Statistical Analysis Plan

"A first-in-human, open-label, dose escalation followed by dose expansion phase I/IIa trial to evaluate the safety, preliminary efficacy and pharmacokinetics of intratumoral CyPep-1 monotherapy and in combination with pembrolizumab in patients with advanced solid cancers."

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Between

Cytovation ASA
Solheimsgaten 11
5058 Bergen
Norway

And

[redacted]

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1 Statistical Analysis Plan Approval Page

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[redacted]; Author — Signature and Date

[redacted]
Reviewing Statistician — Signature and Date

Cytovation ASA

[redacted] — Signature and Date

[redacted]
Project Manager — Signature and Date

1.1 Revision History

Revision summary since final version:

SAP version	Date	Protocol version	Author	Reason for revision
V1.0	19 Dec 2022	V9.0, V9.2	[redacted]	NA, first version
V2.0	05 May 2023	V10.0, V10.1		Protocol amendment
V3.0	04 Jun 2024	V10.0, V10.1		Sponsor comments from first Mid-Study Analysis

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3 List of Abbreviations

This section provides a list of all the abbreviations and acronyms used in the Statistical Analysis Plan (SAP) with their related definitions. All terms appear in alphabetical order.

Table 1. List of Abbreviations

Abbreviation	Description
ACC	Adrenocortical carcinoma
AE	Adverse event
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
CA	Competent Authority
CD	Cluster of differentiation
CL	Clearance
C_{max}	Peak plasma concentration
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DEC	Dose Escalation Committee
DLT	Dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EoT	End of Treatment
ICF	Informed Consent Form
ICH	International Conference for Harmonization
ICI	Immune checkpoint inhibitor
iCPD	iRECIST Confirmed progressive disease
iCR	iRECIST Complete response
IEC	Independent Evaluation Committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
iPR	iRECIST Partial response
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
iSD	iRECIST Stable disease
itRECIST	Intratumoral Response Evaluation Criteria in Solid Tumors
IT	Intratumoral
itCPD	itRECIST Confirmed progressive disease
itCR	itRECIST Complete response
itPR	itRECIST Partial response
itSD	itRECIST Stable disease
itUPD	itRECIST Un-confirmed progressive disease
iUPD	iRECIST Un-confirmed progressive disease
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic

Abbreviation	Description
PKS	CyPep-1 PK Analysis Set
PT	Prothrombin time
RBC	Red blood cell
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SCR	All Screened Set
SDVd	Source data verified
SOC	System Organ Class
$t_{1/2}$	Elimination half-life
TCR	T cell receptor
TEAE	Treatment-emergent AE
TESAE	Treatment-emergent SAE
T-I	Injected target (lesions)
TLT	Treatment-limiting toxicity
t_{max}	Time to reach C_{max}
T-NI	Non-injected target (lesions)
TNM	Tumor, node, metastasis
TTR	Time to response
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
VD	Volume of distribution
WBC	White blood cell
WHO	World Health Organization

4 Introduction

4.1 Preface

CyPep-1 is a synthetic linear 27-amino acid peptide with an acetylated amino group at the N-terminus and an amido group at the C-terminus. All optically active amino acid residues are in D-configuration with the exception of achiral glycine.

CyPep-1 is formulated in a clear and colorless aqueous solution (5 mg/mL).

CyPep-1 has a dual mode-of-action that 1) selectively target tumor cell membranes based on their altered molecular composition, which in turn leads to lysis of tumor cells by removal of the cell membrane, and 2) inhibits the Wnt/b-catenin pathway.

This mode of action of CyPep-1 induces tumor cell death resulting in the release of tumor antigens, and potentially induces a tumor-specific immune response by in-situ immunization. Inhibition of b-catenin reverses immune exclusion by inhibiting an immune suppress transcriptional program.

Preclinical toxicology studies have shown a favorable safety profile and potent anti-tumor activity of CyPep-1 in several tumor models. CyPep-1 was shown to modulate the tumor microenvironment by increasing the presence of CD8+ T-cells and by potentiating the effects of immune checkpoint inhibitors (ICI). As such, it is hypothesized that intratumoral (IT) injection with CyPep-1 leads to transformation of immunological “cold” and ICI treatment-resistant tumors into “hot” and immunological active tumors that can be successfully treated with immune-modulating agents.

4.2 Purpose of the analysis

This Statistical Analysis Plan is a complementary document to the Clinical Study Protocol, “A first-in-human, open-label dose escalation followed by dose expansion phase I/IIa trial to evaluate the safety, preliminary efficacy and pharmacokinetics of intratumoral CyPep-1 monotherapy and in combination with pembrolizumab in patients with advanced solid cancers.” (version 10.1, dated 30-Jan-2023, applicable for France, and version 10.0, dated 30-Jan-2023, applicable for all other countries). This SAP includes a technical and detailed elaboration of the principal features of the proposed statistical analysis, presentations and the way in which anticipated analysis problems will be handled. A description of the planned tables, listings and figures (TLFs) to be presented in the Clinical Study Report (CSR) is provided in a separate document.

4.3 Changes from and Additions to the Clinical Study Protocol

The following additions to the Clinical Study Protocol were made in this SAP:

1. Characterization of potential hepatotoxicity was added.
2. Markedly abnormal criteria for vital signs added.
3. Section for Other exploratory analyses was added (including analyses of PK and toxicity and intratumoral dose concentration).
4. Sections on visit alignment were added.
5. itRECIST analyses for Phase I cohorts were added.
6. Analyses of overall survival by RMH and GRIM-scores and including/excluding subjects with adrenocortical carcinoma were added.

The following changes from Clinical Study Protocol were made in this SAP:

Not applicable, no discrepancies between SAP and Clinical Study Protocol.

5 Trial Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objectives

- To evaluate the safety and tolerability of IT administration of CyPep-1 as monotherapy and in combination with pembrolizumab.
- To identify the recommended phase II dose (RP2D) of CyPep-1 as monotherapy and in combination with pembrolizumab.

5.1.2 Secondary Objectives

- To assess the preliminary anti-tumor efficacy of CyPep-1, as monotherapy and in combination with pembrolizumab.
- To characterize the pharmacokinetics (PK) of CyPep-1.

5.1.3 Exploratory Objectives

- To assess the preliminary anti-tumor efficacy of CyPep-1, as monotherapy and in combination with pembrolizumab, in injected lesions and non-injected lesions, separately.
- To assess survival after treatment with CyPep-1, as monotherapy and in combination with pembrolizumab.
- To assess the immune modulating properties of treatment with CyPep-1, as monotherapy and in combination with pembrolizumab.

5.2 Endpoints

5.2.1 Primary Endpoints

- Type and number of adverse events (AEs) according to National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE) criteria v5.0, and additional safety parameters of CyPep-1 as monotherapy and in combination with pembrolizumab.
- Dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD) for determination of RP2D of CyPep-1 as monotherapy and treatment-limiting toxicities (TLTs) of CyPep-1 in combination with pembrolizumab.

5.2.2 Secondary Endpoints

- Objective response rate (ORR), defined by complete and partial responses, according to immune Response Evaluation Criteria in Solid Tumors (iRECIST) based on the investigator's assessment.
- Time to and duration of response and duration of stable disease.
- The plasma concentration time profile of CyPep-1 and, if detectable, the derived PK parameters (i.e., area under the curve [AUC], peak plasma concentration [C_{max}], time to reach C_{max} [t_{max}], systemic clearance (CL), elimination half-life ($t_{1/2}$) and volume of distribution [VD]).

5.2.3 Exploratory Endpoints

- For all Phase IIa arms: ORR in injected lesions and non-injected lesions, separately, per itRECIST* (Intratumoral Response Evaluation Criteria in Solid Tumors) (Goldmacher, 2020).
- Progression-free survival (PFS) per iRECIST based on investigator's assessment.
- Overall survival (OS).
- The relative change in number of tumor infiltrating CD8+ T-cells in the injected and, whenever available, non-injected tumor biopsies.
- The association between the relative change in tumor infiltrating CD8+ T-cells and response rate in the injected lesions (per itRECIST) and all lesions (per iRECIST). The change in T-cell receptor (TCR) clonality levels in peripheral blood and (when available) biopsied lesions.
- Changes in the tumor microenvironment (injected and, whenever available, non-injected tumor biopsies) via expression of selected candidate immune markers: [redacted]
- For Arms A, B, and C: changes in the levels of peripheral blood cytokines ([redacted]
- Peripheral blood phenotyping of selected immune cell markers.

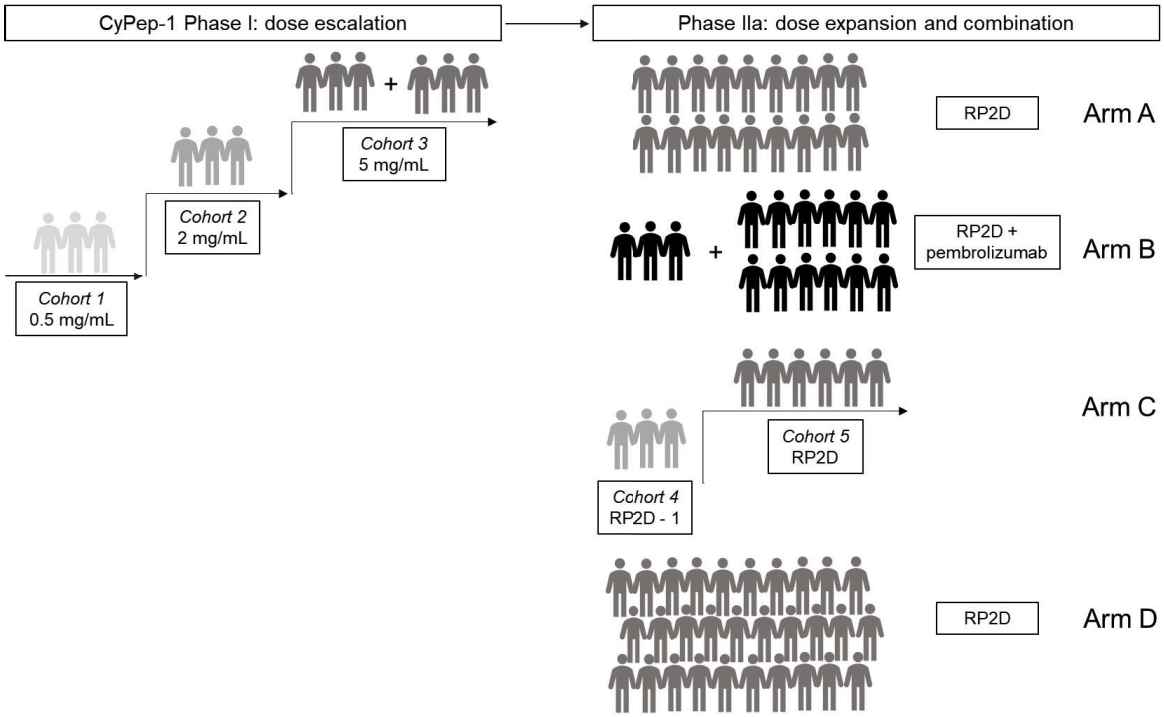
*itRECIST will be programmatically calculated using data obtained from iRECIST assessments following the itRECIST principle summarized in Clinical Study Protocol Appendix F Figure 1.

6 Study Methods

6.1 General Study Design

This is a combined Phase I/IIa, open-label, dose escalation followed by dose expansion trial in subjects with advanced solid cancers. The trial consists of two phases and multiple arms, as shown in the diagram below (Figure 1).

Figure 1. Schematic trial design of Phase I (dose escalation, N=12) and Phase IIa (dose expansion Arm A, N=9 up to 18; combination Arm B, N=15; dose expansion liver metastases Arm C, N=9; and dose expansion melanoma Arm D, N=30)[1]



For both phases and all trial arms, subjects will stay in the trial until end of trial or until confirmed disease progression, unacceptable toxicity, death or discontinuation for any other reason.

Phase I – dose escalation:

In this phase of the trial, safety and tolerability will be documented and the MTD/RP2D will be determined. Cohorts of 3 subjects will receive IT injections with CyPep-1. The DLT observation period for each dose level will be 6 weeks (5 weeks of trial treatment and 1 week of safety follow-up).

Screening will occur during the 4 weeks prior to start of CyPep-1 treatment.

In three dose cohorts of 3 subjects each, subjects will receive CyPep-1 IT at different concentrations (dose escalation) and volumes (depending on tumor size), i.e., 0.5 mg/mL, 2 mg/mL, or 5 mg/mL, respectively. These dose concentrations have been selected based on previous pre-clinical experience with CyPep-1.

Each subject will receive IT injection(s) with CyPep-1 on Day 1 of Weeks 1, 3, and 5, respectively. After each CyPep-1 administration, subjects will be required to stay at the clinic for at least 4 hours for safety and, for those in which PK will be assessed, also for PK monitoring. The data from the additional three subjects in cohort 3 will be used for further confirmation of RP2D. The following CyPep-1 administrations are planned as continuous Q2W administrations.

For each dose cohort, at least 24 hours must elapse between each subject to start treatment with CyPep-1. No intra-subject dose escalation is allowed.

[1] Note: as per sponsor confirmation letter from 14Apr2023, recruitment in Arm D was stopped after recruiting one subject due to recruitment difficulties. This SAP presents information regarding Arm D as presented in protocol v10.0/v10.1 (pre-dating the information letter).

The decisions on dose escalation and MTD will be taken by the Dose Escalation Committee (DEC) after reviewing safety data (including DLTs) from all subjects who have entered the previous dose cohort and have completed the DLT observation period. The DEC is comprised of all the investigators or designees, as well as the medical monitor and representatives of the sponsor.

In Phase I, subject replacement for subjects who drop out for any reason, except DLTs, will only occur before the DLT observation period is completed and is allowed if a subject does not receive all three CyPep-1 administrations, unless due to CyPep-1-related toxicity. No subject replacement will occur for subjects who withdraw later.

After completion of Phase I, all results will be evaluated by the DEC. This will include safety data and if available, other supportive clinical data (i.e., efficacy, pharmacokinetics, tumor biopsy analyses) from all subjects included in Phase I of the trial. The DEC will confirm the MTD or RP2D (in case the MTD is not reached).

All additional arms can start once Phase I data has been evaluated by the DEC and an RP2D is determined for CyPep-1.

Phase I has been completed in August 2021 and the RP2D of CyPep-1 was determined at 5 mg/mL.

Phase IIa – dose expansion (Arm A):

In this phase, safety and tolerability will be further evaluated in an expanded cohort of 9 subjects at the RP2D of CyPep-1, determined in Phase I. Screening- and treatment- schedules will be the same as in Phase I, except for the 24-h observation period before start of treatment of the next subject, which is not applicable.

At the RP2D, in case of a responder per iRECIST or of 2 subjects with stable disease per iRECIST, the number of subjects will be expanded to a total of 18 (to evaluate overall data from a total of 24 subjects treated at RP2D for CyPep-1 monotherapy taking the 6 subjects from cohort 3 into account).

Replacement of subjects in the Phase IIa expansion monotherapy arms is not planned.

Phase IIa – Combination arm (Arm B):

The safety and tolerability of CyPep-1 in combination with pembrolizumab will be evaluated in a cohort of 15 subjects in total, using a staggered approach. Initially, 3 subjects will receive CyPep-1 at RP2D in combination with pembrolizumab Q6W and each subject will be observed for 24 h before the next subject can be administered with CyPep-1. After the first 3 subjects completed the TLT observation period of 6 weeks with no TLTs observed and after reviewing the safety data (including TLTs) by the DEC, the inclusion of all remaining subjects at RP2D of CyPep-1 in combination with pembrolizumab can be initiated. In the absence of any TLTs in the initial 3 subjects, the 24-h observation period before start of treatment of the next subject is no longer applicable. Should any TLTs be observed in the first 3 subjects at the RP2D of CyPep-1 in combination with pembrolizumab, an additional 3 subjects in this dose group will be included. If ≤1 out of 6 subjects have a TLT, the remainder of the 15 subjects will be treated at the RP2D. In the unlikely case that 2 or more of the 6 subjects experience any TLTs at RP2D of CyPep-1, a recommendation to dose de-escalate CyPep-1 and to what dose or to continue the combination part of the trial will be made by the DEC. The same screening schedule is planned and CyPep-1 will be administered according to the same treatment schedule as in Phase I.

For arm B, replacement of the first three subjects is allowed if a subject drops out for any reason and does not receive all three CyPep-1 injections during the TLT observation period, unless due to CyPep-1- and/or pembrolizumab-related toxicity. No subject replacement will occur for subjects who discontinue later.

Phase IIa – dose expansion liver metastases (Arm C):

The safety and tolerability of at least two dose levels of CyPep-1, the RP2D and the dose immediately below that, are planned to be evaluated when CyPep-1 is administered intratumorally using ultrasound guidance to one metastatic lesion in the liver. The two dose levels are planned to be investigated adhering to the “3+3” design and will follow the procedures as described for the dose escalation (Phase I). The first three subjects will receive CyPep-1 at the lower dose level and each subject will be observed for 24 h before CyPep-1 administration to a next subject (cohort 4). After the third subject at that dose finished the DLT observation period of 6 weeks (5 weeks CyPep-1 treatment plus 1 week safety follow-up), the DEC will recommend on the start of the cohort to be administered at RP2D based on the review of the safety data (cohort 5). After the DLT observation period for the first three subjects at RP2D for CyPep-1 and the review of all safety data, the DEC will recommend on the inclusion of all remaining subjects. In the absence of any DLTs in the first 3 subjects, the 24-h observation period before start treatment of the next subject is not applicable. Should a DLT be observed in the first three subjects at the RP2D of CyPep-1, an additional three subjects in this dose group will be included. In case that two or more

subjects experience DLTs at RP2D of CyPep-1, a decision to dose de-escalate and to what dose and how to continue Arm C will be made by the DEC.

For Arm C, replacement for subjects who drop out for any reason, except DLTs, before the DLT observation period is completed is allowed when a subject did not receive all three CyPep-1 administrations. No subject replacement will occur for subjects who discontinue later.

Phase IIa – (Arm D): (see footnote 1 for details on stopping Arm D)

The safety and tolerability of CyPep-1 at RP2D will be further evaluated with focus on assessing efficacy signals of CyPep-1 monotherapy in up to 30 subjects with melanoma. Although safety information will be collected, there will not be a formal DLT observation period.

As part of the continuous safety monitoring of the trial, reports with cumulative safety data of Arm D subjects will be shared with all investigators, competent authorities, and ethical committees of countries where the trial is conducted at the following time points:

- After the first three subjects completed three weeks of treatment with CyPep-1.
- After the first three, six, and 12 subjects completed six weeks of treatment with CyPep-1.

In the occurrence of AEs fulfilling DLT criteria or other safety alters, the DEC will convene to review the safety data and provide recommendations on the continuation of dosing.

Replacement of subjects who dropped out before V8 (at week 8) due to any reasons other than CyPep-1 toxicity is allowed. No subject replacement will occur for subjects who withdraw later than V8.

6.2 Inclusion – Exclusion Criteria

Inclusion criteria are described in Clinical Study Protocol section 4.1. Exclusion criteria are described in Clinical Study Protocol section 4.2.

Note that inclusion criteria differ between protocol v10.1 (applicable for France) and v10.0 (applicable for other countries).

6.3 Sample size calculation

This is a proof-of-concept trial and the number of subjects chosen is based on clinical considerations and not on a formal statistical power calculation.

The exact number will be dependent on the number of dose cohorts investigated and the number of subjects enrolled in each dose cohort in Phase I (dose escalation), based on the toxicity encountered.

Phase I (dose escalation): it is anticipated that 12 subjects will be included in this phase of the trial (Figure 1) at 3 dose levels, with the last dose level including three additional subjects for further confirmation of RP2D.

Phase IIa (dose expansion Arm A): it is planned that 9 subjects will be enrolled in this phase of the trial for further evaluation of CyPep-1 in monotherapy arm (Figure 1).

Formal assessment of response will be based on the first 12 evaluable subjects as follows: in case of no responders in 12 subjects, the likelihood of a 20% ORR is 6.9%; in case of one responder in 12 subjects, the likelihood of a 20% ORR is 26.5%. Assuming stable disease to occur in 30% of subjects, in case no subject has stable disease in the first 12 evaluated subjects, the likelihood is 1.4%; in case one subject has stable disease in the first 12 evaluated subjects, this becomes 8.5%, while with two subjects having stable disease, this becomes 25.2%. Therefore, in case of either one of 12 subjects having an objective response or two of 12 subjects having stable disease, the number of subjects in Arm A may be increased to a total of 24 subjects (meaning 18 subjects in Arm A; based on the total number of subjects at RP2D during dose escalation plus the number of subjects at RP2D in Arm A). In case these outcomes are not observed, Arm A will enroll the planned 9 subjects.

In the current trial, the ORR assessment is based on sum of diameter of all target lesions and SD decision is based on the duration >16 weeks of SD from onset.

Phase IIa (combination Arm B): the safety and tolerability of CyPep-1 in combination with pembrolizumab will be evaluated in an arm of 15 subjects in total (Figure 1).

Phase IIa (liver metastasis, Arm C): for Arm C, a total of 9 subjects are planned to be enrolled to evaluate at least two dose levels of CyPep-1 based on results of Phase I.

Phase IIa (dose expansion melanoma, Arm D): the sample size for Phase IIa Arm D is based on a desired precision by which preliminary clinical efficacy (ORR for injected lesions) may be evaluated. Using 90% 1-sided

Clopper-Pearson exact confidence intervals, lower bounds identified in Table 6 of Clinical Study Protocol would apply.

For example, the lower bound for an observed ORR of 13.3% when there are 4 responders would be higher than 5% (i.e., 5.9%); the lower bound if 6 responders are observed would be 10.9%, which is greater than 10%, allowing for a sufficient sample to review preliminary effectiveness of CyPep-1 monotherapy for Arm D subjects.

6.4 Randomization

This is an open-label non-randomized trial; blinding and randomization are not applicable.

6.5 Schedule of Assessments

See Clinical Study Protocol Tables 1a to 1e for schedule of assessments.

7 General Consideration

7.1 Timing of Analysis

Mid-Study Analysis

Mid-study analysis was carried out in summer 2023. For mid-study analysis, hard database lock was not required; therefore, data was not completely clean for that analysis. Mid-study analysis included all study data collected up to the relevant cut-off date.

No other mid-study analyses are foreseen.

Final Analysis

For reporting purposes, analyses may be performed once the primary and key secondary endpoints are mature or the study is terminated by the sponsor.

A Data Review Meeting will be held before the database hard lock. Protocol deviations will be reviewed during the Data Review Meeting. Furthermore, assignment of subjects to the analysis sets will be performed. All decisions taken at the Data Review Meeting will be documented.

The final analysis will be performed after database lock, and after the finalization and approval of this SAP document.

Follow-up Analysis of Post-Trial Survival Data

Survival data will be analyzed post-treatment end as described in Clinical Study Protocol Section 8.1.4 and presented as addendum(s) to the final trial report. Time-point(s) for analysis will be confirmed when considered justified by Cytovation and the investigator(s).

7.2 Analysis Sets

The analysis sets are defined as follows:

7.2.1 All Screened Set (SCR)

All subjects who were screened for the study and signed informed consent. This analysis set will be used for subject disposition table and for creation of listings.

7.2.2 Safety Analysis Set (SAF)

All subjects who received at least one dose of trial drug (CyPep-1 or pembrolizumab in the combination arm). All analyses (except for PK) will be based on this analysis set.

7.2.3 CyPep-1 PK Analysis Set (PKS)

The first 9 subjects of Phase I, all subjects of Phase IIa Arm C, and the first 12 subjects of Phase IIa Arm D who received at least one dose of CyPep-1, have no clinically important protocol deviations or important events considered affecting PK, and have provided at least one evaluable pre-dose and post-dose PK blood sample will be included in the PKS. All PK analyses will be based on this analysis set.

Note: as per decision to stop recruitment in Arm D (described above), PKS will only include one subject from Arm D.

7.3 Dose Escalation Committee

The decisions on dose escalation and CyPep-1 MTD/RP2D will be taken by the Dose Escalation Committee after reviewing safety data (including DLTs) from all subjects who have entered Phase I of the trial and have completed the DLT observation period.

The DEC will review all data after all subjects in the highest dose cohort completed DLT observation period and before enrolment of subjects in the expansion cohort at RP2D in monotherapy and combination with pembrolizumab cohort can be initiated.

For Phase IIa of the trial, the decision to de-escalate the dose of CyPep-1 based on observed severity and relatedness of safety events (DLT/TLT criteria for CyPep-1) and to what dose (either dose level of the next lowest dose level from Phase I or 50-70% of current dose level), will also be made by the DEC after reviewing available safety data (including TLTs). Dose modifications for pembrolizumab in the combination arm will also be taken into consideration.

Based on the review of this data, recommendations will be made regarding the further conduct and the scientific and ethical integrity of the trial.

At the end of the DEC teleconference, the DEC will provide one of the following recommendations to the sponsor:

1. The trial is proceeding in line with the trial protocol.
2. The trial is not proceeding in line with the trial protocol and/or there is a possible change in the benefit/risk ratio.

The sponsor will act upon these recommendations as appropriate, i.e., the final decision will rest with the sponsor. The sponsor designee will notify the trial team (i.e., the responsible project manager at [redacted]) of the final decision regarding the DEC recommendations, including any actions to be taken. The [redacted] project manager will communicate the DEC recommendations and/or final decision of the sponsor to all investigators, Independent Ethics Committees (IECs) and Competent Authorities (CAs), if applicable.

DEC analyses are described in the *Cohort Management Plan* and are not in scope for this SAP.

7.4 Multi-Centre Studies

This study has approximately 14 sites in 3 countries (France, Spain, and The Netherlands). No by-country summaries will be created; data will be presented in a pooled fashion.

8 General Data Handling Considerations

8.1 Assigned and Actual Treatment

Subjects are assigned to a cohort based on the text and schematic provided in Section 6.1. All analyses will be conducted on the of cohort/arm subjects were assigned to.

8.2 Baseline definition

Baseline value for all assessments will be defined as the last non-missing value recorded prior to the treatment start date(time) (as defined in Section 8.3 below).

8.3 Reference Dates

The following reference dates are defined:

1. **Screening date** is defined as the eCRF provided date on which a subject was screened for trial entry. If screening procedures took several days, the first of these days is considered as screening date.
2. **Informed consent date** is defined as the date of Informed Consent signed by the subject collected on Informed Consent eCRF page.
3. **Treatment start date(time)** is defined as the date(time) of first dose of any study drug (Cy-Pep1 or pembrolizumab). **CyPep-1 treatment start date(time)** is defined as the date(time) of first dose of CyPep-1. **Pembrolizumab treatment start date(time)** is defined as the date(time) of first infusion of pembrolizumab.
4. **Treatment end date(time)** is defined as the date(time) of last dose of any study drug (Cy-Pep1 or pembrolizumab). **CyPep-1 treatment end date(time)** is defined as the date(time) of last dose of CyPep-1. **Pembrolizumab treatment end date(time)** is defined as the end date(time) of last infusion of pembrolizumab.
5. **End of study date** is defined as Date of study completion/discontinuation recorded on the End of Study Form in the eCRF.

6. Age will not be calculated and will come directly from the eCRF. The eCRF uses the demographics assessment date at Screening as its reference date for age calculation.
7. Safety data, such as AEs and laboratory assessments, will use the treatment start date as a reference date.
8. Efficacy data will use the treatment start date as a reference date.
9. **Study day** will be based on treatment start date as a reference date.

8.4 Relative Day (Study Day and Duration Variables)

Reference date calculations will generally be defined as the following, assuming non-missing dates:

> *Date of interest – reference date* + 1 when the *date of interest* >= *reference date*;
> Otherwise, *date of interest – reference date*.

Study day will either have a negative value if collected before dosing or a positive value if collected on or after the day of drug dosing; there will be no study day zero. In some cases, dates will be imputed (see Section 8.7) and reference date calculations performed on the imputed dates. If either date is missing (after imputation), reference date calculations will not be performed. In listings, only relative days calculated based on non-imputed dates will be presented.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculations.

Duration on study (months) is defined as:

> (*End of study date – informed consent date* + 1) / 30.4375.

Duration of treatment (months) is defined as:

> (*Treatment end date – treatment start date* + 1) / 30.4375.

Subjects still receiving ongoing treatment or participating in study follow-up at the time of analysis will use imputed end of treatment and end of study dates (see Section 8.7 for details). Duration of treatment will be calculated separately for CyPep-1 and pembrolizumab based on start and end dates of CyPep-1 and pembrolizumab, respectively.

Survival and time-to-event endpoints (e.g., PFS, OS) are followed until the first event or censoring. As a result, survival and time-to-event time (days) will be calculated as:

> *Event or censoring date – reference date* + 1.

When reporting time-to-event data or duration outcomes, the results (in days) above will be converted to an appropriate unit. When reporting in months, it will be divided by 30.4375; for reporting in weeks it will be divided by 7; and for reporting in years it will be divided by 365.25.

8.5 Study Time Periods

Where applicable, data reporting will be classified by the following study periods for analysis:

1. **Pre-treatment** is defined as the period prior to a subject's treatment start date(time). Assessments done on treatment start date before treatment start per protocol, but where assessment start time is not collected on eCRF, are considered to occur pre-treatment; this is applicable for physical examination and ECOG assessments.
2. **On-treatment** is defined as the period between a subject's treatment start date(time) and End of Treatment visit date (both date(time)s inclusive). In case EoT visit does not occur due to death, withdrawal of consent or loss to follow-up, subject's end of on-treatment period is considered to occur at date of death, date of withdrawal of consent or date lost to follow-up, respectively.
3. **Post-treatment** is defined as the period following the on-treatment period.

8.6 Baseline and Post-Baseline Changes

Unless stated otherwise, baseline and post-baseline change values will be based on the Table 2 below.

Table 2. Baseline and Post-Baseline Changes

Variable	Definition
Baseline value	Baseline definition is provided in Section 8.2.
Post-baseline value	Values collected after the treatment start date(time).

Variable	Definition
Change from baseline	*Post-baseline value – baseline value*.
Percentage change from baseline	(*Post-baseline value – baseline value*) / *baseline value* x 100. If baseline value is equal to 0, percent change from baseline will be missing.
Most extreme change	The maximum most extreme change will be based on the maximum post-baseline value. The minimum most extreme change will be based on the smallest post-baseline value. This calculation will consider all assessments collected during the on-treatment period, scheduled or unscheduled
Maximum reduction from baseline	The maximum reduction from baseline will be based on the minimum post-baseline value collected and calculated per the change from baseline formula above. Maximum reduction from baseline will only be calculated for tumor measurements. Post-baseline values will be considered until an overall response of iCPD or start of new anticancer treatment.
Maximum percentage reduction from baseline	The maximum percentage reduction will be the percentage change from baseline for the maximum reduction from baseline.

8.7 Handling of Partial Dates

APPENDIX 1. PARTIAL DATE **CONVENTIONS** details partial date conventions for adverse events, medications and procedures.

Overall Response Date

For each visit-specific disease assessment, the date of overall response will be established. For complete response (iCR, itCR), partial response (iPR, itPR), and stable disease (iSD, itSD), the date of overall response will be set to the latest of all tumor assessments for the specified visit. Otherwise, the date of overall response will be set to the earliest date of all assessments made during the specified visit when iUPD/itUPD/iCPD/ItCPD is determined.

Treatment End Date

Missing treatment end dates will not necessarily be imputed at the end of the study. However, due to ongoing reporting needs, treatment end date will be imputed as the earliest of the data cutoff date, date of death, or last treatment date recorded on the exposure eCRF.

End of Study Date

Missing study end dates will not necessarily be imputed at the end of the study. However, due to ongoing reporting needs, end of study dates will be imputed as the earliest of the data cutoff date, date of death, or last date recorded on the eCRF.

8.8 Lost to Follow-up or Lapse of Adequate Assessments

Censoring for efficacy endpoints will take into account if a subject has missed two or more scheduled disease assessments prior to iCPD or death. Based on a protocol specified disease assessment schedule of every 8 weeks, a lapse window of 112 days (16 weeks, +/- 1 week window) will be used to determine if a subject has missed two or more scheduled disease assessments.

DOR and TTR analyses will be censored at the last adequate disease assessment prior to the lapse window.

8.9 Multiple Assessments and Visit Windows

Nominal visits (i.e., those identified by the study eCRF) will be the basis of summarization and statistical analysis; no visit date windowing will be conducted. Unscheduled data may be included in summaries of most extreme and baseline; summaries of specific abnormalities any time post-baseline; summaries of tumor/response assessment data; and subject data listings.

For visit-based summaries, visit alignment (as described in APPENDIX 4. VISIT **ALIGNEMENT**) will be used where appropriate to facilitate efficient reporting of data for arms with different visit schedules. Footnotes about visit alignment will be added to affected outputs. Visit alignment will only be used for tables; listings will present original (protocol planned) visit names.

8.10 Ordering and Grouping

Listings (subject-based study data) will be ordered by study phase, cohort/arm, subject ID followed by date and/or time of an event or assessment. When category and subcategory apply, data will be ordered by study phase, cohort/arm, subject ID, followed by the category or subcategory alphabetically or as indicated in the footnote of the listings followed by date and/or time of an event or assessment. All data collected in the eCRF will be presented, including screening failure data (non-mandatory data entered for screening failures doesn't need to be source-data verified (SDVd); such non-SDVd screening failure data will not be included in outputs; however, this data will be included in derived datasets[2]). Screening failures will be presented last.

Cohorts will be displayed with the following columns:

- Phase I:
  - Cohort 1: CyPep-1 0.5 mg/mL
  - Cohort 2: CyPep-1 2.0 mg/mL
  - Cohort 3: CyPep-1 5.0 mg/mL
  - Total: Phase I
- Phase IIa:
  - Arm A: CyPep-1 5.0 mg/mL Monotherapy
  - Arm B: CyPep-1 5.0 mg/mL + IV Pembrolizumab
  - Arm C, Cohort 4: CyPep-1 2.0 mg/mL for liver metastases
  - Arm C, Cohort 5: CyPep-1 5.0 mg/mL for liver metastases
  - Arm D: CyPep-1 5.0 mg/mL for melanoma
  - Total: Phase IIa
- Phase I + IIa:
  - Cohort 3: CyPep-1 5.0 mg/mL + Arm A: CyPep-1 5.0 mg/mL Monotherapy
  - Total: Phase I + IIa

Phase I + IIa columns will only be presented in select tables.

See the mock shells for additional details and a visual representation of the cohort display.

8.11 Handling of Values Below or Above the Limits of Detection or Quantification

Values recorded as below the Lower Limit of Quantification (<LLOQ) will be imputed to half of the Lower Limit of Quantification value (LLOQ/2) for the calculation of summary statistics.

Values recorded as above the Upper Limit of Quantification (>ULOQ) will be imputed to 1.1 times the Upper Limit of Quantification value (ULOQ*1.1) for the calculation of summary statistics.

Values including any characters which represent missing results (e.g. 'UNK') will be imputed to missing.

8.12 Handling of Outliers

All measured values will be included in the analyses.

8.13 Censoring Rules

Censoring rules for DOR and PFS are provided in APPENDIX 2. CENSORING RULES: DOR and **PFS** and censoring rules for duration of stable disease are provided in APPENDIX 3. CENSORING RULES: DURATION OF STABLE **DISEASE**. Simpler censoring rules are described in respective endpoint sections.

8.14 Descriptive Statistics

All data collected in this trial will be documented with the help of subject data listings, summary tables, and figures. All individual subject data will be listed.

For continuous parameters, descriptive statistics will be presented when $n \geq 2$. Descriptive statistics will include the number of non-missing data points (n), mean, standard deviation (SD), median, minimum (MIN) and maximum (MAX). When appropriate, coefficient of variation (CV) or CV%, geometric mean, 95% confidence interval (CI) of the mean will be presented. In case $n < 2$, only the n count will be presented for continuous variables.

[2] Note: at the time of writing this SAP, the only non-SDVd screening failure data collected was death report data from 6 screening failures. For the purpose of excluding non-SDVd death information from listings, the analysis set of deaths listing will be changed to Safety Analysis Set.

For the estimates of the median with 95% CI, the Kaplan-Meier survival method, providing survival descriptive and curves, will be used. The Brookmeyer and Crowley method will be used for CI calculation (Brookmeyer, Crowley, 1982). When the median may not be reached, this will be stated in the output, and if possible, the 25% estimates will be calculated instead.

Raw data will be presented with the number of decimal places as collected, and derived data will be presented with an appropriate number of decimal places. For summary statistics, mean, median, SD, CV, CV% and geometric mean will be reported with one decimal place greater than the raw/derived data. MIN and MAX values will be reported with the same number of decimal places as the raw/derived data.

For categorical variables, descriptive statistics will include the number of non-missing data points (n) and the frequency in percentage (%) with one decimal precision. When the absolute frequency is zero, the percentage is not presented. When the frequency is hundred, no decimal will be presented.

In case cohort/arm has no subjects at time of reporting, the cohort/arm will be omitted from output; in case cohort/arm has one subject at time of reporting, cohort/arm will be included in outputs, with display as described above.

8.15 Calculation of Percentages

All percentages will be calculated against the total number of subjects in the population with non-missing observations at the specific timepoint, unless otherwise noted in table footnotes.

8.16 Shift Tables

Worst-case abnormality tables for categorical data will report shifts from baseline to worst-case post-baseline value, categorized as normal, abnormal (not clinically significant) and abnormal (clinically significant).

Worst-case CTCAE grade tables will report shift from baseline to worst-case post-baseline values, categorized by toxicity grade ranging from 0 to 4. Changes in both directions (increase and decrease of a value) are accounted for in the programmatic derivation of CTCAE grades; the tables will include the worst grade in both directions (separately) for bi-directional variables.

8.17 Software

All outputs will be produced using SAS® version 9.4, SAS Institute Inc., Cary, NC, USA or higher. Statistical analyses will be performed in accordance with the International Conference for Harmonization (ICH) E9 Statistical Principals for Clinical Trials.

8.18 CDISC Version

SDTM datasets will be based on SDTMIG version 3.2, ADaM datasets will be based on ADaMIG version 1.2 and define XML will be based on define XML version 2.1.

9 Study Subject Data

9.1 Disposition of Subjects

Subject disposition data will be summarized (frequency and percentage of subjects) for the SCR by cohort/arm and overall. Disposition summaries will include the following:

1. The number of screened subjects,
2. The number of screening failures,
3. The number of subjects in each analysis set,
4. The number of subjects ongoing in study,
5. The number of subjects reached end of study,
6. Reason for end of study[3]; was end of study related to COVID-19,
7. The number of subjects who discontinued treatment (reason for discontinuation; was treatment discontinuation related to COVID-19).

CONSORT diagram of disposition data (number of screened, screening failures, allocated to each treatment arm, receiving both study treatments, ended the study [and reason why], belonging to each analysis set and excluded from each analysis set) will be created for the SCR.

[3] Note: on the “End of Study” eCRF page, “Primary reason for study discontinuation” is collected for subjects who “Discontinued Early”. However, in tables, listings and figures “Reason for End of Study” will be presented instead, as early discontinuation is not a proper term for subjects who ended the study per protocol (e.g., due to disease progression).

A listing of subject disposition data including reason for end of study and treatment discontinuation, if applicable, will be presented for all subjects.

A listing of inclusion criteria not met and exclusion criteria met will additionally be created for all subjects.

A listing of analysis sets and reasons for exclusion of subjects from analysis sets will additionally be created for all subjects.

9.2 Protocol Deviations

Protocol deviations will be classified (minor/major) by the Medical Monitor before the study database is locked. The decisions on classification will be documented and used for excluding subjects from PKS, as applicable.

Minor and major protocol deviations will be summarized by deviation category (see below) and cohort/arm for the SAF. The deviation categories include:

1. Eligibility criteria (only applicable for Phase IIa),
2. Subject eligibility (only applicable for Phase I),
3. Informed consent,
4. Study intervention (only applicable for Phase IIa),
5. Trial medication/IMP (only applicable for Phase I),
6. Concomitant medication,
7. Study procedures (only applicable for Phase IIa),
8. Missed visit/assessment (only applicable for Phase I),
9. Visit/assessment out of window,
10. Safety,
11. Biological sample handling,
12. Source documents/CRF,
13. Other.

A listing of protocol deviations (including minor/major classification) will be provided for all subjects.

9.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized by cohort/arm and overall for the SAF, and PKS.

These data will include age (years), gender (Male / Female), childbearing potential (Yes / No), baseline height (cm), baseline weight (kg), baseline BMI (kg/m^2), and country. Age is reported as collected in the clinical database from informed consent. Demographics and baseline characteristics will be listed for all subjects.

Disease history and characteristics at baseline will be summarized by cohort and overall for the SAF. These will include: baseline Eastern Cooperative Oncology Group (ECOG); tumor, node, metastasis (TNM) stage at initial diagnosis; time since diagnosis at screening; stage at initial diagnosis; grade at initial diagnosis; progression, recurrence and/or metastasis observed after primary diagnosis (Yes / No); time since progression, recurrence, metastasis (years); specification of progression, recurrence, metastasis; location of progression, recurrence, metastasis. Primary location of cancer and histological type are collected as free text variables (not coded) and therefore only listed.

Time since diagnosis at screening is defined as:

(*Date of screening – date of diagnosis*) / 365.25, if both dates known,

(*Year of screening* + *month of screening* / 12) – (*Year of diagnosis* + *month of diagnosis* / 12), if day is missing for either of the dates,

Year of screening – Year of diagnosis, if month is missing for either of the dates.

If year is missing for either of the dates, time since diagnosis will be missing.

Time since progression, recurrence, metastasis at screening is calculated analogously to time since diagnosis.

Baseline lesion status will be summarized by cohort/arm and overall for the SAF. The following variables will be included on the summary table: presence of target lesions (Yes / No), number of target lesions identified (0, 1, 2, 3, 4, 5), sum of target lesion diameters (mm), location of target lesions, presence of non-target lesions (Yes / No), number of non-target lesions identified (0, 1, 2, 3, 4, 5, >5), location of non-target lesions, number of lesions targeted for injection at Day 1 (1, 2, 3), location of lesions targeted for injection at Day 1 (Head / Face / Neck / Arm / Hand / Chest / Back / Abdomen / Leg / Foot / Other).

Cancer diagnosis data will be listed for all subjects. Tumor lesion data will be presented in separate listings per type of lesion (Target, Non-Target).

In addition to the above, Royal Marsden Hospital prognostic score (RMH score) and Gustave Roussy immune score (GRIm-score) at baseline will be derived and summarized (frequencies, percentages) by cohort/arm and overall for the SAF. Components of each score at baseline will be included in the same table. RMH score and GRIm-score will be listed for SAF.

RMH score will be graded as described in Table 3 below.

Table 3. Royal Marsden Hospital Prognostic Score Scoring Algorithm

Component	Criteria	Score
Lactate Dehydrogenase	Within normal range	0
	> ULN	1
Serum Albumin	≥ 3.5 g/dL	0
	< 3.5 g/dL	1
Sites of Metastasis	0 - 2	0
	3 or more	1

RMH prognostic score will be calculated as sum of component scores. In case one or more components are missing at baseline, RMH prognostic score will also be missing at baseline.

GRIm-score will be graded as described in Table 4 below.

Table 4. Gustave Roussy Immune Score Scoring Algorithm

Component	Criteria	Score
Lactate Dehydrogenase	Within normal range	0
	> ULN	1
Serum Albumin	≥ 3.5 g/dL	0
	< 3.5 g/dL	1
Neutrophil-to-Lymphocyte Ratio	≤ 6	0
	> 6	1

GRIm-score will be calculated as sum of component scores. In case one or more components are missing at baseline, GRIm-score will also be missing at baseline.

9.4 Medical History and Procedures Prior, Concomitant and Subsequent to Study Treatment

9.4.1 Medical history

Medical history (MH) records will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version specified in the *Data Management Plan*).

The summary statistics will be presented as number of subjects (n) and frequency (%) in each system organ class (SOC) and preferred term (PT). SOCs are sorted by the internationally agreed SOC order and PTs by descending overall frequency within each SOC. MH will be presented by cohort/arm and overall for the SAF.

Medical history will also be presented in data listings for all subjects.

9.4.2 Procedures Prior, Concomitant and Subsequent to Study Treatment

Procedures prior to study treatment are those which have been identified to end prior to the treatment start date(time). Procedures concomitant to study treatment are those which have been applied at any point during the period from treatment start date(time) until treatment end date(time) (both inclusive). Procedures subsequent to study treatment are those which have been identified to start after the treatment end date(time). Partial dates will be imputed according to APPENDIX 1. PARTIAL DATE **CONVENTIONS** for the determination of procedures prior, concomitant and subsequent to study treatment.

Procedures prior, concomitant and subsequent to study treatment will be coded and summarized in the same way as medical history.

9.4.3 Anticancer Procedures Prior, Concomitant and Subsequent to Study Treatment

Anticancer procedures prior to study treatment are those collected at the *Primary Cancer – Previous Therapy – Procedures* eCRF page. Anticancer procedures prior to study treatment will be coded and summarized in the same way as prior procedures.

Additionally, a summary table of anticancer procedures prior to study treatment will be created. The variables to be summarized will include: type of previous cancer procedure (Radiation Therapy / Surgery / Other), treatment intent (Curative / Palliative / Preventative / Unknown), treatment setting (Adjuvant / Locally advanced / Metastatic / Neo-adjuvant / Preventative / Unknown), best response (Complete Response / Partial Response / Stable Disease / Progressive Disease / Not Evaluable / Minimal Response / Symptom Relief / Unknown).

Anticancer procedures concomitant to study treatment are those which have been applied at any point during the period from treatment start date(time) until treatment end date(time) (both inclusive). Anticancer procedures subsequent to study treatment are those which have been identified to start after the treatment end date(time). Anticancer procedures concomitant and subsequent to study treatment are entered on the same eCRF pages as other (not anticancer) procedures but identified with *New anti-cancer therapy* variable checked. Anticancer procedures concomitant and subsequent to study treatment will be coded, but only included in listings. Date of response and date of progression will only be listed for anticancer procedures concomitant and subsequent to study treatment.

9.5 Medication Prior, Concomitant and Subsequent to Study Treatment

9.5.1 Medications Prior, Concomitant and Subsequent to Study Treatment

Medications prior, concomitant and subsequent to study treatment will be coded using the World Health Organization (WHO) Drug Dictionary (format and version specified in the *Data Management Plan*).

Medications prior to study treatment are those which have been identified to have been discontinued prior to the treatment start date(time). Medications concomitant to study treatment are those which have been identified to have been taken at any point during the period from treatment start date(time) until treatment end date(time) (both inclusive), including medications which started prior to the treatment start date(time) but are ongoing at first dose. Medications subsequent to study treatment are those which have been identified to have been started after the treatment end date(time). Partial dates will be imputed according to APPENDIX 1. PARTIAL DATE CONVENTIONS for the determination of medications prior, concomitant and subsequent to study treatment.

The incidence of use of medications prior, concomitant and subsequent to study treatment will be summarized by WHO Drug Dictionary Anatomic Therapeutic Chemical (ATC) Level 2 classification (i.e., therapeutic subgroup) and preferred name. A subject will be counted at most once at each level of reporting. Use of medications prior, concomitant and subsequent to study treatment will be summarized separately and presented by cohort/arm and overall for the SAF

All data of medications prior, concomitant and subsequent to study treatment will be provided together in a by-subject listing including the verbatim and preferred drug name and WHO ATC Class (ATC Level 2) for all subjects. Medications prior, concomitant and subsequent to study treatment will be flagged as such in the listing.

9.5.2 Anticancer Therapies Prior, Concomitant and Subsequent to Study Treatment

Anticancer therapies prior to study treatment are those collected on the *Primary Cancer – Previous Therapy – Medications* eCRF page. Anticancer therapies prior to study treatment will be coded and summarized in the same way as prior medications to study treatment.

Additionally, a summary table of anticancer therapies prior to study treatment will be created. The variables to be summarized will include: previous cancer medication (Chemotherapy / Immunotherapy / Other), treatment intent (Curative / Palliative / Preventative / Unknown), treatment setting (Adjuvant / Locally advanced / Metastatic / Neo-adjuvant / Preventative / Unknown), best response (Complete Response / Partial Response / Stable Disease / Progressive Disease / Not Evaluable / Minimal Response / Symptom Relief / Unknown). The number (%) of previous lines of anticancer therapy and number (%) of previous lines of immunotherapy will also be included in the summary table.

The number of previous lines of therapy will be derived as the maximum of (maximum value of *Line of treatment* variable in the *Primary Cancer – Previous Therapy – Medications* eCRF page, maximum value of *Line of treatment* variable in the *Primary Cancer – Previous Therapy – Procedures* eCRF page).

The number of previous lines of immunotherapy will be derived as the number of distinct values entered in the *Line of treatment* variable in the *Primary Cancer – Previous Therapy – Medications* eCRF page where *Immunotherapy* variable is ticked.

Anticancer therapies concomitant to study treatment are those which have been identified to have been taken at any point during the period from treatment start date(time) until treatment end date(time) (both inclusive), including therapies which started prior to the treatment start date(time) but are ongoing at first dose. Anticancer therapies subsequent to study treatment are those which have been identified to have been started after the treatment end date(time). Partial dates will be imputed according to APPENDIX 1. PARTIAL DATE **CONVENTIONS** for the determination of anticancer therapies prior, concomitant and subsequent to study treatment. Anticancer therapies concomitant and subsequent to study treatment are entered on the same eCRF pages as other (not anticancer) medications but identified with *New anti-cancer therapy* variable checked. Anticancer therapies concomitant and subsequent to study treatment will be coded, but only included in listings. Date of response and date of progression will only be listed for anticancer therapies concomitant and subsequent to study treatment.

9.5.3 Pre-medication

Pre-medication data (Paracetamol and antihistamine administration details) will be listed separately along with the verbatim and preferred drug name and WHO ATC Class (ATC Level 2) for all SAF subjects.

9.5.4 Prophylactic Hydration

Prophylactic hydration data will be listed for all SAF subjects.

9.6 Study Treatment Exposure and Compliance

Administration of intratumoral CyPep-1 and administration of IV pembrolizumab will be done in a hospitalized environment by trained trial personnel. Treatment compliance will be accomplished by documenting in record (i.e. the drug accountability, preparation, administration logs, the subjects' eCRF and medical records) information on, but not limited to: the batch number of CyPep-1 and of pembrolizumab used, the time point for preparation, the time point for administration, and signatures of designated site staff preparing and administering intratumoral CyPep-1 and pembrolizumab. Any deviations will be documented on the appropriate eCRF page.

9.6.1 CyPep-1

Exposure to and compliance with CyPep-1 will be summarized by cohort for the SAF by the following variables:

1. Number (%) of subjects exposed to CyPep-1 (overall and by cycle),
2. Number of CyPep-1 administrations (continuous variable),
3. Number (%) of subjects with one or more full dose of CyPep-1 not administered (overall and by cycle),
4. Number (%) of missed CyPep-1 administrations (overall; 0, 1, 2, 3, >3),
5. Number (%) of subjects with weekly CyPep-1 administration schedule during Cycle 1,
6. Average CyPep-1 dose per administration (continuous variable, see definition below),
7. Cumulative CyPep-1 dose (continuous variable, see definition below),
8. Average injected volume per administration (continuous variable, see definition below),
9. Cumulative injected volume (continuous variable, see definition below),
10. Number of injected lesions (overall; 1, 2, 3, 4, 5, >5),
11. Duration of treatment (continuous variable, defined in Section 8.4),
12. Number (%) of times CyPep-1 not administered according to study protocol (overall; 0,1,2,3,>3).

A subject is counted as having been exposed to CyPep-1 in a cycle if the subject received CyPep-1 in given cycle.

Subjects with weekly CyPep-1 administration schedule during Cycle 1 are defined as subjects that received the first two doses of CyPep-1 within a 1-week interval.

For each subject, injected volume of CyPep-1 will be calculated for each administration of CyPep-1 as sum of injected volumes over all injected lesions. The CyPep-1 dose (mg) will be calculated as CyPep-1 concentration (mg/mL) multiplied with the injected volume of CyPep-1 (mL) for each administration of CyPep-1. An average injected volume will be calculated for each subject as mean of injected volume results of all CyPep-1 administrations and average dose will be calculated as mean of CyPep-1 dose results of all CyPep-1 administrations.

The cumulative dose (mg) will be calculated as sum of all doses received throughout the study. Cumulative injected volume (mL) will be calculated as sum of all injected volumes throughout the study.

CyPep-1 exposure and compliance data will be listed for all SAF subjects.

Lesions targeted for injection (for all arms/cohorts) and lesion map information (for arm D only) will be listed for SAF.

9.6.2 Pembrolizumab

Exposure to and compliance with pembrolizumab will be summarized for combination arm B for the SAF by the following variables:

1. Number (%) of subjects exposed to pembrolizumab (overall and by cycle),
2. Number of pembrolizumab administrations (continuous variable),
3. Number (%) of subjects with one or more full dose of pembrolizumab not administered (overall and by cycle),
4. Number (%) of missed pembrolizumab administrations (overall; 0, 1, 2, 3, >3),
5. Average pembrolizumab dose per administration (continuous variable, see definition below),
6. Cumulative pembrolizumab dose (continuous variable, see definition below),
7. Duration of treatment (continuous variable, defined in Section 8.4),
8. Number (%) of times pembrolizumab infusion temporarily interrupted or flow rate modified (overall; 0,1,2,3,>3),
9. Number (%) of times entire volume of pembrolizumab not administered (overall; 0,1,2,3,>3)
10. Number (%) of times pembrolizumab not administered according to study protocol (overall; 0,1,2,3,>3).

A subject is counted as having been exposed to pembrolizumab in a cycle if the subject received pembrolizumab in given cycle.

An average dose of pembrolizumab will be calculated as mean of pembrolizumab doses of all pembrolizumab administrations.

The cumulative dose (mg) will be calculated as sum of all doses received throughout the study.

Pembrolizumab exposure and compliance data will be listed for all SAF subjects in Arm B, including pembrolizumab infusion interruptions and modifications.

10 Efficacy Analysis

Antitumor activity will be assessed as a component of secondary and exploratory endpoints for this study. Evaluation of antitumor response will be based on investigator assessment of timepoint tumor response following iRECIST (for secondary and exploratory endpoints) and programmatically derived itRECIST (for exploratory endpoints for all Phase IIa arms).

iRECIST assessments will be based on CT scan or, if not available, on MRI, photograph (caliper), or ultrasound measurements, in this hierarchical order. In case any other method of evaluation is used, handling of such cases will be discussed separately with the Sponsor and documented appropriately. For comparability, all within-subject measurements need to be performed using the same method; this will be programmatically checked and potential deviations handled on a case-by-case basis[4]. Local measurements data will not be used for iRECIST assessments.

Upon start of CyPep-1 treatment, subjects will be followed for PFS (every 8 weeks) and OS. PFS will be radiologically assessed at the trial sites until disease relapse or progression (based on all lesions), death due to any cause, withdrawal of consent, loss to follow-up, or until the end of the trial, whichever occurs first. A phone call for survival status (OS) will be done every 3 months after confirmation of PD and until the end of the trial.

In order to account for the possibly delayed onset of CyPep-1 action and for subjects who are of acceptable clinical performance status (as deemed by the investigator), if iUPD is recorded and provided that the tumor enlargement is smaller than 50% compared to the previous measurement, the subject will remain in the trial and will be reassessed radiologically after 4 weeks. All lesion(s) are to be evaluated for clinical progression:

- If the lesion(s) continue(s) to enlarge, the original iUPD will be considered as the “first documented iCPD” and there will be an End of Treatment (EoT) visit.
- If lesion(s) remain(s) unchanged or decrease(s) in size, assessments should continue as per protocol (i.e., the next radiological assessment will be performed after an 8-week interval). In this case, the first measured iUPD will be considered pseudo-progression.

[4] At the time of writing this SAP, two cases where not all measurements were done with the same method within subject exist: 1) for subject 02-003 most measurements were done by photograph, but non-target lesion 06 was always done by CT scan; 2) for subject 07-004 all measurements were done by CT scan except for new non-target lesion 01 which was done by MRI. These cases have no impact on sum of diameters, therefore, no additional analysis rules are needed at this point.

In case of iUPD after the first (or subsequent) 3 Q2W injections of CyPep1, the subject should continue Q2W administrations (start of another cycle of CyPep-1) until iCPD. If PD is confirmed 4 weeks later (iCPD), then the subject will be taken off-trial and moved to the EoT visit. In case iUPD is followed by another iUPD, iRECIST will be followed.

Efficacy analyses will be conducted using SAF.

10.1 Secondary Efficacy Analyses

10.1.1 ORR in All Lesions (iRECIST)

A subject's best overall response (BOR) is determined by the highest qualitative value assessed during the study given a hierarchy of overall response results: iCR > iPR > iSD > iUPD > iCPD > NE. Note that even though iUPD is presented before iCPD in iRECIST hierarchy, in case iCPD occurs, it always overwrites iUPD for BOR derivation. A BOR of iCR or iPR requires confirmation of response at least 28 days after the date of the initial response in this non-randomized study (as per RECIST 1.1). BOR will be based on assessments collected after the treatment start date until confirmed disease progression (iCPD) or start of new anticancer therapy, whichever occurs earlier. BOR will be summarized descriptively by cohort/arm (including, Cohort 3: CyPep-1 5.0 mg/mL + Arm A: CyPep-1 5.0 mg/mL Monotherapy) for the SAF.

Secondary efficacy outcome is the objective response rate in all lesions (injected and non-injected) based on iRECIST. ORR will be defined as the percentage of subjects with a BOR of iCR or iPR. The ORR will be summarized by cohort/arm (including, Cohort 3: CyPep-1 5.0 mg/mL + Arm A: CyPep-1 5.0 mg/mL Monotherapy) including 95% 2-sided Clopper-Pearson CIs.

A waterfall plot of maximum percentage reduction from baseline in target lesion sum of diameters (mm) by best overall response will be provided for the SAF. A spider plot of percent change from baseline in target lesion sum of diameter measurements by best overall response will also be provided for the SAF. Only post-baseline data until an overall response of iCPD or start of new anticancer therapy will be included in the figures. In case a lesion is NE at a certain timepoint, sum of diameters will not be presented for that timepoint (in line with RECIST 1.1 recommendation).

A swimmer plot of iRECIST response assessment results will also be created for SAF.

Response evaluation data (including lesions measured, sum of diameters, iRECIST evaluation, maximum reduction in target lesion sum of diameters) will be listed for SAF. BOR and objective response will be listed for SAF.

10.1.2 Duration of Response

DOR will be computed for SAF subjects with a confirmed overall response of iCR or iPR (as per iRECIST). DOR (in months) will be defined as:

(censoring date OR date of iUPD followed by confirmation or death – date of first response + 1) / 30.4375.

Event and censoring rules for DOR are detailed in APPENDIX 2. CENSORING RULES: DOR and **PFS**.

Kaplan-Meier estimates for DOR will be calculated for each cohort/arm (including, Total: Cohort 3: CyPep-1 5.0 mg/mL + Arm A: CyPep-1 5.0 mg/mL Monotherapy), and 75th, 50th and 25th percentiles presented, along with 95% confidence intervals. Number (%) of subjects with an event and number (%) censored will be reported for each cohort/arm. 3-month, 6-month, and 1-year estimates with associated 95% CIs will also be presented.

DOR data will be presented in listings for SAF.

10.1.3 Time to Response

Time to response will be computed for SAF subjects with a confirmed overall response of iCR or iPR (as per iRECIST). TTR (in months) will be computed as:

(date of first response – treatment start date + 1) / 30.4375.

TTR will be analyzed based on the Kaplan-Meier methods described for DOR, except for not presenting number (%) of subjects censored which is not applicable for TTR analyses.

TTR derived data will be presented in listings for SAF.

10.1.4 Duration of Stable Disease

Duration of stable disease will be computed for SAF subjects as:

(censoring date OR date of iUPD followed by confirmation) – treatment start date + 1) / 30.4375.

Event and censoring rules for duration of stable disease are detailed in APPENDIX 3. CENSORING RULES: DURATION OF STABLE **DISEASE**.

Duration of stable disease will be analyzed based on the Kaplan-Meier methods described for DOR.

Duration of stable disease derived data will be presented in listings for SAF.

10.2Exploratory Efficacy Analyses

10.2.1 ORR per itRECIST (Phase IIa arms only)

ORR per itRECIST will be reported for injected and non-injected target lesion, separately, using the SAF set. itRECIST will be programmatically derived using data obtained from iRECIST assessments following the derivation rules provided in APPENDIX 5. itRECIST DERIVATION **RULES**.

ORR per itRECIST will be summarized as described for ORR by iRECIST, except for presenting injected and non-injected target lesions, separately. Also, results from patients receiving 2 mg/mL and 5 mg/mL CyPep-1 will be pooled and included in addition to by cohort/arm presentation to explore a general effect of any treatment with CyPep-1 on ORR.

A double waterfall plot of maximum percentage reduction from baseline in injected and non-injected target lesion sum of diameters (mm) will be provided for the itRECIST analysis instead of the regular waterfall plot. Injected and non-injected responses will be presented on the same figure for SAF.

10.2.2 Survival

Overall survival (in months) is defined as the time from start of study treatment to the date of death:

(censoring date OR date of death – treatment start date + 1) / 30.4375.

Subjects who do not die will be censored at the last known alive date, i.e., at the date of last study visit or the latest survival follow up call, whichever occurs later. SAF will be used for the evaluation of OS.

Progression-free survival is defined as the time from treatment start until disease relapse or disease progression (based on all lesions, using iRECIST) or death due to any cause, whichever occurs earliest:

(*date of iUPD followed by confirmation or death – treatment start date + 1) / 30.4375.*

Event and censoring rules for PFS are detailed in APPENDIX 2. CENSORING RULES: DOR and **PFS**. SAF will be used for the evaluation of PFS.

OS and PFS will be analyzed based on the Kaplan-Meier methods described for DOR.

OS will further be presented (both in tables and on Kaplan-Meier plots) by RMH prognostic score at baseline and GRIm-score at baseline, separately. Subjects with missing RMH prognostic score and GRIM-score values at baseline will be excluded. For the purpose of this exploratory analysis, subjects from all cohorts/arms will be pooled into one group (Total: Phase I + IIa). The analysis will be run including and excluding subjects with adrenocortical carcinoma (ACC) diagnosis. Subjects with ACC diagnosis will be identified based on coded value (i.e., MedDRA PT) of "Adrenocortical carcinoma" corresponding to *Histological type* reported on the *Primary Diagnosis* section of the *Primary Cancer* eCRF page. The aim of this analysis is to further validate the prognostic properties of RMH prognostic score and GRIm-score for population under study.

By-subject data will be listed.

10.2.3 Pharmacokinetics

PK analysis is planned via the determination of the plasma concentration (ng/mL) time profile of CyPep-1 and, if detectable, plasma drug levels are identified, the derived PK parameters will be assessed. These include area under the curve, peak plasma concentration, time to reach C_{max}, systemic clearance, elimination half-life and volume of distribution.

PK data is provided to [redacted]

Details on derivation of PK parameters and summaries to be created are provided in the *PK Analysis Plan* produced by [redacted] PK group ([redacted] All PK summaries will be provided by [redacted] PK group in *PK Analysis Report*.

10.2.4 Immunological Parameters

Immunological parameters will be analyzed using the SAF.

CD8+ T-cell Infiltration

CD8+ data are provided to [redacted]; details on data transfer are specified in corresponding *External Data Transfer Agreement*.

CellCarta is responsible for providing CD8+ T-cell infiltration data summaries to sponsor in accordance with the study protocol.

For this SAP, CD8+ T-cell infiltration data will only be listed.

T-cell Receptor Clonality Levels

TCR clonality data are provided to [redacted] via the Immunoseq tool.

Adaptive is responsible for providing T-cell receptor clonality levels data summaries to sponsor in accordance with the study protocol.

However, Simpson´s clonality results in biopsy on Cycle 1 Visit 4 will be correlated to Simpson´s clonality results in blood on Cycle 1 Visit 4 for the 6 subjects who had TCR data measured in both biopsy and blood. Scatter plot will be used for this analysis. Results will be displayed in pooled fashion (i.e., no presentation by cohort/arm) due to small sample size.

T-cell receptor clonality levels data will also be listed.

Tumor Microenvironment

Tumor microenvironment data are provided to [redacted]; details on data transfers are specified in corresponding *External Data Transfer Agreements*.

[redacted] are responsible for providing tumor microenvironment data summaries to sponsor in accordance with the study protocol.

However, PD-L1 expression data (Tumor Positive Score) will be presented by summary statistics for Arm B subjects at baseline in scope of this SAP.

For this SAP, tumor microenvironment data will only be listed.

Cytokine Levels

Cytokines data are provided to [redacted]; details on data transfer are specified in corresponding *External Data Transfer Agreement*.

Changes in cytokine levels (only for Arms A, B, and C) will be explored. [redacted].

The change in cytokine levels between screening and post-baseline timepoints will be assessed and estimated using paired t-tests with a 0.05 significance level. In addition to test results, the summary table will include summary statistics for cytokine levels by timepoint and for change from screening to each post-baseline timepoint.

Cytokines data will also be listed.

Peripheral Blood Phenotyping

Peripheral blood phenotyping data are provided to [redacted]; details on data transfer are specified in corresponding *External Data Transfer Agreement*.

Cerba Research is responsible for providing peripheral blood phenotyping data summaries to sponsor in accordance with the study protocol.

For this SAP, peripheral blood phenotyping data will only be listed.

Exploratory Analyses of Immunological Parameters

Correlation between immunological parameters and select efficacy endpoints may be explored in case immunological signals are observed. Such analyses, if carried out, will be described in an SAP amendment or in the Clinical Study Report, as applicable.

10.2.5 Exploratory Subgroup Analyses

The following sub-group analyses may be carried out:

1. Analysis of subjects having received weekly vs Q2W CyPep-1 administration,
2. Analysis of subjects in Arm D corresponding to Inclusion Criteria 8e,

Analysis of subjects having received weekly vs Q2W CyPep-1 administration

Comparisons of efficacy data between subjects who received weekly and by-weekly CyPep-1 administrations may be carried out, given sufficient sample size in both groups. No such analyses are planned for this version of SAP.

Analysis of subjects in Arm D corresponding to Inclusion Criteria 8e

Exploratory analyses of subjects in Arm D corresponding to Inclusion Criteria 8e may be carried out. No such analyses are planned for this version of SAP.

10.2.6 Other Exploratory Analyses

Pharmacokinetics and Toxicity

A summary table of AEs (by SOC and PT) by cycle and cohort will be created for the PKS, split by C_{max} detectable vs not detectable.

Intratumoral Dose Concentration

Summary statistics for intratumoral dose concentration at baseline (mg/mm^3) will be presented by best overall response per iRECIST (iSD and better vs worse than iSD) and cohort/arm for the SAF. Corresponding box plots will also be created.

Intratumoral dose concentration at baseline will be calculated following the steps below:

1. For each subject, the volume of *i*th lesion injected at first treatment administration will be estimated using the formula of volume of sphere:
$$V_i = \frac{1}{6} \cdot \pi \cdot {d_i}^3$$
where d_i is the longest diameter of lesion *i* obtained by baseline CT scan (if CT scan is not available, then results from local measurements performed before treatment injection will be used).
2. For each subject, the intratumoral dose concentration at baseline will be calculated as:
$$Conc_{IT} = Average\left(\frac{D_i}{V_i}\right)$$
where D_i is the dose injected (mg) into *i*th lesion at first treatment administration and average is taken over all lesions injected at first treatment administration.

Injected Target Lesion Volume and Best Response in Injected Target Lesions per itRECIST

Injected target lesion volume is hypothesized to be correlated with injected target lesion response per itRECIST. In order to explore that relationship, the following analysis steps will be taken:

1. For each subject, the injected target lesions volume (mm^3) at baseline will be calculated as sum of volumes of all target lesions injected at baseline, based on the formula of volume of sphere:
$$V = \sum_i \frac{1}{6} \cdot \pi \cdot {d_i}^3$$
where d_i is the longest diameter of lesion *i* obtained by baseline CT scan (if CT scan is not available, then results from local measurements performed before treatment injection will be used). For this calculation, baseline can differ between different injected target lesions of the same subject following the itRECIST rules provided in APPENDIX 5. itRECIST DERIVATION **RULES**.
2. Then, median of injected target lesion volume over all patients in SAF will be calculated and patients will be divided into two groups: low volume (≤ median) and high volume (> median).
3. Finally, the itRECIST injected target lesion best response (grouped as itSD and better vs worse than itSD) will be presented by low/high volume groups for the SAF. Fisher's exact test will be used to compare distribution of response between the low and high-volume groups; p-value corresponding to the test will be presented.

The same analysis will be run excluding subjects with adrenocortical carcinoma (ACC) diagnosis. Subjects with ACC diagnosis will be identified based on coded value (i.e., MedDRA PT) of "Adrenocortical carcinoma" corresponding to *Histological type* reported on the *Primary Diagnosis* section of the *Primary Cancer* eCRF page.

11 Safety Analysis

Safety will be assessed by means of physical examinations, body weight, vital signs, ECOG performance status, laboratory evaluations (hematology, biochemistry, coagulation, urinalysis), electrocardiograms (ECG), and recording of concurrent illness/therapy and adverse events. All assessments will be performed as indicated in the protocol Schedule of Assessments. Additional assessments may be performed as clinically indicated.

All safety analyses will be performed on the SAF.

11.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject administered with a medicinal product and which does not necessarily have a causal relationship with this treatment.

Subjects will be monitored for AEs from the time of Informed Consent Form (ICF) signature until the FU visit (or until EoT, if it occurs more than 30 days after the last CyPep-1 administration for Phase I and Arms A and C and D; for Arm B refer to Clinical Study Protocol Section 7.2.1.3). After the FU visit (or EoT visit, if it occurs more than 30 days after the last CyPep-1 administration), only ongoing AEs or serious adverse events (SAEs) related to CyPep-1 administration will be collected.

A serious AE is any untoward medical occurrence or effect that at any dose:

- Results in death (not due to disease progression),
- Is life-threatening (the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe),
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect.

The following are not considered (and do not need to be reported) as SAEs:

- Hospitalization due to a social indication,
- Elective pre-planned hospitalizations for treatment of an existing condition prior to entering the trial,
- Hospitalizations due to tumor-related symptoms or tumor progression.

Any event that does not meet the above criteria may also be considered by the investigator to be an SAE, based on appropriate medical and scientific judgment.

All AEs reported after the start of first dose of study treatment (CyPep-1 or pembrolizumab) are considered treatment-emergent.

AEs will be assessed using CTCAE v5.0, including start and stop dates, severity, relationship to CyPep-1, outcome and action taken. Section 7 of the Clinical Study Protocol provides detailed instructions on AE reporting and definitions related to it.

11.1.1 Treatment Relatedness

Relationship of AEs to CyPep-1 and/or pembrolizumab will be collected as not related, unlikely related, possibly related, probably related and definitely related. Following ICH-E3, the drug relatedness will be dichotomized as follows:

- Related: possibly related, probably related, and definitely related OR with missing relatedness (= worst-case),
- Not related: unlikely related, and not related.

11.1.2 Adverse Event Onset and Duration

AE start and end date will be imputed, as applicable, using rules provided in APPENDIX 1. PARTIAL DATE CONVENTIONS.

Study day of AE start/end will be calculated based on rules provided in Section 8.4, where date of interest is the (imputed) AE start/end date, respectively.

AE duration (days) is calculated as follows:

= *AE stop date – AE start date* + 1 day,
when both dates are completely known or could be imputed
= *trial termination date – AE start date* + 1 day,

when the AE start date is fully known or could be imputed but the AE is ongoing at the end of the trial: in this case the duration will be presented as ">x days" in listings rather than "x days"

= *death date – AE start date* + 1 day,
when the AE start date is fully known or could be imputed but the AE is not resolved at the time of death: in this case the duration will be presented as "x days" in the listing

= missing,
when the AE has resolved but with a completely missing end date.

AE duration and study day of AE start/end will only be included in listings.

11.1.3 Analysis

All AEs will be presented by cohort/arm and overall.

An overview table of treatment-emergent AEs (TEAEs) will be produced, including counts and percentages of subjects (n) and events (#AE) for:

1. TEAEs,
2. TEAEs related to any study treatment (CyPep-1 or pembrolizumab),
3. TEAEs related to CyPep-1,
4. Serious TEAEs (TESAEs),
5. TESAEs related to any study treatment (CyPep-1 or pembrolizumab),
6. TESAEs related to CyPep-1,
7. CTCAE grade 3 or higher TEAEs,
8. CTCAE grade 3 or higher TEAEs related to any study treatment (CyPep-1 or pembrolizumab),
9. CTCAE grade 3 or higher TEAEs related to CyPep-1,
10. TEAEs leading to any study treatment (CyPep-1 or pembrolizumab) discontinuation,
11. TEAEs leading to CyPep-1 discontinuation,
12. TEAEs leading to pembrolizumab discontinuation,
13. TEAEs related to any study treatment (CyPep-1 or pembrolizumab) leading to any study treatment discontinuation,
14. TEAEs related to CyPep-1 leading to CyPep1 discontinuation,
15. TEAEs related to any study treatment (CyPep-1 or pembrolizumab) leading to pembrolizumab discontinuation,
16. TEAEs leading to CyPep-1 dose reduction,
17. TEAEs leading to pembrolizumab dose reduction,
18. TEAEs leading to CyPep-1 dose interruption,
19. TEAEs leading to pembrolizumab dose interruption,
20. TEAEs leading to study discontinuation,
21. TEAEs leading to study discontinuation related to any study treatment (CyPep-1 or pembrolizumab),
22. TEAEs leading to study discontinuation related to CyPep-1,
23. Dose limiting toxicities (for Phase I and Phase IIa Arms A and C),
24. Treatment limiting toxicities (only for Arm B),
25. Fatal TEAEs,
26. Fatal TEAEs related to any study treatment (CyPep-1 or pembrolizumab),
27. Fatal TEAEs related to CyPep-1.

Adverse events will be coded based on the MedDRA (version specified in the *Data Management Plan*) for reporting by SOC and PT. SOC will be ordered in accordance with the international agreed upon sort order for SOC followed by descending order of overall PT incidence within the SOC.

Subjects with PTs of "Cancer Pain" and "Tumour Pain" will be pooled for outputs under PT of "Cancer Pain". Similar pooling will be applied for inconsistently reported injection site reactions; list of applicable AEs will be provided by Sponsor/Data Management/Medical Monitor and reviewed at the Data Review Meeting before the database lock. In listings, such AEs will be flagged as pooled for tables but presented with the PT reported on eCRF (i.e., no pooling will be applied for listings).

For summaries of TEAEs by SOC and PT, a subject will be counted once within an SOC, even if the subject experienced more than one TEAE within a specific SOC (likewise for PT). For summaries of TEAEs by CTCAE v5.0 grade, a subject will be counted at most once at each severity grade within a SOC and/or PT. A missing severity will be assumed to be Grade 3. A missing relationship will be assumed to be likely related unless the subject was never treated with the specific therapy. Summaries of TESAEs by SOC and PT will be handled in a similar manner as TEAEs. A missing seriousness assessment will be assumed serious.

Summaries of adverse events by SOC and PT will include the following types:

1. TEAEs,
2. TEAEs by CTCAE grade,
3. TEAEs related to any study treatment (CyPep-1 or pembrolizumab),
4. TEAEs related to CyPep-1,
5. TESAEs,
6. TESAEs by CTCAE grade,
7. TESAEs related to any study treatment (CyPep-1 or pembrolizumab),
8. TESAEs related to CyPep-1,
9. CTCAE Grade 3 or higher TEAEs,
10. CTCAE Grade 3 or higher TEAEs related to any study treatment (CyPep-1 or pembrolizumab),
11. CTCAE Grade 3 or higher TEAEs related to CyPep-1,
12. TEAEs related to CyPep-1 by CTCAE grade,
13. TEAEs leading to CyPep-1 discontinuation,
14. TEAEs leading to CyPep-1 discontinuation by CTCAE grade,
15. TEAES leading to CyPep-1 discontinuation related to CyPep-1,
16. TEAEs leading to study discontinuation,
17. TEAEs leading to study discontinuation by CTCAE grade,
18. TEAEs leading to study discontinuation related to any study treatment (CyPep-1 or pembrolizumab)
19. TEAEs leading to study discontinuation related to CyPep-1,
20. Dose limiting toxicities,
21. Treatment limiting toxicities (TLTs),
22. Fatal TEAEs by relatedness to any study treatment,
23. Pre-treatment AEs.

A summary of TEAEs by PT and CTCAE grade will also be presented for TEAEs and TEAEs related to CyPep-1. The summary will be sorted by the total incidence of the PT.

A comprehensive listing of all AEs will be provided for all subjects. In addition, the following listings will be provided for SAF subjects:

1. TEAEs related to CyPep-1,
2. TESAEs,
3. CTCAE Grade 3 or higher TEAEs,
4. TEAEs leading to CyPep-1 discontinuation,
5. TEAEs leading to study discontinuation,
6. DLTs,
7. TLTs,
8. Fatal TEAEs.

11.2 Deaths

Deaths will be summarized for all SAF patients by cohort/arm and overall. The summary table will present the primary cause of death (target disease progression, study drug toxicity, study-specific procedure related incident, adverse event, non-study related incident, suicide, unknown, other [including specification]).

Deaths will also be listed for all patients in the SAF.

11.3 Pregnancies

No summary descriptive statistics will be produced, pregnancy test data will be presented in listings for all female subjects.

11.4 Clinical Laboratory Evaluation

Laboratory tests will be performed at times defined in the protocol Schedule of Assessments. Biochemistry, hematology, and coagulation parameters will be reported based on the International System of Units (SI). All clinical laboratory data collected during the on-treatment period will be presented for the SAF by visit, timepoint and cohort/arm, as applicable. Data collected during the pre-treatment and post-treatment periods will only be listed.

The following laboratory evaluations will be reported in data summaries:

1. **Hematology**: parameters to be assessed include hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), and platelet count. Neutrophil-to-lymphocyte count will additionally be derived.

2. **Biochemistry**: parameters to be assessed include creatinine, alkaline phosphatase, phosphate, total bilirubin, direct bilirubin (only applicable if total bilirubin levels > 1.5 x ULN [upper limit of normal]), ALT (alanine transaminase), AST (aspartate transaminase), gamma-glutamyl transferase, total protein, albumin, uric acid, urea, sodium, potassium, calcium, chloride, glucose, lactate dehydrogenase, amylase, lipase, creatinine phosphokinase, cholesterol and triglycerides. Creatinine clearance will be estimated by the CKD-EPI and the Cockcroft-Gault formula.
3. **Coagulation:** parameters to be assessed include prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (APTT).
4. **Urinalysis**: parameters to be assessed include leukocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, occult blood (hemoglobin and erythrocytes) (dipstick). If abnormal, sediment will be performed (including WBC, RBC, epithelial cells, crystals, casts, bacteria, other).
5. **Thyroid function**: free T3, free T4, T3 and TSH.

Observed values and changes from baseline for hematology, biochemistry and coagulation laboratory evaluations will be summarized at each visit; maximum and minimum most extreme change will be summarized as well.

Urinalysis parameters will be summarized at each visit using the number (%) of subjects with results of normal; abnormal, not clinically significant; abnormal, clinically significant.

The number and percentage of subjects with NCI-CTCAE toxicities will be tabulated by laboratory evaluation with defined NCI-CTCAE grading at each visit and at any time (including unscheduled visits) for hematology, biochemistry, coagulation and thyroid function. Subjects with missing values post-baseline will be excluded from the summary. The denominator for percentages will be the number of subjects with at least one post-baseline assessment for the laboratory parameter in question.

Hematology, biochemistry, coagulation and thyroid function shift tables displaying the shift from baseline to the maximum value of NCI-CTCAE grade will be presented (see Section 8.16 for details on shift table creation).

Potential hepatotoxicity will be evaluated by presenting shifts from baseline to worst post-baseline NCI-CTCAE grade for ALT, AST, total bilirubin, alkaline phosphatase and gamma-glutamyl transferase split by baseline status (normal at baseline, abnormal at baseline). If any of the parameters of interest is abnormal at baseline, the subject is considered to belong to the abnormal at baseline group. Only subjects who have normal results for all parameters of interest are considered to belong to the normal at baseline group. NCI-CTCAE Grade 1 or above is considered abnormal for the purpose of this analysis.

Potential hepatotoxicity will additionally be assessed by similar table but splitting by liver metastasis at baseline (no metastasis, metastasis). Finally, a potential hepatotoxicity table by baseline liver metastasis and iRECIST best overall response (iCR + iPR + iSD or UPD + iCPD + NE) will be created.

Mean (±SD) hematology and biochemistry laboratory results will be plotted over time by cohort/arm for SAF. Parameters measured only before treatment start will be excluded from the plots.

Mean (±SD) ALT, AST, total bilirubin, and alkaline phosphatase results will be plotted over time for SAF by liver metastasis at baseline (no metastasis, metastasis) and separately by baseline result for parameter of interest (normal at baseline, abnormal at baseline; by parameter); subjects from all cohorts/arms will be pooled for this analysis (i.e., presenting only for Total: Phase I + IIa).

All laboratory parameters will be provided in subject data listings for all subjects, a separate listing including CTCAE Grade 3 or higher laboratory abnormalities will be created.

A table-listing of NCI-CTCAE graded lab data including the parameter name, CTCAE preferred term, clinical significance of assessment, worst severity and number of applicable events by subject, will be created for clinical chemistry, coagulation, hematology and thyroid function.

11.5 Other Safety Measures

11.5.1 Vital Signs and Body Weight

Vital signs will be assessed on various visits and timepoints thought the study. Vital signs and body weight results collected during the on-treatment period will be presented by cohort/arm for the SAF. Data collected during the pre-treatment and post-treatment periods will only be listed.

The following will be assessed:

1. Pulse rate (beats/min),
2. Respiratory Rate (breaths/min),
3. Systolic and diastolic blood pressure (mmHg),

4. Body temperature (°C).

Observed values and changes from baseline for vital signs and body weight will be summarized at each visit and timepoint, as applicable; maximum and minimum most extreme change will be summarized as well.

Additionally, body weight, pulse rate, body temperature, systolic blood pressure, and diastolic blood pressure will be summarized based on markedly abnormal criteria defined in Table 5 below.

Table 5. Markedly Abnormal Criteria for Vital Signs

Vital Sign	Markedly Abnormal Criteria
Pulse rate (beats/min)	< 60 beats/min > 100 beats/min
Body temperature (ºC)	≤ 35 ºC ≥ 38 ºC
Systolic blood pressure (mmHg)	120-139 mmHg, inclusive (CTCAE grade 1) 140–159 mmHg, inclusive (CTCAE grade 2) ≥ 160 mmHg (CTCAE Grade 3)
Diastolic blood pressure (mmHg)	80–89 mmHg, inclusive (CTCAE grade 1) 90–99 mmHg, inclusive (CTCAE grade 2) ≥ 100 mmHg (CTCAE grade 3)
Body weight (kg)	5 to <10% decrease from baseline 10 to <20% decrease from baseline ≥ 20% decrease from baseline

Incidence of markedly abnormal values will be presented overall (including unscheduled visits) and at each scheduled visit. For pulse rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories, if applicable.

Mean (±SD) vital signs and body weight data will also be plotted over time per cohort/arm for SAF. For vital signs, an additional figure presenting each cycle on different page, including 2 x 2 (or 2 x 3, as applicable) matrix of figures of treatment days in each cycle will be created for SAF. The second figure allows for detailed inspection of data collected in a short timeframe before and after dosing; the first figure will provide general visual trend over entire study duration.

All vital signs and body weight data will be presented in subject data listings for all subjects. Markedly abnormal vital sign values will be flagged as such in the listing.

11.5.2 ECG

ECG will be assessed as specified in the protocol Schedule of Assessments. The following ECG parameters will be collected: PR interval (msec), QRS interval (msec), QT interval (msec), QT interval corrected for heart rate using Fridericia's formula (QTcF) (msec), and Heart Rate (beats/min). ECG parameters will come directly from the eCRF and will not be calculated during analysis (calculation rules for QTcF are documented in the *Study Design Specification* document). ECG results collected during the on-treatment period will be presented by cohort/arm for the SAF. Data collected during the pre-treatment and post-treatment periods will only be listed.

Observed values and changes from baseline for ECG parameters will be summarized at each visit; maximum and minimum most extreme change will be summarized as well.

Shift from baseline to worst post-baseline interpretation (normal; abnormal, not clinically significant; abnormal, clinically significant) will be summarized.

All ECG data will be presented in a by subject data listing for all subjects.

11.5.3 Physical Examinations

Physical examination results will only be presented in subject data listings for all subjects.

11.5.4 ECOG Performance Status

ECOG data will be summarized using score categories 0-5 at scheduled visits during the on-treatment period and with shift from baseline score to the worst post-baseline score by cohort/arm for the SAF. Best to worst ECOG value is defined in the order: Missing, Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5. In case a subject dies while on treatment (i.e., primary reason for treatment discontinuation is death), this subject is counted as

having a shift from baseline value to death, even if ECOG score of 5 is not recorded in the eCRF. Data collected during the pre-treatment and post-treatment periods will only be listed.

ECOG data will be presented in subject data listings for all subjects. Worst post-baseline scores will be flagged in the listing.

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13 APPENDIX

13.1 APPENDIX 1. PARTIAL DATE CONVENTIONS

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

For AEs with missing or partial start and end dates, the following imputation rules will be applied (i.e., "worst case" scenario):

AE start datetime:

Impute to *treatment start datetime* if:

- *AE start time* unknown and *AE start date = treatment start date*.
- *AE start day* is missing from *AE start date* and *AE start month = treatment start month*.
- *AE start month* is missing from *AE start date* and *AE start year = treatment start year*.
- *AE start datetime* fully missing.

Else impute *AE start datetime* as earliest possible datetime (i.e., 00:00 if time unknown, first day of month at 00.00 if time and day unknown or 1st of January at 00.00 if time, day and month are unknown).

AE end date:

If *AE end day* and/or *AE end month* is missing, *AE end day* and /or *AE end month* is imputed with the last day of the month and/or last month of the year. If the imputed *AE end date* falls after *end of study date*, the *AE end date* is imputed with the *end of study date*.

Fully missing AE end dates won't be imputed, unless end date is missing and AE is marked as not resolved at time of death – in that case, AE end date will be imputed as date of death.

Imputed AE start and end dates will only be used for analysis purposes (e.g., generating summary tables or figures). In the listings, the incomplete study dates will be presented as collected (i.e., as incomplete).

An algorithm for determining treatment emergence of an AE is given in Table 6 below.

Table 6. Algorithm for Treatment Emergence of Adverse Events

Start date	Rule
Known	If *AE start datetime* < *treatment start datetime*, not TEAE. If *AE start datetime* ≥ *treatment start datetime*, then TEAE.
Partial/Missing	If *imputed AE datetime* < *treatment start datetime*, not TEAE. If *imputed AE datetime* ≥ *treatment start datetime*, then TEAE.

ALGORITHM FOR MEDICATIONS AND PROCEDURES PRIOR / CONCOMITANT / SUBSEQUENT TO STUDY TREATMENT:

Partial start datetime

Impute to *treatment start datetime* if:

- *Start time* unknown and *start date=treatment start date*.
- *Day* is missing from *start date* and *start month=treatment start month*.
- *Month* is missing from *start date* and *start year=treatment start year*.

Else impute *start datetime* as earliest possible datetime (i.e., 00:00 if time unknown, first day of month at 00.00 if time and day unknown or 1st of January at 00.00 if time, day and month are unknown).

For procedures, only impute start date (time is not collected for procedures).

Partial stop datetime

Impute *stop datetime* as latest possible datetime (i.e.,23:59 if time unknown, last day of month at 23.59 if day unknown or 31st December at 23.59 if day and month are unknown). If the imputed *stop datetime* falls after *end of study date*, the *stop datetime* is imputed with the *end of study date* at 23:59.

For procedures, only impute end date (time is not collected for procedures).

An algorithm for classifying medications and procedures is given in Table 7 below.

Table 7. Algorithm for Medications and Procedures Prior / Concomitant / Subsequent to Study Treatment

Stop date	Rule*
Known	If *stop date(time)* < *treatment start date(time)*, assign as prior. If *treatment start date(time)* <= *stop date(time)* <= *treatment end date(time)*, assign as concomitant. If *treatment end date(time)* < *(imputed) start date(time)*, assign as subsequent.
Partial	If *imputed stop date(time)* < *treatment start date(time)*, assign as prior. If *treatment start date(time)* <= *imputed stop date(time)* <= *treatment end date(time)*, assign as concomitant. If *treatment end date(time)* < (*imputed) start date(time)*, assign as subsequent.
Missing	If *treatment end date(time)* < (*imputed) start date(time)*, assign as subsequent. Else, assign as concomitant.

*For medications use datetime, for procedures use date.

13.2 APPENDIX 2. CENSORING RULES: DOR and PFS

Censoring rules for DOR and PFS are presented in Table 8 below.

Table 8. Censoring Rules for DOR and PFS

#	Situation	Date of Event (PD/Death) or Censoring	Outcome: Event (PD/Death) or Censored
1	No (or inadequate) baseline tumor assessments and the subject has not died	Treatment Start Date	Censored
2	No post-baseline assessments and the subject has not died	Treatment Start Date	Censored
3	iUPD followed by discontinuation due to clinical disease progression, radiological disease progression or death within 8 weeks	Date of assessment of progression[1]	Event
4	iUPD without subsequent iSD, iPR or iCPD and followed by: 1. Treatment discontinuation due to clinical instability (i.e., clinical disease progression, radiological disease progression). 2. No further response assessments (due to subject refusal, protocol non-compliance, or subject death). 3. Next timepoint responses all equal to iUPD. 4. Subject death from cancer.	Date of assessment of progression[1]	Event
5	No iUPD as described in #3 and #4,no iCPD or death and no new protocol excluded anticancer treatment documented	Date of last 'adequate' assessment of response[2]	Censored
6	No iUPD as described in #3 and #4, no iCPD or death and new protocol excluded anticancer treatment documented	Date of last 'adequate' assessment of response[2] on or prior to starting anticancer therapy	Censored
7	New protocol excluded anticancer treatment started (prior to iUPD as described in #3 and #4, iCPD or death)[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anticancer therapy	Censored
8	iCPD documented between scheduled visits	Date of assessment of progression[1]	Event
9	Death before first iCPD assessment	Date of death	Event
10	Death between adequate assessment visits	Date of death	Event
11	Death or progression after two missed visits (with 1-week window) where last assessment is not iUPD	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored

[1]The earliest of
(i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or
(ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or
(iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).

[2]An adequate assessment is defined as a radiological assessment where iCR, iPR, or iSD was determined.

[3]If iCPD and subsequent protocol excluded anti-cancer therapy occur on the same date, assume the progression was documented first.

13.3 APPENDIX 3. CENSORING RULES: DURATION OF STABLE DISEASE

Censoring rules for duration of stable disease are presented in Table 9 below.

Table 9. Censoring Rules for Duration of Stable Disease

#	Situation	Date of Event (PD) or Censoring	Outcome: Event (PD) or Censored
1	No (or inadequate) baseline tumor assessments and the patient has not died	Treatment Start Date	Censored
2	No post-baseline assessments	Treatment Start Date	Censored
3	iUPD followed by discontinuation due to clinical disease progression, radiological disease progression or death within 8 weeks	Date of assessment of progression[1]	Event
4	iUPD without subsequent iSD, iPR or iCPD and followed by: 1. Treatment discontinuation due to clinical instability (i.e., clinical disease progression, radiological disease progression). 2. No further response assessments (due to subject refusal, protocol non-compliance). 3. Next timepoint responses all equal to iUPD.	Date of assessment of progression[1]	Event
5	iCPD documented between scheduled visits	Date of assessment of progression[1]	Event
6	No iUPD as described in #3 and #4, no iCPD and no new protocol excluded anticancer treatment documented	Date of last 'adequate' assessment of response[2]	Censored
7	No iUPD as described in #3 and #4, no iCPD and new protocol excluded anticancer treatment documented	Date of last 'adequate' assessment of response[2] on or prior to starting anticancer therapy	Censored
8	New protocol excluded anticancer treatment started (prior to iUPD as described in #3 and #4, iCPD)[3]	Date of last 'adequate' assessment of response[2] on or prior to starting anticancer therapy	Censored
9	Death before first iCPD assessment	Date of last 'adequate' assessment of response[2]	Censored
10	Progression after two missed visits (with 1-week window) where last assessment is not iUPD	Date of last 'adequate' assessment of response[2] prior to missed assessments	Censored

[1]The earliest of
(i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or
(ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or
(iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions).

[2]An adequate assessment is defined as a radiological assessment where iCR, iPR, or iSD was determined.

13.4 APPENDIX 4. VISIT ALIGNEMENT

Mapping of protocol-defined visits into one common visit set for analysis purposes is presented below in Table 10.

Table 10. Visit Alignment

			Visit (per protocol)		
Visit # (alig.)	**Visit Label (aligned)**	**Visit Day**	**Part I**	**Part IIa Arms A, B, C**	**Part IIa Arm D**
1	Screening		SCREENING	SCREENING	SCREENING
2	Visit 1 Day 1	1	C1 D1	C1 D1	DAY 1
3	Visit 2 Day 8	8		C1 D8*	DAY 8
4	Visit 3 Day 15	15	C1 D15	C1 D15	DAY 15
5	Visit 4 Day 22	22		C1 D22	DAY 22
6	Visit 5 Day 29	29	C1 D29	C1 D29	
7	Visit 6 Day 36	36	C1 D36	C1 D36	
8	Visit 7 Day 43	43	C2 D1	C2 D1	
9	Visit 8 Day 50	50	C1 D50**		
10	Visit 9 Day 57	57	C2 D15	C2 D15	
11	Visit 10 Day 71	71	C2 D29	C2 D29	
12	Visit 11 Day 78	78	C2 D36	C2 D36	
13	Visit 12 Day 85	85	C3 D1	C3 D1	
14	Visit 13 Day 99	99	C3 D15	C3 D15	
15	Visit 14 Day 113	113	C3 D29	C3 D29	
16	Visit 15 Day 120	120	C3 D36	C3 D36	
17	Visit 16 Day 127	127	C4 D1	C4 D1	
18	Visit 17 Day 141	141	C4 D15	C4 D15	
19	Visit 18 Day 155	155	C4 D29	C4 D29	
20	Visit 19 Day 162	162	C4 D36	C4 D36	
21	Visit 20 Day 169	169	C5 D1	C5 D1	
22	Visit 21 Day 183	183	C5 D15	C5 D15	
23	Visit 22 Day 197	197	C5 D29	C5 D29	
24	Visit 23 Day 204	204	C5 D36	C5 D36	
25	Visit 24 Day 211	211	C6 D1	C6 D1	
26	Visit 25 Day 225	225	C6 D15	C6 D15	
27	Visit 26 Day 239	239	C6 D29	C6 D29	
28	Visit 27 Day 246	246	C6 D36	C6 D36	
29	Visit 28 Day 253	253		C7 D1	
30	Visit 29 Day 267	267		C7 D15	
31	Visit 30 Day 281	281		C7 D29	
32	Visit 31 Day 288	288		C7 D36	
33	Visit 32 Day 295	295		C8 D1	
34	Visit 33 Day 309	309		C8 D15	
35	Visit 34 Day 323	323		C8 D29	
36	Visit 35 Day 330	330		C8 D36	
37	Visit 36 Day 337	337		C9 D1	
38	Visit 37 Day 351	351		C9 D15	
39	Visit 38 Day 365	365		C9 D29	
40	Visit 39 Day 372	372		C9 D36	
41	Visit 40 Day 379	379		C10 D1	
42	Visit 41 Day 393	393		C10 D15	
43	Visit 42 Day 407	407		C10 D29	
44	Visit 43 Day 414	414		C10 D36	
45	Visit 44 Day 421	421		C11 D1	
46	Visit 45 Day 435	435		C11 D15	
47	Visit 46 Day 449	449		C11 D29	
48	Visit 47 Day 456	456		C11 D36	
49	Visit 48 Day 463	463		C12 D1	
50	Visit 49 Day 477	477		C12 D15	
51	Visit 50 Day 491	491		C12 D29	

			Visit (per protocol)		
Visit # (alig.)	Visit Label (aligned)	Visit Day	Part I	Part IIa Arms A, B, C	Part IIa Arm D
52	Visit 51 Day 498	498		C12 D36	
53	Visit 52 Day 505	505		C13 D1	
54	Visit 53 Day 519	519		C13 D15	
55	Visit 54 Day 533	533		C13 D29	
56	Visit 55 Day 540	540		C13 D36	
57	Visit 56 Day 547	547		C14 D1	
58	Visit 57 Day 561	561		C14 D15	
59	Visit 58 Day 575	575		C14 D29	
60	Visit 59 Day 582	582		C14 D36	
61	Visit 60 Day 589	589		C15 D1	
62	Visit 61 Day 603	603		C15 D15	
63	Visit 62 Day 617	617		C15 D29	
64	Visit 63 Day 624	624		C15 D36	
65	Visit 64 Day 631	631		C16 D1	
66	Visit 65 Day 645	645		C16 D15	
67	Visit 66 Day 659	659		C16 D29	
68	Visit 67 Day 666	666		C16 D36	
69	Visit 68 Day 673	673		C17 D1	
70	Visit 69 Day 687	687		C17 D15	
71	Visit 70 Day 701	701		C17 D29	
72	Visit 71 Day 708	708		C17 D36	
73	Visit 72 Day 715	715		C18 D1	
74	Visit 73 Day 729	729		C18 D15	
75	Visit 74 Day 743	743		C18 D29	
76	Visit 75 Day 750	750		C18 D36	
77	Visit 76 Day 757	757		C19 D1	
78	Visit 77 Day 771	771		C19 D15	
79	Visit 78 Day 785	785		C19 D29	
80	Visit 79 Day 792	792		C19 D36	
81	Visit 80 Day 799	799		C20 D1	
82	Visit 81 Day 813	813		C20 D15	
83	Visit 82 Day 827	827		C20 D29	
84	Visit 83 Day 834	834		C20 D36	
85	Visit 84 Day 841	841		C21 D1	
86	Visit 85 Day 855	855		C21 D15	
87	Visit 86 Day 869	869		C21 D29	
88	Visit 87 Day 876	876		C21 D36	
90	End of Treatment		EOT	EOT	EOT
91	Follow-up		FOLLOW-UP	FOLLOW-UP	FOLLOW-UP
92.n	PFS Follow-up *n*		PFS FOLLOW-UP *n*	PFS FOLLOW-UP *n*	PFS FOLLOW-UP *n*
93.n	OS Follow-up *n*		OS FOLLOW-UP *n*	OS FOLLOW-UP *n*	OS FOLLOW-UP *n*

alig. = aligned.
* C1 D8 is only applicable for Arm A subject 04-004.
** C1 D50 is only applicable for Cohort 1 subjects; none of these subjects had C2 D1 visit.

For protocol deviations data, affected visits are collected as free text. Protocol deviation visits will be presented as collected in listings (i.e., no visit alignment will be applied to the free-text data). Protocol deviation tables do not include by-visit summarization.

13.5 APPENDIX 5. itRECIST DERIVATION RULES

The following section is adopted from (Goldmacher, 2020).

For all sum of diameters (SOD) calculations below, lesions that are assessed as "too small to measure" at a specific assessment, are considered to have diameter of 5 mm at that specific assessment (as suggested by RECIST 1.1). In case a lesion is non-evaluable at a timepoint, SOD will be missing for that timepoint.

Timepoint Response: Injected and Non-Injected Target Lesions

For timepoint response per itRECIST, the rules provided in Table 11 below will be used for determining injected and non-injected response.

Table 11. itRECIST Timepoint Response Categories by Lesion Category

itRECIST Response Category	Injected Target Lesions (T-I)	Non-Injected Target Lesions (T-NI)
itCR	All non-nodal lesions gone, nodal lesions <10 mm.	All non-nodal lesions gone, nodal lesions <10 mm.
itPR	≥30% decrease in sum of diameters from last imaging assessment.	≥30% decrease in sum of diameters from baseline.
itPD	≥20% increase in sum of diameters from last imagining assessment (≥5 mm absolute).	≥20% increase in sum of diameters from nadir (≥5 mm absolute).
itSD	Not enough growth for itPD & not enough shrinkage for itPR.	Not enough growth for itPD & not enough shrinkage for itPR.
NE	≥1 lesion cannot be measured.	≥1 lesion cannot be measured or has been injected.

For T-I lesions the response assessment is iterative because lesions selected for injection may vary between visits. At each assessment, the current SOD for all target lesions injected during the previous treatment visit should be compared with their SOD at the previous response assessment. The injected response assessment at given timepoint is based on SOD change from previous assessment.

For T-NI lesions, timepoint responses will only be calculated until the timepoint first T-NI lesion is injected.

Best Response: Injected and Non-Injected Target Lesions

The best response for T-I lesions is determined using the rules provided in Table 11 above, but comparing the SOD based on the smallest size for each injected target lesion to the pre-injection SOD of the same lesions (instead of comparing current results with results from previous assessment).

The best response for T-NI lesions is determined based on non-injected target lesion timepoint responses using the hierarchy of itCR > itPR > itSD > itPD > NE.

Maximum Percent Reduction from Baseline: Injected and Non-Injected Target Lesions

For each T-I lesion, the baseline is its diameter just before it is first injected. Baseline SOD is the sum of all baseline diameters. The best response SOD is the SOD of these lesions at each lesion's smallest size post-injection. Maximum percent reduction will be calculated as (*Best Response SOD – Baseline SOD*) / *Baseline SOD* x 100%.

For T-NI lesions, the baseline SOD is defined as the SOD of T-NI lesions before any injections. The smallest post-baseline SOD is the smallest SOD observed at any timepoint post-baseline (and before any T-NI lesion becomes injected). The maximum percent reduction will be calculated as (*Smallest Post-baseline SOD – Baseline SOD*) / *Baseline SOD* x 100%.