No subjects with melanoma (cutaneous, mucosal or uveal) can be enrolled into this cohort.

For all cohorts, response is defined as a subject presenting with a partial or complete response to treatment according to RECIST criteria.

If responses are seen and considered to be of interest by number and depth of response, the Safety Review Committee (SRC) may decide in agreement with the Sponsor to expand individual cohorts following a **Simon-2-stage design** to confirm a certain response rate with the following assumptions:

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, a minimum of 1 responder each is required to allow for continuation. Treating an additional N = 13 subjects shall generate a total of ≥ 4 responders to assume the overall response rate to be 20% or higher. For cutaneous squamous-cell carcinoma, a minimum of 2 responders is required to allow for continuation. Treating an additional N = 24 subjects shall result in a total of ≥ 6 responders to assume the overall response rate to be 25% or higher
- For the **second group**, for colorectal cancer with N = 10 fixed for the first stage, if at least 1 responder was observed in the first stage, an additional N = 19 subjects may be added to a cohort. In a total of N = 29 subjects at least ≥ 4 responders are expected to assume the true response rate could be at 20% or higher
- For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) with up to N = 75 subjects no such further expansion is considered. Instead, depending on response rate, - depth and - duration observed a potential registration size trial design will be considered and reviewed with the competent authorities (separate protocol). For the PD-L1 TPS > 1 group ("hot" tumors) a response rate of ≥ 30% is seen as clinically of significance, for the PD-L1 TPS ≤ 1 ("cold" tumors) a response rate > 20%.

In case of progressive disease (PD), treatment beyond progression might be applied as per Investigator assessment in agreement with the patient.

Proposed indications were selected based upon an **extensive translational research program** by the Sponsor, indicating a negative impact of GDF-15 on the immune response in the tumor microenvironment in the proposed indications, resulting in lack of immune cell infiltration, activation and in some indications proven resistance to checkpoint inhibitor treatment. In all subjects of all cohorts a baseline biopsy is mandatory to evaluate for potential predictive biomarker. In selected cohorts (i.e., melanoma, cutaneous squamous-cell carcinoma and in the

biomarker cohort with mixed solid tumors ["basket" cohort]) sequential, dual tumor biopsies will be taken in subjects with accessible lesions. Enrolment into all cohorts may occur in parallel.

Due to the excellent tolerability of the combination of CTL-002 and nivolumab, the defined checkpoint inhibitor in Part A (Phase 1) of the trial and as per request of Investigators study treatment is made accessible to all subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge, and the prior, additional requirement to have no therapeutic alternative is removed. For the first and third group in Phase 2a, the requirement of failure or progression on prior anti-PD-1/PD-L1 treatment is maintained.

For the cutaneous squamous-cell carcinoma cohort, combination treatment will be done with cemiplimab (not nivolumab), as the approved checkpoint inhibitor for cutaneous squamous-cell carcinoma treatment.

Subjects interested in participation in the trial are in each case informed about all treatments available for their disease situation. The potential advantages and disadvantages of participating in this experimental trial will be discussed in relationship to available alternative treatment options, among them any remaining approved treatment opportunities. Participating subjects that have still existing alternative treatment options must have understood that these options are available to them, and that trial participation encompasses an experimental treatment. As stated above, subjects enrolling must have completed and failed prior anti-PD-1/PD-L1 in all cases and must be in non-curative state.

Note: Additional cohorts may be added at a later stage to Part B (Phase 2a) of the study but only upon approval of a substantial amendment(s) defining detailed target populations, combination exploration, dose/schedule of CTL-002 for the expansion phase and detailed enrolment criteria of the respective selected target populations. In such an amendment a separate monotherapy cohort may be added to explore the single agent safety profile in detail.

Treatment cycles are as follows:

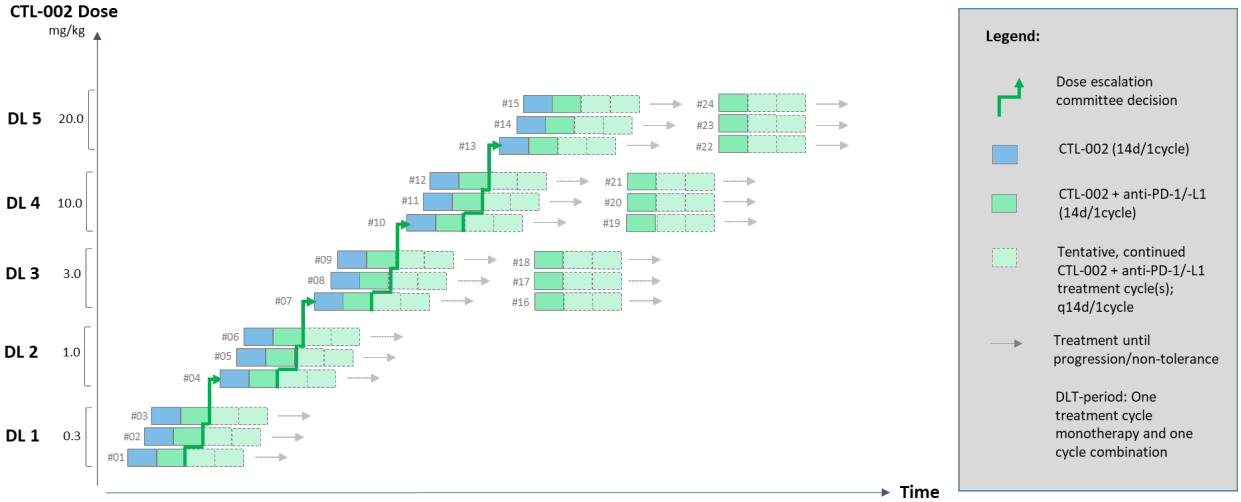
- Q2wk for bladder cancer, hepatocellular cancer, non-small cell lung cancer, melanoma, colorectal cancer and the biomarker cohort with mixed solid tumors ("basket" cohort)
    - 10 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q2wk
    - 240 mg nivolumab as an IV infusion over approximately 30 minutes, Q2wk
- Q3wk for the cutaneous squamous-cell carcinoma cohort
    - 20 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q3wk
    - 350 mg cemiplimab as an IV infusion over approximately 30 minutes, Q3wk

Pharmaco-modelling and obtained PK/Pharmacodynamic data from Part A (Phase 1) indicate complete GDF-15 neutralization at the dose of 10 mg/kg and the dosing interval of 2 weeks (Q2wk) or the dose of 20 mg/kg and the dosing interval of 3 or 4 weeks (Q3wk or Q4wk), respectively in serum and tumor vasculature (tumor microenvironment) in subjects with a wide range of baseline GDF-15 serum levels. In the current development phase (Phase 2a) the dosing interval follows for subject convenience the dosing interval of the checkpoint inhibitor. No safety events of concern and no DLT have been observed at any dose in Phase 1, including the doses of 10 mg/kg and 20 mg/kg. In addition, the for this initial Phase 2 exploration selected dose of 10 mg/kg and 20 mg/kg (with dosing interval of Q2wk and Q3wk, respectively) provide exposure that is still below the no-observed adverse effect level (NOAEL) in non-human primate (NHP).

Depending on further PK/pharmacodynamics data observed and safety and efficacy data, the SRC may modify these Phase 2 doses if seen as recommended or if a second dose is decided to be explored (all via substantial amendment).

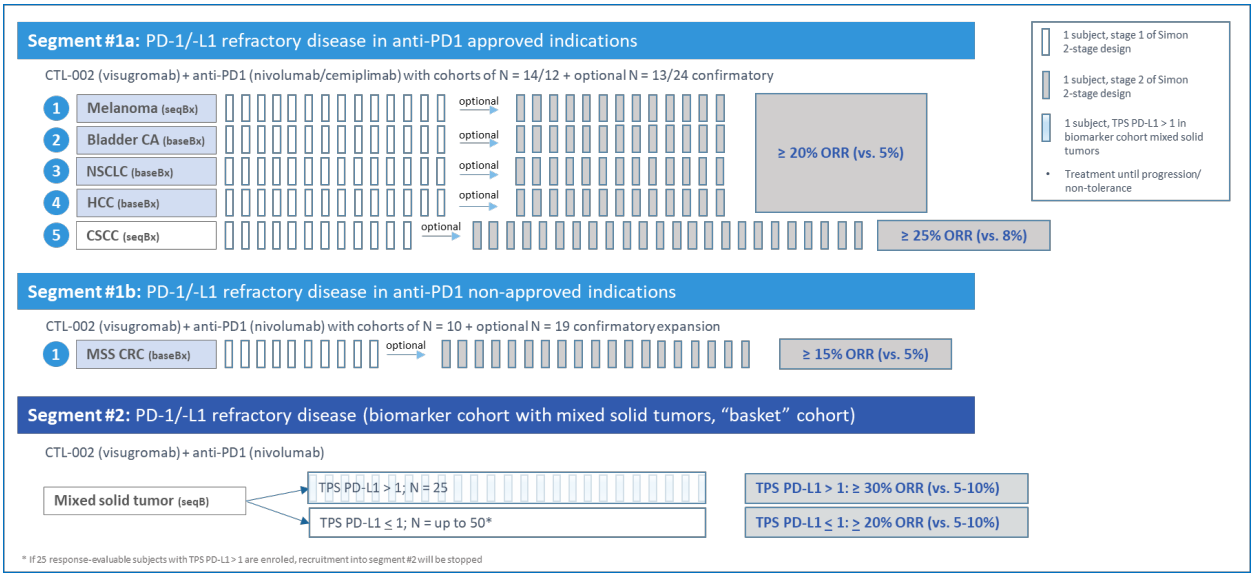
Figure 4: Part A (Phase 1; dose escalation)

Note: Enrollment has been completed. No further subjects will be enrolled



Abbreviations: d = day; DL = dose level; DLT = dose-limiting toxicity; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; q14d = once every 14 days

Figure 5: Part B (Phase 2a; expansion)



Abbreviations: baseBx = baseline biopsy; CA = cancer; CRC = colon adenocarcinoma, rectum adenocarcinoma; CSCC = Cutaneous Squamous-Cell Carcinoma; HCC = Hepatocellular cancer; MSS= microsatellite stability; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; seqBx = sequential biopsy; TPS = Tumor Proportion Score;

2.2. Treatment Period

2.2.1. Part A (Phase 1; dose escalation)

2.2.1.1. Pre-screening

Subjects with advanced-stage, relapsed and/or refractory solid tumors (subjects must have received an anti-PD-1/PD-L1 treatment [alone or in combination] and progressed on or relapsed after completion of anti-PD-1/PD-L1 treatment) with no available approved therapeutic alternative will sign a Pre-screening Informed Consent form (ICF) allowing the site/Sponsor to evaluate serum GDF-15 levels prior to entering the screening period.

2.2.1.2. Screening

For Part A (Phase 1; dose escalation) only, based on pre-screening GDF-15 serum levels, the Sponsor will approve pre-screened subjects for consent on the main study. Ideally 50% of enrolled subjects per dose level should show increased serum GDF-15 levels at pre-screening (> 1.5 ng/ml).

Subjects considered to be eligible to participate in the study will sign an ICF allowing the site/Sponsor to perform the screening procedures to confirm eligibility for the study (therefore, Screening is defined as the day of informed consent, and "Screening" is used throughout the synopsis and protocol to refer to this visit). The Screening Period is up to 21 days (for Part A) and up to 28 days (for Part B).

2.2.1.3. Part A (Phase 1; dose escalation)

This study will employ a standard "3+3" dose escalation design for which 3 to 6 subjects will be enrolled at each assigned dose level, per cohort, depending on the occurrence of DLTs.

The planned doses of CTL-002 to be tested are outlined below:

- Cohort 1: 0.3 mg/kg
- Cohort 2: 1.0 mg/kg
- Cohort 3: 3.0 mg/kg
- Cohort 4: 10 mg/kg
- Cohort 5: 20 mg/kg

The start dose of 0.3 mg/kg for Cohort 1 is fixed. Doses explored in Cohorts 2-5 (as outlined above) may be modified by the SRC established for the study based on emerging data (i.e., available safety, PK/pharmacodynamic, other biomarker data).

The DLT Observation Period will be the first 2 treatment cycles (i.e., first 4 weeks) for each dosing cohort. All treatment cycles are defined as 2 weeks in duration. CTL-002 will be administered Q2wk as an IV infusion over 60 minutes. Subjects will first receive one dose of CTL-002 given as monotherapy for one cycle, followed by a combination of CTL-002 given together with the defined anti-PD-1 checkpoint inhibitor for one cycle, where the defined checkpoint inhibitor will be administered at a dose of 240 mg IV given once every 2 weeks infused over approximately 30 minutes.

For the combination, CTL-002 and the defined checkpoint inhibitor will be given on the same day concomitantly, where CTL-002 will always be administered first and for the first combination infusion, there will be a 30-minute observation period to assess safety, which will then be followed by the defined checkpoint inhibitor infusion administered per SmPC or Product Label and local guidelines. The period of observation may be modified (i.e., shortened or lengthened) based on emerging safety data.

The first 2 treatment cycles (i.e., first 4 weeks) represent the DLT Observation Period. Thereafter, subjects will continue with the combination treatment, until progression or until withdrawal from the study for any other reasons (e.g., toxicity or subject withdraws consent).

Additional, intermediate dose cohorts may be explored based on emerging data and upon SRC request. The maximum dose of CTL-002 to be tested in this study will not exceed 20 mg/kg.

All subjects will be hospitalized overnight after receiving the first dose of CTL-002 and also after receiving the first combination dose of CTL-002 and the defined checkpoint inhibitor, for the purposes of safety observation and to enable logistical collection of sampling time-points (e.g., PK).

Dose Escalation Rules:

Initially, 3 subjects will be enrolled in any given dose cohort.

- If 0/3 subjects experience a DLT, then proceed to next dose
- If 1/3 subjects experience a DLT, then an additional 3 subjects will be tested at the same dose level
- If $\geq$ 2/3 subjects experience a DLT, this is considered the limiting dose and then an additional 3 subjects will be tested at the previous dose level to ensure a total of 6 subjects treated safely at that dose. In the situation where there is no lower dose level (i.e., if limiting dose is confirmed in Cohort 1), the Sponsor/SRC will make a recommendation about study continuation
- If 1/6 subjects experience a DLT, then proceed to the next dose level
- If $\geq$ 2/6 subjects experience a DLT, this would be defined as the limiting dose and dose escalation will stop. The previous lower dose would be considered the MTD. At least 6 subjects evaluable for safety must be enrolled at this dose level before it may be confirmed as the MTD
- Intermediate dose levels may be explored based on emerging data (safety, PK/pharmacodynamic) and if explored, will be discussed and agreed by the SRC and such decisions will be documented in writing

Note: Moving from 1 dose cohort to the next requires subjects eligible for evaluation. Evaluable subjects must have received 2 weeks of CTL-002 monotherapy and 2 weeks of the combination (i.e., a subject must complete the 4-week DLT Observation Period). Subjects who have confirmed disease progression during the 4-week DLT Period or those subjects who discontinue for any reason, other than a DLT, may be replaced in the applicable dosing cohort. Subjects who experience a DLT will not be replaced.

In each dose cohort, the first subject will be dosed and observed for 6 calendar days to allow for initial assessment of safety before any other subjects may be dosed. Upon confirmation that the

first subject has tolerated CTL-002 monotherapy and there are no significant toxicities that preclude further dosing, the second subject may be dosed and this subject will be observed for safety for 2 days. Upon confirmation that the second subject has tolerated CTL-002 monotherapy and there are no significant toxicities within the first 2 days that preclude further dosing, the third subject may be dosed.

In the case a DLT is observed in the first 3 subjects, there will be a 2-day stagger between the enrolment of the 3 additional subjects.

The first subject in the next higher dose cohort will not receive treatment with CTL-002 until the previous dose cohort has met the criteria for dose escalation and agreement from the SRC has been obtained and the decision documented in writing.

Intra-Patient Dose Escalation in Extended Treatment

If any Cohort 1 subjects are still on 0.3 mg/kg treatment when Cohort 2 has been completed and reviewed by the SRC, the subjects can be increased to the Cohort 2 dose of 1.0 mg/kg.

If any Cohort 1 or 2 subjects are still on 1.0 mg/kg treatment when Cohort 3 has been completed and reviewed by the SRC, the subjects can be increased to the Cohort 3 dose of 3.0 mg/kg.

Note: Any subjects still on 0.3 mg/kg treatment must be treated at 1.0 mg/kg prior to advancing to 3.0 mg/kg in agreement with the Sponsor Medical Monitor.

The maximum a subject dose can be increased to, through intra-dose escalation, will be 3.0 mg/kg.

Available safety, PK/pharmacodynamic data, as well as preliminary efficacy data will inform the MTD/dose(s) to be further explored in Part B of the study.

The MTD is defined as the highest dose level of CTL-002 at which no more than 1 out of 6 subjects experienced a DLT during the first 2 treatment cycles (i.e., the first 4 weeks, where CTL-002 is given as monotherapy [Weeks 1 and 2] and in combination with the defined checkpoint inhibitor [Weeks 3 and 4]).

In addition, for Cohorts 3-5, in the absence of any DLT, an additional 3 subjects can be recruited into each of these cohorts (up to a total of 6 subjects per cohort), to increase the understanding of the PK and pharmacodynamic data. This occurs while dose escalation continues. These additional "backfill" subjects will receive the combination treatment of CTL-002 and the defined checkpoint inhibitor once every 2 weeks from Cycle 1 Day 1 onwards, with CTL-002 always administered first and the defined checkpoint inhibitor given thereafter as outlined above.

For Part A subjects (except backfill subjects), 3 sequential tumor biopsies are mandated; one biopsy at baseline, the second biopsy prior to the initiation of the combination therapy (after 2 weeks) and the third after the first cycle of combination therapy (either at the End of Treatment visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3).

For backfill subjects, only 2 biopsies are mandated; one at baseline, and the second after 4 weeks of combination treatment (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3).

These biopsies are mandatory in order to assess immune cell infiltration in the tumor. If a biopsy cannot be taken for safety reasons, this must be discussed with the Medical Monitor.

Dose-Limiting Toxicity Criteria

The DLT Observation Period is the first 2 treatment cycles (i.e., 4 weeks). The SRC will review all DLTs as per the SRC charter. A DLT is defined as any of the following AEs graded using the NCI-CTCAE Version 5.0.

Hematologic Toxicity:

- Any Grade 4 hematologic toxicity

Non-Hematologic Toxicity:

- Any Grade 4 non-hematologic toxicity
- Any other ≥ Grade 3 non-hematologic toxicity lasting more than 96 hours despite appropriate supportive therapy
- Any ≥ Grade 3 pneumonitis, adrenal insufficiency, myocarditis, hepatitis (immune-related ≥ Grade 3 aspartate aminotransferase [AST], alanine aminotransferase [ALT] and total bilirubin elevation)
- Occurrence of Stevens-Johnson syndrome (SJS)

General Toxicity:

- Any Grade 5 toxicity
- Any other toxicity that is not captured with above regulations but is considered by the Investigator and the SRC as qualifying for a dose-limiting event/toxicity (e.g., any permanent discontinuation criteria of the defined anti-PD-1 checkpoint inhibitor)

Note: Transfusions of blood products or use of growth factors are **NOT** permitted during the Screening Period or during the 4-week DLT Observation Period (with the exception of a requirement to treat a DLT/SAE).

2.2.1.4. Maximum Tolerated Dose

The MTD is defined as the highest dose level of CTL-002 at which no more than 1 of 6 subjects experienced a DLT during the first 4 weeks of treatment (2 treatment cycles, DLT Period). The MTD is effectively considered to be the highest dose associated with a DLT in the first 4 weeks of treatment in <33% of subjects.

2.2.2. Part B (Phase 2a; expansion)

In Part B (Phase 2a) of the study, various cohorts with defined tumor indications as provided above will be enrolled.

The treatment dose for CTL-002 in Part B is set at 10 mg/kg Q2wk or 20 mg/kg Q3wk.

Pharmaco-modelling and obtained PK/pharmacodynamic data from Part A indicate complete GDF-15 neutralization at the dose of 10 mg/kg and the dosing interval Q2wk or the dose of 20 mg/kg and the dosing interval Q3wk or Q4wk in serum and tumor vasculature (tumor microenvironment) in subjects with a wide range of baseline GDF-15 serum levels. In the current development phase (Phase 2a) the dosing interval follows for subject convenience the dosing interval of the checkpoint inhibitor. No safety events of concern and no DLT have been observed

at any dose in Phase 1, including the doses of 10 mg/kg and 20 mg/kg. In addition, the for this initial Phase 2 exploration selected dose of 10 mg/kg and 20 mg/kg (with dosing interval of Q2wk and Q3wk, respectively) provide exposure that is still below the no-observed adverse effect level (NOAEL) in non-human primate (NHP).

Depending on further PK/pharmacodynamics data observed and safety and efficacy data, the SRC may modify these Phase 2 doses if seen as recommended or if a second dose is decided to be explored (all via substantial amendment).

In the expansion cohorts, subjects with advanced-stage, relapsed/refractory solid tumors in non-curable state that have either of the following indications will receive treatment with a combination of CTL-002 and the defined checkpoint inhibitor

(1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound or

(2) colorectal cancer (MSS/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy, or

(3) biomarker cohort with mixed solid tumors ("basket" cohort) that are relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound and that have exhausted existing treatment options or are not eligible for them anymore.

- For the **first group** (currently approved anti-PD-1/PD-L1 indications) N = 14 response-evaluable subjects each will be recruited for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, for cutaneous squamous-cell carcinoma N = 12.
- For the **second group** (currently non-approved anti-PD-1/PD-L1 indication) N = 10 response-evaluable subject will be recruited for colorectal cancer (MSS/mismatch-repair competent).
- The **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) investigated, are subjects with anti-PD-1/PD-L1 relapsed/refractory mixed advanced solid tumors. Up to N = 75 subjects are planned to be enrolled to have at least N = 25 response evaluable with TPS PD-L1 > 1 status and ideally up to N = 50 response-evaluable subjects with PD-L1 TPS ≤ 1. If recruitment of 25 response-evaluable subjects with TPS PD-L1 > 1 is achieved, recruitment into the third group will be stopped and the TPS ≤ 1 cohort will be evaluated with given patient number in descriptive way.

For **all groups** the following additional requirements and restrictions apply:

(a) **All subjects** generally **must have received** a **currently for their tumor type approved anti-PD-1/PD-L1 compound;** non-approved, experimental anti-PD-1/PD-L1 treatments are not permissive for enrolment into this group (does not apply for other cohorts) unless condition (e) applies. (Group 2 with MSS-CRC is exempted from this regulation)

(b) **Baseline tumor biopsies** are **mandatory for all subjects** to further evaluate for predictive biomarkers of response as detected in Phase 1 and to further deepen the understanding of "cold-to-hot" tumor transitions for response under treatment.

(c) For **melanoma**, **cutaneous squamous-cell carcinoma** and the **biomarker cohort with mixed solid tumors** ("basket" cohort), an additional **follow-up, on-treatment biopsy** is

mandatory to assess for immunologic changes in the tumor. **Important note**: All biopsies are only taken if considered **safe** and **feasible** by the treating physician/Investigator.

(d) All subjects that **achieve/maintain stable disease by week 24** but do not show tumor shrinkage beyond – 10% as per RECIST criteria can undergo if desired by the treating physician and agreed by the patient stereotactic radiotherapy of one or more tumor lesions to increase neoantigen exposure and potential for response improvement (as was seen in two Phase 1 patients). This should always be pre-discussed with the medical representative of the sponsor and the radiotherapy area should not include all lesions that are used for RECIST response assessment to allow for abscopal antitumor effect assessment. **Note:** In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, if seen as safe and medically feasible by the treating physician.

For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort) the following additional requirements and restrictions apply:

(f) Up to **5 subjects** (but no more) in the PD-L1 TPS > 1 group with **tumor indications that are currently not yet approved at all for anti-PD-1/PD-L1 treatment** may be enrolled if treated with a currently approved anti-PD-1/PD-L1 (for other indication(s)), if also all other criteria for the group apply. For the PD-L1 TPS ≤ 1 group this may be up to 10 patients.

(g) No subjects with melanoma (cutaneous, mucosal or uveal) can be enrolled into this cohort.

Treatment cycles are as follows:

- Q2wk for bladder cancer, hepatocellular cancer, non-small cell lung cancer, melanoma, colorectal cancer and biomarker cohort with mixed solid tumors ("basket" cohort)
    - 10 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q2wk
    - 240 mg nivolumab as an IV infusion over approximately 30 minutes, Q2wk
- Q3wk for the cutaneous squamous-cell carcinoma cohort
    - 20 mg/kg CTL-002 as an IV infusion over approximately 60 minutes, Q3wk
    - 350 mg cemiplimab as an IV infusion over approximately 30 minutes, Q3wk

In all subjects of all cohorts a baseline biopsy is mandatory to evaluate for potential predictive biomarkers (either fresh biopsy or archived biopsy taken within 120 days prior to treatment start). For melanoma, cutaneous squamous-cell carcinoma and the biomarker cohort with mixed solid tumors ("basket" cohort), an additional on-treatment biopsy is mandatory. If there is a safety risk at the discretion of the investigator to perform an on-treatment biopsy, this must be discussed with the Medical Monitor. An optional third biopsy can be taken at the next medically feasible timepoint during ongoing treatment in case the first biopsy is evaluable, but the second biopsy is non-evaluable, to assure assessable histology data.

In cutaneous squamous-cell carcinoma, multiple punch biopsies will be taken at a single timepoint (as per clinical possibility, ideally 3-5), as extensive molecular analyses are pursued (messenger ribonucleic acid [mRNA] expression analyses, such as T cell clonality analyses, RNAseq, nanostring analyses or genome sequencing etc.).

Enrolment into the Phase 2a cohorts may occur in parallel. Subjects that do not reach the first response assessment for reasons other than disease progression will be replaced to assure a full set of response assessable subjects. All subjects will be treated until progression under observation of RECIST criteria.

For the purposes of safety observation and to enable logistical collection of sampling time points (i.e., PK sampling), all subjects will be hospitalized overnight after receiving the first dose of CTL-002 (in case of future monotherapy cohort) or after receiving the first combination dose with CTL-002 and the defined checkpoint inhibitor (combination therapy cohort), respectively.

As part of Phase 2a, a dedicated CTL-002 monotherapy cohort may be conducted within a defined tumor indication to explore the safety profile of CTL-002 given as monotherapy (e.g., in subjects with advanced-stage melanoma) at a later timepoint, introduced per substantial amendment.

2.2.2.1. Recommended Phase 2 Dose

The treatment dose for CTL-002 for the initial Phase 2a exploration is set at 10 mg/kg, to be administered Q2wk (applicable for all cohorts treated in combination with nivolumab) or 20 mg/kg Q3wk (for the cutaneous squamous-cell carcinoma cohort; CTL-002 treatment in combination with cemiplimab).

Pharmaco-modelling and obtained PK/pharmacodynamic data from Part A (Phase 1) indicate complete GDF-15 neutralization at the dose of 10 mg/kg and the dosing interval Q2wk or the dose of 20 mg/kg and the dosing interval Q3wk or Q4wk, respectively in serum and tumor vasculature (tumor microenvironment) in subjects with a wide range of baseline GDF-15 serum levels. In the current development phase (Phase 2a) the dosing interval follows for subject convenience the dosing interval of the checkpoint inhibitor. No safety events of concern and no DLT have been observed at any dose in Phase 1, including the doses of 10 mg/kg and 20 mg/kg. In addition, the for this initial Phase 2 exploration selected doses of 10 mg/kg and 20 mg/kg (with dosing interval of Q2wk and Q3wk, respectively) provide exposure that is still below the no-observed adverse effect level (NOAEL) in non-human primate (NHP).

Depending on further PK/pharmacodynamic data observed and safety and efficacy data, the SRC may modify these Phase 2 doses if seen as recommended or if a second dose is decided to be explored (all via substantial amendment).

2.3. Optional Stereotactic Radiotherapy

All subjects in the phase 2 part that achieve/maintain stable disease by week 24 but do not show tumor shrinkage beyond -10% as per RECIST criteria can undergo if desired by the treating physician and agreed by the patient stereotactic radiotherapy of one or more tumor lesions to increase neoantigen exposure and potential for response improvement (as was seen in two phase 1 patients). This should always be pre-discussed with the medical representative of the sponsor and the radiotherapy area should not include all lesions that are used for RECIST response assessment to allow for abscopal antitumor effect assessment.

Radiotherapy should be performed according to local hospital's regulations.

Note: In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, if seen as safe and medically feasible by the treating physician.

2.4. Follow-up

Following the Safety Follow-up Visit / End of Core Study Visit, subjects will be followed up with an Efficacy and Survival follow-up for response duration and survival every 3 months for 12 months (in Part A) and every 3 months for 24 months (in Part B). The follow-up will be performed by telephone contact or (e)mail.

3. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all of the inclusion criteria and none of the exclusion criteria before enrolling into the study. Under no circumstances can there be exceptions to this rule. Procedures for handling subjects who do not meet entry criteria but have been enrolled or started treatment with CTL-002 (and possibly checkpoint-inhibitor) in error are described in Section 3.4.

3.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study:

1. Provide signed and dated informed consent. For Part A only: signed pre-screening consent for subjects that undergo pre-screening procedures or collection of historical data prior to informed consent procedure.
2. Male or female aged ≥ 18 years.
3. Subjects with histologically or cytologically confirmed/documented diagnosis of advanced-stage, relapsed/refractory solid tumors in non-curable state as per current clinical knowledge.
4. For Part A (Phase 1), subjects must have received during their prior treatment at least one anti-PD-1/PD-L1 treatment (alone or in combination) and progressed on or relapsed after completion of the anti-PD-1/PD-L1 treatment (with a minimum of 12 weeks of anti-PD-1/PD-L1 exposure).

   For Part B (Phase 2a), subjects must either have

   (1) bladder cancer, hepatocellular cancer, non-small cell lung cancer, cutaneous squamous-cell carcinoma, or melanoma (for melanoma, only cutaneous and mucosal forms, not uveal/ocular) (approved anti-PD-1/PD-L1 indications) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound (with a minimum of 12 weeks of anti-PD-1/PD L1 exposure).

   For cutaneous squamous-cell carcinoma, subjects have to have locally advanced disease or metastatic disease. Cutaneous squamous-cell carcinoma subjects with locally advanced disease must not be candidates for surgery for one or both of the following reasons: disease recurrence after two or more surgical procedures and as per treating physician curative resection is unlikely or surgery would result in substantial complications or deformity.

   (2) colorectal cancer (MSS/mismatch-repair competent) and have not received any prior anti-PD-1/PD-L1 therapy

   (3) biomarker cohort with mixed solid tumors (“basket” cohort) that relapsed on or were primary refractory to prior anti-PD-1/PD-L1 therapy with an approved anti-PD-1/PD-L1 compound and that have exhausted available approved therapies for their disease or do not qualify for them anymore.

   Note: All Subjects in cohorts (1) and (3) must have received an approved anti-PD-1/PD-L1 compound with a minimum of 12 weeks of anti-PD1/PD L1 exposure. Non-approved, experimental anti-PD-1/PD-L1 treatments are not permissive for enrolment into this group (does not apply for other cohorts).

5. Ability to understand the purpose of the study, provide signed and dated informed consent prior to performing any protocol-related procedures (including Screening evaluations), and able to comply with the study procedures and any locally required authorization.
6. For Part A, ideally ~50% of subjects enrolled per dose level should have increased GDF-15 serum levels (based on pre-screening result or historic serum GDF-15 data [up to 2 months prior to the start of treatment with CTL-002 where available]).
7. All subjects must have biopsy-accessible tumor lesions and be willing to undergo tumor biopsy: triple sequential biopsies (Part A) or dual-sequential biopsies (Part A backfill); in Part B, baseline biopsy (new or archived if obtained within 120 days prior to treatment start) from all subjects. For melanoma, cutaneous squamous-cell carcinoma and the biomarker cohort with mixed solid tumors ("basket" cohort) an additional on-treatment biopsy is mandatory. All biopsies are mandatory unless not seen as safe and feasible by the treating physician or another specific reason that precludes a biopsy sample being taken and which should be discussed with the Medical Monitor prior to Screening or if applying to the sequential biopsy, prior to that biopsy. All other study eligibility criteria must be met before the baseline biopsy sample is obtained.
8. For Part B, presence of radiologically measurable disease at baseline – with at least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter with computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for accurate, repeated measurements as per RECIST V1.1/iRECIST is required. This shall not be the lesion that is going to be biopsied.
9. ECOG Performance Status 0-1.
10. Life expectancy >3 months as assessed by the Investigator.
11. Adequate organ function:
    a. Bone marrow function: hemoglobin ≥ 9.0 g/dL (equal to 5.59 mmol/L); platelet count ≥ 100×10^9/L; leukocyte count ≥ 2.5×10^9/L.
    b. Hepatic function: AST and ALT ≤2 × upper limit of normal (ULN) (3 × ULN in the case of liver metastases); bilirubin ≤ 1.5 × ULN (2 × ULN in case of liver metastases/subjects with Gilbert's disease).
    c. Renal function: serum creatinine < 1.5 × ULN and/or creatinine clearance ≥ 50 ml/min (Cockcroft-Gault equation).
    d. Coagulation: no evidence for clinically relevant hypo- or hypercoagulability or presence of thrombosis/thrombotic event as per D-Dimer, antithrombin III (ATIII), prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT) analysis and treating physician's assessment.
12. All toxicities related to prior radiotherapy, chemotherapy, and any type of immunotherapy or other anti-cancer therapy, or surgical procedure must have recovered to Grade ≤ 1 based on NCI-CTCAE v5.0, except alopecia (any grade), and Grade 2 peripheral sensory neuropathy, and AEs that are clinically not considered as significant in this context and/or are stable on supportive therapy.
13. If subject has type II diabetes and receives metformin, metformin has to be replaced with other antidiabetic(s) prior to start of study treatment (at minimum 7 days prior to study baseline GDF-15 measurement) and for the whole study treatment duration.
14. Women of childbearing potential must have a negative serum pregnancy test within 7 days

prior to CTL-002 treatment. If a pregnancy test is not performed within 7 days of dosing with CTL-002, a repeat test must be performed prior to Day 1 dosing.

Women of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

15. All subjects, male and female, who are not surgically sterilized or postmenopausal as defined above, and subjects' partners of childbearing potential must agree to use "highly effective methods of contraception" during the study and for at least 5 months (5 times the predicted half-life of CTL-002 in humans) after the last dose of CTL-002.

    "Highly effective methods of contraception" are combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence.

    The double-barrier method (synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel), periodic abstinence (such as calendar, symptothermal, or post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method and spermicide only are NOT acceptable as "highly effective methods of contraception."

3.2. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible to enroll in this study:

1. Pregnant or breastfeeding.
2. Has received any tumor-directed therapy within 21 days before start of study treatment.
3. Treatment with any investigational agent within 21 days before start of study treatment.
4. Radiotherapy within 14 days before the start of the study treatment; however, subjects may receive palliative radiotherapy upon discussion and approval from the Medical Monitor if needed on non-target lesions.
5. Any acute or chronic major tissue injury that may require maintained GDF-15 function for tissue protection as per Investigator assessment (diagnosed with liver, kidney, myocardial infarction, or other major organ failure, all within < 6 months prior to Screening).
6. Pre-existing arrhythmia (unless considered clinically not relevant), uncontrolled angina pectoris, diagnosed with heart failure New York Heart Association (NYHA) Grade IV, any myocardial infarction/coronary event as well as any CNS-ischemic event and any thromboembolic event at any time < 6 months prior to Screening or presence of uncontrolled heart failure NYHA Grade III or higher.
7. Left ventricular ejection fraction (LVEF) <50% as measured by an echocardiogram (ECHO) or multigated acquisition (MUGA) scan if ECHO cannot be performed at site for any reason.
8. QT interval corrected for heart rate using Fridericia's formula (QTcF) interval > 450 ms for men or > 470 ms for women.

9. Any active autoimmune disease that requires systemic immunosuppressive treatments, for which (re-)activation may present a medical threat to the subject as per Investigator's assessment.
10. Any history of non-infectious pneumonitis < 6 months prior to Screening.
11. Any active inflammatory bowel disease such as Crohn's disease or ulcerative colitis which are generally excluded or active autoimmunthyroiditis present < 6 months prior to Screening.
12. Type I diabetes.
13. History of CNS disease such as stroke, seizure, encephalitis, or multiple sclerosis (< 6 months prior to Screening).
14. Any history of motor neuron disorder or disease that affects motor neuron function.
15. Ongoing immune-related AEs (irAEs) and/or AEs ≥ Grade 2 not resolved from previous therapies except vitiligo, stable peripheral sensory neuropathy up to Grade 2, hair loss, and stable endocrinopathies with substitutive hormone therapy.
16. Active allergy requiring systemic treatment (with the exception of histamine H1 receptor blocker treatment) or active infections requiring systemic anti-infectious therapy.
17. History of or clinical evidence of CNS primary tumors or metastases including leptomeningeal metastases, unless they have been previously treated, demonstrated no progression at least for 3 months before Screening, are asymptomatic and have had no requirement for steroids or enzyme inducing anticonvulsants in the last 14 days before Screening – subjects with suspected brain metastases at Screening should undergo a CT/MRI of the brain prior to study entry.
18. Systemic steroids at a daily dose of > 10 mg of prednisolone, > 2 mg of dexamethasone or equivalent, except non-systemic (inhaled, topical, nasal), for the last 28 days and ongoing.
19. Subjects with rapidly progressing disease (as per Investigator assessment), which may predispose to inability to tolerate treatment and/or study procedure.
20. Major surgery within last 4 weeks prior to Screening.
21. Known/expected hypersensitivity against CTL-002 and/or anti-PD-1/PD-L1 agents or their ingredients or previously had a severe hypersensitivity (≥ Grade 3) reaction to treatment with monoclonal antibodies (including pembrolizumab, nivolumab, cemiplimab etc.) and/or any of their excipients.
22. Evidence for active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as per adequate testing performed.
23. Dementia or altered mental status that would prohibit informed consent.
24. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory abnormality giving reasonable suspicion of a disease or condition that in the opinion of the Investigator would contraindicate the use of an investigational drug.
25. Receipt of any organ transplantation, including hematopoietic cell transplantation, but with the exception of transplants that do not require immunosuppression (e.g., corneal transplant, hair transplant).

26. Paraneoplastic syndrome (PNS) of autoimmune nature, requiring systemic treatment (systemic steroids or immunosuppressive agents) or a clinical symptomatology suggesting worsening of PNS.
27. Vaccine administration within 4 weeks of investigational drug administration (exception: coronavirus disease 2019 [COVID-19] vaccination). Vaccination with live vaccines while on trial is prohibited. Administration of inactivated vaccines like inactivated influenza vaccines or RNA-vaccines is allowed, including COVID-19.
28. Known active drug or alcohol abuse.

3.3. Discontinuation of Study Treatment and Subject Withdrawal Criteria

Subjects are at any time free to withdraw from the study, without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen by an Investigator and undergo the End of Treatment Visit (see Section 6.1.9) and assessments and procedures scheduled for the follow-up (see Section 6.1.11). Adverse Events should be followed up (see Section 7.2.1). More detailed guidance on Dose Modification and Discontinuation criteria is given in Section 5.3.

Subjects must be discontinued from the study in the following situations:

1. Occurrence of any AEs that are deemed to be clinically significant in the opinion of the Investigator and/or the SRC and warrant that a subject must discontinue treatment and be withdrawn from the study.
2. DLT in Part A (Phase 1; dose escalation).
3. Severe non-compliance to this protocol as judged by the Investigator and/or the SRC.
4. Confirmed disease progression.
5. Subjects incorrectly initiated on CTL-002 or the defined checkpoint inhibitor.
6. Use of prohibited concomitant drug, as defined in Section 5.4.3.
7. Pregnancy.
8. Withdrawal of consent.
9. Participation in any other clinical trial.

3.4. Procedures for Handling Subjects Incorrectly Initiated on CTL-002 and/or the Defined Checkpoint Inhibitor

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled to receive study medication. There can be no exceptions to this rule.

Where subjects who do not meet the inclusion criteria and have been enrolled or started treatment with CTL-002 (or the defined checkpoint-inhibitor) in error, the Investigator shall inform the Medical Monitor and the SRC immediately. The Investigator will discuss with the SRC and the subject the best way forward and whether study treatment should be aborted or continued. The decision making has the intent to provide the subject with the best possible solution for his/her situation. The Investigator and Medical Monitor are to ensure that all such decision making is appropriately documented.

3.5. Replacement of Subjects

Subjects that are withdrawn from the study but are evaluable for safety will not be replaced. Any subject that is withdrawn and is not considered evaluable for safety during the Part A (Phase 1; dose escalation), will be replaced to ensure a minimum number of evaluable subjects.

Evaluable subjects for Part A (Phase 1; dose escalation) must have received the first 2 treatment cycles (i.e., a subject must complete the 4-week DLT Observation Period consisting of 2 weeks CTL-002 monotherapy and 2 weeks combination therapy or Part A backfill subjects must have completed the first 4 weeks of combination treatment). Subjects who have confirmed disease progression during the 4-week DLT Period or those subjects who discontinue for any reason, other than a DLT, may be replaced in the applicable dosing cohort. Subjects who experience a DLT will not be replaced.

Evaluable subjects for Part B (Phase 2a; expansion) must have received the first 4 treatment cycles (in case of combination treatment with nivolumab) or 3 treatment cycles (in case of combination treatment with cemiplimab), (i.e., 8 or 9-weeks combination therapy in any combination therapy cohorts), except if they have confirmed disease progression during these 4 or 3 in case of cemiplimab) cycles or discontinue for toxicity. Subjects discontinued for other reasons may be replaced in the applicable dosing cohort.

3.6. Enrolment Stopping Rules

Enrolment may be temporarily stopped if any of the following occurs:

- A DLT in Part A (Phase 1; dose escalation) (see Section 2.2.1.3 for more information on the DLT criteria)
- Any toxicity that is unexpected, significant, and unacceptable (based on SRC review and discussion)
- Any death related to CTL-002 and/or the combination of CTL-002 with the defined checkpoint inhibitor, other than death related to PD, that occurs within 30 days of CTL-002 and the defined checkpoint inhibitor administration

If any of the above stopping criteria are met, an SRC meeting will occur to review the information and to determine how to proceed.

3.7. Premature Study Discontinuation

The study may be prematurely discontinued due to the following reasons:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study, or to potential study participants
- A decision on the part of the Sponsor to suspend or discontinue the development of CTL-002
- Any other significant reason as determined by the Sponsor or SRC

4. INVESTIGATIONAL MEDICINAL PRODUCTS

4.1. CTL-002 – Handling and Management

4.1.1. Description

CTL-002 is a humanized, hinge-stabilized immunoglobulin (Ig)G4 monoclonal antibody targeting GDF-15 with high-affinity, for IV infusion, to be administered over approximately 60 minutes, Q2wk for Phase 1 and Q2wk or Q3wk for Phase 2a (dependent on dosing scheme: Q2wk when CTL-002 is administered in combination with nivolumab and Q3wk when CTL-002 is administered in combination with cemiplimab).

Packaging and Storage:

CTL-002 Drug Product injection for intravenous infusion is supplied in single-use vials. It is presented at a concentration of 25 mg/ml of CTL-002 in a liquid formulation, in 20 mM Histidine/Histidine HCl, 150 mM sucrose, 50 mM Arginine-HCl, 0.02% w/v Polysorbate 20, at pH 5.5. It is a ready-to-use solution for infusion with an almost clear and colorless appearance, free from visible particles, free of animal-derived components, that contains no preservatives and is intended for single use only. CTL-002 Drug Product is sterile filtered and aseptically filled.

Labels will be designed in compliance with the respective national legislation applicable for the country participating in the study. Information on the label will appear in the official language(s) of the country in which the investigational medicinal product (IMP; also known as the investigational product [IP]) is used.

If shelf-life of the product is extended during the trial, relabeling of IMP at the Trial Sites/Pharmacies may be performed according to local regulations, and must follow detailed instructions provided.

CTL-002 Drug Product vials must be stored at +2°C–8°C (36°F-46°F) in their original secondary packaging within a secure environment, protected from light and separated from other medication or investigational product. The product should not be frozen.

4.1.2. Preparation and Administration

Preparation:

Visually inspect drug product solution for particulate matter and discoloration prior to preparation of the solution for infusion. The solution should be clear to slightly opalescent, colorless or pale yellow and practically free from particulate matter (although it may contain a few small translucent to white amorphous proteinaceous particles). Discard the vial if the solution is cloudy, discolored, or contains extraneous or considerable particulate matter.

Note: proteinaceous particles, typically white or translucent in appearance, can be formed in biological products due to their intrinsic tendency to self-associate. Although a small number of visible particles in parenteral products is unlikely to cause an adverse impact on safety, an in-use filter is mandated for use in this study.

To prepare CTL-002 for intravenous administration, the CTL-002 solution is added to an infusion bag containing 0.9% NaCl. CTL-002 solution for infusion may be administered using IV bags

made of polyethylene (PVC-, DEHP- and latex-free) or polyvinylchloride (latex-free) and infusion lines made of PE (PVC-, DEHP- and latex-free) or PVC (DEHP- and latex-free) material.

Storage of the prepared solution:

- At room temperature for no more than 6 hours from the time of preparation (this includes room temperature storage of the infusion in the IV container and time for administration of the infusion)

or

- Under refrigeration at +2°C-8°C (36°F-46°F) for no more than 24 hours from the time of preparation
- Do not freeze

Administration:

- Administer the infusion over approximately 60 (± 10 min) minutes at ambient temperature
- The use of an 0.2 µm inline filter (positive charged/uncharged PES membrane) is mandated
- Do not co-administer other drugs through the same intravenous line
- Flush the intravenous line at end of infusion

Note: Baseline weight can be used for dose calculation; adjustments are only required in case of >10% weight gain or loss.

Detailed instructions regarding the preparation of CTL-002 for administration will be provided to study sites and pharmacies participating in CTL-002 clinical studies in the Pharmacy Manual. For Part B (Phase 2a) of the study, there are no intra-subject dose escalation or reductions allowed. Dosing may only be interrupted, delayed, or discontinued.

4.2. Nivolumab (Combination Product) – Handling and Management

Sponsor will provide nivolumab for the anti-PD-1 combination treatment (applicable for all cohorts except cutaneous squamous-cell carcinoma. Refer to the regional manufacturer's package information leaflet and the SmPC (Opdivo SMPC, 2020) or Product Label (Opdivo Product Label, 2021) for more detailed information. Drug accountability, handling, and disposal are described in Section 4.4 and Section 4.5, respectively.

4.2.1. Description

Nivolumab (Bristol-Myers Squibb Company, Princeton, NJ USA) is a fully human IgG4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor PD-1 with immune checkpoint inhibitory and antineoplastic activities. Nivolumab binds to and blocks the activation of PD-1, an Ig superfamily transmembrane protein, by its ligands PD-L1, overexpressed on certain cancer cells, and programmed cell death ligand 2 (PD-L2), which is primarily expressed on antigen presenting cells. This results in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens. Activated PD-1 negatively regulates T-cell activation and plays a key role in tumor evasion from host immunity.

4.2.2. Packaging and Storage

Nivolumab injection for intravenous infusion is supplied in single-use vials. Each ml of nivolumab solution contains 10 mg nivolumab.

Store nivolumab under refrigeration at 2°C-8°C (36°F-46°F). Protect nivolumab from light by storing in the original package until time of use. Do not freeze or shake. Refer to the pharmacy manual for storage conditions and to the current SmPC or Product Label for further details.

4.2.3. Preparation and Administration

Preparation:

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial. Withdraw the required volume of nivolumab and transfer into an intravenous container. Dilute nivolumab with either 0.9% Sodium Chloride Injection or 5% Dextrose Injection to prepare an infusion with a final concentration ranging from 1 mg/ml to 10 mg/ml.

Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of nivolumab.

Storage of the prepared solution:

The product does not contain a preservative and the prepared solution can be stored:

- At room temperature for no more than 8 hours from the time of preparation (this includes room temperature storage of the infusion in the IV container and time for administration of the infusion)

or

- Under refrigeration at 2°C-8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation
- Do not freeze

Administration:

- For the combination administration with CTL-002, CTL-002 must always be administered first. In addition, for the first combination infusion, there will be a 30-minute observation period to assess safety of CTL-002 before the infusion of the combination drug.
- Administer the nivolumab infusion over approximately 30 (± 5 min) minutes once every 2 weeks (q2wk) through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer)
- Do not co-administer other drugs through the same intravenous line
- Flush the intravenous line at end of infusion

Dosing interval for nivolumab will be no less than 12 days and up to a maximum of 16 days, in line with the accepted visit window (±2 days).

There are no premedications recommended for nivolumab prior to the first infusion. There are no intra-subject dose escalation or reductions allowed. Dosing may only be interrupted, delayed, or discontinued.

Further details and updates may be provided in the Pharmacy Manual.

4.3. Cemiplimab (Combination Product) – Handling and Management

Sponsor will provide cemiplimab for the anti-PD-1 combination treatment in the cutaneous squamous-cell carcinoma cohort. Refer to the regional manufacturer's package information leaflet and the SmPC (Libtayo, SmPC, 2022) or Product Label for cemiplimab (Libtayo, Product Label, 2021) for more detailed information. Drug accountability and handling and disposal are described in Section 4.4 and Section 4.5, respectively.

4.3.1. Description

Cemiplimab (Regeneron Pharmaceuticals, Inc. and Sanofi-Aventis US LLC) is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response.

4.3.2. Packaging and Storage

Cemiplimab concentrate for solution for infusion is supplied in single-use vials. Each vial contains 350 mg of cemiplimab in 7 ml solution (50 mg/ml).

Store cemiplimab under refrigeration at 2°C-8°C (36°F-46°F) in the original carton. Protect from light. Do not freeze or shake. Refer to the pharmacy manual for storage conditions and to the current cemiplimab SmPC or Product Label for further details.

4.3.3. Preparation and Administration

Preparation:

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Cemiplimab is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent to white, particles. Do not shake the vial.

Withdraw 7 ml (350 mg) of cemiplimab and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/ml to 20 mg/ml. Mix the diluted solution by gentle inversion. Do not shake the solution. Discard any unused medicinal product or waste material in accordance with local regulations.

Storage of prepared solution:

- Once prepared, the diluted cemiplimab solution should be administered immediately. If diluted solution is not administered immediately, it may be stored temporarily either
- at room temperature up to 25°C (77°F) for no more than 8 hours from the time of infusion preparation to the end of infusion

or

- under refrigeration at 2°C-8°C (36°F-46°F) for no more than 24 hours from time of infusion preparation to the end of infusion. Allow the diluted solution to come to room temperature prior to administration
- Do not freeze

Administration:

- For the combination administration with CTL-002, CTL-002 must always be administered first. In addition, for the first combination infusion, there will be a 30-minute observation period to assess safety of CTL-002 before the infusion of the combination drug
- Administered the cemiplimab infusion over approximately 30 minutes (± 5 min) once every 3 weeks (q3wk) through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micrometer to 5 micrometer pore size)
- Do not co-administer other medicinal products through the same infusion line
- Flush the intravenous line at end of infusion
- Dosing intervals for cemiplimab will be no less than 19 days and up to a maximum of 23 days, in line with the accepted visit window (±2 days).
- There are no intra-subject dose escalation or reductions allowed. Dosing may only be interrupted, delayed, or discontinued.
- Further details and updates may be provided in the Pharmacy Manual.

4.4. Drug Accountability

Each trial site will be supplied with a sufficient amount of IMP to treat the first subjects enrolled. Additional shipments of IMP will be performed according to the site's recruitment rate.

At each site, the pharmacist, or the person designated as the site‘s compounding person, is responsible for keeping accurate IMP accountability records, throughout the study, regarding the receipt of IMP, the dispensing of IMP to the study personnel and the return of all used and unused IMP. The drug accountability form will be periodically reviewed by the study monitor.

4.5. Handling and Disposal

The trial site shall return all unused IMP to the drug supplier for destruction or destroy it on site upon written authorization by the Sponsor. Pursuant to Sponsor's instruction used vials may be discarded at site in compliance with local procedures after drug accountability has been performed by the monitor. If tear-off labels are used for documentation, used vials must be kept until drug accountability has been checked by the monitor. In any case destruction of IMP and its documentation will be performed in accordance with Good Manufacturing Practice.

4.6. Treatment Beyond Progression

The drugs used in this study are meant to induce an immune response against the subject's tumor and may not have an immediate effect on the tumor. In addition, the expected mechanism of action involves an infiltration of T-cells and inflammatory cells and local release of inflammatory cytokines. Therefore, it is expected that initial radiographic progression may not be indicative of subsequent lack of response. Treatment may continue in spite of early radiographic progression,

including appearance of new lesions, in the absence of symptomatic progression as long as the subject has not had an AE that meets the criteria for treatment discontinuation.

Treatment past initial RECIST-defined radiographic progression may continue according to Investigator judgment, in consultation with the Medical Monitor, based on the subject's overall clinical status, overall tumor burden, and rate of progression, taking into account the subject's other treatment options and need for urgent intervention (decisions regarding subject treatment should be made according to site standard of care as determined by the Investigator).

For example, a subject may continue treatment if a tumor assessment shows improvement or stable disease compared to the previous scan, even if there is progression compared to the baseline scan. Investigators may schedule an additional tumor assessment within 8 weeks after a scan showing progression, in order to reassess the subject's response. Subjects may be treated after progression if they meet these criteria:

- Investigator-assessed potential clinical benefit
- No disease-related clinical deterioration
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- Subject has not had an AE that meets the criteria for treatment discontinuation

If treatment is continued in spite of radiographic progression, the Investigator should record the rationale, and the subject must be informed that treatment beyond initial progression is not standard of care, and the Investigator should discuss potential risks and alternative treatment options.

Subjects should permanently discontinue study therapy upon evidence of further progression, defined as an additional 20% or greater increase in total measured tumor burden (TMTB) from time of initial progression. The total measured tumor burden from time of initial progression should be used as the reference baseline for comparison with the post-progression assessment.

4.7. Biological Sampling Procedures

The subject's consent to participate in the biomarker components of the study is mandatory. Blood and tissue samples will be obtained from the subjects according to the Schedules of Assessments (SoA) (see Table 5, Table 6 and Table 7). Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

4.7.1. Handling, Storage and Destruction of Biological Samples

The samples will be used up or disposed of after analyses or retained for further use as described below.

All biological samples for future supporting research and sample leftovers (as applicable) will be retained by the Sponsor, or designee site on behalf of the Sponsor, for a maximum of 10 years after the last subject's last visit in the study. The results from future analysis will not be reported in the Clinical Study Report but may be reported separately in a Clinical Study Report Addendum /Scientific Report or Scientific Publication.

4.7.2. Labelling and Shipment of Biohazard Samples

The Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the requirements for Biological Substances, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix 3 (International Airline Transportation Association [IATA] 6.2 Guidance Document).

Any samples identified as Infectious Category A materials must not be shipped and no further samples taken from the subject unless agreed with Sponsor or delegate and appropriate labelling, shipment and containment provisions are approved.

All archival tumor samples should be shipped as per the Laboratory Manual.

4.7.3. Chain of Custody of Biological Samples

A full chain of custody will be maintained for all samples throughout their lifecycle.

The Investigator at each study site will keep full traceability of collected biological samples from the subjects while in storage at the study site until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival. For the biobanking of any biological subject sample at the Sponsor laboratory or contracted third party delegate, the Sponsor and/or delegate guarantees documentation, sample management including sample-specific shipment and storage requirements.

The Sponsor or delegate will keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

4.7.4. Withdrawal of Informed Consent for Previously Collected Donated Biological Samples

If a subject withdraws consent to the use of previously collected biological samples, then the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

The Investigator:

- Ensures that the Sponsor or delegated representative is notified immediately of the subject's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, and the action documented. A signed document confirming sample disposal/destruction needs to be returned to the study site
- Ensures that the subject and Sponsor or delegated representative are informed about the sample disposal

5. GUIDANCE TO INVESTIGATORS

5.1. Potential Specific Toxicities of CTL-002

Clinical experience with CTL-002 is still limited. No Serious Adverse Reactions are considered expected by the sponsor for the purpose of expedited reporting of SUSARs. Yet, four main potential areas of concern can be delineated that may contribute to the adverse event profile of CTL-002 (refer to Investigator's Brochure for details):

- Potential potentiation (earlier occurrence, more rapid evolution, and higher overall toxicity grade of adverse events) of anti-PD-1/-L1 compounds
- Organ distress during CTL-002 treatment leading to excessive immune cell infiltration
- Potentially relevant findings from GDF-15 knock-out models
- Possible potentiation of adverse events after radiotherapy

All monitoring recommendations specified below are based upon identified mode-of-action, findings from knock-out mouse models and hypothetic consequences of GDF-15 long-term suppression (refer to Investigator's Brochure for details).

5.1.1. Potential Organ Toxicity During CTL-002 Treatment

Investigators should monitor carefully for any potential organ disturbances under CTL-002 treatment based upon a potential excessive shift of immune cells into organs under stress.

Any signs of:

- Myocardial infarction or other hypoxic event of clinical significance
- Heart failure
- CNS hypoxic events
- Pneumonia, sepsis, any severe organ infection
- Liver failure of any type
- Kidney failure of any type
- Pancreatitis, pneumonitis, colitis, hepatitis, thyreoditis or any other "-itis" of clinical relevance
- Any other major hypoxic, toxic, metabolic or immunologic event with significant organ stress or damage

should result in an immediate careful evaluation of kinetics and degree of toxicity and a potential need for dosing interruption and/or medical intervention.

Immunosuppressive treatment may be required if excessive immune-cell infiltration of tissues (in line with mode-of-action of CTL-002) is at least suspected as possible causative factor for any such organ damage and if any such damage requires immediate intervention as per opinion of the Investigator.

5.1.2. Potential Toxicities Linked to Long-term Suppression of GDF-15

Investigators should monitor carefully for any potential specific toxicities that may be linked to long-term suppression of GDF-15. Although isolated toxicities were observed in knock-out mouse models with complete absence of GDF-15 from impregnation onwards, these toxicities are not truly expected in the context of temporary, organism-wide, only partial suppression of GDF-15; however, it is still recommended to monitor for them.

Any signs of:

- Thrombosis formation or increased clotting
- Motorneuron impairment
- Sensory neuron impairment
- Parkinson's disease induction (potential substantia nigra alteration)
- Potential altered mobility or mood alterations

should be monitored for carefully in context of general AE monitoring

Immunosuppressive treatment may be required if immune-cell infiltration of tissues is at least suspected as possible causative factor for any such organ damage and if any such damage requires immediate intervention as per opinion of the Investigator.

5.1.3. Guidance on Pregnancy, Lactation, and Effects on Fertility

Due to the described potential role of GDF-15 in feto-maternal tolerance, pregnancy should not occur during CTL-002 exposure and pregnant women should not be exposed to CTL-002 at any time. Enrolment of pregnant women into CTL-002 trials is not permitted and highly effective contraception methods must be used throughout CTL-002 exposure by all participants. For subject safety such contraception methods must be practiced for a minimum of 5 months post last dose of CTL-002.

5.1.4. Guidance on Concomitant Medication

No drug interactions studies have been performed so far. No drug interactions are known or suspected for CTL-002 at this point in time.

Subjects receiving substrates of Cytochrom P450 (CYP) enzymes with narrow therapeutic index should be monitored closely and have doses adjusted for these medications as necessary, as GDF-15 blockade may have so far unknown effects on CYP enzymes.

5.2. Supportive Care and AE Monitoring and Intervention Guidelines

The supportive care guidelines described in this section can be modified by the treating physician/Investigator as deemed medically necessary or as appropriate without requiring a protocol amendment or being considered a protocol deviation.

5.2.1. General Supportive Care Recommendations

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care (these can include antibiotics, analgesics,

pain control, transfusions (except during the Screening Period), psychotherapy, growth factors (except during the Screening Period), or any other symptomatic therapy as clinically indicated).

Transfusions of blood products or use of growth factors are **NOT** permitted during the Screening Period or during the 28-day DLT Observation Period (with the exception of a requirement to treat a DLT/ SAE).

Investigators are not encouraged to use supportive care as prophylaxis prior to the first CTL-002 infusion or generally any of the infusions. However, if AEs such as fever/chills, allergic reaction, nausea/vomiting, pain are observed after the first dose of CTL-002 as monotherapy or in combination with nivolumab or cemiplimab (for the cutaneous squamous-cell carcinoma cohort), appropriate premedication for subsequent study treatments may be administered at the Investigator's discretion as per local Institutional treatment guidelines. General guidance for pre-medication is described in Table 2. Consult with the Medical Monitor to discuss any questions regarding pre-medication.

The supportive care guidelines for CTL-002 treatment described below are mainly modeled on available data from other similar agents and the pre-clinical data package.

5.2.2. Premedication Options for CTL-002/Nivolumab/Cemiplimab Infusion

In general, there are no premedications recommended for CTL-002 or nivolumab/cemiplimab prior to the first infusion. However, in case classic immediate infusion reaction occur, a limited number of premedications are recommended. See Table 2 for details.

Table 2 Guidance for the Use of Pre-medication Prior to CTL-002/Nivolumab/Cemiplimab Infusions in Case Certain Adverse Events are Observed

Condition	Agents	Dose	Route	When
Fever/chills	Acetaminophen	up to 650 mg or 10 to 15 mg/kg recipient weight	Orally	Prior to each dose & repeat 4 hours after dosing. Repeat every 4 hours if fever present Max 4g/day
	And			
	Indomethacin	25 mg daily dose or 50 mg when subject experienced a fever > 39.0°C in a previous dose	Orally	Prior to each dose & repeat it 4-6 hours after dosing If persistent fever > 39.0°C, repeat 50 mg every 8 hours (if adequate renal function) with acetaminophen every 6 hours.
Allergic reaction	Diphenhydramine	25 mg or up to 0.5 to 1 mg/kg recipient weight	Orally or IV	One hour prior to each dose and Repeat 4-6 hours after dosing. Antihistamine, such as diphenhydramine or cetirizine should be taken for 1 day before and 1 to 2 days after dosing.
	In combination with one of the following			
	Ranitidine 300 mg		Orally	
	Cimetidine 300 mg		Orally	
	Famotidine 20 mg		Orally	
Hypotension	Normal saline (0.9%)	2 mL/kg/hr (up to 100 mL/hr)[1]	Continuous IV	Begin 30 minutes prior to and for 6 hours after each dose
Nausea/ Vomiting	Ondansetron	0.2 mg/kg (up to 8 mg)	IV	30 minutes prior to each dose
	OR other 5-HT3 antagonists at the discretion of the Investigator.			
Pain	Hydromorphone	0.5 mg	IV	30 minutes prior to each dose
	OR other opioid medications at the discretion of the Investigator			

Abbreviations: BP = blood pressure; hr = hour; IV = intravenously.

[1] In the last 2 hours, if BP does drop slightly, it is recommended to increase the normal saline rate to 250 ml/hr (given no evidence of fluid overload) and give over 2 hours until pressure is 90 mm systolic or more stable. Alternatively, if this has occurred previously, a higher rate of fluid administration from the start of the dosing protocol (i.e., 200 ml/hr over 6 hours) can be used as long as there are no signs of fluid overload (i.e., crackles in the lungs or peripheral edema or > 10% weight gain).

Note: Nonsteroidal anti-inflammatory medication including acetaminophen, ibuprofen, or naproxen may be given per physician discretion following the recommended dosing thresholds:

- Acetaminophen: not to exceed 3000 mg (3 grams) in 24 hours.
- Ibuprofen: not to exceed 2400 mg in 24 hours.
- Naproxen: not to exceed 1100 mg in 24 hours.

Note: The use of systemic steroid medications may result in loss of therapeutic effects of the study drug and should be avoided; however, in the event of a severe/life-threatening inflammatory reaction to CTL-002 and/or nivolumab/cemiplimab, the IV administration of dexamethasone or other steroid-based medication is warranted.

5.2.3. General Rules on Hydration Around CTL-002/Nivolumab/Cemiplimab Infusions

Ensure adequate fluid intake 24 to 72 hours prior to each CTL-002/nivolumab/cemiplimab infusion. Continuous IV fluid may be given 30 minutes prior to and for up to 6 hours after each dose of CTL-002 at 2 ml/kg/hr up to 100 ml/hr,

If blood pressure (BP) does drop slightly post-infusion, it may be recommended to increase the normal saline rate to 250 ml/hr (given no evidence of fluid overload) until BP is stabilized.

Alternatively, if this has occurred previously, a higher rate of fluid administration from the start of the dosing protocol (i.e., 200 ml/hr) may be used as long as there are no signs of fluid overload (i.e., crackles in the lungs or peripheral edema or > 10% weight gain).

5.2.4. Infusion Site Reactions Around CTL-002/Nivolumab/Cemiplimab Infusions

As with other drugs administered IV, local infusion site reactions (e.g., infusion pain, infusion site reaction, skin or vein irritation) may occur and these can be managed according to local institutional guidelines. Implantable port insertions (e.g., Portacath) may be considered.

5.2.5. Management of Infusion-Related Reactions Around CTL-002/Nivolumab/Cemiplimab Infusions

The supportive care guidelines described in this section can be modified by the treating physician/Investigator as deemed medically necessary or as appropriate without requiring a protocol amendment or being considered a protocol deviation.

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse **e**ffects (e.g., antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs and graded according to the NCI-CTCAE v5.0 grading scale. Guidance on the management of infusion related reactions is provided in Table 3.

Table 3 Management Guidelines for Infusion-Related Reactions

NCI-CTCAE v5.0 Grade	Treatment modifications for CTL-002/nivolumab/cemiplimab
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Decrease the CTL-002/nivolumab/cemiplimab infusion rate by 50% and monitor closely for any worsening
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, Narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Stop CTL-002/nivolumab/cemiplimab infusion Resume infusion at 50% of previous rate once infusion related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequence	Stop the CTL-002/nivolumab/cemiplimab infusion immediately and disconnect infusion tubing from the subject Subjects have to be withdrawn immediately from CTL-002/nivolumab/cemiplimab treatment and must not receive any further CTL-002/nivolumab treatment
Grade 4 Life-threatening consequences; urgent intervention indicated.	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory

Acute infusion reactions can include cytokine release syndrome, angioedema, or anaphylaxis, and differ from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting.

Appropriate premedication may be administered at the Investigator's discretion approximately 30 to 60 minutes prior to CTL-002 infusion for subjects who have previously experienced ≤ Grade 2 infusion related reaction. Premedication can be started with an antihistamine and with paracetamol (acetaminophen) (e.g., 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent), with H2-blocker antihistamines (e.g., famotidine or ranitidine) considered to be added at the Investigator's discretion.

Steroids can be considered to improve symptoms of infusion-related reaction (IRR) but are not permitted for prophylactic purposes.

If the subject has a second IRR Grade ≥2 on the slower infusion rate, with or without premedication, the infusion should be stopped, and the subject removed from the CTL-002/nivolumab/cemiplimab treatment.

5.2.6. Management of Severe Hypersensitivity Reaction and Flu-like Symptoms around CTL-002/Nivolumab/Cemiplimab infusions

The supportive care guidelines described in this section can be modified by the treating physician/Investigator as deemed medically necessary or as appropriate without requiring a protocol amendment or being considered a protocol deviation.

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms of severe hypersensitivity reaction and flu-like symptoms may include:

- Impaired airway
- Decreased oxygen saturation (<92%)
- Confusion
- Lethargy
- Hypotension
- Pale /Clammy skin
- Cyanosis

Management of symptoms:

- Epinephrine injection and IV dexamethasone
- Subject should be placed on cardiac, BP, heart rate, and oxygen saturation monitor immediately
- Alert intensive care unit for possible transfer is required

For prophylaxis of flu-like symptoms, a non-steroidal anti-inflammatory drug (NSAID), for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of CTL-002 IV infusion.

5.2.7. Management of Immune-related Adverse Events

The supportive care guidelines described in this section can be modified by the treating physician/Investigator as deemed medically necessary or as appropriate without requiring a protocol amendment or being considered a protocol deviation.

An irAE is defined as an off-target side effect associated with exposure of immunogenic drug and is consistent with immune mechanism. In the process of identification of irAE any possible etiology of neoplastic, infectious, metabolic, toxin, or any other factor should be ruled out, serologic, histologic (biopsy), and/or immunologic results should be obtained to evaluate the differential diagnosis and/or support an immune-mediated cause.

An irAE should be documented as “Adverse Event of Special Interest”, and it is recommended to involve the medial monitor at first incidence and subsequently as needed for follow-up. Details of the diagnostic work-up will be requested by the study team.

In order to help health care providers who are not involved with the subject’s cancer treatment, to identify that subjects have received immune-oncology therapy as well as to recognize rare or subtle

symptoms of immune-oncology toxicity, subjects will be provided with immune-oncology wallet cards.

5.2.7.1. Known Checkpoint Blocking Antibody-related Toxicities and Their Management

The recommended treatment modifications for immune-related AEs observed for immune checkpoint blockade in combination with CTL-002 (e.g., nivolumab, cemiplimab, nivolumab/relatlimab etc.) are provided in Table 4. This guidance was derived from all existing guidelines for the individual products in the respective regions (i.e., EU SmPC, SwissMedic Medical Product Information and US Product Label for nivolumab, cemiplimab and nivolumab/relatlimab; as available as of June 2022), always following the most conservative recommendation made for the respective adverse event observed. Thereby, adherence to all existing guidelines and maximum patient safety is assured.

For additional management guidelines, refer to current European Society for Medical Oncology (ESMO; Haanen et al, 2017), American Society of Clinical Oncology (ASCO; Schneider et al. 2022), and National Comprehensive Cancer Network (NCCN) guidelines (Thompson et al., 2020). Adverse event grading follows CTCAE 5.0 if not otherwise declared.

Table 4 Recommended Treatment Modifications for Checkpoint Blockade in combination with CTL-002

Immune-related Adverse Reaction	Severity	Dose Modifications	Additional intervention
Pneumonitis	Grade 2	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10mg/day prednisone or equivalent. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids dose or inability to reduce prednisone to ≤ 10mg/day (or equivalent) within 12 weeks of initiating steroids.	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 diarrhea or colitis	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Table 4 Recommended Treatment Modifications for Checkpoint Blockade in combination with CTL-002

Immune-related Adverse Reaction	Severity	Dose Modifications	Additional intervention
		Resume if colitis or diarrhea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10mg/day prednisone or equivalent. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤ 10mg/day (or equivalent) within 12 weeks of initiating steroids.	
	Grade 3 or 4 diarrhea or colitis	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis with no tumor involvement in liver	Grade 2 with AST or ALT > 3× and ≤ 5× ULN, or total bilirubin to > 1.5× and ≤ 3× ULN, regardless of baseline value	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating steroids.	
	Grade 3 or 4 with AST or ALT > 5× ULN, or total bilirubin > 3× ULN, regardless of baseline value	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis with tumor involvement in the liver [b]	1.) Baseline AST/ALT is > 1× and ≤ 3× ULN and increases to > 5× and ≤ 10× the ULN or 2.) Baseline AST/ALT is > 3× and ≤ 5× ULN and increases to > 8× and ≤ 10× the ULN	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume in subjects with complete or partial resolution (Grade 0 to 1) after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating steroids.	
	AST or ALT increases to > 10× ULN or total bilirubin increases to > 3× ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Table 4 Recommended Treatment Modifications for Checkpoint Blockade in combination with CTL-002

Immune-related Adverse Reaction	Severity	Dose Modifications	Additional intervention
Endocrinopathies	1.) Symptomatic Grade 2 or 3 hypothyroidism 2.) Symptomatic Grade 2 or 3 hyperthyroidism 3.) Grade 3 thyroiditis 4.) Symptomatic Grade 2 or 3 hypophysitis 5.) Grade 2 adrenal insufficiency 6.) Grade 3 Type 1 diabetes mellitus (hyperglycemia)	Withhold	1.) Initiate thyroid hormone replacement as clinically indicated 2.) and 3.) Initiate symptomatic management 4.) and 5.) Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated 6.) Initiate treatment with anti-hyperglycaemics as clinically indicated
		1.) to 3.), and 6.) Resume when event returns to Grade 0 to 1 or is otherwise clinically stable. 4.) + 5.) Resume if event improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable.	
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or Grade 4 adrenal insufficiency Grade 4 Type 1 diabetes mellitus (hyperglycemia)	Permanently discontinue	• Depending on affected organ, consider initiation of corticosteroids with dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Initiate appropriate hormone replacement therapy • For Grade 4 Type 1 diabetes mellitus, initiate treatment with anti-hyperglycaemics as clinically indicated
Nephritis and renal dysfunction	Grade 2 blood creatinine elevation > 1.5× and ≤ 3× the ULN	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.	
	Grade 3 or 4 blood creatinine level > 3× the ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or

Table 4 Recommended Treatment Modifications for Checkpoint Blockade in combination with CTL-002

Immune-related Adverse Reaction	Severity	Dose Modifications	Additional intervention
			equivalent followed by a taper
Skin Adverse Reactions	Grade 2 lasting longer than 1 week, Grade 3 rash, or suspected SJS or TEN or DRESS	Withhold	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating steroids.	
	Grade 4 rash, or confirmed SJS, TEN or DRESS	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent promptly initiated and prompt cardiology consultation with diagnostic workup according to current clinical guidelines
Neurological toxicities (including but not limited to paraneoplastic encephalomyelitis, meningitis, Guillain-Barre syndrome, central nervous system inflammation, chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, neuropathy peripheral)	Grade 2	Withhold	• Depending on observed event consider initiation of corticosteroids with dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Initiate neurologic consultation
		Resume in subjects with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating steroids.	
	Grade 3 or 4	Permanently discontinue	• Depending on observed event consider initiation of corticosteroids with dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Initiate neurologic consultation

Table 4 Recommended Treatment Modifications for Checkpoint Blockade in combination with CTL-002

Immune-related Adverse Reaction	Severity	Dose Modifications	Additional intervention
Other immune-related adverse reactions (including but not limited to myositis, solid organ transplant rejection, graft-vs-host disease, myasthenia gravis, pericarditis, immune thrombocytopenic purpura, vasculitis, arthralgia, arthritis, muscular weakness, myalgia, polymyalgia rheumatica, Sjogren's syndrome, keratitis, stomatitis)	Grade 2 or 3 based on type of reaction (first occurrence)	Withhold dose(s)	Initiate symptomatic management including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume if other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.	
	– Grade 3 based on type of reaction or Grade 4 – Grade 3 or 4 pericarditis – Recurrent Grade 3 immune-related adverse reaction - Persistent Grade 2 or 3 lasting 12 weeks or longer despite treatment modification - Inability to reduce corticosteroid dose to 10 mg or less prednisone or equivalent per day within 12 weeks of initiating steroids	Permanently discontinue treatment	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
Infusion-related reactions (refer to Section 5.2.5)	Grade 1 or 2	Interrupt or slow the rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue treatment	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = Drug Rash with Eosinophilia and Systemic Symptoms; ULN = upper limit of normal; SJS = Stephen-Johnson syndrome; SmPC = Summary of Product Characteristics; TEN = toxic epidermal necrolysis.

Note: Toxicity should be graded with the current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

[a] Recommendation for the use of hormone replacement therapy is provided below.

[b] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue based on recommendations for hepatitis with no liver involvement.

In case of occurrence of specific immune-related Adverse Events during the combination treatment with CTL-002 and checkpoint blocking antibodies (e.g., nivolumab, cemiplimab, nivolumab/relatlimab), specific supportive care guidelines are provided below; please also refer to the individual SmPC (EU), SwissMedic Medical Product Information (Switzerland) or the product label (US) of the respective checkpoint blocking agent. Immune-mediated adverse reactions or also called immune-related adverse reactions (irAE), which may be severe or fatal, may occur in any organ system or tissue. IrAEs can occur at any time after starting therapy with checkpoint blocking antibodies or CTL-002. While irAEs usually manifest during treatment with checkpoint blocking antibodies, irAEs can also evolve after discontinuation of checkpoint blocking treatment. IrAEs affecting more than one body system can occur simultaneously.

Early identification and management of irAEs are essential to ensure safe use of checkpoint blocking antibodies and CTL-002. Monitor closely for symptoms and signs that may be clinical manifestations of underlying irAEs. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected irAEs, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue treatment depending on severity (refer to Table 4). In general, if the treatment requires interruption or discontinuation, administer systemic corticosteroid therapy (prednisone or equivalent) until improvement to Grade 1 or less and in case of high grade irAEs consider immediate intravenous systemic treatment with corticosteroids.

Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in subjects whose irAEs are not controlled with corticosteroids.

Toxicity management guidelines for different adverse reactions are discussed below.

Immune-related pneumonitis:

Checkpoint blocking antibodies can cause immune-mediated pneumonitis, defined as requiring use of systemic corticosteroids or other immunosuppressants and the absence of clear alternate etiology. Fatal cases have been reported. Subjects should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated pneumonitis should be ruled out. Subjects with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with treatment modifications and corticosteroids followed by taper (refer to Table 4).

Immune-related colitis:

Checkpoint blocking antibodies can cause immune-mediated colitis, defined as requiring use of systemic corticosteroids or other immunosuppressants and the absence of clear alternate etiology. The primary component of the immune-mediated colitis is diarrhea. Cytomegalovirus infection/reactivation has been reported in subjects with corticosteroid-refractory immune-mediated colitis treated with checkpoint blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Subjects should be monitored for signs and symptoms of diarrhea or colitis and managed with treatment modifications, anti-diarrhea agents, and corticosteroids followed by taper (refer to Table 4).

Immune-related hepatitis (with or without tumor involvement in liver):

Checkpoint blocking antibodies can cause immune-mediated hepatitis, defined as requiring use of systemic corticosteroids and the absence of clear alternate etiology. Subjects should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with treatment modifications and corticosteroids (refer to Table 4).

Immune-related endocrinopathies:

Hypophysitis

Checkpoint blocking antibodies can cause immune-mediated hypophysitis. Monitor subjects for signs and symptoms of hypophysitis. Hypophysitis can present with acute symptoms associated

with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue treatment (refer to Table 4).

Adrenal insufficiency:

Checkpoint blocking antibodies can cause immune-mediated adrenal insufficiency. Subjects should be monitored for signs and symptoms of adrenal insufficiency during and after treatment. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold treatment depending on severity (refer to Table 4).

Thyroid Disorders (Hypothyroidism/Hyperthyroidism/Thyroiditis):

Checkpoint blocking antibodies can cause autoimmune thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Thyroid disorders can occur at any time during the treatment. Subjects should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation. Initiate hormone replacement or medical management as clinically indicated. For symptomatic hypothyroidism, treatment should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, treatment should be withheld and methimazole should be initiated as needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized. Withhold or permanently discontinue treatment depending on severity (refer to Table 4).

Type 1 Diabetes mellitus:

Checkpoint blocking antibodies can cause Type 1 diabetes mellitus. Subjects should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold treatment depending on severity (refer to Table 4).

Immune-mediated nephritis and renal dysfunction:

Checkpoint blocking antibodies can cause immune-mediated nephritis, defined as renal dysfunction or ≥ Grade 2 increased creatinine, requirement for systemic corticosteroids or other immunosuppressants, and absence of a clear alternate etiology. Monitor subjects for elevated serum creatinine and changes in renal function prior to and periodically during treatment. Subjects should be managed with treatment modifications and corticosteroids (refer to Table 4).

Immune-mediated skin adverse reactions:

Checkpoint blocking antibodies can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) has occurred with checkpoint blocking antibodies, some cases with fatal outcome. Subjects should be monitored for evidence of suspected severe skin reactions and exclude other causes. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue treatment depending on severity (refer to Table 4). For symptoms or signs of SJS or TEN, refer the subject for specialized care for assessment and treatment and manage subject with treatment modifications (refer to Table 4).

Immune-mediated encephalitis:

Checkpoint blocking antibodies can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of subjects with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold or permanently discontinue treatment depending on severity (refer to Table 4).

Other immune-mediated adverse reactions:

Checkpoint blocking antibodies can cause other clinically significant immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of treatment. Evaluate suspected immune-related adverse reactions to exclude other causes. Subjects should be monitored for signs and symptoms of immune-related adverse reactions and managed with treatment modifications and corticosteroids as clinically indicated (refer to Table 4).

Infusion-related reactions:

Checkpoint blocking antibodies can cause severe or life-threatening infusion reactions. Monitor subjects for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction are nausea, pyrexia, rash and dyspnea. Interrupt or slow down the rate of infusion or discontinue based on severity of reactions (refer to Table 4).

5.3. Dose Modification and Discontinuation

Modification of study treatment (interruption, reduction, and/or permanent discontinuation) may be indicated if an AE is judged (by the Investigator) to be possibly related to CTL-002 and/or nivolumab/cemiplimab. In any such cases it is also recommended to consult the Sponsor's Medical Monitor.

5.3.1. Dose Reduction

Nivolumab/Cemiplimab intra-subject dose escalation or reductions are not allowed. Dosing may only be interrupted, delayed, or discontinued. The same applies for CTL-002.

5.3.2. Permanent Dosing Interruption (Discontinuation)

Permanent discontinuation of both CTL-002 and nivolumab/cemiplimab is required/recommended under the following criteria and following Table 4 recommendations:

- Subjects who experience any at least possibly CTL-002-, or nivolumab/cemiplimab related **Grade 4 AE**
- Subjects who experience any at least possibly CTL-002-, or nivolumab/cemiplimab-related **Grade ≥2** immune-related **myocarditis**
- Subjects who experience any at least possibly CTL-002- or nivolumab/cemiplimab-related **Grade ≥3** immune-related **pneumonitis**, **adrenal insufficiency**
- Subjects who experience any at least possibly CTL-002-, or nivolumab/cemiplimab-related immune-related **hepatitis**
    - Subjects with no tumor involvement in the liver with ≥ Grade 3 AST or ALT or total bilirubin elevation
    - Subjects with tumor involvement of the liver with AST or ALT increases to > 10× ULN or total bilirubin increases to > 3× ULN

- Subjects who experience **Stevens-Johnson syndrome (SJS)**.
- Subjects who experience any other at least possibly CTL-002- or nivolumab/cemiplimab-related **Grade 3 AE** that persists despite optimal supportive treatment measures
- Subjects who experience any other at least possibly CTL-002- or nivolumab/cemiplimab-related AE of any Grade that **in the opinion of the Investigator requires permanent discontinuation** (SRC ad-hoc confirmation for discontinuation recommended for this case)
- Subjects who experience **recurrent Grade 3 toxicities**

5.3.3. Temporary Dosing Interruption

Temporary dosing interruption should occur for

- Subjects that **experience AEs for which temporary dosing interruption is recommended** as listed in Section 5.2.7.1 ("Known Checkpoint Blocking Antibody-related Toxicities and Their Management")
- Subjects who experience any other at least possibly CTL-002- or nivolumab/cemiplimab-related AE of any Grade that i**n the opinion of the Investigator requires at least temporary dosing interruption** (confirmation for temporary discontinuation with the Medical Monitor is recommended for this case)

5.3.4. Recommencement of Dosing

In general, subjects may be considered for recommencement of treatment once

- A toxicity resolves to **Grade ≤ 1** (provided that the toxicity was not recurrent) or
- When a toxicity **is stable and manageable through supportive/medical therapy** and **in the Investigator's opinion** and in agreement with the Sponsor Medical Monitor **it appears safe to recommence treatment**

For Part A (Phase 1), CTL-002 recommencement of treatment may be at the initial dose level or one dose level reduced, based upon the discretion of the Investigator ideally in agreement with the Sponsor Medical Monitor. For Part B (Phase 2a) of the study, recommencement of treatment should be at the same dose based upon the discretion of the Investigator ideally in agreement with the Sponsor Medical Monitor. There are no intra-subject dose escalation or reductions allowed. Dosing may only be interrupted, delayed, or discontinued.

For nivolumab, the dose is fixed at 240 mg and no dose adjustment is permitted under any circumstance apart from those provided in the label.

For cemiplimab, the dose is fixed at 350 mg and no dose adjustment is permitted under any circumstance apart from those provided in the label.

Treatment modifications for irAE and infusion-related reactions (Grade 1 to 4) should be handled according to the guidelines in Section 5.2.5.

5.4. Prior and Concomitant Therapy

Any medication that is considered necessary for the subject's welfare and will not interfere with CTL-002 or nivolumab/cemiplimab (see below), may be given at the discretion of the Investigator.

5.4.1. Concomitant Therapy Guidance

Concomitant therapies should be used according to local guidance. Supportive care guidelines (Section 5.2) and prohibited medications (Section 5.4.3) must be considered.

Other anti-cancer agents, investigational agents and radiotherapy should not be given while the subject is on study, although radiation for palliation at focal sites is permitted after discussion with the Medical Monitor.

Nondrug interventions and any changes to a concomitant medication or other interventions should also be recorded in the electronic Case Report Form (eCRF). Use of any herbal or dietary supplements required to be captured with dose, start and stop dates as appropriate.

5.4.2. Recording of Concomitant Medication

Any concomitant treatment and medication information will be collected from the time that subjects sign the ICF until:

- 30 days following the last CTL-002/anti-PD-1 checkpoint inhibitor infusion
- Concomitant medications given to treat AEs deemed related to CTL-002/defined anti-PD-1 checkpoint inhibitor will be recorded up to 12 months (Part A) or 24 months (Part B) following the last CTL-002/ defined anti-PD-1 checkpoint inhibitor infusion or longer in case the AE has not resolved
- Concomitant therapies given to manage a subject's underlying disease will be recorded through the end of the study

Any medication a subject receives at the time of signing the ICF or during the study as well as any changes thereof must be recorded in the eCRF along with:

- Generic name of the drug (or trade name for combination drugs)
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant medication or prior therapy.

In addition, any prior or concomitant diseases and signs and symptoms (a condition that is either active at enrolment or adversely impacts the subject's condition at enrolment), if applicable at baseline will be recorded. The Sponsor will code according to the standard dictionaries (e.g., WHO Drug and Medical Dictionary for Regulatory Activities [MedDRA]; for details refer to the Safety Management Plan.

5.4.3. Prohibited Medications

The following are prohibited during the study:

- Chemotherapy, surgery or radiation therapy for cancer are not allowed during active participation with the exception of palliative intent. Likewise, use of any unapproved (i.e., no marketing authorization has been granted) IMP, other than CTL-002/the defined anti-PD-1 checkpoint inhibitor, or device is not allowed until a subject has completed the End of Core Study/Safety Follow-up Visit and enters the long-term Follow-up Period part of the study
- Corticosteroids and other immunosuppressive compounds are prohibited during active participation, except for:
    a. Inhaled or topical steroids for short term use.
    b. Prednisone or equivalent used to treat any condition other than immune-mediated AEs at a dose of ≤0.125 mg/kg/day of prednisone (maximum allowed 10 mg/day) for more than 7 consecutive days or at a dose of >0.125mg/kg/day prednisone for less than 7 consecutive days.
    c. Corticosteroids used to treat immune-mediated AEs.
    d. Immunomodulating agents.
    e. Anti-PD-1 checkpoint inhibitor determined as combination treatment product in this protocol.

5.5. Overdose

No data on overdosing with CTL-002 are available since this is the first study in humans. There is no known antidote.

For the purpose of this protocol, an overdose is defined as:

- Any subject receiving a higher dose of CTL-002 than the dose(s) assigned to a subject in any particular dosing cohort (applies to both Part A and B), or any subject administered a dose higher than 20 mg/kg of CTL-002
- Any subject receiving a dose of nivolumab higher than 240mg
- Any subject receiving a dose of cemiplimab higher than 350 mg

Investigators should be advised that any subject who receives a dose of CTL-002 and/or nivolumab/cemiplimab higher than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly. If the overdose results in an AE, the subject should be followed up carefully until all signs of toxicity are resolved.

For overdoses of nivolumab/cemiplimab refer to the leaflet insert.

For the purposes of the study such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF, on the overdose eCRF module and reported using the SAE report form where applicable. This applies to situations were an AE is associated with ("results from") the overdose of CTL-002 and/or nivolumab/cemiplimab, the AE(s) is reported as an SAE, even if no other seriousness criteria are met

- An overdose with no associated symptoms is only reported on the overdose eCRF module

If an overdose occurs in the course of the study, then Investigators or other site personnel must inform appropriate Sponsor representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

For overdoses associated with an SAE, standard reporting timelines apply.

5.6. Treatment Compliance

The Investigator is responsible for maintaining accurate subject records to fully document the study drugs have been administered with details of dosing information.

CTL-002 and nivolumab/cemiplimab should only be used as directed in this protocol and as detailed in the Pharmacy Manual. Details of treatment with CTL-002 and nivolumab/cemiplimab for each subject will be recorded in the eCRF.

5.7. Randomization and Blinding

This is an open-label, single-arm study without randomization or blinding of data.

6. TRIAL PROCEDURES AND ASSESSMENT

6.1. Study Visits

During the study all subjects will undergo regular assessments (see below for further details). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- Complete SoAs and their timing are provided in the SoAs see Table 5, Table 6 and Table 7. More detailed description of laboratory procedures and sample management is provided in the Laboratory Manual.
- Descriptions of the different Efficacy and Safety Assessments are provided in Section 6.2.5 and Section 6.2.4, respectively
- Note the following guidance regarding visit windows, as far as not otherwise indicated in the SoA

6.1.1. Pre-screening Visit Part A (Phase 1; dose escalation)

Time point: Pre-screening assessment to confirm subject's GDF-15 serum levels.

This result should be available before a subject is approved for consent and starts screening procedures.

- Pre-screening informed consent (for collection of historical serum GDF-15 results within 2 months prior to the start of treatment with CTL-002 or in case of pre-screening blood sampling)
- Serum analysis of GDF-15. **Note**: Serum GDF-15 levels can be measured locally (if site routinely performs this assessment) or centrally.

  The analysis of GDF-15 does not need to be repeated if there are historical serum GDF-15 results available within 2 months prior to the start of treatment with CTL-002

6.1.2. Screening Visit Part A (Phase 1; dose escalation) / Part B (Phase 2a; expansion)

Time point: Screening assessments (i.e., inclusion/exclusion criteria) to confirm subject eligibility will be performed within up to 21 days (Day -21 to Day -1) (for Part A) and up to 28 days (Day -28 to Day -1) (for Part B) prior to first dose.

All results should be available before a subject is declared eligible for study participation.

- Subject informed consent
- Medical history/current medical conditions, prior cancer therapies including radiation and surgery
- Demographics
- Eligibility criteria
- Vital signs
- SARS-CoV-2 (COVID-19) testing (RNA and antibody testing)
- Pregnancy test (women of childbearing potential only. Serum test for pregnancy within 7 days prior to Day 1 dose)

- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Safety urinalysis
- Assessment of thyroid hormones, hemoglobin A1c (HbA1c) and NT-proBNP (N-terminal B-type natriuretic peptide)
- Infectious disease/serology
- Immunoglobulins
- Immune monitoring (cytokines/chemokines) (Part A only)
- Serum analysis of GDF-15
- Urine analysis of GDF-15 (Part A only)
- Full physical examination (including height and weight) plus collection of historical weight data from ≤ 6 months prior Screening, as available
- ECOG Performance Status
- Neurological examination/assessment (check for motor neuropathy)
- ECG
- Echocardiography or MUGA if ECHO cannot be performed (MUGA/ECHO standard of care results can be used as long as assessed within screening period)
- Cutaneous tumor lesion assessment/photography
- Tumor assessment/Imaging: CT/MRI/positron emission tomography (PET)-Scan to document tumor burden according to RECIST/iRECIST (Refer to Appendix 2) (scans performed as standard of care can be used as long as made within screening period)
- L3SMI (Part A only)
- Mini Cachexia Score (MCASCO) (Part A only)
- X-ray thorax (only if CT/MRI/PET CT imaging older than 7 days)
- Mandatory tumor biopsy:
    - For Part A (Phase 1) to be taken between day -7 and Day -1
    - For Part B (Phase 2a) baseline biopsy from all subjects (new or archived if obtained within 120 days prior to treatment start), for melanoma and cutaneous squamous cell carcinoma ideally within -7 days before infusion of CTL-002

      Note: for cutaneous squamous-cell carcinoma, multiple punch biopsies to be taken at a single timepoint (as per clinical possibility, ideally 3-5).
- Tumor mutational status:
    - For all subjects: collection of historical data e.g., but not limited to BRAF, CEA, PSA, CA19-9, CA-125, MSI, PD-L1, EGFR, Alk, HER2 and other molecular hallmark changes depending upon subject's primary cancer.
    - For subjects enrolled under this version of the protocol and under previous protocols v4.0 and 5.0, an optional retrospective analysis of PD-L1 and other relevant biomarkers might be conducted on archival tumor tissue any time after screening.

6.1.3. Part A (Phase 1; dose escalation): DLT Observation Period (Cycles 1 and 2)

Time-point: After confirmation of all study eligibility criteria – Weeks 1-4 (Cycles 1 and 2)

Note: On the day of study drug dosing, all procedures are to be performed pre-dose. Before start of first CTL-002 infusion, safety laboratory parameters will be assessed to reconfirm eligibility and ability to receive study treatment.

Cycle 1

Week 1: Day 1

- Medical history/current medical conditions, prior cancer therapies including radiation and surgery
- AEs
- Concomitant medications
- Physical examination
- ECOG
- ECG
- Safety laboratory testing (hematology, clinical chemistry, coagulation): Pre-CTL-002 infusion (within 24 hours prior to dosing to reconfirm eligibility criteria) and 6 hours after the start of CTL-002 infusion.
- Safety urinalysis
- Urine pregnancy test (if positive, to be confirmed with serum test)
- Urine analysis of GDF-15 (prior to infusion)
- Immune monitoring (cytokines/chemokines): Sample taken within 30 minutes prior to CTL-002 infusion
- PK: Sample taken within 30 minutes prior to CTL-002 infusion, then immediately before the end of CTL-002 infusion (1 hour) and 4 hours (±15 minutes), and 8 hours (±30 minutes) after the start of CTL-002 infusion.
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to CTL-002 infusion, then immediately before the end of CTL-002 infusion (1 hour) and 4 hours (±15 minutes) and 8 hours (±30 minutes) after the start of CTL-002 infusion.
- Immunogenicity/ADA testing: Sample taken within 30 minutes CTL-002 prior to infusion
- Blood molecular/transcriptional profiling: Sample taken within 30 min prior to CTL-002 infusion
- Vital Signs (immediately before CTL-002 infusion and then 15 min (± 5 min), 30 min (± 5 min), 60 min (± 15 min), 90 min (± 15 min), 2 hrs (± 15 min), 4 hrs (± 15 min) and 8 hrs (± 30 min) after the start of CTL-002 infusion)
- CTL-002 infusion over approximately 60 minutes (± 10 min) (**Note**: for "backfill" subjects, combination treatment is started immediately on Day 1, no prior monotherapy cycle)
- Overnight hospitalization/observation

Week 1: Day 2

- Vital signs
- AEs
- Concomitant medications
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Safety urine analysis

- Urine analysis of GDF-15
- Immune monitoring (cytokines/chemokines): Sample taken 24 hours post-CTL-002 infusion (±2 hours)
- PK: Sample taken at 24-hour time-point (±2 hours)
- Serum analysis of GDF-15: Sample taken 24 hours post -CTL--002 infusion (±2 hours)
- Blood molecular/transcriptional profiling: Sample taken 24 hours post-CTL-002 infusion (±2 hours)

Week 2: Day 8 (±24 hours)

- Vital signs
- AEs
- Concomitant medications
- Physical examination
- ECOG
- Safety laboratory testing (hematology, clinical chemistry, coagulation).
- Safety urinalysis
- Urine analysis of GDF-15
- Immune monitoring (cytokines/chemokines): Sample taken at Day 8 (±24 hours)
- PK: Sample taken at Day 8 (±24 hours)
- Serum analysis of GDF-15: Sample taken at Day 8 (±24 hours)

Cycle 2

Week 3: Day 15 (±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- AEs
- Concomitant medications
- Mandatory biopsy - To be taken within 48 hours prior to CTL-002 infusion (Day 15 biopsy not required for Dose level 3-5 “backfill” subjects)
- Physical examination
- ECOG
- Weight assessment
- ECG
- Safety laboratory testing (hematology, clinical chemistry, coagulation) – Pre-CTL-002 infusion (within 24 hours of dosing) and 6 hours after the start of CTL-002 infusion
- Assessment of thyroid hormones, HbA1c and NT-proBNP
- Safety urine analysis
- Urine pregnancy test (if positive, to be confirmed with serum test)
- Urine analysis of GDF-15
- Immune monitoring (cytokines/chemokines): Sample taken within 30 minutes prior to CTL-002 infusion
- PK: Sample taken within 30 minutes prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hour)

- Serum analysis of GDF-15: Sample taken within 30 minutes prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hour)
- Immunogenicity: Sample taken within 30 minutes prior to CTL-002 infusion
- Blood molecular/transcriptional profiling: Sample taken within 30 minutes prior to CTL-002 infusion
- Vital signs (immediately before CTL-002 infusion and 15 min (± 5 min), 60 min (± 15 min), 2 hrs (± 15 min) and 4 hrs (± 15 min) after the start of CTL-002 infusion)
- CTL-002 infusion over approximately 60 minutes (± 10 min) - 30 minutes before nivolumab infusion
- Nivolumab infusion over approximately 30 minutes (± 5 min)
- Overnight hospitalization/observation

Week 4: Day 22 (±2 days)

- Vital signs
- AEs
- Concomitant medications
- Physical examination
- ECOG
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Safety urine analysis
- Urine analysis of GDF-15
- Immune monitoring (cytokines/chemokines)
- PK
- Serum analysis of GDF-15
- MCASCO

6.1.4. Part A (Phase 1; dose escalation): Extended Treatment Phase

Time-point: From Cycle 3 onwards (every 14 days ±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- Vital signs
- AEs
- Concomitant medications
- Mandatory biopsy (end of Cycle 2/beginning of Cycle 3 if treatment is extended)
- Physical examination
- ECOG
- Weight assessment (every 2 weeks)
- ECG (only every 4 weeks)
- Safety laboratory testing (hematology, clinical chemistry, coagulation) (within 24 hours prior to dosing)
- Safety urine analysis
- Urine pregnancy test (if positive, to be confirmed with serum test), (prior to any treatment with CTL-002)

- Immune monitoring (cytokines/chemokines) (only in Cycle 3)
- PK: Sample taken within 30 minutes prior infusion and immediately before end of infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to infusion and immediately before end of infusion (1 hour)
- Immunogenicity/ADA testing (only Cycle 3-5)
- Blood molecular/transcriptional profiling: Sample taken within 30 min prior to CTL-002 infusion (only Cycle 3-4)
- Assessment of thyroid hormones, HbA1c and NT-proBNP (every 2 weeks for 3 months, thereafter monthly)
- Tumor assessment/Imaging: CT/MRI/PET-Scan to document tumor burden according to RECIST/iRECIST (Refer to Appendix 2): after 8 weeks and every 8 weeks thereafter; End of Treatment Visit only if last scan is more than 4 weeks old
- L3SMI (every 8 weeks)
- MCASCO (every 4 weeks)
- Cutaneous tumor lesion assessment/photography (every 4 weeks)
- CTL-002 infusion over approximately 60 minutes (± 10 min) - prior to any nivolumab infusion
- Nivolumab infusion over approximately 30 minutes (± 5 min)

6.1.5. Part B (Phase 2a; expansion), All Cohorts Except Cutaneous Squamous-Cell Carcinoma: Core Treatment Period – Nivolumab Combination (Cycles 1-4)

Time-point: After confirmation of all study eligibility criteria – Cycles 1 to 4

Note: On the day of study drug dosing, all procedures are to be performed pre-dose. Before start of first CTL-002 infusion, safety laboratory parameters will be assessed to reconfirm eligibility and ability to receive study treatment.

Cycle 1

Week 1: Day 1

- Medical history/current medical conditions, prior cancer therapies including radiation and surgery
- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- ECG, (in extended treatment only every 4 weeks)
- Safety laboratory testing (hematology, clinical chemistry, coagulation): Pre-CTL-002 infusion (within 24 hours prior to dosing to reconfirm eligibility criteria) and 6 hours after the start of CTL-002 infusion.
- Safety urinalysis
- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)

- Immune monitoring (cytokines/chemokines): Sample taken within 30 minutes prior to CTL-002 infusion
- PK: Sample taken within 30 minutes prior to CTL-002 infusion, and immediately before the end of CTL-002 infusion (1 hour).
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to CTL-002 infusion.
- Immunogenicity/ADA: Sample taken within 30 minutes prior to CTL-002 infusion
- Blood molecular/transcriptional profiling: Sample taken within 30 min prior to CTL-002 infusion
- Vital Signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation immediately before CTL-002 infusion and then 15 min (± 5 min), 30 min (± 5 min), 60 min (± 15 min), 90 min (± 15 min), 2 hrs (± 15 min), and 4 hrs (± 15 min) after the start of CTL-002 infusion
- Immediate combination treatment (no prior monotherapy cycle):
    - CTL-002 infusion over approximately 60 minutes (± 10 min) - 30 minutes before nivolumab infusion
    - Nivolumab infusion over approximately 30 minutes (± 5 min)
- Overnight hospitalization/observation

Week 1: Day 2

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation
- AEs
- Concomitant medications
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Immune monitoring (cytokines/chemokines): Sample taken 24 hours (±2 hours) post-CTL-002 infusion
- PK: Sample taken at 24-hour (±2 hours) after start of CTl-002 infusion
- Serum analysis of GDF-15: Sample taken 24 hours (±2 hours) after start of CTL--002 infusion

Week 2: Day 8 (±24 hours)

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation
- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- PK: Sample taken at Day 8 (±24 hours)
- Serum analysis of GDF-15: Sample taken at Day 8 (±24 hours)

Cycle 2

Week 3: Day 1 (±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- Weight assessment
- Safety laboratory testing (hematology, clinical chemistry, coagulation) (within 24 hours prior to dosing)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP
- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)
- Immune monitoring (cytokines/chemokines): Sample taken within 30 minutes prior to CTL-002 infusion
- PK: Sample taken within 30 minutes prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to CTL-002 infusion
- Immunogenicity/ADA: Sample taken within 30 minutes prior to CTL-002 infusion
- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation (immediately before CTL-002 infusion)
- Combination treatment:
    - CTL-002 infusion over approximately 60 minutes (± 10 min) - prior to any nivolumab infusion
    - Nivolumab infusion over approximately 30 minutes (± 5 min)

Cycle 3-4: Day 1 (±2 days)

Time-point: From Cycle 3-4 (every 14 days ±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation (immediately before CTL-002 infusion)
- AEs
- Concomitant medications
- Mandatory biopsy (only for melanoma; end of Cycle 4/beginning of Cycle 5)
- Physical examination
- ECOG Performance Status
- Weight assessment (every 2weeks)
- ECG (only every 4 weeks)
- Safety laboratory testing (hematology, clinical chemistry, coagulation) (within 24 hours prior to dosing)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP (every 2 weeks for 3 months, thereafter monthly)

- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test) (prior to any treatment with study drug)
- Immune monitoring (cytokines/chemokines) (only in Cycle 3)
- PK: Sample taken within 30 minutes prior infusion and immediately before end of infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to infusion
- Immunogenicity/ADA testing
- Tumor assessment/Imaging: CT/MRI/PET-Scan to document tumor burden according to RECIST/iRECIST (refer to Appendix 2): after 8 weeks and every 8 weeks thereafter
- Cutaneous tumor lesion assessment/photography (every 4 weeks)
- Combination treatment:
    - CTL-002 infusion over approximately 60 minutes (± 10 min) - prior to any nivolumab infusion
    - Nivolumab infusion over approximately 30 minutes (± 5 min)

6.1.6. Part B (Phase 2a; expansion), All Cohorts Except Cutaneous Squamous-Cell Carcinoma: Extended Treatment Phase - Nivolumab Combination

Time-point: From Cycle 5 onwards (every 14 days ±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation
- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- Weight assessment (every 2 weeks)
- ECG (only every 4 weeks)
- Safety laboratory testing (hematology, clinical chemistry, coagulation) (within 24 hours prior to dosing)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP (every 2 weeks for 3 months, thereafter monthly)
- Safety urine analysis (only every 8 weeks)
- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)
- PK: Sample taken within 30 minutes prior infusion and immediately before end of infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to infusion
- Immunogenicity/ADA testing (Cycle 5 only)
- Blood molecular/transcriptional profiling: Sample taken within 30 min prior to CTL-002 infusion (only Cycle 5 [after 8 weeks] and Cycle 9 [after 16 weeks])

- Tumor assessment/Imaging: CT/MRI/PET-Scan to document tumor burden according to RECIST/iRECIST (Refer to Appendix 2): after 8 weeks and every 8 weeks thereafter; End of Treatment Visit only if last scan is more than 4 weeks old
- Cutaneous tumor lesion assessment/photography (every 4 weeks)
- Mandatory biopsy (for melanoma and the biomarker cohort with mixed solid tumors; end of Cycle 4/beginning of Cycle 5)
- Combination treatment:
    - CTL-002 infusion over approximately 60 minutes (± 10 min) prior to any nivolumab infusion
    - Nivolumab infusion over approximately 30 minutes (± 5 min)

6.1.7. Part B (Phase 2a; Expansion), Cutaneous Squamous-Cell Carcinoma Cohort: Core Treatment Period – Cemiplimab Combination (Cycles 1-3)

Time-point: After confirmation of all study eligibility criteria – Cycles 1 to 3

Note: On the day of study drug dosing, all procedures are to be performed pre-dose. Before start of first CTL-002 infusion, safety laboratory parameters will be assessed to reconfirm eligibility and ability to receive study treatment.

Cycle 1

Week 1: Day 1

- Medical history/current medical conditions
- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- ECG
- Safety laboratory testing (hematology, clinical chemistry, coagulation): Pre-CTL-002 infusion (within 24 hours prior to dosing to reconfirm eligibility criteria) and 6 hours after the start of CTL-002 infusion.
- Safety urinalysis
- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)
- Immune monitoring (cytokines/chemokines): Sample taken within 30 minutes prior to CTL-002 infusion
- PK: Sample taken within 30 minutes prior to CTL-002 infusion, and immediately before the end of CTL-002 infusion (1 hour).
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to CTL-002 infusion.
- Immunogenicity/ADA: Sample taken within 30 minutes prior to CTL-002 infusion
- Blood molecular/transcriptional profiling: Sample taken within 30 min prior to CTL-002 infusion
- Vital Signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation immediately before CTL002 infusion and then

15 min (± 5 min), 30 min (± 5 min), 60 min (± 15 min), 90 min (± 15 min), 2 hrs (± 15 min), and 4 hrs (± 15 min) after the start of CTL-002 infusion

- Immediate combination treatment (no prior monotherapy cycle):
  - CTL-002 infusion over approximately 60 minutes (± 10 min); 30 minutes before cemiplimab infusion
  - Cemiplimab infusion over approximately 30 minutes (± 5 min)
- Overnight hospitalization/observation

Week 1: Day 2

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation
- AEs
- Concomitant medications
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Immune monitoring (cytokines/chemokines): Sample taken 24 hours (±2 hours) post-CTL-002 infusion
- PK: Sample taken at 24-hour (±2 hours) after start of CTl-002 infusion
- Serum analysis of GDF-15: Sample taken 24 hours (±2 hours) after start of CTL--002 infusion

Week 2: Day 8 (±24 hours)

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation
- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- PK: Sample taken at Day 8 (±24 hours)
- Serum analysis of GDF-15: Sample taken at Day 8 (±24 hours)

Cycle 2

Week 4: Day 1 (±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- Weight assessment
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP

- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)
- Immune monitoring (cytokines/chemokines): Sample taken within 30 minutes prior to CTL-002 infusion
- PK: Sample taken within 30 minutes prior to CTL002 infusion and immediately before end of CTL-002 infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to CTL-002 infusion
- Immunogenicity/ADA: Sample taken within 30 minutes prior to CTL-002 infusion
- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation (immediately before CTL-002 infusion)
- Combination treatment:
    - CTL-002 infusion over approximately 60 minutes (± 10 min) - prior to any cemiplimab infusion
    - Cemiplimab infusion over approximately 30 minutes (± 5 min)

Cycle 3: Day 1 (±2 days)

Week 7: Day 1 (±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation (immediately before CTL-002 infusion)
- AEs
- Concomitant medications
- Mandatory biopsy (end of Cycle 3/beginning of Cycle 4)
- Physical examination
- ECOG Performance Status
- Weight assessment
- ECG
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP
- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)
- PK: Sample taken within 30 minutes prior infusion and immediately before end of infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to infusion
- Immunogenicity/ADA testing
- Tumor assessment/Imaging: CT/MRI/PET-Scan to document tumor burden according to RECIST/iRECIST (refer to Appendix 2): after 6-9 weeks and every 6-9 weeks thereafter
- Cutaneous tumor lesion assessment/photography (every 6-9 weeks)
- Combination treatment:
    - CTL-002 infusion over approximately 60 minutes (± 10 min) - prior to any cemiplimab infusion
    - Cemiplimab infusion over approximately 30 minutes (± 5 min)

6.1.8. Part B (Phase 2a; Expansion), Cutaneous Squamous-Cell Carcinoma Cohort: Extended Treatment Phase – Cemiplimab Combination

Time-point: From Cycle 4 onwards (every 21 days ±2 days)

Note: On the day of dosing, all procedures to be performed pre-dose.

- Vital signs including systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation
- AEs
- Concomitant medications
- Physical examination
- ECOG Performance Status
- Weight assessment (every 3 weeks)
- ECG (only every 6 weeks)
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP (every 3 weeks for 3 months, thereafter every second cycle)
- Safety urine analysis (only every 9 weeks)
- Urine pregnancy test (mandatory for women of childbearing potential). If positive, confirm with serum test (prior to any treatment with study drug)
- PK: Sample taken within 30 minutes prior infusion and immediately before end of infusion (1 hour)
- Serum analysis of GDF-15: Sample taken within 30 minutes prior to infusion
- Immunogenicity/ADA testing (Cycle 4 and 5 only)
- Blood molecular/transcriptional profiling: Sample taken within 30 min prior to CTL-002 infusion (only Cycle 4 [after 9 weeks] and Cycle 7 [after 18 weeks])
- Tumor assessment/Imaging: CT/MRI/PET-Scan to document tumor burden according to RECIST/iRECIST (Refer to Appendix 2): after 6-9 weeks and every 8-9 weeks thereafter; End of Treatment Visit only if last scan is more than 4 weeks old
- Cutaneous tumor lesion assessment/photography (every 6-9 weeks, according to local practice)
- Mandatory biopsy (end of Cycle 3/beginning of Cycle 4): for cutaneous squamous-cell carcinoma, multiple punch biopsies to be taken (as per clinical possibility, ideally 3-5)
- Combination treatment:
    - CTL-002 infusion over approximately 60 minutes (± 10 min) - prior to any cemiplimab infusion
    - Cemiplimab infusion over approximately 30 minutes (± 5 min)

6.1.9. End of Treatment Visit

Time-point: 2 weeks after the last CTL-002 infusion (±2 days)

- Vital signs
- AEs
- Concomitant medications
- Physical examination (including neurological examination [check for motor neuropathy])

- ECOG Performance Status
- Weight assessment
- SARS-CoV-2 (COVID-19) testing (RNA and antibody testing)
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Assessment of thyroid hormones, HbA1c, and NT-proBNP
- Safety urine analysis
- Urine analysis of GDF-15 (Part A only)
- Urine pregnancy test (if positive, confirm with serum test)
- Immune monitoring (cytokines/chemokines)
- PK
- Serum analysis of GDF-15
- Immunogenicity/ADA testing
- Blood molecular/transcriptional profiling (Part A only)
- Infectious diseases/serology
- Immunoglobulins
- Tumor assessment/Imaging: CT/MRI/PET-Scan to document tumor burden according to RECIST/iRECIST (Refer to Appendix 2): End of Treatment Visit only if last scan is more than 4 weeks old
- L3SMI (only if last scan is more than 4 weeks old) (Part A only)
- MCASCO (Part A only)
- Cutaneous tumor lesion assessment/photography
- ECG
- Echocardiography or MUGA if ECHO cannot be performed

6.1.10. Safety Follow-up Visit

Time-point: 30 days post last infusion (±2 days)

- Vital signs
- AEs
- Concomitant medications
- Safety laboratory testing (hematology, clinical chemistry, coagulation)
- Urine pregnancy test (if positive, to be confirmed with serum test)
- Physical examination (including neurological examination [check for motor neuropathy])
- ECOG Performance Status

6.1.11. Follow-up

Time-point: Every 3 months (±2 weeks) e.g., by phone/email for a total of 12 months in Part A (Phase 1; dose escalation) and a total of 24 months in Part B (Phase 2a; expansion).

- AEs (related to CTL-002 or study procedures)
- Concomitant medications (anti-cancer medication or due to related AEs)
- Cutaneous tumor lesion assessment/photography according to site practices
- Tumor assessment/Imaging: CT/MRI/PET-Scan according to local practice

- Survival

6.1.12. Study Schedules

The schedules of assessments for Part A (dose escalation, month 1/DLT period) and Part B (Phase 2a; expansion, combination therapy) excluding and including cutaneous squamous-cell carcinoma are provided in see Table 5, Table 6 and Table 7 respectively.

Table 5 Schedule of Assessments – Part A (Phase 1; dose escalation, month 1 / DLT period)

	Core study										Follow-up
Examination	**Pre-screening**	**Screening**	**Core Treatment Period: DLT Observation Period**					**Extended Treatment Period (optional)[1]**	**End of Treatment Visit**	**Safety FU/End of Core study**	**Efficacy and Survival FU**
Cycle			**Cycle 1**			**Cycle 2**		**Cycle 3-x**			
Weeks			**Wk 1**		**Wk 2**	**Wk 3**	**Wk 4**	**2 wk cycle**	**2 wks post-last CTL-002 infusion**	**30 d post-last CTL-002 infusion**	**Every 3 mos for 1 year by phone/(e)mail**
Study Day (D)		**D -21 to D -1**	**D1[2]**	**D2**	**D8**	**D15[2]**	**D22**	**D1[2]**			
					(±1 d)	(±2 d)	(±2 d)	(±2 d)	(±2 d)	(+2 d)	(± 2 wks)
CTL-002 infusion[3]			+			+		+			
Anti-PD-1/-L1 infusion[4]			(+) [5]			+		+			
Overnight observation/hospitalization			+			(+)[6]					
Pre-screening informed consent[44]	+										
Informed consent		+									
Medical history/current medical conditions		+	+								
Prior cancer therapies, including radiation and surgery		+	+								
Demographics, height		+									
Weight[7]		+				+		+	+		
Eligibility criteria		+	+[43]								
Pregnancy test[8]		+	+			+		+	+	+	
ECG		+	+			+		+[9]	+		
Echocardiography or MUGA if ECHO cannot be performed		+							+		
Physical examination		+	+		+	+	+	+	+	+	
ECOG Performance Status		+	+		+	+	+	+	+	+	
Vital signs[10]		+	8+	+	+	5+	+	+	+	+	
Neurological examination[11]		+							+	+	
Safety laboratory (Hematology, clinical chemistry, coagulation)[12] and urinalysis[13]		+	2+	+	+	2+	+	+	+	+	
Thyroid hormones (T3, TSH)[14]		+				+		+[15]	+		
HbA1c		+				+		+[15]	+		
NT-proBNP		+				+		+[15]	+		

	Core study										Follow-up
Examination	**Pre-screening**	**Screening**	**Core Treatment Period: DLT Observation Period**					**Extended Treatment Period (optional)[1]**	**End of Treatment Visit**	**Safety FU/End of Core study**	**Efficacy and Survival FU**
Cycle			**Cycle 1**			**Cycle 2**		**Cycle 3-x**			
Weeks			**Wk 1**		**Wk 2**	**Wk 3**	**Wk 4**	**2 wk cycle**	**2 wks post-last CTL-002 infusion**	**30 d post-last CTL-002 infusion**	**Every 3 mos for 1 year by phone/(e)mail**
Study Day (D)		**D -21 to D -1**	**D1[2]**	**D2**	**D8**	**D15[2]**	**D22**	**D1[2]**			
					(±1 d)	(±2 d)	(±2 d)	(±2 d)	(±2 d)	(+2 d)	(± 2 wks)
Infectious diseases (HIV, HBV, HCV, TBC, SARS-CoV-2)[16]		+							+		
Immunoglobulins[17]		+							+		
Immune monitoring (Cytokines/Chemokines)[18]		+	+	+	+	+	+	+[19]	+		
PK sampling[20]			4+	+	+	2+	+	2+	+		
Serum analysis of GDF-15[21]	+[44]	+	4+	+	+	2+	+	2+	+		
Urine analysis of GDF-15[22]		+	+	+	+	+	+		+		
Immunogenicity/ADA[23]			+			+		+[24]	+		
Blood molecular/transcriptional profiling[25]			+	+		+		+[45]	+		
Cutaneous tumor lesion assessment/ photography[26]		+						+[27]	+[27]		+[30]
Tumor assessment/Imaging [28]		+						+[29]	+[29]		+[30]
Lumbar Skeletal Muscle Index L3 (L3SMI)[31]		+						+[29]	+[29]		
X-ray thorax [32]		+									
Tumor Biopsy[33]		+				(+) [34]		(+)[35]	(+)[35]		
Tumor mutational status[36]		+									
MCASCO[37]		+					+	(+)[27]	+		
Adverse events[38]			+	+	+	+	+	+	+	+	+[39]
Concomitant medication[40]			+	+	+	+	+	+	+	+	+[41]
Survival[42]											+

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; d = day(s); ANC = absolute neutrophil count; CRP = C=reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; GDF-15 = growth differentiation factor 15; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hr = hour; Ig = immunoglobulin; iRECIST = modified RECIST = Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; MCASCO = Mini Cachexia Score; min = minute; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NT-proBNP = N-terminal B type natriuretic peptide; PET = positron emission tomography; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; TSH = thyroid-stimulating hormone; wk = week.

Note: A number in a cell indicates the number of times the assessment is conducted at that visit, e.g. 8+ indicates that vital signs are measured 8 times on Day 1 of Cycle 1.

(1) If treatment is not extended, refer to End of Treatment Visit.
(2) On CTL-002 treatment days all examinations to be done pre-dose, if not stated otherwise.
(3) Subjects with clinical benefit will be allowed to continue treatment if treatment is tolerated. Infusion on Day 15 if no DLT occurred and if no other safety event of concern. In combination treatment, CTL-002 to be administered always prior to anti-PD-1.
(4) Anti-PD-1 to be administered in approved standard dose every 2 weeks and always after CTL-002.
(5) Applies to backfill subjects only.
(6) Not required for backfill subjects.
(7) Weight: collection of historical data (6 months prior Screening, or any available pre-Screening data) in addition to Screening, every 2 weeks and at End of Treatment.
(8) Women of childbearing potential only. Mandatory for women of childbearing potential; Screening: serum screen for pregnancy within 7 days prior to study treatment; Day 1, Day 15 and Day 29, all CTL-002 administration days in extended treatment: urine test to confirm absence of pregnancy prior to any treatment with CTL-002 which if positive, confirm with serum test.
(9) In extended treatment ECG only every 4 weeks.
(10) Systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, oxygen saturation; Day 1: immediately before CTL-002 infusion and 15 min (± 5 min), 30 min (± 5 min), 60 min (± 15 min), 90 min (± 15 min), 2 hrs (± 15 min), 4 hrs (± 15 min) and 8 hrs (± 30 min) after the start of CTL-002 infusion; Day 15: immediately before CTL-002 infusion and 15 min (± 5 min), 60 min (± 15 min), 2 hrs (± 15 min) and 4 hrs (± 15 min) after CTL-002 infusion; all other visits before CTL-002 infusion.
(11) Neurological examination: including check for motor neuropathy (can be conducted by any treating physician, no neurology board certification required).
(12) Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differential WBC, ANC, absolute monocyte count, and platelet count; clinical chemistry: CRP, creatinine, lactate dehydrogenase (LDH), calcium, electrolytes (sodium and potassium), total bilirubin, gamma glutamyltransferase (GGT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glucose; coagulation: activated partial thromboplastin time (αPTT), prothrombin time/international normalized ratio (PT/INR), ATIII and D-dimer; Day 1 and Day 15: before CTL-002 infusion (within 24 hours prior to dosing) and 6 hrs after the start of CTL-002 infusion.
(13) Safety urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood and glucose in urine will be assessed by dipstick.
(14) Thyroid hormones: free T3 and basal TSH.
(15) Every 2 weeks for 3 months; thereafter monthly.
(16) HIV, HBV, HCV, TB, SARS-CoV-2 mandatory testing. For SARS-CoV-2 RNA and antibody testing to be conducted.
(17) IgG, IgA, IgM, IgE.
(18) Cytokines: Day 1 and Day 15: sample taken within 30 min prior to CTL-002 infusion, Day 2 = 24 hrs (± 2 hrs), Day 8 (± 24 hrs); Day 22 (± 24 hrs), Cycle 3 (if applicable): Day 1: within 30 min prior to CTL-002 infusion, End of Treatment. Part of the blood sample collected for immune-monitoring will also be used for exploratory analysis.
(19) Cytokines/chemokines: Cycle 3 only.
(20) PK: Day 1: sample taken within 30 min prior to CTL-002 infusion, immediately before end of CTL-002 infusion (1 hr), 4 hrs (± 15 min), and 8 hrs (± 30 min) after the start of CTL-002 infusion, Day 2 = 24 hrs (±2 hrs), Day 8 (±24 hrs), Day 15: sample taken within 30 min prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hr), Day 22, Cycle 3-following, Day 1: sample taken within 30 min prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hr), End of treatment Visit.
(21) Serum analysis of GDF-15: Day 1: sample taken within 30 min prior to CTL-002 infusion, immediately before end of CTL-002 infusion (1 hr), 4 hrs (± 15 min), and 8 hrs (± 30 min) after the start of CTL-002 infusion, Day 2 = 24 hrs (±2 hrs), Day 8 (± 24 hrs), Day 15: sample taken within 30 min prior to CTL-002 infusion, immediately before end of CTL-002 infusion (1 hr), Day 22; Cycle 3-5 (if applicable): Day 1: sample taken within 30 min prior to CTL-002 infusion, immediately before end of CTL-002 infusion (1 hr); End of Treatment.
(22) Urine analysis of GDF-15: Day 1 and Day 15: prior to CTL-002 infusion.
(23) Immunogenicity/ADA assessment: Day 1 and Day 15: sample taken within 30 min prior to CTL-002 infusion; Cycle 3-5 (if applicable): End of Treatment.
(24) Immunogenicity/ADA Cycle 3-5 only.
(25) Blood molecular/transcriptional profiling: Day 1: sample taken within 30 min prior to CTL-002 infusion, Day 2 = 24 hrs (±2 hrs), Day 15: within 30 min prior to CTL-002 infusion, Cycle 3-4 (if applicable) within 30 min prior CTL-002 infusion, End of Treatment.
(26) If applicable, number of lesions, measurement of target cutaneous lesions and color photography (including size measurement): Baseline within -7 days before infusion of CTL-002, every 4 weeks in extended treatment, End of Treatment and Follow-up.
(27) Every 4 weeks
(28) CT/MRI/PET-Scan of thorax and abdomen mandatory to document tumor burden according to RECIST/iRECIST, other areas as needed: At Screening, after 8 weeks and every 8 weeks thereafter; End of treatment Visit only if last scan is more than 4 weeks old. All imaging assessments to be sent to a central reader.
(29) Every 8 weeks; if treatment is stopped after core treatment period (no extended treatment) and last scan is less than 8 weeks old, imaging at End of Treatment Visit not necessary.

(30) Blinded copy of routine imaging assessments sent to a central reader.
(31) Lumbar Skeletal Muscle Index L3 (L3SMI), L3 level included, as part of the standard thorax/abdomen CT: Baseline assessment as part of Screening imaging, every 8 weeks thereafter; End of treatment Visit only if last scan is more than 4 weeks old.
(32) X-ray thorax only if CT/MRI/PET CT imaging older than 7 days
(33) Biopsy: Baseline within -7 days before infusion of CTL-002; Day 15: to be taken within 48 hrs before infusion of CTL-002; end of Cycle 2/beginning of Cycle 3 (in case of extended treatment) or End of treatment (if treatment is not extended). In case a biopsy is non-evaluable, an optional biopsy can be collected at the next medically feasible timepoint during ongoing treatment and as per treating physician's decision.
(34) For backfill subjects in Dose level 3-5, no Day 15 biopsy.
(35) For subjects without extended treatment third biopsy at End of Treatment Visit; for subjects with extended treatment biopsy end of Cycle 2/beginning of Cycle 3.
(36) Tumor mutational status: Collection of historical data e.g., but not limited to BRAF, CEA, PSA, CA19-9, CA-125, MSI, PD-L1, EGFR, Alk, HER2 and other molecular hallmark changes depending upon subject primary cancer.
(37) MCASCO: Baseline within -7 days before infusion of CTL-002, Day 22, every 4 weeks in extended treatment, and at End of Treatment.
(38) After 6 months, only new possibly related AEs will be captured (in addition, SAEs may be reported at any time during the study regardless of relationship).
(39) Related to CTL-002/defined checkpoint inhibitor or study procedures (in addition, SAEs may be reported at any time during the study regardless of relationship).
(40) After 6 months, only further anti-cancer-related medication will be captured.
(41) Anti-cancer medication or medication due to related AEs.
(42) Every 3 months for 1 year.
(43) Baseline safety laboratory testing prior to CTL-002 infusion to re-confirm eligibility.
(44) To determine eligibility, potential candidates will undergo a pre-screening assessment to determine GDF-15 serum levels, after signing the pre-screening ICF. Available GDF-15 serum results within 2 months prior to the start of treatment with CTL-002 are acceptable and do not need to be repeated. If historic results are not available, serum analysis of GDF-15 will need to be conducted during pre-screening, either locally or centrally.
(45) Blood molecular/transcriptional profiling Cycle 3-4 only.

Table 6 Schedule of Assessments – Part B (Phase 2a; expansion, combination therapy with nivolumab (except CSCC)

	Core study								Follow-up
Examination	**Screening**	**Core Treatment Period**				**Extended Treatment Period (optional)[1]**	**End of Treatment Visit**	**Safety FU/End of Core study**	**Efficacy and Survival FU**
Cycle		**Cycle 1**		**Cycle 2**	**Cycle 3-4**	**Cycle 5-x**			
Weeks		**Wk 1**	**Wk 2**	**Wk 3**	**2 wk cycle**	**2 wk cycle**	**2 wks post-last CTL-002 infusion**	**30 d post-last CTL-002 infusion**	**Every 3 mos for 2 years by phone/(e)mail**
Study Day (D)	**D-28 to D -1**	**D1[2]** **D2**	**D8**	**D1[2]**	**D1[2]**	**D1[2]**			
			(±1 d)	(±2 d)	(±2 d)	(±2 d)	(±2 d)	(+2 d)	(± 2 wks)
CTL-002 infusion[3]		+		+	+	+			
Nivolumab infusion[4]		+		+	+	+			
Overnight observation/hospitalization		+							
Informed consent	+								
Medical history/current medical conditions	+	+							
Demographics, height	+								
Prior cancer therapies, including radiation and surgery	+	+							
Weight[5]	+			+	+[5]	+[5]	+		
Eligibility criteria	+								
Pregnancy test[6]	+	+		+	+	+	+	+	
ECG[7]	+	+			+[7]	+[7]	+		
Echocardiography or MUGA if ECHO cannot be performed	+						+		
Physical examination	+	+	+	+	+	+	+	+	
ECOG Performance Status	+	+	+	+	+	+	+	+	
Vital signs[8]	+	7+ +	+	+	+	+	+	+	
Neurological examination[9]	+						+	+	
Safety laboratory (hematology, clinical chemistry, coagulation)[10]	+	2+[37] +	+	+	+	+	+	+	
Safety lab urinalysis [11]	+	+				+[11]	+		
Thyroid hormones (T3, TSH)[12]	+			+	+[13]	+[13]	+		
HbA1c	+			+	+[13]	+[13]	+		
NT-proBNP	+			+	+[13]	+[13]	+		

	Core study								Follow-up
Examination	**Screening**	**Core Treatment Period**				**Extended Treatment Period (optional)[1]**	**End of Treatment Visit**	**Safety FU/End of Core study**	**Efficacy and Survival FU**
Cycle		**Cycle 1**		**Cycle 2**	**Cycle 3-4**	**Cycle 5-x**			
Weeks		**Wk 1**	**Wk 2**	**Wk 3**	**2 wk cycle**	**2 wk cycle**	**2 wks post-last CTL-002 infusion**	**30 d post-last CTL-002 infusion**	**Every 3 mos for 2 years by phone/(e)mail**
Study Day (D)	**D-28 to D -1**	**D1[2]**	**D2**	**D8**	**D1[2]**	**D1[2]**	**D1[2]**		
				(±1 d)	(±2 d)	(±2 d)	(±2 d)	(±2 d)	(+2 d)	(± 2 wks)
Infectious diseases (HIV, HBV, HCV, TB, SARS-CoV-2)[14]	+							+		
Immunoglobulins[15]	+							+		
Immune monitoring (cytokines/chemokines)[16]		+	+		+	+[17]		+		
PK sampling[18]		2+	+	+	2+	2+	2+	+		
Serum analysis of GDF-15[19]	+	+	+	+	+	+	+	+		
Immunogenicity/ADA[20]		+			+	+[21]	+[21]	+		
Blood molecular/transcriptional profiling[22]		+					+[22]			
Cutaneous tumor lesions assessment/ photography[23]	+					+[24]	+[24]	+[24]		+[25]
Tumor assessment/Imaging[26]	+					+[27]	+[27]	+[27]		+[25]
X-ray thorax[28]	+									
Tumor biopsy[29]	+					+[29]	+[29]			
Tumor mutational status[30]	+	+[31]								
Adverse events[32]		+	+	+	+	+	+	+	+	+[33]
Concomitant medication[34]		+	+	+	+	+	+	+	+	+[35]
Survival[36]										+

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ANC = absolute neutrophil count; d = day(s); CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; GDF-15 = growth differentiation factor 15; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; hr = hour; Ig = immunoglobulin; iRECIST = modified RECIST = Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; MCASCO = Mini Cachexia Score; min = minute; MRI = magnetic resonance imaging; NT-proBNP = N-terminal B type natriuretic peptide; PET = positron emission tomography; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; TSH = thyroid-stimulating hormone; wk = week.

Note: A number in a cell indicates the number of times the assessment is conducted at that visit, 8+ indicates that vital signs are measured 8 times on Day 1 of Cycle 1.

(1) If treatment is not extended, refer to End of Treatment Visit.

(2) On CTL-002 treatment days all examinations to be done pre-dose, if not stated otherwise.

(3) Subjects with clinical benefit will be allowed to continue treatment if treatment is tolerated. CTL-002 is to be administered always prior to anti-PD-1.

(4) PD-1/PD-L1 to be administered in approved standard dose every 2 weeks and always after CTL-002.

(5) Weight: collection of historical data (6 months prior Screening, or any available pre-Screening data) in addition to Screening, every 2 weeks and at End of Treatment.
(6) Mandatory for women of childbearing potential only; Screening: serum screen for pregnancy within 7 days prior to study treatment; Cycle 1 Day 1, Cycle 2 Day 1, all CTL-002 administration days Cycle 3-4 and in extended treatment: urine test to confirm absence of pregnancy prior to any treatment with CTL-002 which if positive, confirm with serum test.
(7) Cycle 3-4 and in extended treatment ECG only every 4 weeks.
(8) Systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, oxygen saturation; Day 1: immediately before CTL-002 infusion and 15 (± 5 min), 30 (± 5 min), 60 (± 15 min) and 90 min (± 15 min), and 2 hrs (± 15 min), and 4 hrs (± 15 min) after the start of CTL-002 infusion; all other visits before CTL-002 infusion.
(9) Neurological examination: including check for motor neuropathy (can be conducted by any treating physician, no neurology board certification required).
(10) Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differential WBC, ANC, absolute monocyte count, and platelet count; clinical chemistry: CRP, creatinine, lactate dehydrogenase (LDH), calcium, electrolytes (sodium and potassium), total bilirubin, gamma glutamyltransferase (GGT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase or amylase, and glucose; coagulation: activated partial thromboplastin time (αPTT), prothrombin time/international normalized ratio (PT/INR), ATIII and D-dimer; Cycle 1, Day 1: before CTL-002 infusion and 6 hrs after CTL-002 infusion.
(11) Safety urine analysis: pH, ketones, specific gravity, bilirubin, protein, blood and glucose in urine will be assessed by dipstick. Screening, Day 1, every 8 weeks, EoT visit.
(12) Thyroid hormones: free T3 and basal TSH.
(13) Every 2 weeks for 3 months; thereafter monthly.
(14) HIV, HBV, HCV, TB, SARS-CoV-2 mandatory testing. For SARS-CoV-2 RNA and antibody testing to be conducted.
(15) IgG, IgA, IgM, IgE.
(16) Cytokines: All infusion days (Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1): sample taken within 30 min prior to CTL-002 infusion, Cycle 1 Day 2 = 24 hrs (± 2 hrs), End of Treatment. Part of the blood sample collected for immune-monitoring will also be used for exploratory analysis.
(17) Cytokines/Chemokines: Cycle 3 only.
(18) PK: Cycle 1 Day 1: sample taken within 30 min prior to CTL-002 infusion, and immediately before end of CTL-002 infusion (1 hr), Day 2 = 24 hrs (±2 hrs-) after the start of CTL-002 infusion, Day 8 (±24 hrs), Cycle 2--following (if applicable), Day 1: sample taken within 30 min prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hr-), EoT.
(19) Serum analysis of GDF-15: Cycle 1 Day 1: sample taken within 30 min prior to CTL-002 infusion, Cycle 1 Day 2 = 24 hrs (±2 hrs) after the start of CTL-002 infusion, Day 8 (± 24 hrs), Cycle 2-following (if applicable): Day 1: sample taken within 30 min prior to CTL-002 infusion; End of Treatment.
(20) Immunogenicity/ADA assessment: Cycle 1 Day 1 and Cycle 2 Day 1: sample taken within 30 min prior to CTL-002 infusion; Cycle 3-5 (if applicable); End of Treatment.
(21) Immunogenicity/ADA Cycle 3-5 only.
(22) Blood molecular/transcriptional profiling: Cycle 5 Day 1 (after 8 weeks) and Cycle 9 Day 1 (after 16 weeks) (if applicable) sample taken within 30 min prior CTL-002 infusion.
(23) If applicable, number of lesions, measurement of target cutaneous lesions and color photography (including size measurement): Baseline within -7 days before infusion of CTL-002, every 4 weeks in Cycle 3-4 and in extended treatment, End of Treatment and Follow-up.
(24) Every 4 weeks.
(25) Blinded copy of routine imaging assessments sent to a central reader.
(26) CT/MRI/PET-Scan of thorax and abdomen mandatory to document tumor burden according to RECIST/iRECIST, other areas as needed: At Screening, after 8 weeks and every 8 weeks thereafter; End of treatment Visit only if last scan is more than 4 weeks old. All imaging assessments to be sent to a central reader.
(27) Every 8 weeks; if treatment is stopped after core treatment period (no extended treatment) and last scan is less than 8 weeks old, imaging at End of Treatment Visit not necessary.
(28) X-ray thorax only if CT/MRI/PET CT imaging older than 7 days
(29) Tumor biopsy: baseline biopsy in all subjects (new or archived if obtained within 120 days prior to treatment start); a sequential follow-up biopsy only for melanoma, and the biomarker cohort with mixed solid tumors: baseline biopsy ideally within -7 days before infusion of CTL-002 and second biopsy after 8 weeks of treatment (end of Cycle 4/beginning of Cycle 5). In case the second biopsy is non-evaluable, an optional third biopsy can be collected at the next medically feasible timepoint during ongoing treatment and as per treating physician's decision. If stereotactic radiotherapy is initiated, another follow-up biopsy after 4 wks of the initiation of radiotherapy should be performed. **Note**: All biopsies are to be performed only if seen as safe and feasible from treating physician's discretion.
(30) Tumor mutational status: Collection of historical data e.g., but not limited to BRAF, CEA, PSA, CA19-9, CA-125, MSI, PD-L1, EGFR, Alk, HER2 and other molecular hallmark changes depending upon subject primary cancer.
(31) For subjects enrolled under this version of the protocol and under previous protocols v4.0 and 5.0, an optional retrospective analysis of PD-L1 and other relevant biomarkers might be conducted on archival tumor tissue any time after Screening provided and that the subject agrees in writing to this testing.
(32) After 6 months, only new possibly related AEs will be captured (in addition, SAEs may be reported at any time during the study regardless of relationship).
(33) Related to CTL-002/defined checkpoint inhibitor or study procedures (in addition, SAEs may be reported at any time during the study regardless of relationship).
(34) After 6 months, only further anti-cancer-related medication will be captured.
(35) Anti-cancer medication or medication due to related AEs.
(36) Every 3 months for 2 years.
(37) Baseline safety laboratory testing prior to CTL-002 infusion to re-confirm eligibility

Table 7 Schedule of Assessments – Part B (Phase 2a; expansion, combination therapy with cemiplimab (CSCC only)

	Core study								Follow-up
Examination	**Screening**	**Core Treatment Period**					**Extended Treatment Period (optional)[1]**	**End of Treatment Visit**	**Safety FU/End of Core study**	**Efficacy and Survival FU**
Cycle		**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4-x**			
Weeks		**Wk 1**		**Wk 2**	**Wk 4**	**Wk 7**	**3 wk cycle**	**2 wks post-last CTL-002 infusion**	**30 d post-last CTL-002 infusion**	**Every 3 mos for 2 years by phone/ (e)mail**
Study Day (D)	**D-28 to D -1**	**D1[2]**	**D2**	**D8**	**D1[2]**	**D1[2]**	**D1[2]**			
				(±1 d)	(±2 d)	(±2 d)	(±2 d)	(±2 d)	(+2 d)	(± 2 wks)
CTL-002 infusion[3]		+			+	+	+			
Cemiplimab infusion[4]		+			+	+	+			
Overnight observation/hospitalization		+								
Informed consent	+									
Medical history/current medical conditions	+	+								
Demographics, height	+									
Prior cancer therapies, including radiation and surgery	+									
Weight[5]	+				+	+[5]	+[5]	+		
Eligibility criteria	+									
Pregnancy test[6]	+	+			+	+	+	+	+	
ECG[7]	+	+				+[7]	+[7]	+		
Echocardiography or MUGA if ECHO cannot be performed	+							+		
Physical examination	+	+		+	+	+	+	+	+	
ECOG Performance Status	+	+		+	+	+	+	+	+	
Vital signs[8]	+	7+	+	+	+	+	+	+	+	
Neurological examination[9]	+							+		
Safety laboratory (hematology, clinical chemistry, coagulation)[10]	+	2+[35]	+	+	+	+	+	+	+	
Safety laboratory urinalysis [11]	+	+					+[11]	+		
Thyroid hormones (T3, TSH)[12]	+				+	+[13]	+[13]	+		
HbA1c	+				+	+[13]	+[13]	+		
NT-proBNP	+				+	+[13]	+[13]	+		

	Core study								Follow-up
Examination	**Screening**	**Core Treatment Period**				**Extended Treatment Period (optional)[1]**	**End of Treatment Visit**	**Safety FU/End of Core study**	**Efficacy and Survival FU**
Cycle		**Cycle 1**		**Cycle 2**	**Cycle 3**	**Cycle 4-x**			
Weeks		**Wk 1**	**Wk 2**	**Wk 4**	**Wk 7**	**3 wk cycle**	**2 wks post-last CTL-002 infusion**	**30 d post-last CTL-002 infusion**	**Every 3 mos for 2 years by phone/ (e)mail**
Study Day (D)	**D-28 to D -1**	**D1[2]**	**D2**	**D8**	**D1[2]**	**D1[2]**	**D1[2]**		
				(±1 d)	(±2 d)	(±2 d)	(±2 d)	(±2 d)	(+2 d)	(± 2 wks)
Infectious diseases (HIV, HBV, HCV, TB, SARS-CoV-2)[14]	+						+		
Immunoglobulins[15]	+						+		
Immune monitoring (cytokines/chemokines)[16]		+	+		+	+		+		
PK sampling[17]		2+	+	+	2+	2+	2+	+		
Serum analysis of GDF-15[18]	+	+	+	+	+	+	+	+		
Immunogenicity/ADA[19]		+			+	+	+[20]	+		
Blood molecular/transcriptional profiling[21]		+					+[21]			
Cutaneous tumor lesions assessment/ photography[22]	+					+[23]	+[23]	+[23]		+[24]
Tumor assessment/Imaging[25]	+					+[26]	+[26]	+[26]		+[24]
X-ray thorax[27]	+									
Tumor biopsy[28]	+					+[28]	+[28]			
Tumor mutational status[29]	+									
Adverse events[30]		+	+	+	+	+	+	+	+	+[31]
Concomitant medication[32]		+	+	+	+	+	+	+	+	+[33]
Survival[34]										+

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; ANC = absolute neutrophil count; d = day(s); CRP = C-reactive protein; CT = computed tomography; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = Follow-up; GDF-15 = growth differentiation factor 15; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; hr = hour; Ig = immunoglobulin; iRECIST = modified RECIST = Response Evaluation Criteria in Solid Tumors for immune-based therapeutics; MCASCO = Mini Cachexia Score; min = minute; MRI = magnetic resonance imaging; NT-proBNP = N-terminal B type natriuretic peptide; PET = positron emission tomography; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis; TSH = thyroid-stimulating hormone; wk = week.

Note: A number in a cell indicates the number of times the assessment is conducted at that visit, 8+ indicates that vital signs are measured 8 times on Day 1 of Cycle 1.

(1) If treatment is not extended, refer to End of Treatment Visit.
(2) On CTL-002 treatment days all examinations to be done pre-dose, if not stated otherwise.
(3) Subjects with clinical benefit will be allowed to continue treatment if treatment is tolerated. CTL-002 is to be administered always prior to anti-PD-1.

(4) Cemiplimab to be administered in approved standard dose every 3 weeks and always after CTL-002.
(5) Weight: collection of historical data (6 months prior Screening, or any available pre-Screening data) in addition to Screening, every 3 weeks and at End of Treatment.
(6) Mandatory for women of childbearing potential only; Screening: serum screen for pregnancy within 7 days prior to study treatment; all CTL-002 administration days Cycle 1-3 and in extended treatment: urine test to confirm absence of pregnancy prior to any treatment with CTL-002 which if positive, confirm with serum test.
(7) Cycle 3 and in extended treatment ECG only every 6 weeks.
(8) Systolic and diastolic blood pressure (sitting), pulse rate, temperature, respiratory rate, oxygen saturation; Day 1: immediately before CTL-002 infusion and 15 (± 5 min), 30 (± 5 min), 60 (± 15 min) and 90 min (± 15 min), and 2 hrs (± 15 min), and 4 hrs (± 15 min) after the start of CTL-002 infusion; all other visits before CTL-002 infusion.
(9) Neurological examination: including check for motor neuropathy (can be conducted by any treating physician, no neurology board certification required).
(10) Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count with differential WBC, ANC, absolute monocyte count, and platelet count; clinical chemistry: CRP, creatinine, lactate dehydrogenase (LDH), calcium, electrolytes (sodium and potassium), total bilirubin, gamma glutamyltransferase (GGT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lipase or amylase and glucose; coagulation: activated partial thromboplastin time (αPTT), prothrombin time/international normalized ratio (PT/INR), ATIII and D-dimer; Cycle 1, Day 1: within 24 hours before CTL-002 infusion and 6 hrs after CTL-002 infusion.
(11) Safety urine analysis: pH, ketones, specific gravity, bilirubin, protein, blood and glucose in urine will be assessed by dipstick. Screening, Day 1, every 9 weeks, End of treatment visit.
(12) Thyroid hormones: free T3 and basal TSH.
(13) Every 3 weeks for 3 months; thereafter every second cycle (6 weeks).
(14) HIV, HBV, HCV, TB, SARS-CoV-2 mandatory testing. For SARS-CoV-2 RNA and antibody testing to be conducted.
(15) IgG, IgA, IgM, IgE.
(16) Cytokines: All infusion days (Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1): sample taken within 30 min prior to CTL-002 infusion, Cycle 1 Day 2 = 24 hrs (± 2 hrs), End of Treatment. Part of the blood sample collected for immune-monitoring will also be used for exploratory analysis.
(17) PK: Cycle 1 Day 1: sample taken within 30 min prior to CTL-002 infusion, and immediately before end of CTL-002 infusion (1 hr), Day 2 = 24 hrs (±2 hrs) after the start of CTL-002 infusion, Day 8 (±24 hrs), Cycle 2-following (if applicable), Day 1: sample taken within 30 min prior to CTL-002 infusion and immediately before end of CTL-002 infusion (1 hr), End of treatment Visit.
(18) Serum analysis of GDF-15: Cycle 1 Day 1: sample taken within 30 min prior to CTL-002 infusion, Cycle 1 Day 2 = 24 hrs (±2 hrs) after the start of CTL-002 infusion, Day 8 (± 24 hrs), Cycle 2-following (if applicable): Day 1: sample taken within 30 min prior to CTL-002 infusion; End of Treatment.
(19) Immunogenicity/ADA assessment: Cycle 1 Day 1 and Cycle 2 Day 1: sample taken within 30 min prior to CTL-002 infusion; Cycle 3-5 (if applicable); End of Treatment.
(20) Immunogenicity/ADA Cycle 4-5 only.
(21) Blood molecular/transcriptional profiling: Cycle 4 Day 1 (after 9 weeks) and Cycle 7 Day 1 (after 18 weeks) (if applicable) sample taken within 30 min prior CTL-002 infusion.
(22) If applicable, number of lesions, measurement of target cutaneous lesions and color photography (including size measurement): Baseline within -7 days before infusion of CTL-002, Cycle 3, every 6-9 weeks in extended treatment, End of Treatment and Follow-up.
(23) Every 6-9 weeks according to local practice.
(24) Blinded copy of routine imaging assessments sent to a central reader (if possible).
(25) CT/MRI/PET-Scan of thorax and abdomen mandatory to document tumor burden according to RECIST/iRECIST, other areas as needed: At Screening, after 6-9 weeks and every 6-9 weeks thereafter; End of treatment Visit only if last scan is more than 4 weeks old. All imaging assessments to be sent to a central reader.
(26) Every 8 weeks; if treatment is stopped after core treatment period (no extended treatment) and last scan is less than 8 weeks old, imaging at End of Treatment Visit not necessary.
(27) X-ray thorax only if CT/MRI/PET CT imaging older than 7 days
(28) Tumor biopsy: new or archived if obtained within 120 days prior to treatment start; sequential biopsy in cutaneous squamous-cell carcinoma cohort, multiple punch biopsies at a single timepoint (as per clinical possibility, ideally 3-5): baseline biopsy ideally within -7 days before infusion of CTL-002 and second biopsy after 9 weeks of treatment (end of Cycle 3/beginning of Cycle 4). In case the second biopsy is non-evaluable, an optional third biopsy can be collected at the next medically feasible timepoint during ongoing treatment and as per treating physician's decision. If stereotactic radiotherapy is initiated, another follow-up biopsy after 4 wks of the initiation of radiotherapy should be performed. **Note**: All biopsies are to be performed only if seen as safe and feasible from treating physician's discretion.
(29) Tumor mutational status: Collection of historical data e.g., but not limited to BRAF, CEA, PSA, CA19-9, CA-125, MSI, PD-L1, EGFR, Alk, HER2 and other molecular hallmark changes depending upon subject primary cancer. An optional retrospective analysis of PD-L1 and other relevant biomarkers might be conducted on archival tumor tissue any time after Screening provided that the subject agrees in writing to this testing.
(30) After 6 months, only new possibly related AEs will be captured (in addition, SAEs may be reported at any time during the study regardless of relationship).
(31) Related to CTL-002/defined checkpoint inhibitor or study procedures (in addition, SAEs may be reported at any time during the study regardless of relationship).
(32) After 6 months, only further anti-cancer-related medication will be captured.
(33) Anti-cancer medication or medication due to related AEs.
(34) Every 3 months for 2 years.
(35) Baseline safety laboratory testing prior to CTL-002 infusion to re-confirm eligibility

6.2. Study Assessments

6.2.1. Tumor Biopsy

Timing of biopsies are as follows:

- Part A (all subjects except backfill subjects): 3 sequential tumor biopsies are mandated; one biopsy at baseline, the second biopsy prior to the initiation of the combination therapy (after 2 weeks) and the third biopsy after the first cycle of combination treatment (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3). These biopsies are mandatory in order to assess immune cell infiltration in the tumor

  Part A (backfill subjects): 2 serial tumor biopsies are mandated; one biopsy at baseline and a second biopsy after 4 weeks of combination treatment (either at the End of Treatment Visit or, if combination treatment is continued, at the end of Cycle 2/beginning of Cycle 3).

  For all Part A subjects: in case a tumor biopsy is non-evaluable, an optional biopsy can be collected at the next medically feasible timepoint during ongoing treatment and as per treating physician's decision to assure assessable histology data
- Part B: Baseline biopsies are mandatory in all subjects; for melanoma, cutaneous squamous-cell carcinoma and the biomarker cohort with mixed solid tumors ("basket" cohort), an additional on-treatment biopsy after the first 8 weeks (for cutaneous squamous-cell carcinoma: 9 weeks) of treatment (dependent on dosing scheme i.e., combination with nivolumab after 4 cycles [8 weeks] and with cemiplimab after 3 cycles [9 weeks]) is mandatory. In case the second biopsy is non-evaluable, an optional third biopsy can be collected if seen as safe and feasible at the next possible timepoint during ongoing treatment and as per treating physician's decision.

  Note: In case of initiation of stereotactic radiotherapy in addition to study treatment, an optional tumor biopsy should be performed no earlier than 4 weeks after initiation of radiotherapy, again only if seen as safe and medically feasible by the treating physician, as in all biopsy cases.
  - For subjects enrolled under this version of the protocol and under previous protocols v4.0 and v5.0: an optional retrospective analysis of PD-L1 and other relevant biomarkers might be conducted on archival tumor tissue any time after Screening provided the available material is < 120 days old and that the subject agrees in writing to this testing.
  - For cutaneous squamous-cell carcinoma subjects: will be taken at a single timepoint (as per clinical possibility, ideally 3-5), as extensive molecular analyses are pursued (messenger ribonucleic acid [mRNA] expression analyses, such as T cell clonality analyses, RNAseq, nanostring analyses or genome sequencing etc.).

There has to be a lesion that is amenable to sequential biopsy, if possible, or a lesion in close proximity, but this lesion should ideally not be the only target lesion that will be radiologically assessed during the course of the study. If a sequential biopsy cannot be taken for safety reasons, this must be discussed with the Medical Monitor.

If stereotactic radiotherapy is initiated, another follow-up biopsy after 4 wks of the initiation of radiotherapy should be performed. **Note**: All biopsies are to be performed only if seen as safe and feasible from treating physician's discretion. Biomarkers may be analyzed from biopsy tumor tissue samples. Additional immune cell markers and/or tumor markers specific to any of the tumor type may be included.

Biopsied tumor tissue will be fixed with formalin and embedded in paraffin (formalin-fixed paraffin-embedded [FFPE]) to determine treatment-induced changes in the number, frequency and spatial location of infiltrating immune cells including but are not limited to leukocytes, different lymphocytes (e.g., CD4+ and CD8+ T cells, B cells, natural killer cells) by histology before and after treatment with CTL-002 or in combination with the defined checkpoint inhibitor. Moreover, the expression of the CTL-002 drug target, GDF-15 protein and mRNA, will be determined.

Retrospective exploratory analysis of, but not limited to additional immune cell characterization, gene expression, tumor mutational burden (TMB), microsatellite instability (MSI), indication-specific molecular signatures and other biomarkers will be optionally performed from FFPE tissue biopsies to support pharmacodynamic studies and confirm proof of mechanism.

Retrospective biomarker testing to address emergent questions will be not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. Retrospective biomarker studies will be conducted with appropriate biostatistical design and analysis and compared to PK/pharmacodynamic results, previously assessed biomarkers or clinical outcomes.

6.2.2. Demographics and Medical History

Demographics (age, sex, race/ethnicity [if allowed per country-specific regulations]) and height will be recorded along with a full review of medical history including cancer history (e.g., prior therapies including radiation and surgery) and known tumor biology (e.g., historical data for PD-L1). All relevant medical history of all body systems and history of all prior therapies for cancer and other relevant therapies will be collected and recorded in the eCRF.

6.2.3. Assessment of Weight

At Screening, weight will be assessed and data on weight 6 months prior to Screening, if available, or any data until Screening, as available, will be recorded. Thereafter, weight will be assessed every 2 weeks for Part A (see Table 5), every 2 weeks for Part B combination therapy with nivolumab (see Table 6) and every 3 weeks for Part B combination with cemiplimab (Table 7) and at End of Treatment Visit (see Section 6.1.9).

6.2.4. Assessment of Safety

The safety and tolerability of IV infusions of CTL-002 monotherapy and CTL-002 in combination with the defined checkpoint inhibitor will be evaluated by the incidence of AEs (all AEs will be evaluated according to NCI-CTCAE v5.0), SAEs, DLTs, and use of concomitant medications. Safety assessments will include: ECGs, physical examinations including neurological examination (motor neuropathy can be conducted by any treating physician, no neurology board certification required), ECOG performance status, vital signs and clinical laboratory samples (hematology, clinical chemistry, coagulation, thyroid function (thyroid stimulating hormone [TSH] and free T3), cytokines, assessment of HbA1c, NT-proBNP, and urinalysis).

Subjects are assessed for safety at Screening, as well as during treatment until the Safety Follow-up Visit. Thereafter safety related to the study is further captured during the follow-up of up to 12 months (Part A)/24 months (Part B) post-treatment. Planned time points for all safety assessments are provided the SoAs in Table 5, Table 6 and Table 7.

6.2.4.1. Vital Signs

Vital signs including systolic and diastolic BP (sitting), pulse rate, temperature, respiratory rate, and oxygen saturation should be evaluated at Screening and at the time points indicated in the SoAs in Table 5, Table 6 and Table 7. Additional vital sign measurements may be performed if clinically warranted.

6.2.4.2. Physical and Neurologic Examination

A physical examination will be performed at Screening and will include examination of head, eyes, ears, nose, throat, neck, cardiovascular, chest/lungs, abdomen (including liver and spleen size), extremities, skin, and lymph nodes, as well as a brief neurologic examination to assess motor neuropathy (motor neuropathy examination can be conducted by any treating physician, no neurology board certification required).

Additional physical examination assessment time points are outlined below and in the SoAs in Table 5, Table 6 and Table 7.

6.2.4.3. Performance Status

Performance status will be assessed at Screening and at the time points in the SoAs in Table 5, Table 6 and Table 7 according to ECOG criteria as follows:

- 0 = Fully active, able to carry out all pre-disease activities without restrictions
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
- 2 = Ambulatory and capable of 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 self-care, totally confined to bed or chair
- 5 =Death

6.2.4.4. Cardiac Function Monitoring

Subjects will undergo a thorough monitoring for cardiac/vascular AEs and protective measures are in place to exclude subjects at risk from trial participation.

At baseline, subjects undergo an ECG, an echocardiography (or MUGA if ECHO cannot be performed) and testing for N-terminal pro b-type Natriuretic Peptid levels (NT-proBNP, heart-failure screening). Testing for NT-proBNP will be repeated every 2 weeks (3 weeks for the cutaneous squamous-cell carcinoma cohort) for 3 months and thereafter monthly (every second cycle for the cutaneous squamous-cell carcinoma cohort) or in case of any suspicion regarding cardiac/vascular damage of any type (then combined with ECG and echocardiography, again).

A single, 12-lead ECG will be performed at time points outlined in Section 6.1.12.

All ECG monitoring is to be performed locally at the Investigator site.

The subject should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG.

Additional ECG testing may be performed at the Investigator's discretion if deemed clinically warranted.

6.2.4.5. Clinical Laboratory Assessment

Samples for laboratory testing listed as below will be collected at time points according to the SoAs in Table 5, Table 6 and Table 7. All tests are performed locally.

- Hematology/coagulation, clinical chemistry results must be available and reviewed and deemed acceptable by the Investigator or authorized designee, prior to CTL-002/PD-1/PD-L1 administration
- Clinically significant abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical Monitor must be consulted
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the Investigator which includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important

Table 8 Safety Laboratory Testing

Hematology	Hemoglobin, hematocrit, RBC, WBC with differential, ANC, AMC, platelet count
Clinical Chemistry	CRP, creatinine, LDH, calcium, electrolytes (sodium and potassium), total bilirubin, GGT, albumin, alkaline phosphatase, AST, ALT, lipase or amylase and glucose
Coagulation	• Includes: αPTT, PT/INR • INR/PT should be measured daily for any subject experiencing ALT or AST elevations ≥3 x ULN with concomitant elevation in bilirubin ≥ 2 x ULN until resolution to baseline of the liver function test abnormality. • AT III • D-Dimer
Serology	Analysis for HIV1 and HIV2, HBV, HCV, TB, SARS-CoV-2
Urinalysis	pH, ketones, specific gravity, bilirubin, protein, blood and glucose will be assessed by dipstick.

Abbreviations: αPTT = activated partial prothrombin time; AMC = absolute monocyte count; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; AT III = Antithrombin III; CRP = C-reactive protein; GGT = gamma-glutamyltransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV1 = human immunodeficiency virus 1; HIV2 = human immunodeficiency virus 2; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell count; TB = tuberculosis; ULN = upper limit of normal; WBC = white blood cell count

6.2.4.6. Pregnancy Testing

Serum β-human chorionic gonadotropin (β-HCG) pregnancy test will be performed at Screening for all women of childbearing potential. A urine pregnancy test must be repeated prior to each dose of CTL-002/the defined checkpoint inhibitor and then at the End of Treatment Visit and at the Safety Follow-up Visit (refer to the SoAs in Table 5, Table 6 and Table 7). Any positive urine test must be confirmed with a serum pregnancy test.

Additional urine pregnancy tests may be done during the course of the study at the Investigator's discretion if deemed clinically warranted, with a urine dipstick test, to be performed locally.

Pregnancy must be reported from the time of the signing of the ICF until 5 months after last study treatment.

6.2.4.7. Pharmacokinetics

The PK of CTL-002 given as monotherapy and/or in combination with the defined checkpoint inhibitor will be measured from blood samples collected at the start of treatment and at various subsequent time points (Part A, Phase 1). Additional PK data may be evaluated in the expansion cohorts (Part B, Phase 2 a).

Blood samples will be taken at the start of treatment and at various subsequent time points to determine, if antibodies directed against CTL-002 may have developed.

6.2.4.8. Pharmacodynamics and Monitoring of Systemic Cytokines/Chemokines

The pharmacodynamics of CTL-002 administered as monotherapy and/or in combination with the defined checkpoint inhibitor will be determined from peripheral blood, urine and tumor biopsies as available. Urine GDF-15, serum total GDF-15, intratumoral GDF-15 and tumor immune cell infiltration will be determined.

Serum samples will be collected as defined in the SoAs in Table 5, Table 6 and Table 7 for measurement of cytokines, chemokines and other circulating biomarkers to assess pharmacodynamic effects as well as safety. Table 9 below provides a summary of pharmacodynamic laboratory assessments for this study.

Table 9 Pharmacodynamic Laboratory Assessments

Assessment	Analysis	Sample
GDF-15	GDF-15	Serum
Cytokines and chemokines	May include but are not limited to: TNF-α, IFN-ɣ, IL-1 β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, CXCL9 (MIG) and CXCL10 (IP-10)	Serum
Molecular/transcriptional profiling	May include but are not limited to: TMB, TCR	Blood

Abbreviations: IFN = interferon; IL = interleukin; IP = interferon-gamma induced protein 10 kD, CXCL10; MIG = monokine induced by gamma; TNF-α = tumor necrosis factor alpha.

6.2.4.9. Exploratory Assessments

Various molecular and immunohistochemical biomarkers and immune parameters (e.g., including but not limited to molecular profiling, mutation status, mutational burden or other markers of interest relating to immune activation or disease may be explored) will be assessed in peripheral blood, serum, urine and tumor tissue.

The Sponsor might conduct future retrospective serum biomarker testing on specimens (retention aliquots) specifically collected for future biomedical research during this clinical trial to identify serum factors (e.g., but not limited to metabolites, soluble growth factors, cytokines, chemokines,) important for anti-GDF-15 (CTL-002) therapy. This biomarker testing to address emergent questions will not be described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. Retrospective biomarker studies will be conducted with appropriate biostatistical design and analysis and compared to PK/Pharmacodynamic results, previously assessed biomarkers or clinical outcomes.

6.2.5. Efficacy Assessment

6.2.5.1. Tumor Assessments (CT/MRI/PET-Scan, local Testing)

Tumor response is evaluated according to institutional standards using RECIST V1.1 as well as iRECIST criteria (refer to Appendix 2). For the purposes of this study, subjects will undergo evaluation at Screening for a baseline scan and should be re-evaluated every 8 weeks (6-9 weeks for the cutaneous squamous-cell carcinoma cohort only) and/or from the End of Treatment Visit, then after this time response assessments may be performed as per local institutional guidelines until the end of the Efficacy and Survival Follow-up. Refer to the SoAs in Table 5, Table 6 and Table 7.

All lesions identified at Screening/baseline will be consistently followed using the unique lesion number assigned at Screening/baseline and need to be documented in the subject file and in the eCRF. Lesions that are being biopsied should not be included in the RECIST assessment.

The same method of assessment (imaging modality, e.g., MRI, CT) must be used to characterize each identified and reported lesion at baseline and during all follow-up examinations for an individual subject. If there is a change in modality, then the trial site may be asked to explain the reason for the change in the eCRF. A change in modality may be considered a protocol deviation.

Each efficacy time point/visit may be completed up to a window of ±7days in the Core Study Period and a window of ±2 weeks in the Efficacy and Survival Follow-up period.

A central reading of the images by a reading center will be performed post-hoc in addition to local reading by the Investigator during the trial.

Definition of Progressive Disease according to RECIST V1.1 and iRECIST:

RECIST assessments will be used to identify subjects with possible progression of disease (Eisenhauer et al, 2009). As defined by modified RECIST V1.1 criteria for immune-based therapeutics or iRECIST criteria Seymour et al., 2017),), the date of initial potential progression by RECIST scanning will be defined as the immune unconfirmed progressive disease (iUPD) date. Subjects with an iUPD date who are stable will continue to participate in the study as planned and be reassessed for progression 4 to 8 weeks after the initial assessment. If the confirmatory assessment supports PD, the date of disease progression will be the iUPD date. If the confirmatory assessment does not support PD, the subject does not have disease progression and the iUPD date is ignored; such subjects will remain in the study as planned and continue the next imaging evaluation as planned per protocol.

Anti-tumor activity will be assessed per Investigator assessment using RECIST V1.1 and the Immune Response Criteria according to iRECIST (see details in Appendix 2), as described below.

- Contrast CT scans of the chest, abdomen and pelvis, MRI or positron emission tomography-computed tomography (PET-CT)
- Disease response and disease progression will be evaluated in this study using RECIST and iRECIST criteria
- Subjects with brain and/or leptomeningeal metastases that are symptomatic or untreated or that require current therapy will not be eligible for the study. Brain imaging must not be older than 12 weeks. Results with abnormal/unexpected findings of brain MRI should be discussed with the Medical Monitor as part of the screening process
- 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. If there is a change in modality, then the trial site may be asked to explain the reason for the change in the eCRF. A change in modality may be considered a protocol deviation

6.2.5.2. Cutaneous Tumor Lesions Assessment

For all subjects, the target cutaneous lesions selected for RECIST evaluation, as applicable, will be measured by caliper and photographed. In addition, the number of target cutaneous lesions will be recorded. For clinical measurements of target cutaneous lesions, documentation by color photography (including size measurement) and caliper measurement of lesion will be performed

at Baseline within -7 days before infusion of CTL-002, every 4 weeks during extended treatment (3 weeks for the cutaneous squamous-cell carcinoma cohort), at End of Treatment Visit, and during follow-up.

A central reading of the photography by a central reading center will be performed post-hoc in addition to local reading by the Investigator during the trial.

6.2.5.3. Assessment of L3 Skeletal Muscle Index (Part A only)

The L3SMI is a surrogate marker of sarcopenia. To estimate skeletal muscle changes during study treatment, an estimation of 3-dimensional muscle mass at the level of L3 vertebra on 2-dimensional planar sections (cm^2 of muscle tissue) of routine CT scans is made. L3SMI is calculated based on the skeletal muscle area at the level of L3 vertebra, divided by the subject height (squared).

L3SMI assessment will be conducted post-hoc by a central reading center.

6.2.5.4. Mini-Cachexia-Score Quality of Life Questionnaire (Part A only)

The MCASCO, a simplified version of the CASCO, is a tool for the quantitative staging of cachectic cancer patients (Argilés et. al, 2017). The MCASCO should be completed by the subject before any other clinical assessments and before receiving any study medications. A subject may be exempt from completing the MCASCO if he or she is unable to read the questionnaire in one of the country languages available.

The MCASCO is based on the following 5 constituents: (1) body weight loss and composition, (2) inflammation/metabolic disturbances/immunosuppression, (3) physical performance, (4) anorexia, and (5) quality of life. MCASCO allows classification of subjects into the following 3 groups that are associated with a numerical scoring: mild cachexia, moderate cachexia and severe cachexia.

The MCASCO will be completed as outlined in the SoAs in Table 5, Table 6 and Table 7.

7. SAFETY REPORTING AND MEDICAL MANAGEMENT

Adverse Events and SAEs, regardless of suspected relationship to study treatment, are recorded from the time the subject consents to the study, to 30 days after last dose.

As part of the safety oversight for this study, in addition to the staggering of subject dosing with CTL-002 in Part A (Phase 1; dose escalation), subjects will only be enrolled and treated with CTL-002 at carefully selected investigational sites who have experience in FIH studies and immunotherapy, handling of related AEs, access to intensive care units (ICU) and immediate and appropriate resuscitation measures at all times during hospitalization.

Medical measures have been implemented which ensures a quick diagnosis of events and the implementation of quick actions (e.g., central venous access, hospitalization, close subject monitoring for vital signs, cardiac monitoring).

7.1. Definition of Adverse Event

An AE is defined in the ICH for Good Clinical Practice (GCP) guideline as "any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment." An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Examples of AEs may include the following factors:

- A new sign, symptom, illness, or syndrome
- Worsening of a concomitant disease, sign or symptom at Screening
- An effect of investigational product, including comparator or concomitant medication
- An effect of an invasive procedure required by the protocol
- An accident or injury
- Abnormalities in physiological testing or physical examination findings requiring clinical intervention or further investigation (beyond ordering a repeat, confirmatory, test)
- Clinically significant laboratory abnormalities requiring clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event

Interventions for pre-treatment conditions or medical procedures that were planned prior to study enrolment are not considered to be AEs. Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected after the administration of the IMP and is not the condition under study.

Disease progression (unless considered to be drug related by the Investigator) is not considered an AE or SAE and should not be reported as such. When there are reasonable grounds for suspicion that an event is caused by the study treatment (i.e., there are facts or arguments to suggest a causal relationship), it must be considered as an adverse drug reaction.

Any stable or intermittent chronic condition that is present at the time that the subject is screened will be considered as medical history (with the last value prior to dosing considered as baseline) and not reported as an AE unless possibly related to study procedures. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Note: lab and/or vital signs abnormalities detected during the screening period (i.e., after date of consent) and prior to first dose should be reported under Medical History, unless they are related to screening procedures or they are considered symptoms of a Medical History.

7.1.1. Serious Adverse Event

An SAE is an AE that fulfils one or more of the following criteria:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity, or substantial disruption of the ability to conduct normal life functions
- Is or results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

A hospitalization meeting the regulatory definition for "serious" is any subject admission, regardless of the length of stay, even if as a precautionary measure for continued observation. Elective hospitalizations for the routine administration of protocol therapy, therapeutic blood products, treatment of a pre-existing condition that did not worsen from baseline, elective procedures, or for social or technical reasons are not considered SAEs. However, prolongation of hospitalization or re-admission after the subject has been discharged for reasons other than administrative, will be considered SAEs.

For further guidance on the definition of an SAE, see Appendix 4 of this clinical study protocol.

All SAEs that occur after any subject has entered screening, before treatment, during treatment, or within 30 days following the cessation of treatment, whether or not they are related to the study, must be recorded on forms provided by the Sponsor.

7.1.2. Other Adverse Event

Other AEs (OAEs) will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient/subject from the study, will be classified as OAEs. For each OAE, a narrative may be written and included in the Clinical Study Report.

7.2. Recording and Reporting of Adverse Events

Adverse event reporting and data management will be performed according to the following relevant guidelines:

- Directive 2001/20/EC (European Clinical Trial Directive)

- Committee for Proprietary Medicinal Products (CPMP)/ICH/E2A/377/95 (Clinical Safety Data Management: Definition and Standards for Expedited Reporting)
- CPMP/ICH/135/95 (GCP)
- 21 Code of Federal Regulations (CFR) 312.32 (Food and Drug Administration)

7.2.1. Recording of AEs/SAEs

The Investigator is responsible for ensuring that all AEs that are observed by trial site personnel or reported by a subject, are recorded on the eCRF during the study and/or as described below. All SAEs must be reported using the SAE reporting form.

These AEs will include the following:

- All SAEs (as defined in Section 7.2.3.1) that occur after the subject has signed the first ICF up to 30 days after last dose of CTL-002/nivolumab/cemiplimab (i.e., the Safety Follow-up/End of Core Study Visit).

  Exceptions/additions:

  - Serious AEs and non-serious AEs related to study participation/procedures or leading to withdrawal from study that occur after the subject has signed the ICF must be reported until end of study (as defined in Section 9.5).
  - Serious AEs deemed by the Investigator to be at least possibly related to CTL-002/nivolumab that occur from first day of administration (Day 1) until the end of the study (as defined in Section 9.5).
- DLTs (as defined in Section 2.2.1.3)
- All non-serious AEs (i.e., any AEs that do not meet a serious criteria) that occur from Screening up 30 days after the last dose of CTL-002/nivolumab/cemiplimab (i.e., the Safety Follow-up Visit).

The AE term should be reported in standard medical terminology when possible: diagnosis or syndrome(s) if known, signs or symptoms can be accepted if underlying cause is not known. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, severity and serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

The Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

7.2.2. Relationship

The potential causal relationship to the study treatment is assessed by the Investigator as either “not related”, “possibly related”, “probably related” or “related.”

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Related:** The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship

between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE

- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the investigational product). However, other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "related," as appropriate
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition
- **Not related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

7.2.2.1. A Guide to Interpreting Causality

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course: Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile: Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- Dechallenge experience: Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause: The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience: Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Sponsor would not normally recommend or support a rechallenge.
- Laboratory tests: A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist. In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any

dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

7.2.3. Severity

Severity or intensity will be assessed according to the CTCAE Version 5.0 severity grading scale. 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:

- Grade1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening (urgent intervention indicated)
- Grade 5: Death related to AE

7.2.3.1. Further Guidance on the Definition of a Serious Adverse Event

Life Threatening

"Life-threatening" means that the subject was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospitalization should be used in circumstances where an admission occurred to treat a clinical AE, as such the following would not be considered valid hospitalizations for SAE reporting purposes; 24-hour hold for observation, admission to a hospice facility or nursing home, respite care, outpatient surgery, social admission (e.g., a homeless subject) or admission not associated with a precipitating clinical AE (e.g., elective or pre-planned surgery, or in-patient administration of subsequent chemotherapy).

Note: In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose (see Section 5.5 – Overdose, for more information)

Important Medical Event or Medical Intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement should be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

7.2.4. Reporting of Serious Adverse Events

Any SAEs regardless of any opinion as to the relationship of the SAE to the study intervention and discovered by the Investigator at any time after the study shall be reported within 24 hours of the first awareness of the event. If an AE initially reported as non-serious event, becomes serious, this must also be reported within 24 hours following knowledge.

Upon identification, all SAEs will be reported by the site within 24 hours of awareness using the appropriate SAE report form and eCRF pages. The Investigator is responsible for confirming the accuracy of the data entered into the SAE report form and eCRF pages.

SAEs should be reported by email to the Clinical Safety group using the SAE report form. The Investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded with the corresponding source documents.

These forms must be scanned and sent via e-mail within 24 hours following knowledge of the event by the Investigator to the attention of:

Name	Precision for Medicine, Oncology and Rare Disease – Safety Group
E-mail	PFM_Safety@precisionformedicine.com

- The initial report must be as complete as possible, including details of the current illness and the (serious) AE, and the assessment of the causal relationship between the event and the study treatment
- The Investigator should not wait to receive additional information to fully document the event before notifying an SAE, although additional information may be requested

- Where applicable, anonymized information from relevant laboratory results, hospital case records and autopsy reports should be obtained accounting for local data protection regulations. The Investigator is also required to submit follow-up reports until such time as the SAE has resolved or in the case of permanent impairment, until the AE stabilizes
- Details of all SAEs shall also be reported on the AE pages in the eCRF
- Additional follow-up information, if required or available, should be completed within one business day of receipt and this should be completed as an update to eCRF system or by way of a follow-up SAE form. If required, the original SAE information should be replaced and kept with the appropriate section of the eCRF and SAE report form

The Sponsor is responsible for notifying the relevant regulatory authorities of all SAEs as required by local regulations. It is the PI's responsibility (as per local Standard Operating Procedures) to notify their local Institutional Ethics Committee (IEC) or Institutional Review Board (IRB) of all SAEs that occur at his or her site.

Due to the coronavirus SARS-CoV-2 (COVID-19) pandemic, Investigators must ensure compliance with local governing legislation and reporting requirements associated with COVID-19 infections.

Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IEC/IRB of these additional events.

7.2.5. Disease Progression

Progression or recurrence of the tumor will be recorded in the clinical assessments in the eCRF. Death due to PD is to be recorded on a specific form in the eCRF but not reported as an SAE (or as a DLT). However, if the Investigator considers that there was a causal relationship between administration of study medication, protocol design, or procedures and the disease recurrence or progression, then this must be reported as an SAE using the SAE report form.

Any new primary cancer (nonrelated to the cancer under study) must be reported as an SAE.

7.3. Reporting of Pregnancy and its Outcome

Should a pregnancy occur at any time during the subject's study participation, it must be reported and recorded on the Sponsor's pregnancy form immediately, but no later than 24 hours of when he or she becomes aware of it. Pregnancy must be reported from the time of the signing of the ICF until 5 months after last treatment. Pregnancies of female subjects and partners of male subjects should be reported.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up to birth and where possible 6-8 weeks after birth and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be

handled as AEs. Pregnancy report forms should be submitted to email address outlined in Section 7.2.4.

7.3.1. Paternal Exposure

Pregnancy of a subject's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 150 days (5 months) after discontinuation of dosing should be reported to the Sponsor and followed up for its outcome.

If a pregnancy occurs in a subject's partner within the timeframe specified above, then Investigators or other site personnel will inform the appropriate Sponsor representative immediately, but **no later than 24 hours** of when he or she becomes aware of it. The same timelines apply when outcome information is available. Detailed instructions on reporting pregnancies are provided in the pregnancy report form separate from this protocol.

7.4. Safety Review Committee

A SRC will be established consisting of the Sponsor, the Sponsor's Medical Expert(s), and the Investigators. The SRC will review and evaluate the available safety and efficacy data (i.e., AEs including DLTs, other available clinical data and available PK/pharmacodynamic data) collected during the study. Additional internal or external experts may be consulted by the SRC as necessary.

For Part A of the study (Phase 1; dose escalation), the SRC will meet upon the completion of each dose escalation cohort or upon member-request ad-hoc and review all available, cumulative safety data that are reported in a rolling fashion to the SRC. For dose escalation decisions all safety data for the DLT Period must be available to the SRC.

The SRC can recommend at any dose level that more subjects should be enrolled for DLT evaluation, to dose escalate/de-escalate or to stop enrolment. When Part A has been completed, the SRC will receive a cumulative safety report for review. Any subsequent exploration of CTL-002 can only start, if the SRC agrees with commencement of Part B of the study.

During Part B of the study (Phase 2a; expansion), the SRC will meet regularly or upon member-request ad-hoc. All safety data will again be reported in rolling fashion at these time-points to the SRC.

For Part B (Phase 2a; expansion), the SRC will decide together with the Sponsor which cohorts may undergo Simon-2-stage expansion. An expansion only takes place with SRC and Sponsor agreement, both based upon observed antitumor activity and safety warranting further cohort expansion.

A respective SRC Charter will describe the composition, activities, as well as the way recommendations for further treatments are made.

After the completion of a given cohort, the SRC will evaluate the data as outlined above to recommend the next dose to assess.

The SRC will consist of:

- Medical Monitor, or delegate who will chair the committee
- Principal Investigator, or delegate, from each Investigator site
- Sponsor's Global clinical development representative and/or delegate

- Clinical Project Manager

In addition, at least one other physician from the following may be invited:

- Global safety physician, or delegate

The study clinical pharmacologist, study statistician, study safety scientist, other clinical project manager, and additional study support staff may also be invited as appropriate. The safety review charter for this study will define the exact membership and who should be present for decisions to be made.

Further, internal or external experts may be consulted by the SRC as necessary. The global development physician or delegate should always be present at the SRC if there are safety issues for discussion.

Once there are at least 3 evaluable subjects for a given dose level, the SRC will review and assess all available safety and other clinical data from the cohort together with available laboratory/biomarker data to make a decision on the dose to be assessed in the next cohort of subjects. Any dose interruptions and reductions of CTL-002 and/or the defined checkpoint inhibitor will be taken into account.

The responsibility of the SRC may be to:

- Qualify an AE as a DLT
- Decide to proceed with dose escalation
- Decide on expanding the cohort to a maximum of 6 evaluable subjects
- Decide de-escalation of the dose either to a previous lower dose level (up to a maximum of 6 evaluable subjects), or to an intermediate lower dose level
- Recommend suspension of the study
- Recommend to stop the dose escalation part of the study

The Sponsor is responsible for all decisions pertaining to study suspension or stopping the dose escalation part of the study.

Any subject started on treatment in error, as he/she failed to comply with any or all of the selection criteria, but meets the criteria for an evaluable subject, will be reviewed on a case-by-case basis by the SRC to determine if the subject should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the SRC will be documented and provided to the Investigators.

8. STATISTICS

A Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a more technical and detailed description (including templates for Tables, Listings, and Figures) of the planned statistical summaries. The SAP will be finalized before initiating any statistical analysis.

Unless otherwise stated tabulation of summary statistics and data analysis will be performed using SAS® Version 9.4 or later.

8.1. Statistical Methods

This study is explorative in nature. Thus, no formal statistical comparisons are planned. Descriptive and inferential statistics will be used to summarize the data. Continuous variables will be summarized by number, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized by subject counts and related percentages.

Percentages will be calculated using the total subjects per dose group (Part A), and cohort (Part B).

As a general principle, all summaries from Part A, presented by dose group and Part B, presented by cohort, will be displayed separately. No pooling of data from the two parts is planned.

In Part B (Phase 2a; expansion), cohorts with several defined tumor indications will be treated to detect efficacy signals, in a screening effort to identify tumor indications where CTL-002 has clinically relevant antitumor activity. All indications have been selected based upon translational research results by the sponsor and other scientific groups that indicate an immunosuppressive role of GDF-15 in these tumor indications.

To achieve this and based upon a **conditional probability calculation** the following subject numbers are recruited:

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma, N = 14 response-evaluable subjects will be initially recruited per each tumor indication. This shall allow to detect 2 responses in a cohort with 80% probability if the true response rate is 20% or more, and at least 1 response in the cohort with 77% probability if the true response rate is 10% or more. For cutaneous squamous-cell carcinoma, N = 12 response-evaluable subjects will be recruited initially. This should result in 2 responses or more with 80% probability if the true response rate is 25% or higher
- For the **second group** (colorectal cancer [MSS/mismatch-repair competent, a currently non-approved anti-PD-1/PD-L1 indication]), N = 10 response-evaluable subject will be recruited. This shall allow to detect 1 response with 89% probability (if the true response rate is 20% or more), and 1 response with 80% probability if the true response rate is 15% or more
- For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort), N = 75 subjects are planned to be enrolled to have at least N = 25 response-evaluable subjects with TPS PD-L1 > 1 status and ideally up to N = 50 response-evaluable subjects with PD-L1 TPS ≤ 1. For the TPS PD-L1 > 1 group this would ideally confirm a response rate of ≥ 30% (with 81% probability resulting in a minimum of 6 or more responders in the cohort), resulting in a lower limit of the 95% confidence interval of 0.15 (15% lower end response rate), allowing to well rule out background response rates at 5-10% level. For subjects with TPS ≤1, a response rate > 20% would be seen as clinically of interest and beneficial, and

this would result in a minimum of 8 (10) responders with a probability of 81% (56%), respectively, if the true response rate is 20% or above. If recruitment of 25 response-evaluable subjects with TPS PD-L1 > 1 is achieved, recruitment into the third group will be stopped and the TPS ≤1 cohort will be evaluated with given patient number in descriptive way.

Response is defined as a subject presenting with a partial or complete response to treatment according to RECIST criteria.

If responses are seen and considered to be of interest by number and depth of response, the SRC may decide in agreement with the Sponsor to expand individual cohorts **following a Simon-2-stage design** to confirm a certain response rate with the following assumptions:

- For the **first group**, for bladder cancer, hepatocellular cancer, non-small cell lung cancer, and melanoma with N = 14 fixed for the first stage, an additional N = 13 subjects may be added to a cohort to achieve at least 4/27 responders and confirms a true response rate of 20% with 80% power. For cutaneous squamous-cell carcinoma, N = 12 fixed for the first stage, an additional N = 24 subjects may be added to a cohort to achieve at least 6/36 responders and confirm a true response rate of 25% with 80% power.
- For the **second group**, for colorectal cancer with N = 10 fixed for the first stage, an additional N = 19 subjects may be added to a cohort to achieve at least 4/29 responders and confirm the true response rate of 20% with 80% power.
- For the **third group** (biomarker cohort with mixed solid tumors; "basket" cohort), with up to N = 75 subjects no such further expansion is considered. Instead, depending on response rate, - depth and - duration observed a potential registration size trial design will be considered and reviewed with the competent authorities (separate protocol). For the PD-L1 TPS > 1 group ("hot" tumors), a response rate of ≥ 30% is seen as clinically of significance, for the PD-L1 TPS ≤1 ("cold" tumors) a response rate > 20%. .

8.2. Subject Selection for Analyses

The statistical analysis will be conducted in the following data sets:

- The Safety Analysis Set will consist of all subjects who received at least one dose of CTL-002. Subjects will be analyzed according to the dose level initially received
- The PK Analysis Set will consist of all subjects who received at least one dose of study medication and have at least one measurable concentration of CTL-002
- The Efficacy Evaluable Analysis Set as per statistical definition will consist of all subjects who complete at least 2 cycles of treatment (e.g., 1 cycle monotherapy followed by 1 cycle combination therapy for Part A or 2 cycles combination therapy for Part A backfill and Part B subjects), and have baseline and at least one valid post-baseline tumor assessment demonstrating progression or were declared to be clinically progressing or terminated treatment due to a treatment-related AE

8.3. Statistical Analysis

8.3.1. Subject Disposition, Demography and Baseline Tumor Characteristics

The disposition of subjects will be summarized presenting the number of subjects enrolled, the number and percentage of subjects in each analysis set, the number for whom the study drug was discontinued with the reasons for discontinuation, and the number of subjects who discontinued participation in the study.

Demographic and baseline tumor characteristics will be presented based on the Safety Analysis Set. Baseline demographic and background data, including, but not limited to age, gender, weight, height, BMI, race, ethnicity, GDF-15 serum levels, and ECOG performance status will be listed and summarized using appropriate descriptive statistics.

Baseline tumor characteristics including primary diagnosis, primary tumor location and disease status at baseline will also be summarized. Medical history data will be summarized using frequency tabulations by MedDRA system organ class and preferred term.

8.3.2. Safety Analysis

Summary statistics (mean, median, standard deviation, and range, as appropriate) will be presented descriptively for the following safety endpoints by dose level and overall in Part A and by cohort and overall in Part B. All safety summaries will be presented by dose level (Part A) or cohort (Part B) and visit. The number of subjects experiencing each AE will be summarized by the MedDRA system organ class, MedDRA preferred term, NCI-CTCAE grade, and relationship to study treatment. Serious AEs and irAEs will be summarized separately.

AE summaries:

- Adverse Events - the number of AEs, the proportion of subjects having at least one AE and AEs by MedDRA coded terms will be presented.
- Serious Adverse Events - the number of SAEs, the proportion of subjects having at least one SAE and SAEs by coded terms will be presented.
- Related Adverse Events - the number of related AEs, the proportion of subjects having at least one related AE and related AEs by coded terms will be presented.
- Adverse Events leading to Discontinuation - the number of AEs leading to discontinuation, the proportion of subjects having at least one AE and AEs by coded terms will be presented.

Note: Only treatment-emergent AEs (commencing after exposure to study medication) will be included in the AE summaries. Non-treatment emergent events (starting prior to exposure to study medication) will be included in the subject listings and not included in the above summaries.

Adverse Event Listings:

- Adverse Events, SAEs, DLTs, and AEs leading to discontinuation will also be listed separately
- Details of any deaths will be listed for all subjects
- Any AEs in the study that occur after a subject has received further therapy for cancer (following discontinuation of CTL-002/the defined checkpoint inhibitor) will be flagged in the data listings

Laboratory Evaluations

Clinical laboratory results (including clinical chemistry, hematology, cytokines & chemokines, pharmacodynamic biomarkers, ADA, and urinalysis) will be summarized descriptively by dose level (Part A) or cohort (Part B) and visit, which will also include a display of change from baseline. Listings of abnormal clinical laboratory data according to NCI-CTCAE severity grades (if applicable), abnormal flags (low or high), and clinical significance of the latter will be provided. Shift tables will also be provided tabulating baseline versus on treatment changes in laboratory results.

Vital Signs

Descriptive statistics for vital signs, including weight and BMI, both observed values and changes from baseline, will be summarized by dose level (Part A) or cohort (Part B) and visit. Vital sign measurements will be listed by subject and by visit.

Physical Examination

Abnormal physical examination results will be listed separately.

Electrocardiography

Electrocardiogram parameters and changes from baseline will be summarized by dose level (Part A) or cohort (Part B) and visit using descriptive statistics.

ECOG

ECOG performance status will be summarized by dose level (Part A) or cohort (Part B) and visit using descriptive statistics.

Lumbar Skeletal Muscle Index L3 (L3SMI) (Part A only)

For Part A, The L3SMI results will be summarized by dose level and visit using descriptive statistics.

Mini Cachexia Score (MCASCO) (Part A only)

The 5 MCASCO components and the 3 cachexia classification groups will be summarized by dose level (Part A) and visit using descriptive statistics.

8.3.3. Efficacy Analysis

Efficacy analyses will be based on the Efficacy Evaluable Analysis Set and will include summaries of confirmed PR/CR, ORR, DoR, PFS, TTR, and OS by dose level (Part A) or cohort (Part B). Tumor response will be evaluated according to institutional standards using RECIST V1.1 for solid tumors, as well as iRECIST criteria. The definitions of the response evaluation endpoints are as follows:

Table 10 Definitions of Response Evaluation (RECIST V1.1)

Duration of Response:	Duration of response will be measured from the time that measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that PD or death is documented. This analysis will include subjects with overall best response being CR or PR only. Subjects who neither progressed nor died will be censored at the date of the last tumor assessment
Overall Response Rate	Overall response rate is defined as the percentage of subjects with a CR or PR as assessed by RECIST V1.1. A responder is defined as a subject experiencing either a CR or PR by these criteria. Subjects with no tumor assessment after the start of study treatment are to be considered as non-responders.
Progression Free Survival	Progression-free survival is defined as the length of time between first study drug administration and the date of the first occurrence of disease progression or death from any cause.
Time to Response	Time to response will be measured from the time of first study administration until the day of documented CR or PR (whichever status is recorded first). Subjects without response will be censored at the date of the last tumor assessment or the date of death.
Overall Survival	Overall survival is defined as the time from the study drug administration to the date of death, regardless of the cause of death. Subjects who were alive at the time of the analysis will be censored at the date the subject was last known to be alive. Subjects without follow-up assessment will be censored at the day of their last dose and subjects with no post-baseline information will be censored at the time of their first study drug administration.

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors

For DOR, PFS, TTR and OS, Kaplan-Meier curves and estimates including medians and 95% confidence intervals (CIs) will be provided. For analysis of the ORR, summary tables will be generated, presenting the number and proportion of responders in each dose group and 2-sided 95% Pearson-Clopper CIs. Logistic regression analyses may be used to test potential predictive factors for overall response.

8.3.4. Pharmacokinetic Analysis

Plasma concentrations of CTL-002 will be summarized by dose level (Part A) and cohort (Part B) using descriptive statistics (number of subjects [n], mean, standard deviation, coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum by nominal time point. Summary statistics will also be provided for PK parameters by cycle, including but not limited to AUC, C_{max}, and $t_{1/2}$.

8.3.5. Pharmacodynamic and Exploratory Analyses

Pharmacodynamic effects will be based on appropriate summaries of cytokines, chemokines, and other circulating biomarkers (see Section 6.2.4.8). Correlations of GDF-15 serum levels with certain pharmacodynamic results may be included graphically.

Exploratory endpoints will be based on summaries of immune cell phenotyping, molecular profiling and iRECIST parameters (see Section 6.2.4.9)

Note: Not all subject samples will be analyzed under "exploratory research/endpoints." The decision to analyze certain samples will be based on emerging data, data that indicates specific tumor indications and/or subjects where CTL-002 administered as monotherapy and/or in combination with a PD-1/PD-L1 inhibitor demonstrates increased tumor immune cell infiltration.

8.4. Interim Analysis

No formal interim data analysis is planned. However, the Sponsor will review Part A data produced, and based on safety, pharmaco-modelling data, and response data (as far as available), define an initial recommended dose for Part B (Phase 2a; expansion) and to support the submission of the substantial amendment to competent authorities and IEC/IRB. Other summaries of the data may be provided at any point during the study and used to help the Safety Review Committee and the Sponsor make informed decisions.

8.5. Sample Size

The sample size for Part A (Phase 1; dose escalation) of the study is not based on any statistical assumptions; rather, it follows the classic '3+3 rule," a well-established methodology in the design of dose-finding clinical trials in oncology.

The study plans for up to 5 dose escalation cohorts in Part A, with each cohort comprising a minimum of 3 subjects to be treated with CTL-002 in combination with the defined checkpoint inhibitor at each dose escalating level and with typical DLT driven expansions up to 6 subjects per cohort and at the MTD.

For Part A of the study (Phase 1; dose escalation), it is anticipated that a minimum of 24 subjects will be enrolled.

For Part B of the study (Phase 2a; expansion), up to 249 subjects will be enrolled in different expansion cohorts (79 response evaluable subjects in the first cohorts, with expansion option of 4×13, 1×24 and 1x19 subjects = 95 subjects, and 75 subjects in the biomarker cohort with mixed solid tumors; "basket" cohort). Therefore, a total of approximately 274 subjects might be enrolled (Part A: n = 25 / Part B: n = 79 + 95 + 75 = 249). Additional cohorts may be added via substantial amendment, only.

8.6. Level of Significance

The level of significance, alpha (α), for this trial is 0.05.

8.7. Criteria for the Termination of the Study

No statistical stopping rules will be formulated for this study.

8.8. Procedure for Accounting for Missing, Unused and Spurious Data

Missing, unused and spurious data will be dealt with as such. There is no intention to implement any procedure for replacing missing data.

8.9. Deviations from the Original Planned Analysis

Planned statistical analyses will be documented in the final SAP before database lock. Any changes to the planned statistical methods will be documented in the clinical study report.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory, Ethical and Study Oversight Considerations

9.1.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH/GCP guidelines, applicable regulatory requirements and the Sponsor or delegated representatives' policy on Bioethics and Human Biological Samples.

9.1.2. Ethics and Regulatory Review

The study will not be initiated without approval of the national Competent Authority and appropriate IEC/IRB and compliance with all administrative requirements of the governing body of the institution.

This will include approval of the exploratory biomarker and pharmacogenetic research and associated consent(s) forms. The Investigator will ensure the distribution of these documents to the applicable IEC/IRB, and to the trial site staff.

The Sponsor or designated representative will provide Regulatory Authorities, IECs, and PIs with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

Each Principal Investigator is responsible for providing the IEC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The Sponsor or designated representative will provide this information to the PI so that he/she can meet these reporting requirements.

9.2. Ethics/Independent Ethics Committee /Institutional Review Board /

The Principal Investigator (PI) must obtain IEC/IRB approval for the investigation. Initial IEC/IRB approval, and all materials approved by the IEC/IRB for this study including the subject ICF and recruitment materials (if applicable) must be maintained by the Investigator and made available for inspection.

The PI must submit written approval to the Sponsor or its representative before he or she can enroll any subject into the study.

The PI is responsible for informing the IEC of any amendment to the protocol in accordance with local requirements. In addition, the IEC/IRB must approve all advertising that may be used to recruit subjects for the study. The protocol must be re-approved by the IEC/IRB upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IEC/IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its representative will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IEC/IRB according to local regulations and guidelines.

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (See Appendix 5) and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsors policy on Bioethics.

9.3. Informed Consent

The PI at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subjects signed and dated informed consent must be obtained before conducting any study procedures.

The PI(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

The Investigator will obtain written informed consent from each subject participating in the study:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the exploratory biomarker assessments
- Ensure that each subject is notified that they are free to withdraw from the study or the subsequent biomarker assessments at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided and discuss the study with their family or surrogates
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed ICF is stored in the Investigator's Study File/medical records
- Ensure a copy of each signed ICF is given to the subject

9.3.1. Changes to the Protocol and Informed Consent Form

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative.

Any such changes which may affect a subject's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IEC/IRB and the concerned Competent Authorities. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number).

Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IEC/IRB by the Principal Investigator.

9.4. Subject Confidentiality

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their interventions as per local regulations. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IEC/IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical trial site will permit access to such records.

The study subject's contact information will be securely stored at each trial site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IEC/IRB, Institutional policies, or Sponsor requirements.

Subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the designated Clinical Research Organization supporting the study. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the designated Clinical Research Organization's research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived by the designated Clinical Research Organization.

9.5. Study Termination

Although Sponsor has every intention of completing the study, it reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the core study is defined as the time point when the last subject has completed the last Safety Follow-up Visit (End of Core Study Visit) 30 days from the last dose.

The end of study is defined as the time point when the last subject has completed the last Efficacy and Survival follow-up. This is 12 months after end of the core study for Part A and 24 months after end of the core study for Part B.

9.6. Study Monitoring

Before an investigational trial site can enter a subject into the study, a representative of the Sponsor will review the investigational trial site to:

- Determine the adequacy of the facilities

- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor or its representatives and the Investigator

During the study, a monitor from the Sponsor or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts)
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IEC/IRB

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

9.7. Audits and Inspections

As per ICH GCP and the Sponsor's audit plans, representatives of the Sponsor or the Contract Research Organization's Clinical Quality Assurance Department (or designees), a regulatory authority, an IEC or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

9.8. Insurance

This study is covered under the Sponsor's Liability Insurance Policy. A certificate of insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

9.9. Quality Control and Quality Assurance

To ensure compliance with GCP ICH E6(R2) and all applicable regulatory requirements, the Sponsor or its representatives may conduct a quality assurance audit. See Section 9.7 for more details regarding the audit process.

9.10. Data Handling and Recordkeeping

9.10.1. Inspection of Records

The Sponsor or its representative will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

9.10.2. Retention of Records

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or its representative, or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

10. PUBLICATION POLICY

The Sponsor recognizes and supports the publication and dissemination of scientific information as a means of furthering knowledge. The general strategy regarding publication of the study (e.g., what, when, where etc.) will be mutually agreed upon by the Investigator and Sponsor. However, in order to protect its commercial interests, the Sponsor reserves the right to manage the publication of all study results. The Investigator agrees that oral and written communication to third parties of any procedures or results from the study is subject to prior written consent of the Sponsor. Presentation material and/or manuscript(s) for publication will be reviewed by Sponsor prior to submission for publication. This review will be completed within 30 days of receiving presentation material and 60 days of receiving the manuscript from the Investigator. Alterations in the material will only be made in agreement between the Investigator and the Sponsor. Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

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12. APPENDICES

APPENDIX 1: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1

The following paragraphs represent a reference to the RECIST criteria (Version 1.1). The complete criteria are available at https://recist.eortc.org/recist-1-1-2/ and are included in the published RECIST document.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

For Part B, only subjects with obvious measurable disease at baseline should be included in the present clinical trial.

A 1.1 Measurability of Tumor Lesions at Baseline – Definitions

Measurable disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions – *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray, and as ≥10 mm with CT scan or clinical examination (using calipers). Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). *Malignant lymph nodes* must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. 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.

Non-measurable lesions – all other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.

Target lesions – when more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected 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*.

Note: Pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum.

At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.

Non-target lesions – all non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥10 mm but <15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

A 1.2 Methods of Measurements

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.

Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the eCRF at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Clinical lesions – clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using callipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray – 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 ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI – 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 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound – 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 should be obtained.

Endoscopy, Laparoscopy – the utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers – tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in CR.

Cytology, Histology – these techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors,

where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is advised to differentiate between response or SD and PD.

A 1.3 Tumor Response Evaluation

All subjects will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below. Refer to Table 11 and Table 12.

Complete Response (CR) – disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (***Note:*** *continue to record the measurement even if <10 mm and considered CR).* Tumor markers must have normalized. Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR) – at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.

Stable Disease (SD) – neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD) – at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 11 Integration of Target, Non-Target, and New Lesions Response Assessment (Appendix 1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
Subjects with target lesions ± non-target lesions				
CR	CR	No	CR	Normalization of tumor markers All tumor nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/not all evaluated	No	PR	
SD	Non-PD/not all evaluated	No	SD	
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; NE = Not Evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression (or evidence of unequivocal disease progression) at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

The BOR can be interpreted from Table 12.

Table 12 Response Assessment After Subsequent Scan (Appendix 1)

Response: First Time Point	Subsequent Time Point	BEST Overall Response	Also Requires
CR	CR	CR	Normalization of tumor markers. All tumor nodes <10 mm.
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

Abbreviations: CR = complete response; NE = Not Evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

A 1.4 Frequency of Tumor Re-Evaluation

Tumors should be assessed at baseline, Week 8 and then every 8 weeks. Additional assessments may be performed thereafter according to local institutional guidelines.

A 1.5 Date of Progression

This is defined as the first day when the RECIST (Version 1.1) criteria for PD are met.

A 1.6 Reporting of Tumor Response

All subjects included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each subject will be assigned one of the following categories: CR, PR, SD, PD, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

'Early death' is defined as any death occurring before the first per protocol time point of tumor re-evaluation. The responsible Investigator will decide if the cause of death is malignant disease,

toxicity or other cause. Subjects for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for SD (or the criteria for PR in case of an unconfirmed CR). Subjects' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

APPENDIX 2. IMMUNE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (iRECIST)

As defined by modified RECIST V1.1 criteria for immune-based therapeutics or iRECIST criteria (Seymour et al., 2017), the date of initial potential progression by RECIST scanning will be defined as the iUPD date. Subjects with an iUPD date who are stable will continue to participate in the study as planned and be reassessed for progression 4 to 8 weeks after the initial assessment. If the confirmatory assessment supports PD, the date of disease progression will be the iUPD date. If the confirmatory assessment does not support PD, the subject does not have disease progression and the iUPD date is ignored; such subjects will remain in the study as planned and continue the next imaging evaluation as planned per protocol.

Table 13 Comparison of RECIST V1.1 and iRECIST (Appendix 2)

	RECIST V1.1	iRECIST
Definitions of measurable and nonmeasurable disease; numbers and site of target disease	Measurable lesions are ≥10mm in diameter (≥15mm for nodal lesions) maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST V1.1; however, new lesions are assessed as per RECIST V1.1 but are recorded separately on the eCRF (but not included in the sum of lesions for target lesions identified at baseline)
CR, PR, or SD	Cannot have met criteria for progression before CR, PR, or SD	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of CR or PR	Only required for non-randomized trials	As per RECIST V1.1
Confirmation of SD	Not required	As per RECIST V1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances – e.g., in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

Abbreviations: CR = complete response; eCRF = electronic Case Report Form; iRECIST = modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics NE = Not Evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Note: "I" indicates immune responses assigned using iRECIST; iCR = complete response; iPR = partial response; iSD = stable disease; iUPD = unconfirmed progression

APPENDIX 3. IATA 6.2 GUIDANCE DOCUMENT

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens (e.g., Ebola and Lassa fever virus) are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, HIV types 1 and 2. They are assigned the following United Nations (UN) number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged.

APPENDIX 4. ADDITIONAL SAFETY INFORMATION

Further Guidance on the Definition of a Serious Adverse Event

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

In addition to the guidance provided in Section 7.2.3.1. the following should be noted regarding potential SAEs meeting the hospitalization criterion:

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment should be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring a blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Sponsor would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

APPENDIX 5. ETHICAL AND REGULATORY REQUIREMENTS

Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH/GCP guidelines, applicable regulatory requirements and the Sponsor or delegated representative's policy on Bioethics and Human Biological Samples.

Ethics and Regulatory Review

An IEC/IRB should approve the final Clinical Study Protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. This will include approval of the exploratory biomarker and pharmacogenetics research and associated consent(s) forms. The Investigator will ensure the distribution of these documents to the applicable IEC/IRB, and to the study site staff.

The opinion of the IEC/IRB should be given in writing. The Investigator should submit the written approval to the Sponsor or delegated representative before enrolment of any subject into the study. If applicable this approval should clearly state that the exploratory biomarker and pharmacogenetics research is approved.

The IEC/IRB should approve all advertising used to recruit subjects for the study (as applicable).

The Sponsor or designated representative should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IEC/IRB annually.

Before enrolment of any subject into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The Sponsor or designated representative will handle the distribution of any of these documents to the national regulatory authorities.

The Sponsor or designated representative will provide Regulatory Authorities, IEC/IRB and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the IEC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The Sponsor or designated representative will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

Informed Consent

Any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation should be described in the informed consent form that is approved by an IEC/IRB.

The Principal Investigator at each center will:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the optional exploratory biomarker and genetic research component(s)
- Ensure that each subject is notified that they are free to withdraw from the study or the research components at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure each original, signed Informed Consent Form is stored in the Investigator's Study File/medical records
- Ensure a copy of each signed Informed Consent Form is given to the subject

To participate in the optional pharmacogenetics component of the study the subject should sign and date the consent form for the main study and, as applicable, a separate consent form for the pharmacogenetic components of the study.

Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of each Principal Investigator and the Sponsor.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a Clinical Study Protocol Amendment and were required in a new version of the protocol (Revised Protocol).

The amendment should be approved by each IEC/IRB and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for Revised Protocols.

The Sponsor or designated representative will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator.

If a protocol amendment requires a change to a center's Informed Consent Form, The Sponsor or designated representative and the center's IEC/IRB should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IEC/IRB.