[redacted]

STATISTICAL ANALYSIS PLAN (SAP)
(PHASE 1B)

Protocol Title:	A Phase 1b/2a, Open-Label, Multi-Center Study of CyPep-1 in Combination With Pembrolizumab to Evaluate the Efficacy and Safety of CyPep-1 in Patients With Advanced or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma, or Triple-Negative Breast Cancer (TNBC) (CATALYST)
Protocol Number:	CYP003
Protocol Version/Date:	Version 4.0 / 23 November 2022
Investigational Product:	CyPep-1
Sponsor:	Cytovation ASA Solheimsgaten 11 5058 Bergen, Norway
SAP Version/Date:	Version 1.0 / 9 October 2024

SIGNATURE PAGE

Protocol Title:	A Phase 1b/2a, Open-Label, Multi-Center Study of CyPep-1 in Combination With Pembrolizumab to Evaluate the Efficacy and Safety of CyPep-1 in Patients With Advanced or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma, or Triple-Negative Breast Cancer (TNBC) (CATALYST)
Protocol Number:	CYP003
SAP Version/Date:	Version 1.0 / 9 October 2024

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
[redacted]	
[redacted]	
[redacted]	
[redacted]	

VERSION HISTORY

Version	Version Date	Description
1.0	9 Oct 2024	Original Signed Version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AECI	Adverse Event of Clinical Interest
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CL	Clearance
CM	Concomitant Medication
C_{max}	Peak plasma concentration
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DMC	Data Monitoring Committee
DoR	Duration of Response
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EoT	End of Treatment
FAS	Full Analysis Set
HNSCC	Head and Neck Squamous Cell Carcinoma
iCPD	immune Confirmed Progression of Disease
iCR	immune Complete Response
iDCR	Disease Control Rate per iRECIST
IMP	Investigational Medicinal Product
iRECIST	Immune-Response Evaluation Criteria in Solid Tumors
iSD	Stable Disease per iRECIST
IT	Intra-tumoral(ly)
itRECIST	Intratumoral-Response Evaluation Criteria in Solid Tumors
iUPD	immune Unconfirmed Progression of Disease
IV	Intravenous(ly)

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
OS	Overall Survival
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR Interval	Parameter in ECG
Q2W	Every 2 weeks
Q6W	Every 6 weeks
QRS Duration	Parameter in ECG
QT Interval	Parameter in ECG
QTcB	Heart rate-corrected QT interval using Bazett's formula
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
RR	RR Interval; Parameter in ECG
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable Disease
SoD	Sum of Diameters
$t_{1/2}$	Terminal half-life
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFL	Tables, Figures and Listings
T_{max}	Time to reach peak plasma concentration
TNBC	Triple-negative breast cancer
ULN	Upper limit of normal
VD	Volume of Distribution
WBC	White Blood Cells
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number CYP003 for Phase 1b only. Due to the termination after Phase 1b of the study, this SAP will contain a full report on safety endpoints and an abbreviated selection of efficacy endpoints. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives of Phase 1b only

This section describes the abbreviated study objectives for Phase 1b only.

2.1.1 Primary Objective

- Confirm the recommended CyPep-1 dose (20 mg every 2 weeks [Q2W]) when administered by intra-tumoral (IT) injection in combination with pembrolizumab.

2.1.2 Secondary Objective

- Evaluate the PK of CyPep-1 in combination with pembrolizumab.

2.1.3 Explorative Objective

- Analyze changes in biomarkers and tumor kinetics associated with the mode of action of CyPep-1 and pembrolizumab by tumor biopsy from injected lesions.
- Expand evaluation of anti-tumor activity of CyPep-1 and pembrolizumab.

2.2 Study Endpoints in Phase 1b only

This section describes the abbreviated study endpoints for Phase 1b only. Any pharmacokinetic analyses will be described in a separate document.

2.2.1 Primary Endpoints

- Incidence, frequency, and seriousness of Treatment-emergent adverse events (TEAEs);
- Incidence of dose-limiting toxicities (DLTs); and
- Changes from baseline in vital signs, body weight, 12-lead electrocardiogram (ECG) parameters, and laboratory assessments.

2.2.2 Secondary Endpoints

Plasma concentration-time profile of CyPep-1 and, if detectable, the following derived PK parameters:

- Area under the curve (AUC), Peak plasma concentration (C_{max}), Time to reach peak plasma concentration (T_{max}), clearance (CL), terminal half-life ($t_{½}$), and volume of distribution (VD).

2.2.3 Exploratory Endpoints

- Number and relative change of tumor infiltrating immune cells;
- Expression of selected immune cell biomarkers;
- Change from baseline in target tumor lesion size over time, overall, and by injected versus non-injected lesions;
- Maximum decrease from baseline in target tumor lesions, overall, and by injected versus non-injected lesions;
- Changes in new lesions treated with CyPep-1; and
- ORR according to Intratumoral-Response Evaluation Criteria in Solid Tumors (itRECIST).

2.3 Study Design

2.3.1 Overview

This is an open-label, multi-center, non-randomized Phase 1b/2a study. The Phase 1b portion of the study (the first 6 patients enrolled) will confirm the recommended CyPep-1 dose of 20 mg every 2 weeks (Q2W) in combination with pembrolizumab 400 mg every 6 weeks (Q6W).

The following 3 study arms will be included in the study:

- Arm A: Patients with advanced or metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)
- Arm B: Patients with Melanoma
- Arm C: Patients with Triple-Negative Breast Cancer (TBNC).

Patients will receive intra-tumoral (IT) injections of a fixed concentration of CyPep-1 Q2W beginning at Cycle 1 Visit 1. Pembrolizumab will be administered intravenously (IV) at a fixed dose Q6W beginning at Cycle 1 Visit 1. Patients must be observed for 4 hours post injection for pharmacokinetic (PK) monitoring on Cycle 1 Day 15. The plasma concentration-time profile of CyPep-1 and, if detectable, the derived PK parameters will be assessed.

The dose-limiting toxicity (DLT) period for the Phase 1b portion of the study will be Cycle 1 (initial 6 weeks of study treatment). After the first 6 patients have completed the DLT period, the Data Monitoring Committee (DMC) and Sponsor will review safety and tolerability data prior to the enrollment of the patients into the Phase 2a portion of the study. If ≤2 DLTs are observed in the first 6 patients, then the recommended CyPep-1 dose will be confirmed and enrollment of the remainder of the patients should continue.

If >2 of the 6 patients develop a DLT at the recommended CyPep-1 dose level (5 mg/mL dose concentration), then the maximum tolerated dose (MTD) of CyPep-1 will be assumed to have been exceeded and dose de-escalation will be conducted to determine the MTD. At least 6 patients will be treated at CyPep-1 dose level -1 (2 mg/mL dose concentration). If necessary, due to >2 DLTs in the dose level -1 cohort, a further reduction to dose level -2 (0.5 mg/mL dose concentration) will be performed.

Dose de-escalation will proceed according to the following rules:

- If ≤2 out of 6 patients develop a DLT, the MTD will be declared; or
- If >2 out of 6 patients develop a DLT, the dose will be de-escalated to the next lower dose.

The MTD will guide confirmation, by agreement of the DMC and the Sponsor, of a recommended Phase 2 dose (RP2D). The RP2D may be equivalent to the MTD or may be a dose below the MTD and will be dependent on an acceptable tolerability profile and manageable adverse events (AEs). The patients from Phase 1b will continue to the Phase 2a portion of the study. After the DMC reviews the safety data, feedback will be provided to the Sponsor regarding the further conduct of the study.

For detailed definition of DLT, please refer to the study protocol Section 3.1.1.1.

2.3.2 Study Drug

The overall study treatment regimen is defined as IT CyPep-1 in combination with IV pembrolizumab.

2.3.3 CyPep-1

CyPep-1 will be administered Q2W as an IT injection. CyPep-1 will be administered through a needle, which should be redirected along multiple tracks to ensure even dispersion of CyPep-1 throughout the tumor lesion. On the visits that CyPep-1 and pembrolizumab are administered on the same day, CyPep-1 is to be administered 30 to 60 minutes after pembrolizumab infusion is completed. Refer to the Guidance for Intra-tumoral Administration of CyPep-1 study manual for more details.

The cumulative maximal injected volume of CyPep-1 will be 4 mL (cumulative maximal dose of 20 mg at the recommended 5 mg/mL concentration) per treatment day for each patient, and it may be divided for injection over 1 to 3 tumor lesions depending on tumor lesion sizeCyPep-1 dose modifications are not planned. In the event of CyPep-1-related excessive toxicity, administration of CyPep-1 may be delayed for no more than 7 days; and if delayed >7 days, then that dose will be omitted at the discretion of the Investigator with the approval of the Medical Monitor.

2.3.4 Pembrolizumab

The dose of pembrolizumab in combination with CyPep-1 will be 400 mg Q6W administered via a 30-minute infusion, beginning at Cycle 1 Visit 1. On the visits that CyPep-1 and pembrolizumab are administered on the same day, CyPep-1 is to be administered 30 to 60 minutes after pembrolizumab infusion is completed. Pembrolizumab may be administered up to 3 days before or after the scheduled Visit 1 of each cycle from Cycle 2 onward.

2.3.5 Sample Size Determination

The sample size for the Phase 1b portion of the study is based on practical determinations. The first 6 patients of the study are planned to be enrolled in the Phase 1b portion.

3 STATISTICAL METHODOLOGY

This section describes the statistical analyses to be conducted in relation to the primary, secondary, and exploratory objectives of the Phase 1b part of the study.

3.1 General Considerations

All analyses will be performed using SAS® Version 9.4. Unless explicitly stated, no formal hypothesis testing will be performed for this study. All variables will be analyzed by descriptive statistical methods. Confidence intervals (CIs) will be constructed at the 2-sided 95% confidence level where appropriate.

Comprehensive data listings of all data will be generated. By-patient data listings of all clinical trial data will include all enrolled patients.

3.1.1 Treatment Groups and Arms

In general, all summaries will be displayed in *Total* for Phase 1b. By-arm summaries will not be displayed given the small sample size in Phase 1b.

3.1.2 Analysis Day

Analysis day will be calculated from the date of first dose of CyPep-1. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.3 Analysis Visits

Analysis visits will be based on the nominal scheduled visit (case report form [CRF] visit label).

In general, for by-visit summaries, data will be presented based on the scheduled visits. Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will be assigned a visit name of "Unscheduled". Such visits will be included in data listings and will contribute to the derivation of best- or worst-case values where applicable.

3.1.4 Definition of Baseline

Unless specified otherwise, baseline is defined as the last non-missing measurement prior to the first dose of study drug (CyPep-1 or pembrolizumab).

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.6 Handling of Dropouts and Missing Data

In general, missing data values will be recorded as missing and will not be imputed for the statistical analysis unless specified otherwise.

For missing or partial AEs and concomitant medications (CM) dates, conservative conventions will be applied in order to assign the events to corresponding periods (e.g. treatment period to ensure that no TEAE is missed). AEs will be considered as treatment-emergent, and the medications will be considered as concomitant if the missing/partial dates cannot definitively exclude the treatment period. Handling incomplete dates (e.g., AE and concomitant medications) are described in Appendix E.

<u>Treatment duration</u>

For the calculation of treatment duration, the date of last study drug infusion should be consistent with that of the last dose on the dosing page of the electronic case report form (eCRF). If the date of last dose on the dosing page is missing on the eCRF, use the last available dose date on the dosing page of eCRF to calculate. The last infusion should be clearly recorded on eCRF and not be estimated by the date of returning remaining study drug.

Laboratory values

Unless otherwise specified, for laboratory values that are reported using a non-numeric qualifier (e.g., less than [<] or greater than [>] sign), the reported numeric values will be used for summary or analysis without the qualifier.

In some cases, when the White Blood Cells (WBC) count is too low, the WBC differentials may be difficult to detect and thus not reported by the lab. If the reported WBC count < 0.5*10^9/L, then the differentials such as absolute neutrophils value will be imputed as zero for both the lab value summary and the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading. For example, absolute neutrophils value imputed as 0 would be considered as grade 4.

3.2 Analysis Populations

3.2.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive an injection of CyPep-1. The FAS will be used in the analysis of efficacy and exploratory endpoints.

3.2.2 Safety Analysis Set

The Safety Analysis Set (SAS) will include all patients who receive at least 1 injection of CyPep-1 or at least 1 administration of pembrolizumab. The SAS will be the basis of safety analyses.

[redacted]

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Data tabulations will be summarized for Phase 1b for the following patient numbers:

- Screened
- Screen Failure
- Enrolled
- Treated (CyPep-1 and/or pembrolizumab)
- Discontinued from CyPep-1 or pembrolizumab
- Study completion
- Discontinued from the study

Reasons for treatment discontinuation and for study discontinuation will be summarized.

All disposition data will be listed by patient.

3.3.2 Protocol Deviations

Counts and percentages of patients with CSR reportable protocol deviations by deviation category will be summarized in total based on the Safety Analysis Set.

All protocol deviations will be listed by patient.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized in total based on all enrolled patients.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate for the Safety Analysis Set and the Full Analysis Set. If the two sets are identical, only one version of the table will be presented. The following demographic and baseline characteristics will be summarized:

- Age at informed consent (years) and age categories (<65 years, ≥65 years);
- Sex;
- Childbearing potential if female;
- Race;
- Ethnicity;
- Height (cm);
- Weight (kg); and
- Body mass index (BMI) (kg/m^2).

All available demographic information will also be listed by patient for the Safety Analysis Set.

3.3.5 Primary Cancer History

Primary cancer history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. The following primary cancer history information will be summarized descriptively for the Safety Analysis Set.

- For Melanoma:
  - Type (Superficial spreading, Nodular, Lentigo maligna, Amelanotic, Acral lentiginous, Mucosal, Other);
  - Tumor Stage at diagnosis (0, I, II, III, IIIA, IIIB, IIIC, IIID, IV, Other);
  - BRAF (Wild type, mutated, not tested);
  - Grade (Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated, Not Applicable, Unknown]; and
  - Tumor stage at trial entry (locally advanced, metastatic).

All cancer history data will be listed by patient for the Safety Analysis Set.

3.3.6 Medical History

Medical history will include an evaluation of past and present history of the systems and/or conditions. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

All available medical history will be listed by patient for the Safety Analysis Set.

3.3.7 Prior & Concomitant Medications

All medications and therapies taken within 28 days prior to the Screening Visit until the Safety Follow-up Visit will be recorded in the eCRF. Prior medications include medications that were taken prior to and stopped before the first dose of the study treatment. Concomitant medications include medications that were taken on or after the first dose date of the study treatment until 30 days after the last dose of study treatment.

All prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug Global B3, Version March 2022). Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) and preferred term in total for the Safety Analysis Set. For each medication, the ATC used in the summary is taken as the highest available level from among ATC1, ATC2, ATC3, and ATC4. That is, if ATC4 is available, it will be used as the ATC for the summary, but if not available then the next highest level will be used. Although a patient may have taken two or more medications, the patient is counted only once within each ATC and preferred term classification. The same patient may contribute to two or more preferred terms in the same ATC classification.

All prior and concomitant medication data will be listed by patient for the Safety Analysis Set.

3.3.8 Prior Cancer Treatment

Prior systemic cancer therapy will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug Global B3, Version March 2022).

The following prior cancer treatment status will be summarized descriptively for the Safety Analysis Set:

- prior systemic anti-cancer therapy (yes, no), type of prior systemic cancer therapy (neo-adjuvant, adjuvant, maintenance, metastatic), and the best overall response to the last prior systemic anti-cancer therapy
- prior cancer radiation therapy (yes, no),
- prior cancer surgeries (yes, no)

All available prior cancer treatment data (including radiation therapy and surgery) will be listed by patient for the Safety Analysis Set.

3.3.9 Study Drug Exposure and Compliance

Duration of Treatment

The duration of treatment (in weeks) for CyPep-1 will be calculated as (the last dose date of CyPep-1 minus the first dose date of CyPep-1 + 14)/7.

The duration of treatment (in weeks) for pembrolizumab will be calculated as the (last dose date of pembrolizumab minus the first dose date of pembrolizumab + 42)/7.

Descriptive statistics will be provided for the treatment duration of CyPep-1 and pembrolizumab for the Safety Analysis Set. Note that the exposure calculation is intended to describe the length of time a patient was exposed to the study drug and therefore does not take study drug interruptions into account.

Total number of cycles initiated

For each patient, the total number of cycles initiated is defined as the total number of cycles that the patient took the study drug recorded on the eCRF(s) during the study. The total number of cycles initiated will be summarized descriptively. In addition, the number and percentage of patients with total number of cycles in the following categories will also be presented: 1 cycle, 2 cycles, 3 cycles, and ≥4 cycles.

Dosing Status

The number and proportion of patients with dose omissions (CyPep-1 and pembrolizumab), dose reductions (CyPep-1 and pembrolizumab), and dose interruptions (pembrolizumab only) will be summarized.

Dosing Intensity

The cumulative dose of (CyPep-1 and pembrolizumab) per patient across the treatment period is the sum of the actual dose (mg) the patient received.

The actual dose intensity will be calculated for each patient as follows:

- Dose intensity of CyPep-1 (mg/week) = cumulative dose of CyPep-1 (mg) /duration of treatment for CyPep-1(in weeks)
- Dose intensity of pembrolizumab (mg/week) = cumulative dose of pembrolizumab (mg) /duration of treatment for pembrolizumab (in weeks)

The overall relative dose intensity (%) for CyPep-1 and pembrolizumab will be calculated as (the actual dose intensity/planned dose intensity per protocol)*100%

All study drug administration data will be listed by patient and tabulated by study arm.

3.4 Efficacy Assessment

All efficacy analysis will be based on the Full Analyses Set (FAS).

The Investigator will assess tumor responses according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria and Intratumoral-Response Evaluation Criteria in Solid Tumors (itRECIST); see Appendices B, C, and D respectively. Efficacy evaluations will include the following: Local measurement of tumor lesions, radiological assessments, tumor biopsy, and peripheral cytokines.

Response (Complete response [CR] / partial response [PR], immune complete response [iCR] / immune partial response [iPR]) must be confirmed by a repeat assessment performed no less than 6 weeks after the criteria for response are first met. When stable disease (SD) or immune stable disease (iSD) is believed to be the best response, it must also meet the minimum interval of 6 weeks (42 days) from the start of the treatment. Best overall response (BOR) will be determined based on the overall visit responses from each RECIST and iRECIST assessment by the Investigator. BOR is defined as the best response designation (in the order of CR, PR, SD, progression of disease [PD] using RECIST, and in the order of immune complete response [iCR], immune partial response [iPR], immune stable disease [iSD], immune confirmed progression of disease [iCPD], and immune unconfirmed progression of disease [iUPD] using iRECIST) a patient has had following the first dose of study treatment, but prior to and including progression (PD for RECIST and iCPD for iRECIST) or the last evaluable assessment in the absence of disease progression. Patients with no evaluable assessments after the first study dose will be assigned to

the not evaluable (NE) category. The determination of the best overall response by RECIST 1.1, iRECIST and itRECIST is summarized in Appendices B, C, and D.

For patients with solid tumors who have evidence of disease progression at a post baseline tumor assessment (iUPD) and who remain on study treatment, repeat imaging studies are required within 4 to 8 weeks to assess for confirmation of disease progression. If unconfirmed at the next assessment, continue tumor assessments every 6 weeks (±7 days) until the earliest of any of the following: start of a new anticancer therapy, iRECIST confirmed progression of disease, withdrawal of consent by the patient, investigator decision to terminate treatment, sponsor termination of the study, pregnancy, loss to follow-up, or death.

Anticancer activity parameters that will be assessed include the determination of the following:

- Disease control rate (DCR) (CR+PR+SD) per RECIST v1.1 and iRECIST;
- Progression-free survival (PFS) per RECIST v1.1 and iRECIST; and
- Overall survival (OS) (for up to 26 months from Cycle 1 Visit 1).

3.4.1 Definition of Efficacy Endpoints

Disease Control Rate (DCR)

The Disease Control Rate per RECIST 1.1 is defined as the proportion of patients whose best overall response is CR, PR, or SD at ≥16 weeks.

- DCR = 100 x (Number of patients [CR+PR+SD]) / Total number of patients in Full Analysis Set

DCR per iRECIST (iDCR) is defined as the proportion of patients whose best overall response is iCR, iPR, or iSD at ≥16 weeks.

Disease assessments after the start of new anticancer therapy will be excluded from the determination of CR, iCR, PR, iPR, SD, or iSD.

Progression Free Survival (PFS):

PFS per RECIST 1.1 will be defined as the time from the first dose date of study drug to first observation of documented PD per RECIST 1.1 or death due to any cause within 12 weeks of last tumor assessment, per RECIST 1.1:

- PFS (months) = (Event/censoring date – first dose date + 1)/30.4375

For patients who have not progressed and are still alive at time of data cutoff for study analysis or who are lost to follow-up, PFS will be right censored. The event or censoring date will be determined based on the conventions listed in **Table 3.1.**

Table 3.1: Progression Free Survival (PFS)

Situation	Date of event or censoring	Outcome
Death before first planned disease assessment	Date of death	Event

Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
No postbaseline disease assessments	Date of first dose	Censored
Initiation of alternate anticancer treatment before disease progression or death (without disease progression beforehand)	Date of last evaluable disease assessment prior to start of alternate anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last evaluable disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last evaluable disease assessment	Censored

The PFS time will be derived based on scan/assessment dates and not visit dates to determine radiological progression. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied for this calculation:

- Date of radiological progression will be determined based on the earliest assessment/scan dates of the component that triggered the progression (PD using RECIST).
- When censoring a patient for PFS, the patient will be censored at the latest of the assessment/scan dates contributing to a particular overall visit assessment.

PFS per iRECIST (iPFS):

iPFS will be defined as the time from the first dose date of study drug to first observation of documented iCPD per iRECIST or death due to any cause within 12 weeks of last tumor assessment:

- iPFS (months) = (Event/censoring date – first dose date + 1)/30.4375

The iPFS time will be derived based on scan/assessment dates in the same manner as the PFS time derivation. To be counted as disease progression, the iUPD assessment must be confirmed as iCPD at the next iRECIST assessment. In the event that an iUPD response is assessed but the progression is not confirmed (e.g. a later assessment of iSD, iPR, or iCR is observed) then the initial iUPD will not be counted as an event for determination of iPFS. To be conservative, in the case that an assessment of iUPD is recorded and no subsequent evaluable iRECIST assessments are recorded then the iUPD event will be treated as confirmed disease progression.

For patients who have not progressed and are still alive at time of data cutoff for study analysis or who are lost to follow-up, iPFS will be right censored. The same censoring rules for PFS using RECIST 1.1 as specified in **Table *3.1*** will be applied.

Overall Survival (OS)

OS is defined as the interval from the start of first study dose to death from any cause. Patients who are alive or lost to follow-up as of the data cutoff date will be censored at the date the patient was last known to be alive:

- OS (months) = (Death date/censoring date – first study dose date + 1)/30.4375

The last date known to be alive for each individual patient may be determined using, but not limited to, the following dates recorded on the eCRF:

- AE start and stop dates,
- Study treatment start and stop dates,
- Laboratory assessment dates,
- Dates of vital signs, physical examination, Eastern Cooperative Oncology Group (ECOG),
- Performance status, and electrocardiogram (ECG) assessments,
- Disease assessment dates,
- Start and stop dates of concomitant medications including procedures and alternative anti-cancer therapy, and
- Date patient last known to be alive on long-term follow-up.

3.4.2 Statistical Methodology of Efficacy Analyses

Tumor Response Data

The following tumor response variables will be listed and summarized using descriptive statistics:

- Best Overall Response,
- DCR per RECIST 1.1,
- DCR as per iRECIST (iDCR),
- Progression Free Survival per RECIST (PFS),
- Progression Free Survival per iRECIST (iPFS), and
- Overall Survival (OS).

The Disease Control Rate will be based on the number of patients achieving a PR, CR, or stable disease ≥16 weeks based on RECIST v1.1 and iRECIST (iDCR).

Point estimates along with the exact Clopper-Pearson 95% CIs will be presented for DCR and iDCR.

The best overall response will be determined according to RECIST v1.1 and iRECIST. Response (CR/PR, iCR/iPR) must be confirmed by a repeat assessment performed no less than 6 weeks (42 days) after the criteria for response are first met. When SD or iSD is believed to be the best response, it must also meet the minimum interval of 6 weeks (42 days) from the start of study drug. If the minimum time is not met when SD or iSD is otherwise the best time point response, the patient's best response depends on the subsequent assessments.

All tumor response data will be listed by patient and tabulated by study arm.

Progression Free Survival

PFS and iPFS based on the Investigator assessment will be estimated using the Kaplan-Meier method.

The Kaplan-Meier estimate of the first quartile, median, and third quartile for PFS and iPFS and the 95% CIs for the median calculated using the Brookmeyer-Crowley method will be presented. The PFS and iPFS rates and 95% CIs will also be provided for 6 and 12months after the first treatment with CyPep-1 + pembrolizumab using the Kaplan-Meier method.

Overall Survival

OS based on the Investigator assessment will be estimated using the Kaplan-Meier method.

The Kaplan-Meier estimate of the first quartile, median, and third quartile for OS and the 95% CIs for the median calculated using the Brookmeyer-Crowley method will be presented.

3.5 Pharmacokinetic (PK) Assessment

Pharmacokinetic (PK) analyses will be described in a separate document.

3.6 Biomarker Assessment

All available biomarker data will be listed by patient.

3.7 Safety Assessment

Safety will be assessed by physical examinations, vital signs, 12-lead ECGs, ECOG performance status (see Protocol Appendix C), clinical laboratory evaluations, and AEs (as defined by the National Cancer Institute [NCI] CTCAE v5.0; see Section 8.1.3 of the protocol) as indicated in the Schedule of Assessments (Protocol Appendix A). Additional assessments may be performed as clinically indicated.

Patients will be monitored for DLTs for confirmation of the CyPep-1 dose of 20 mg Q2W in combination with pembrolizumab 400 mg Q6W. Safety will be monitored in conjunction with the DMC and as per the DMC charter.

Safety data will be summarized in total based on the safety analysis set.

3.7.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 25.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start or worsen after the first dose of study drug and within 30 days after the last dose of study treatment.

Adverse events of clinical interest (AECI) include the following:

- An overdose of pembrolizumab, as defined in Section 5.5.3.4 of the protocol; and
- An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) laboratory value that is greater than or equal to 3 times the upper limit of normal (ULN) (greater than 5 times the ULN for patients with liver metastases), an elevated total bilirubin laboratory value that is greater than or equal to twice the ULN, and, at the same time, an alkaline phosphatase laboratory value that is less than twice the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

An overview of TEAEs will be provided including counts and percentages of patients (and event counts) with the following:

- TEAEs;
- CyPep-1 related TEAEs (overall and by maximum severity);
- TEAEs related to any Investigational Medicinal Product (IMP) (CyPep-1 or pembrolizumab);
- CTCAE Grade 3/4/5 TEAEs;
- Treatment-emergent serious AEs (TESAEs);
- CyPep-1 related TESAEs;
- TESAEs related to any IMP (CyPep-1 or pembrolizumab);
- Serious adverse events (SAEs);
- TEAEs leading to interruption of CyPep-1;
- TEAEs leading to interruption of pembrolizumab;
- TEAEs leading to delayed or held CyPep-1 dose;
- TEAEs leading to delayed or held pembrolizumab;
- TEAEs leading to permanent discontinuation of CyPep-1;
- TEAEs leading to discontinuation of pembrolizumab;
- TEAEs leading to discontinuation of study;
- TEAEs leading to death; and
- TEAEs of clinical interest.

Counts and percentages of patients (and event counts) will also be presented by system organ class (SOC) and preferred term (PT) for each of the categories in the overview. For these summaries, patients with multiple adverse events will be counted only once per SOC or PT.

A by-patient adverse event data listing will be presented including, but not limited to, verbatim term, preferred term, SOC, CTCAE grade, and relationship to any study drug. SAEs, and AEs leading to discontinuation of study drug, AEs leading to death, and AECIs will also be listed.

3.7.2 Dose Limiting Toxicities (DLTs)

The Dose-Limiting Toxicities in this study are defined in Section 3.1.1.1 in the protocol.

All DLTs will be listed based on the DLT Evaluable Set.

3.7.3 Clinical Laboratory Tests

Clinical laboratory evaluations will be summarized using descriptive statistics for selected laboratory parameters (i.e., chemistry and hematology) including absolute measurements and changes from baseline for the minimum post-baseline value, maximum post-baseline value, and last post-baseline value. Selected clinical laboratory tests including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), total bilirubin (TBIL), creatinine, hemoglobin, absolute neutrophil count (ANC), and platelets. Both scheduled and unscheduled post-baseline visits will be considered for the summaries of the last, maximum, and minimum post-baseline values. All clinical laboratory analytes are listed in Appendix A.

Abnormal laboratory results will be graded according to NCI-CTCAE version 5.0 as applicable. For some laboratory tests, the CTCAE criteria may include qualifying definitions (e.g., clinical AE and/or requirement for concomitant medication) in addition to the specific laboratory value used

for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades.

A shift table, presenting the 2-way frequency tabulation for baseline and the worst post treatment value according to the NCI-CTCAE grade will be provided for selected clinical laboratory tests including Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), total bilirubin (TBIL), creatinine, hemoglobin, absolute neutrophil count (ANC), and platelets. Both scheduled and unscheduled post-treatment visits will be considered in tabulation of the worst post-treatment value.

For purposes of analysis and reporting, laboratory values will be standardized using International System of Units (SI) or clinically appropriate units.

The number and percentage of patients with treatment-emergent laboratory abnormalities (any grade and grade ≥3 per NCI-CTCAE v5.0) will be presented for applicable hematology and serum chemistry laboratory parameters. Treatment-emergent laboratory abnormalities are defined as post baseline laboratory abnormalities with worsening CTCAE grade from baseline. Post-baseline laboratory abnormality with unknown baseline grade will be considered as treatment-emergent.

The number and percentage of patients with the following potentially clinically significant abnormal liver function tests at any post-Baseline visits will be summarized:

- ALT ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- Potential Hy's Law cases: ALT or AST ≥3×ULN with total bilirubin ≥2×ULN and ALP < 2xULN at the same visit date

Laboratory values that are reported using a nonnumeric qualifier (e.g., less than [<] or greater than [>] sign), the reported numeric value will be used for analysis without the qualifier.

Clinical laboratory evaluations for selected parameters (i.e. chemistry and hematology) will be listed by patient, tabulated by study arm, and abnormal values will be flagged.

3.7.4 Vital Signs

Vital signs will be measured in the supine position after at least a 10-minute rest at screening, Visit 1 of each dosing cycle, the end of treatment (EoT) Visit, and the Safety Follow-up Visit. At dosing visits, vital signs will be assessed before dosing (after ECG assessment) and at 15 minutes (±5 minutes), 30 minutes (±5 minutes), and 1 hour (±10 minutes) after dosing. The following variables will be measured:

- Systolic and diastolic blood pressure (mm/Hg);
- Pulse rate (beats per minute); and
- Temperature (°C).

Changes from baseline to the last, maximum, and minimum post-baseline values will be presented. Both scheduled and unscheduled post-treatment values will be considered for summaries of the last, minimum, and maximum.

The number and proportion of patients with potentially clinically significant changes in vital signs will be presented based on the following thresholds:

- Systolic blood pressure ≥ 160 mmHg and increase ≥ 20 mmHg from baseline,
- Diastolic blood pressure ≥ 100 mmHg and increase ≥ 15 mmHg from baseline, and
- Pulse rate ≥ 120 bpm with increase ≥ 15 bpm from baseline.

All vital signs data will be listed by patient and tabulated by study arm.

3.7.5 Electrocardiograms

The Electrocardiogram parameters PR interval, RR interval (RR), QRS Duration (QRS), QT interval (QT), Bazett-corrected QT interval (QTcB), and Fridericia-corrected QT interval (QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by scheduled time of evaluation, including the last post-baseline and the maximum post-treatment value. Both scheduled and unscheduled post-treatment values will be considered for summaries of the last and maximum post-treatment values.

The Bazett-corrected QT interval (QTcB) is based on the following formula:

$$QTcB\ (msec) = \frac{QT\ (msec)}{\sqrt[2]{RR}(msec)/1000}$$

The Fridericia-corrected QT interval (QTcF) is based on the following formula:

$$QTcF\ (msec) = \frac{QT\ (msec)}{\sqrt[3]{RR}(msec)/1000}$$

In addition, the number and percentage of patients experiencing QTcF or QTcB elevation at any time post-baseline will be presented for the following categories:

- QTcF > 450 ms,
- QTcF > 480 ms,
- QTcF > 500 ms,
- Increase from baseline QTcF > 30 ms,
- Increase from baseline QTcF > 60 ms,
- QTcB > 450 ms,
- QTcB > 480 ms,
- QTcB > 500 ms,
- Increase from baseline QTcB > 30 ms, and
- Increase from baseline QTcB > 60 ms.

All ECG measurements and overall interpretation will be listed by patient and tabulated by study arm.

3.7.6 Physical Examinations

All physical examination data will be listed by patient.

3.7.7 Performance Status

All ECOG performance status data will be listed by patient.

4 DATA MONITORING COMMITTEE

The monitoring of the safety and tolerability of CyPep-1 + pembrolizumab will be performed by the DMC.

This will include all the patients in the Phase 1b portion and thereafter, all patients who have entered the study. This will be conducted on a regular basis, as defined in the DMC charter.

After the DMC reviews the safety data, feedback will be provided to the Sponsor regarding the further conduct of the study. The DMC will be comprised of independent members or designees. The DMC will strive for a consensus opinion regarding the data reviewed.

5 ANALYSIS TIMING

5.1 Interim Analysis

No formal interim analysis is planned.

5.2 Pre-Final Analysis

After the database is locked the pre-final analysis will be generated. Pre-final tables, figures and listings (TFLs) will be provided approximately 3 weeks after database lock.

5.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final.

6 [redacted]

[redacted]

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. [redacted] will be followed for the validation of all SAS programs and outputs.

Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen/urea	C-reactive protein
Calcium	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Lactate dehydrogenase
Lipase	Phosphate
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

Hematology

Absolute neutrophil count	Hematocrit
Hemoglobin	Platelets
Red blood cell count	White blood cell count and differential [1]

1. Including neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

Activated partial thromboplastin time	International normalized ratio [1]
Prothrombin time	

1. In case there are no normal ranges available for the prothrombin time, the international normalized ratio may be used instead of prothrombin time.

Urinalysis

Bilirubin	pH
Creatinine	Specific gravity
Ketones	Blood
Microscopy [1]	Glucose

Leukocyte esterase	Protein
Nitrite	Urobilinogen

1. Microscopy is performed only as needed based on positive dipstick test results.

Pregnancy Test [1]

Serum human chorionic gonadotropin	Urine human chorionic gonadotropin

1. For female patients of childbearing potential only.

Endocrinology

Follicle-stimulating hormone [1]	Free thyroxine
Thyroid-stimulating hormone	Triiodothyronine [2]

1. Follicle-stimulating hormone will only be performed in female patients who have spontaneous amenorrhea for at least 2 years to verify their post-menopausal status.

2. Or free triiodothyronine.

Serology

Human immunodeficiency virus

APPENDIX B: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) VERSION 1.1 (V1.1)

Measurable TumorBurden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified atbaseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥10 mm in longest diameter (LD) and 2× the slice thickness for extranodal lesions. ≥15 mm in short axis diameter (SAD) for nodal lesions. ≥10 mm in LD for clinical lesions (must be measured using electronic calipers). ≥20 mm in LD for chest X-ray (if clearly defined and surrounded by aerated lung);CT is preferable. Ultrasound cannot be used to measure lesions.
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are nonmeasurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions)is followed through the course of therapy.

Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed onCT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emissiontherapy (PET), or plain films are nonmeasurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meetthe minimum size criteria. Noncystic lesions are preferable.
Lesions With PriorLocal Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are notmeasurable unless the lesion has progressed since therapy.
Too Small to Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned.If the lesion disappears, the measurement is recorded as 0 mm.
Lesions That Split orCoalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to calculate the sum. If target lesions coalesce and cannot be distinguished, the LDof the coalesced lesion is added to the sum.
Definition of CompleteResponse (CR)	CR requires the disappearance of all extranodal lesions, the regression of all nodallesions to <10 mm SAD, and the normalization of tumor marker level.
Definition of PD	PD is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm fromnadir (including baseline if it is the smallest sum).
	Patients with measurable disease: for “unequivocal progression” based on nontarget disease, there must be an overall level of substantial worsening that meritsdiscontinuation of therapy (if target disease is SD/PR).
	Patients without measurable disease: for “unequivocal progression” of nontarget disease, the increase in overall tumor burden must be comparable to the increaserequired for PD of measurable disease.
Assessment of NewLesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings, which may not be a tumor (ie, “new” bone lesions may be healing or flare of preexisting lesions). If it is equivocal, repeat scans are needed toconfirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET: (-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-upis PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to preexisting lesion on CT that is notprogressing; not PD.
Recurrence of Lesions	For a patient with SD/PR, a lesion that disappears and then reappears will continue to be measured and added to the sum. Response will depend on the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.

Overall Response	One overall response table integrates target, nontarget, and new lesions and anothertable integrates nontarget and new lesions for the assessment of patients without measurable disease.
Confirmation ofResponse	Confirmation of PR/CR is ONLY required for nonrandomized studies where response is the primary endpoint. In these studies, subsequent confirmation of PR with 1 interim timepoint of SD is acceptable.

APPENDIX C: DESCRIPTION OF THE iRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Immune-Response Evaluation Criteria in Solid Tumors (iRECIST) is based on the Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression and to guide decisions about changes in management.

Assessment at Screening and Prior to the RECIST v1.1 Progression

Until radiographic disease progression based on modified RECIST v1.1, there is no distinct iRECIST assessment.

Assessment and Decision at the RECIST v1.1 Progression

For patients who show radiological progressive disease (PD) by RECIST v1.1, the Investigator will decide whether to continue a patient on study treatment until repeat scans are obtained. Tumor flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir; Note: The iRECIST publication uses the terminology “sum of measurements,” but “sum of diameters” will be used in this SAP, consistent with the original RECIST v1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline; and
- Development of new lesion(s).

iRECIST defines new response categories, including unconfirmed PD (iUPD) and confirmed progressive disease (iCPD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST v1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Scans

On the confirmatory scans, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (stable disease [iSD]/partial response [iPR]/complete response [iCR]).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening; or
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point;
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST v1.1; or
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point;
        - Visible growth of new non-target lesions; or
        - The appearance of additional new lesions.
- Any new factor appears that would have triggered PD by RECIST v1.1.

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

None of the progression-confirming factors identified above occurs; AND

The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST v1.1).

Additional scans for confirmation are to be scheduled 4 weeks to ≤8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan will proceed in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

None of the progression-confirming factors identified above occurs; AND

The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Scan

If repeat scans do not confirm PD per iRECIST, as assessed by the Investigator, study intervention is to continue, and the regular scan schedule is to be followed. If PD is confirmed, patients may be discontinued from study intervention.

Note: If a patient has confirmed radiographic progression (iCPD), clinically meaningful study intervention may be continued after consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie, after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions;
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- Non-target lesions; or
  - If non-target lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD; or
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions;
  - New lesions appear for the first time;
  - Additional new lesions appear;
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum; or
  - Previously identified non-target lesions show any significant growth.

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Scans above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial PD, with 1 exception, which could occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan, then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until new or worsening causes of progression indicates iCPD.

Additional details about the iRECIST are provided in the iRECIST publication.

APPENDIX D: itRECIST GUIDANCE

Intratumoral-Response Evaluation Criteria in Solid Tumors (itRECIST) is based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and immune-RECIST but adapted to account for the unique tumor response seen with intra-tumoral immunotherapeutic drugs. itRECIST will be used by the Investigator to assess tumor response.

APPENDIX E: DATE OF IMPUTATION GUIDELINE

The following date imputation guidelines will apply to adverse events, prior medications and concomitant medications.

AE Start Date	AE Stop Date	Action
Known	Known/Partial/Missing	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
Partial, but the known date components show that it cannot be on or after study drug start date	Known/Partial/Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (ie, last day of month if day is unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (ie, last day of month if day is unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing	Assumed TEAE

CM Start Date	CM Stop Date	Action
Known	Known	If stop date < study drug start date, assign as PRIOR
		If stop date ≥ study drug start date, and start date ≤ end of treatment +30 days, assign as CONCOMITANT
		If stop date ≥ study drug start date and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31-Dec if day and month are unknown), then:
		If stop date < study drug start date, assign as PRIOR
		If stop date ≥ study drug start date, and start date ≤ end of treatment +30 days, assign as CONCOMITANT
		If stop date ≥ study drug start date, and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Missing	If stop date is missing, then PRIOR will never be assumed or assigned
		If start date ≤ end of treatment, assign as CONCOMITANT
		If start date > 30 days after the end of treatment, assign as POSTTREATMENT
Partial	Known	Impute start date as earliest possible date (ie, first day of month if day unknown or 01-Jan if day and month unknown), then:
		If stop date < study drug start date, assign as PRIOR
		If stop date ≥ study drug start date and start date ≤ end of treatment + 30 days, assign as CONCOMITANT
		If stop date ≥ study drug start date and start date > 30 days after the end of treatment, assign as POSTTREATMENT
	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 01-Jan if day and month are unknown) and impute stop date as latest possible date (ie, last day of month if day unknown or 31-Dec if day and month are unknown), then:
		If stop date < study drug start date, assign as PRIOR
		If stop date ≥ study drug start date and start date ≤ end ofe treatment + 30 days, assign as CONCOMITANT
		If stop date ≥ study drug start date and start date > 30 days after the end of treatment, assign as POSTTREATMENT

CM Start Date	CM Stop Date	Action
	Missing	Impute start date as earliest possible date (ie, first day of month if day unknown or 01 Jan if day and month unknown), then: If stop date is missing, then PRIOR will never be assumed or assigned If start date ≤ end of treatment + 30 days, assign as CONCOMITANT If start date > 30 days after the end of treatment, assign as POSTTREATMENT
Missing or Unknown	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT If start date is missing, then POST-TREATMENT will never be assumed or assigned
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT If start date is missing, then POSTTREATMENT will never be assumed or assigned
	Missing	Assign as CONCOMITANT