CLINICAL STUDY PROTOCOL

A Phase 1b/2a, Open-Label, Multi-Center Study of CyPep-1 in Combination With Pembrolizumab to Evaluate the Efficacy and Safety of CyPep-1 in Patients With Advanced or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma, or Triple-Negative Breast Cancer (TNBC) (CATALYST)

Investigational Product: CyPep-1 and pembrolizumab
Protocol Number: CYP003
EudraCT Number: 2021-006804-34

Sponsor:
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Original Protocol: 07 January 2022
Amendment 1 (Version 2.0): 09 March 2022
Amendment 2 (Version 3.0): 20 May 2022
Amendment 3 (Version 4.0): 23 November 2022

SIGNATURE PAGE

STUDY TITLE: A Phase 1b/2a, Open-Label, Multi-Center Study of CyPep-1 in Combination With Pembrolizumab to Evaluate the Efficacy and Safety of CyPep-1 in Patients With Advanced or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma, or Triple-Negative Breast Cancer (TNBC) (CATALYST)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

[redacted]

Date

25-Nov-2022

[redacted]

28-Nov-2022

[redacted]

28-Nov-2022

[redacted]

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Cytovation ASA to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Cytovation ASA and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Cytovation ASA, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 1b/2a, Open-Label, Multi-Center Study of CyPep-1 in Combination With Pembrolizumab to Evaluate the Efficacy and Safety of CyPep-1 in Patients With Advanced or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), Melanoma, or Triple-Negative Breast Cancer (TNBC) (CATALYST)

PROTOCOL NUMBER: CYP003

INVESTIGATIONAL PRODUCT: CyPep-1 and pembrolizumab

PHASE: 1b/2a

INDICATIONS: Advanced or metastatic head and neck squamous cell carcinoma (HNSCC), melanoma, or triple-negative breast cancer (TNBC)

OBJECTIVES AND ENDPOINTS:

The study objectives and endpoints are provided in Table S1.

Table S1. Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
Phase 1b	
Confirm the recommended CyPep-1 dose (20 mg Q2W) when administered by IT injection in combination with pembrolizumab	• Incidence, frequency, and seriousness of TEAEs; • Incidence of DLTs; and • Changes from baseline in vital signs, body weight, 12-lead ECG parameters, and laboratory assessments.
Phase 2a	
Assess the anti-tumor activity of CyPep-1 administered by IT injection in combination with pembrolizumab	ORR based on radiological assessment according to RECIST v1.1
Secondary Objectives	**Secondary Endpoints**
Phase 1b	
Evaluate the PK of CyPep-1 in combination with pembrolizumab	• Plasma concentration-time profile of CyPep-1 and, if detectable, the following derived PK parameters: o AUC; o C_{max}; o T_{max}; o CL; o $t_{½}$; and o VD.

Table S1. Objectives and Endpoints (Continued)

Secondary Objectives	Secondary Endpoints
Phase 2a	
Expand evaluation of efficacy CyPep-1 + pembrolizumab	• ORR according to iRECIST; • DCR according to iRECIST and RECIST v1.1; • DoR according to iRECIST and RECIST v1.1; • PFS according to iRECIST and RECIST v1.1; and • OS for up to 26 months from Cycle 1 Visit 1.
Evaluate the safety and tolerability of CyPep-1 in combination with pembrolizumab	• Incidence, frequency, and seriousness of TEAEs; and • Changes from baseline in vital signs, body weight, 12-lead ECG parameters, and laboratory assessments.
Exploratory Objectives	**Exploratory Endpoints**
Analyze changes in biomarkers and tumor kinetics associated with the mode of action of CyPep-1 and pembrolizumab by tumor biopsy from injected lesions	• Number and relative change of tumor infiltrating immune cells; • Expression of selected immune cell biomarkers; • Change from baseline in target tumor lesion size over time, overall, and by injected versus non-injected lesions; • Maximum decrease from baseline in target tumor lesions, overall, and by injected versus non-injected lesions; and • Changes in new lesions treated with CyPep-1.
Expand evaluation of anti-tumor activity of CyPep-1 and pembrolizumab	ORR according to itRECIST

AUC = area under the curve; CL = systemic clearance; C_{max} = peak plasma concentration; DCR = Disease Control Rate; DLT = dose-limiting toxicity; DoR = Duration of Response; ECG = electrocardiogram; iRECIST = immune-Response Evaluation Criteria in Solid Tumors; IT = intra-tumoral; itRECIST = intratumoral-Response Evaluation Criteria in Solid Tumors; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression Free Survival; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; $t_{½}$ = elimination half-life; TEAE = treatment-emergent adverse event; T_{max} = time to reach peak plasma concentration; v = version; VD = volume of distribution.

POPULATION:

No waivers for inclusion or exclusion criteria will be given.

General Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Are 18 years of age or older on the day of signing informed consent;
2. Provide written informed consent and are able to comply with study procedures and assessments;
3. Have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 as assessed by the local site Investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions;
4. Have at least 1 non-ulcerated, measurable, and accessible lesion for intra-tumoral (IT) injection with a maximum diameter of 5 cm;

5. Are able to provide tissue from a core or excisional biopsy at screening or have an acceptable stored tumor sample available that was collected within 90 days prior to screening;
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
7. Have a life expectancy ≥3 months, as determined by the Investigator;
8. Female patients of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before screening), post-menopausal, defined as spontaneous amenorrhea for at least 2 years, or with follicle-stimulating hormone in the post-menopausal range at screening;
9. Female patients of childbearing potential (defined as <2 years after last menstruation or not surgically sterile) must have a negative serum pregnancy test at screening and agree to use a highly effective method for contraception from the time of signing the informed consent form (ICF) until at least 120 days after the last administration of study treatment. Highly effective methods of contraception are birth control methods with a failure rate of <1% per year when used consistently and correctly, including the following:
    - Combined estrogen- and progestin-containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally; progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant; intrauterine devices; and intrauterine hormone-releasing systems;
    - Female sterilization (surgical bilateral oophorectomy with/without hysterectomy, total hysterectomy, bilateral tubal occlusion/ligation) at least 26 weeks prior to first study treatment;
    - Sterilization of male partner (at least 6 months prior to first study treatment dose); and
    - Complete sexual abstinence. Periodic abstinence (eg, calendar) and withdrawal are not acceptable. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.
10. Male patients able to father children must agree to use 2 acceptable methods of contraception throughout the study (eg, condom plus spermicidal gel). Sperm donation is not recommended from the time of signing the ICF until at least 120 days after the last administration of study treatment; and
11. Have adequate organ function as defined in Table S2. Specimens must be collected within 72 hours prior to the start of study treatment at Cycle 1 Visit 1.

Table S2. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin[1]	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Creatinine OR Measured or calculated CrCl[2] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for patients with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for patients with liver metastases)

This table includes eligibility-defining laboratory value requirements for treatment.
1. Criteria must be met without pRBC transfusion within the prior 2 weeks. Patients can be on a stable dose of erythropoietin (approximately ≥3 months).
2. CrCl should be calculated per institutional standard.

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; pRBC = packed red blood cell; ULN = upper limit of normal.

Inclusion Criteria for Arm A

Patients who meet all of the general Inclusion Criteria and the following additional criteria will be eligible for inclusion in Arm A:

1. Have histologically confirmed diagnosis of HNSCC (including nasopharyngeal squamous cell carcinoma);
2. Have advanced or metastatic HNSCC incurable by standard of care therapies; and
3. Have recurrent or metastatic HNSCC that has progressed on or failed both platinum-based chemotherapy AND an immune checkpoint inhibitor (ICI) (given either sequentially or concurrently).

   Note: Patients who received platinum-based chemotherapy with concurrent radiation for locally advanced HNSCC and experienced disease progression within 6 months may also be considered as having disease progression on platinum-based chemotherapy.

Inclusion Criteria for Arm B

Patients who meet all of the general Inclusion Criteria and the following additional criteria will be eligible for inclusion in Arm B:

1. Have histologically confirmed diagnosis of malignant melanoma;
2. Do not have uveal melanoma;
3. Have advanced or metastatic melanoma incurable by standard of care therapies;

4. Have received a combination of a BRAF inhibitor and a MEK inhibitor if diagnosed with a BRAF-mutated melanoma and if clinically indicated; and
5. Have failed or progressed on or after treatment with a checkpoint inhibitor administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies.

Inclusion Criteria for Arm C

Patients who meet all of the general Inclusion Criteria and the following additional criteria will be eligible for inclusion in Arm C:

1. Have histologically confirmed diagnosis of TNBC as per American Society of Clinical Oncology/College of American Pathologists guidelines;
2. Have advanced or metastatic TNBC incurable by standard of care therapies;
3. Have received sacituzumab govitecan chemotherapeutic treatment if clinically indicated; and
4. Have failed or progressed on or after treatment with a checkpoint inhibitor administered either as monotherapy or in combination with other therapies (if ICI eligible based on programmed cell death ligand 1 [PD-L1] status) OR have received prior systemic therapy with either an anthracycline- or taxane-containing regimen (if ICI non-eligible based on PD-L1 status).

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Have only non-palpable cutaneous infiltrations (eg, breast cancer cutaneous carcinomatosis);
2. Have had anti-cancer therapy within 4 weeks prior to the first dose of study treatment (2 weeks for palliative radiotherapy);

   Note: Patients must have recovered from all adverse events (AEs) due to previous therapies to ≤Grade 1 or baseline (alopecia is an allowable exception). Upon discussion with the Sponsor, patients with ≤Grade 2 neuropathy or endocrine-related AEs requiring treatment or hormone replacement may be eligible.

   Note: If the patient had major surgery, the patient must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
3. Have participated in a clinical trial and received an investigational therapy within 30 days prior to the first dose of study treatment;
4. Have received or will receive a live or live attenuated vaccine within 30 days prior to the first dose of study treatment;

   Note: Seasonal flu vaccines that do not contain live vaccine are permitted. Coronavirus Disease 2019 (COVID-19) vaccines are only permitted with documentation of the date of the vaccine if the last dose of vaccine was administered >14 days prior to the first dose of study treatment. The COVID-19 booster vaccine must be administered at least 14 days prior to the first dose of study treatment and is not allowed during the first 3 months of the Treatment Period.

5. Have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 14 days prior to the Screening Visit;

   Note: Patients who have had a known SARS-CoV-2 infection >14 days prior to the Screening Visit are permitted at Investigator discretion and must present with no symptoms.

6. Have had a major surgical procedure within 14 days prior to the first dose of study treatment;
7. Are expected to require a systemic or localized anti-neoplastic therapy during participation in this study, excluding localized palliative radiotherapy to tumors not selected for evaluation of treatment response;

   Note: Use of denosumab for patients with bone metastasis is allowed.

8. Are pregnant or breastfeeding;
9. Have clinical evidence of a secondary malignancy actively progressing or requiring active treatment other than curative therapies for early stage (carcinoma in situ or Stage 1) carcinomas or non-melanoma skin cancer;
10. Have had any autoimmune disease requiring immunosuppressive therapy (ie, use of disease modifying agents, corticosteroids, or immunosuppressive drugs) within 2 years prior to the first dose of study treatment;

    Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

11. Have a condition requiring continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive agents within 2 weeks prior to the first dose of study treatment. Inhaled, intranasal, or topical (only on areas outside the injected lesion[s]) and physiological replacement doses of up to 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease;
12. Have abnormal or clinically significant coagulation parameters as determined by the Investigator (eg, prothrombin time, international normalized ratio, activated partial thromboplastin time) unless patients are on anti-coagulants in which case it must be within appropriate clinical levels;

    Note: Patients who are on anti-coagulants must be able to switch to a low molecular weight heparin or equivalent prior to Cycle 1 Day 1 and continue during the Treatment Period.

13. Have a significant history or clinical manifestation of any allergic disorders and/or Quincke's edema (as determined by the Investigator) capable of significantly altering the absorption of drugs, of constituting a risk when taking CyPep-1 or pembrolizumab, or of interfering with the interpretation of the data;
14. Have a known hypersensitivity to any component of CyPep-1 or pembrolizumab;
15. Have a history of adverse reactions from treatment with ICIs, including pembrolizumab, which resulted in discontinuation of ICI or pembrolizumab or has ongoing pembrolizumab-related toxicity event(s) as per treatment-limiting toxicity definitions, except patients with ongoing

endocrine disorders that are managed with replacement therapy (ie, hypothyroidism related to prior pembrolizumab treatment);

16. Have an active infection requiring systemic therapy;
17. Have a known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as Hepatitis C virus RNA [qualitative] is detected) infection;

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.
18. Have had radiotherapy within 2 weeks prior to the first dose of study treatment, are in recovery from radiation toxicity, or have had radiation pneumonitis;
19. Have a history of non-infectious pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease;
20. Have had a prior allogeneic tissue/solid organ transplant, stem cell, or bone marrow transplant;
21. Have active human immunodeficiency virus (HIV). Patients are eligible when on stable anti-retroviral therapy (no change in medication or dose) for at least 4 weeks prior to screening, have confirmed virologic suppression with HIV RNA less than 50 copies/mL or the lower limit of quantification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening, and have a cluster of differentiation 4+ T cell count >350 cells/mm^3 at screening. HIV-infected patients with a history of Kaposi sarcoma and/or Multicentric Castleman Disease will be excluded;
22. Have 4 or more sites involved, including the primary cancer;

    Note: A site is defined as an organ (eg, lung, liver, or brain) or a system (eg, lymphatic or central nervous system [CNS]).
23. Have a CNS metastasis that is symptomatic, progressing, or that requires current therapy (eg, evidence of new or enlarging CNS metastasis, carcinomatous meningitis, or new neurological symptoms attributable to CNS metastasis);
24. Have a QTcF >480 ms at screening, history of long or short QT syndrome, Brugada syndrome, QTc prolongation, or Torsade de Pointes, with the exception of patients with controlled atrial fibrillation, pacemaker, or bundle branch block as the QTc will be prolonged due to the widened QRS;
25. Are an adult under legal protection, are vulnerable, or lack the capacity to give informed consent, such as:
    - Persons deprived of liberty by a judicial or administrative decision;
    - Adult persons subject to a legal protection measure (under supervision/under guardianship); or
    - Persons under a judicial protection measure; or
26. Have a history of or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or make participation in the study not in the best interest of the patient, in the opinion of the Investigator.

STUDY DESIGN AND DURATION:

This is an open-label, multi-center, non-randomized Phase 1b/2a study. The Phase 1b portion of the study (ie, the first 6 patients enrolled) will confirm the recommended CyPep-1 dose of 20 mg every 2 weeks (Q2W) in combination with pembrolizumab 400 mg every 6 weeks (Q6W). The patients from the Phase 1b portion will continue to the Phase 2a portion of the study (approximately 90 patients in total will be enrolled, with 30 patients per arm). The Phase 2a portion of the study will have 3 arms including patients with advanced or metastatic HNSCC, melanoma, or TNBC and will assess the efficacy, safety, and pharmacodynamics of CyPep-1 (20 mg Q2W) when administered directly into measurable tumor lesions in combination with the anti-programmed cell death protein 1 (PD-1) antibody pembrolizumab (400 mg Q6W).

After signing the ICF, patients will be assessed for study eligibility. The Screening Visits will be completed within 28 days of the start of treatment. Screening will include the identification of measurable tumor lesions as per RECIST v1.1. Patients with lesions appropriate for IT injection with CyPep-1 (injected lesions) should be identified and will receive up to 4 mL of CyPep-1, after it is ensured that they meet the Inclusion Criteria and none of the Exclusion Criteria per the Investigator.

When more than 1 measurable lesion is present at screening, up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. Both injected and non-injected lesions identified at screening per RECIST v1.1 may be target lesions and will be recorded and measured at baseline and followed for response. If a patient only has 1 measurable lesion, then this lesion will be identified as an injected lesion and will be evaluated for efficacy as a target lesion. In these cases, IT therapy will not be considered a loco-regional therapy exclusionary for measurability, and single lesions may be designated as injectable target lesions per intratumoral-RECIST (itRECIST).

After each of the first 3 CyPep-1 injections, a telephone call will be conducted once daily for the first 2 days and once approximately 1 week post injection to assess patients' symptoms and temperatures.

AEs will be recorded from the time of signing the ICF until 30 days after the last dose of study treatment. All AEs that are considered serious will be monitored and recorded until 90 days (30 days if patients initiate new anti-cancer therapy) after the last dose of study treatment. Other safety assessments will be conducted as described in the Schedule of Assessments. The Data Monitoring Committee (DMC) will review accumulating safety data in regular intervals as per the DMC charter.

Phase 1b

The Phase 1b portion of the study will comprise of the first 6 patients enrolled in the study to confirm the recommended CyPep-1 dose (20 mg Q2W) based on safety and tolerability observations.

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

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

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

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

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

The MTD will guide confirmation, by agreement of the DMC and the Sponsor, of a recommended Phase 2 dose (RP2D). The RP2D may be equivalent to the MTD or may be a dose below the MTD and will be dependent on an acceptable tolerability profile and manageable AEs.

The patients from Phase 1b will continue to the Phase 2a portion of the study. After the DMC reviews the safety data, feedback will be provided to the Sponsor regarding the further conduct of the study.

Dose-limiting toxicities

All toxicities will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 based on the Investigator assessment.

The DLT window of observation will be during Cycle 1 (initial 6 weeks of study treatment).

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

1. Grade 4 non-hematologic toxicity (not laboratory);
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration; or
    - Grade 3 thrombocytopenia associated with clinically significant bleeding.

3. Any non-hematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions:
   - Grade 3 fatigue lasting ≤3 days;
   - Grade 3 diarrhea, nausea, or vomiting unless it persists for >3 days despite the use of anti-emetics or anti-diarrheals per standard of care; or
   - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Clinically significant medical intervention is required to treat the patient;
   - The abnormality leads to hospitalization;
   - The abnormality persists for >1 week; or
   - The abnormality results in a drug-induced liver injury.
   - Exceptions: Clinically non-significant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc. Isolated laboratory abnormalities ≥Grade 3 (not present at baseline) that resolve to <Grade 1 in <3 days without clinical sequelae or need for therapeutic intervention.
5. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour; or
   - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity;
7. Delay in administration of CyPep-1 for >7 days;
8. Any single instance of aspartate aminotransferase and/or alanine aminotransferase >3 × upper limit of normal (ULN) AND concurrent total bilirubin >2 × ULN that is not thought to be due to disease progression or other medical illness (ie, liver function abnormalities that meet the criteria of Hy's Law);
9. Any treatment-related toxicity that causes the patient to discontinue treatment during Cycle 1;
10. Missing >25% of study treatment doses as a result of drug-related AE(s) during the first cycle; or
11. Grade 5 toxicity.

Phase 2a

The Phase 2a portion of the study will comprise of all approximately 90 patients (including the first 6 patients assessed in the Phase 1b portion) to assess the efficacy, safety, and pharmacodynamics of CyPep-1 (20 mg Q2W) in combination with the anti-PD-1 antibody

pembrolizumab (400 mg Q6W). Patients will receive IT injections of a fixed concentration of CyPep-1 Q2W beginning at Cycle 1 Visit 1. Pembrolizumab will be administered IV at a fixed dose Q6W beginning at Cycle 1 Visit 1. Each treatment cycle will be 6 weeks, and treatment will continue for a maximum of 18 cycles (108 weeks) or until the occurrence of confirmed progressive disease (PD), excessive toxicity, death, or withdrawal of consent. Patients who complete all 18 cycles, which is the Food and Drug Administration-approved maximum duration of pembrolizumab use, may continue receiving CyPep-1 at the current dose if determined beneficial by the Investigator and following approval of the Sponsor. CyPep-1 monotherapy may proceed until the occurrence of confirmed PD, excessive toxicity, death, or withdrawal of consent.

Radiological assessments and local measurements of tumor lesion(s), according to RECIST v1.1, will be conducted and evaluated at baseline (screening) and at 8-week intervals after the first dose of CyPep-1 through the last Progression Follow-up Visit during the Follow-up Period (up to approximately 26 months after the start of treatment). Radiological assessments can be more frequent if clinically indicated. Magnetic resonance imaging (MRI) or computed tomography (CT) are the preferred scanning procedures to be used in this study. Selection of either MRI or CT should be based on individual patient considerations and local regulations and is at the Investigator's discretion. Once selected for each patient, the same scanning procedure should be used consistently at all remaining visits. Scans will be collected and held centrally for potential central radiologic review. When radiological PD is identified by the Investigator, PD is to be confirmed by another set of scans performed approximately 4 weeks to ≤8 weeks later according to immune-RECIST (iRECIST) guidelines. If PD is not confirmed, study treatment will continue until progression is confirmed.

Patients who have confirmed PD or discontinue treatment for any other reason will be followed-up by phone call every 3 months for survival until the end of study (approximately 26 months after the start of treatment).

Unless death or withdrawal of consent occurs, patients who received any injection of CyPep-1 will have a Safety Follow-up Visit 30 days after the last CyPep-1 injection. If the End of Treatment Visit occurs more than 30 days after the last dose of study treatment, the Safety Follow-up Visit will be skipped. Patients who terminate treatment prior to 18 cycles will continue to be followed for progression every 8 weeks from start of study treatment until the occurrence of confirmed PD as defined by iRECIST or start of new anti-cancer treatment. These patients will also be followed for survival for up to approximately 26 months after the start of treatment.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

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

CyPep-1 Administration

CyPep-1 will be administered Q2W as an IT injection. CyPep-1 will be administered through a needle, which should be redirected along multiple tracks to ensure even dispersion of CyPep-1 throughout the tumor lesion. On the visits that CyPep-1 and pembrolizumab are administered on the same day, CyPep-1 is to be administered 30 to 60 minutes **after** pembrolizumab infusion is completed. Following CyPep-1 administration, patients must be observed for 4 hours post injection at Cycle 1 Visit 1 and Cycle 2 Visit 1 and 1 hour post injection at Cycle 1 Visit 2 and

Cycle 1 Visit 3 for potential immediate injection-related reactions. Refer to the Guidance for Intra-tumoral Administration of CyPep-1 study manual for more details.

The cumulative maximal injected volume of CyPep-1 will be 4 mL (cumulative maximal dose of 20 mg at the recommended 5 mg/mL concentration) per treatment day for each patient, and it may be divided for injection over 1 to 3 tumor lesions (satellitosis/grouped lesions <1 cm count as 1 lesion) depending on tumor lesion size; see Table S3. The injected lesions identified at baseline should be injected 3 times before selecting new lesions to inject, unless there is a complete response or the lesion, by the Investigator's assessment, has been adequately treated (eg, reduced size and highly inflamed). The volume of CyPep-1 delivered to each injected lesion will be determined based on the longest diameter of the lesion. Effort should be made to administer the maximum volume of CyPep-1 as planned per lesion size; see Table S3.

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Pembrolizumab Administration

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

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

SAFETY VARIABLES:

Safety will be assessed by physical examinations, vital signs, 12-lead electrocardiograms (ECGs), ECOG performance status, laboratory evaluations, and AEs (as defined by NCI CTCAE v5.0) as indicated in the Schedule of Assessments. Additional assessments may be performed as clinically indicated.

Safety will be monitored in conjunction with the DMC and as per DMC charter.

STATISTICAL ANALYSES:

Analysis Sets

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

The Evaluable Analysis Set (EAS) will include all patients who receive an injection of CyPep-1 on at least 2 treatment days, receive at least 1 administration of pembrolizumab, and have at least 1 post-baseline tumor response assessment after the first injection of CyPep-1 (Cycle 1 Visit 1).

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

Analysis of Efficacy

Analysis of efficacy will be conducted in Phase 2a. Efficacy analyses will be done using the FAS. The Objective Response Rate (ORR) will be based on the number of patients achieving a partial response (PR) or complete response (CR) based on RECIST v1.1 and iRECIST. Best overall response will also be calculated. The Disease Control Rate will be based on the number of patients achieving a PR, CR, or stable disease ≥16 weeks based on RECIST v1.1 and iRECIST. Progression Free Survival (PFS) (percentage of patients alive and progression-free) at 6, 12, 18, and 24 months after the first treatment with CyPep-1 + pembrolizumab will be determined. A progression event is defined as disease relapse or progression (based on all lesions) or death due to any cause. For patients who are not known to have died or progressed as of the data cut-off date, PFS will be censored at the date of the last objective progression-free disease assessment. Patients who discontinue the study treatment without post-treatment assessments will be treated as non-responders. The detailed censoring rules will be specified in the Statistical Analysis Plan. Sensitivity analysis for primary efficacy endpoints will be provided using the EAS. An exploratory analysis of itRECIST will be applied to allow for a separate response assessment of injected and non-injected lesions.

Analysis of Safety

Safety analysis will be conducted in both Phase 1b and Phase 2a using the SAS. Treatment-emergent AE (TEAE) incidence rates will be described by the frequency of TEAEs and categorized by preferred term and system organ class according to the NCI CTCAE v5.0. TEAEs will be summarized by seriousness, grade, and relationship to CyPep-1 and pembrolizumab. The incidence of TEAEs will be evaluated for each study arm and for all patients combined. The following data will be summarized using descriptive statistics: treatment exposure, disposition, vital signs, body weight, 12-lead ECG parameters, and laboratory assessments. Shift tables showing changes from baseline will be generated where appropriate. Summaries will be by arm and for all patients.

The incidence of DLT events during the DLT period will be presented.

Analysis of Pharmacokinetics

Phase 1b patients who have received CyPep-1 and have provided 1 evaluable pre-dose and at least 1 post-dose PK blood sample will be evaluable for PK. Standard methodology will be used to estimate PK parameters. Concentration-time profiles will be derived for patients with post-dose samples.

SAMPLE SIZE DETERMINATION:

The Simon's 2-Stage Design is used in the Phase 2 portion, which allows the study to be stopped for futility and provides a recommendation for continuation from Stage 1 to Stage 2.

CATALYST is a hypothesis-generating study for the combination of CyPep-1 with pembrolizumab. The hypothesis implemented in the Simon's 2-Stage Design disease model uses the historical objective responses observed in pembrolizumab single-agent Phase 2 trials. The

rationale and statistical details are provided in the key references of the 3+3 dose-escalation design for Phase 1 trials in oncology.

The sample size for the Phase 1b portion of the study is based on practical determinations. The first 6 patients of the study are planned to be enrolled in the Phase 1b portion. Approximately 90 patients will be enrolled, with 30 patients per arm. Assuming 10% of enrolled patients will not have evaluable post-baseline tumor response data, it is expected that approximately 27 patients will be included in the evaluable set in each arm.

While all endpoints will be reviewed to assess activity of CyPep-1, and the sample size is based on practical rather than statistical considerations, the level of precision that is achieved for 27 patients on the primary endpoint, ORR, is as follows:

A sample size of 27 patients will produce a 2-sided exact 80% confidence interval of 34.4% to 62.0% when the sample proportion is 48% (13/27) and an interval of 38.1% to 65.5% when the sample proportion is 52% (14/27). The lower bounds are computed through an exact binomial test.

The Simon's 2-Stage Design will be used in the Phase 2 portion to determine whether CyPep-1 has sufficient anti-tumor activity to warrant further development for patients with advanced or metastatic HNSCC, melanoma, or TNBC. A true ORR ≤9% is considered insufficient to warrant further study (null hypothesis), whereas a true ORR ≥25% is considered sufficiently effective (alternative hypothesis). The number of patients in each stage and the minimum number of patients achieving objective response (CR + PR) per RECIST v1.1 needed to continue to the next stage will be determined based on the Simon's 2-Stage Design with 80% power and a 1-sided significance level of 10% for each arm separately. Based on this design, up to 16 evaluable patients will be accrued for Stage 1. If ≤1 patient of these 16 patients achieves objective response (CR + PR) per RECIST v1.1, the enrollment for the expansion cohort will terminate. Otherwise, 10 additional evaluable patients will be evaluated in Stage 2. In order to enroll the required number of evaluable patients, it is anticipated that approximately 18 and 12 patients (total of approximately 30 patients) will be enrolled into Stages 1 and 2, respectively. Upon completion of Stage 2, if >4 patients out of the total 26 evaluable patients achieve objective response (CR + PR) per RECIST v1.1, then the null hypothesis will be rejected. If the required minimum number of responses is observed prior to completion of enrollment, then the transition between the first and second stages will occur without interruption. If the minimum is not observed at the time enrollment is completed, then enrollment in the second stage will be held until the continuation criterion is met.

SITES: Approximately 35 study sites

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AECI	Adverse event of clinical interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
CD	Cluster of differentiation
CFR	Code of Federal Regulations
C_{max}	Peak plasma concentration
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CR	Complete response
CRA	Clinical Research Associate
CSR	Clinical Study Report
CT	Computed tomography
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
DEC	Dose Escalation Committee
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DRF	Dose range finding
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EoT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICI	Immune checkpoint inhibitor
IEC	Independent Ethics Committee
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune-Response Evaluation Criteria in Solid Tumors
IT	Intra-tumoral(ly)
itRECIST	Intratumoral-Response Evaluation Criteria in Solid Tumors
IV	Intravenous(ly)
LOQ	Limit of quantification
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q8W	Every 8 weeks
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
T_{max}	Time to reach peak plasma concentration
TNBC	Triple-negative breast cancer
ULN	Upper limit of normal
v	Version

[redacted]

and

[redacted]

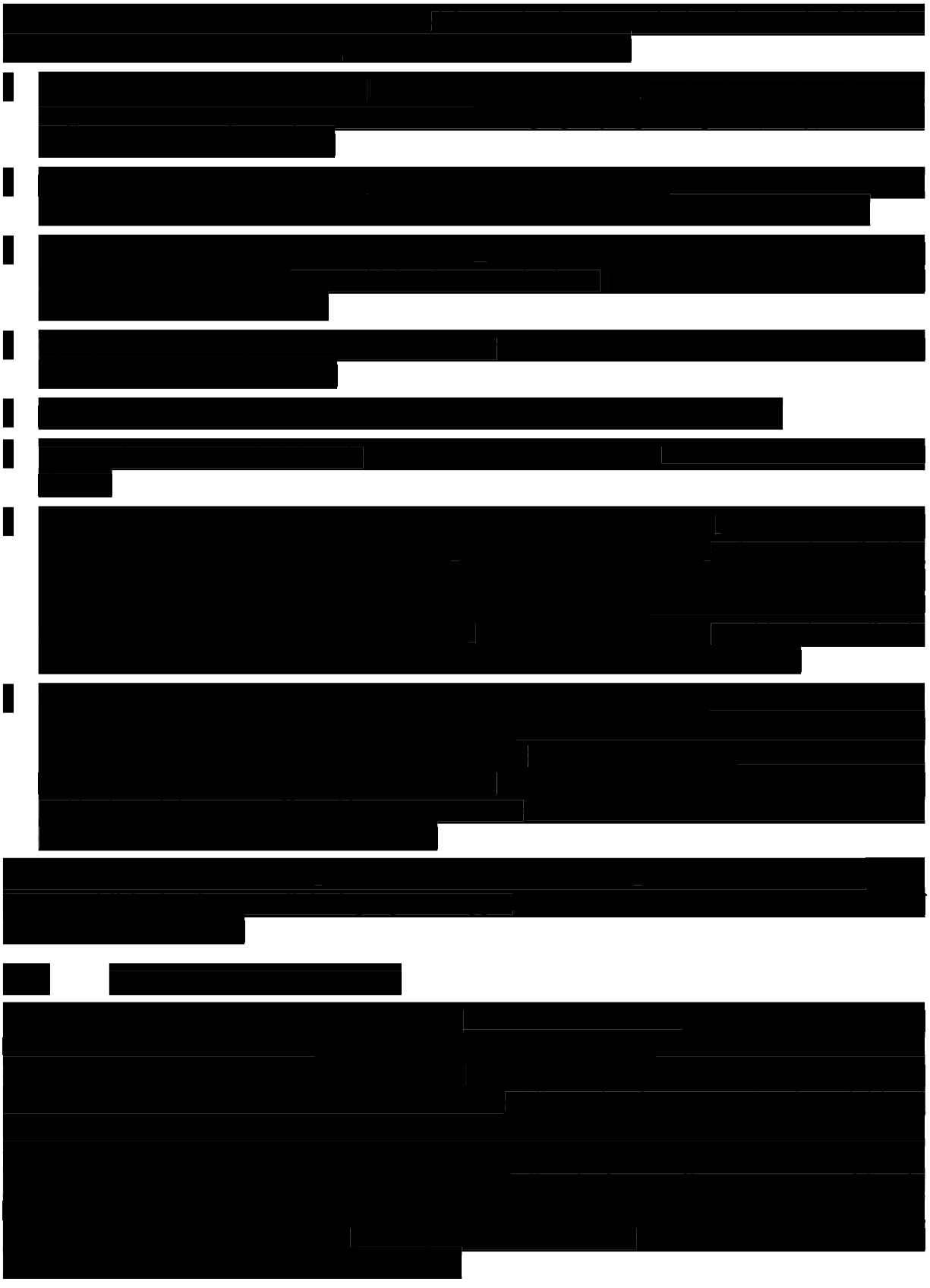


Figure 1. Individual Time-Serum Profiles for CyPep-1 (CICILIA Study)

be computed in only 2 instances, for 1 subject in Cohort 2 and 1 subject in Cohort 3. For 4 additional subjects (3 in Cohort 2 and 1 in Cohort 3) at least 1 sample was quantifiable enabling peak plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) to be computed as sole PK parameters. Descriptive statistics of the computed PK parameters by cohort is provided in Table 3.

Table 3. Descriptive Statistics of Computed Pharmacokinetic Parameters by Cohort

-1

To date in the CICILIA study, the most frequently reported treatment-emergent adverse event (TEAE) was "injection site pain" and occurred in all 3 dose cohorts. No fatal TEAE or SAE/Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported. Additionally, no TEAE leading to CyPep-1 discontinuation was reported; see Table 4 which shows data from the Safety Report of the CICILIA study part I (dose escalation).

The most common CyPep-1-related adverse event (AE) was "injection site pain" and was reported in Cohorts 2 and 3.

Table 4. Cumulative Treatment-Emergent Adverse Events and CyPep-1-Related Treatment-Emergent Adverse Events by Preferred Term (CICILIA Study)

Cohort	AE PT	Grade 1 (n events)	Grade 2 (n events)	Grade 3/4 (n events)	All Grades (n events)	SAE/SUSARS
Cumulative TEAEs per PT						
1	Constipation	3	0	0	3	0
1	Injection site pain	2	0	0	2	0
2	Anaemia	0	1	1	2	0
2	Cough	1	1	0	2	0
2	Fatigue	1	1	0	2	0
2	Injection site pain	5	1	0	6	0
2	Nausea	2	0	0	2	0
2	Cancer pain	1	2	0	3	0
2	Urinary tract infection	0	2	0	2	0
2	Vomiting	1	0	1	2	0
3	Cancer pain	7	6	1	14	0
3	Constipation	3	1	0	4	0
3	Fatigue	2	0	0	2	0
3	Injection site pain	15	1	0	16	0
Cumulative CyPep-1-related TEAEs per PT						
3	Injection site pain	11	1	0	12	0
2	Injection site pain	5	1	0	6	0
2	Fatigue	0	1	0	1	0
1	Pyrexia	1	0	0	1	0
2	Nausea	1	0	0	1	0
2	Rash macular	1	0	0	1	0
2	Vomiting	1	0	0	1	0
3	Injection site oedema	1	0	0	1	0
3	Pain in extremity	1	0	0	1	0
3	Platelet count decreased	1	0	0	1	0
3	Skin wound	1	0	0	1	0
3	Vitiligo	1	0	0	1	0

AE = adverse event; n = number of subjects; PT = preferred term; SAE = serious adverse event; SUSAR = Suspected Unexpected Serious Adverse Reaction; TEAE = treatment-emergent adverse event.
Source: Investigator's Brochure for CyPep-1

Analysis of the reported TEAEs across the dose cohorts showed no increase in the number of TEAEs per subject in the higher dose levels; see Table 5.

Table 5. Frequency of Reported Treatment-Emergent Adverse Events per Dose Cohort (CICILIA Study)

	Cohort 1 (n=3)			Cohort 2 (n=5)			Cohort 3 (n=6)		
Relatedness	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Not related TEAE	10	2	7	12	9	5	20	9	3
Related TEAE	1	0	0	8	2	0	16	1	0

n = number of subjects; TEAE = treatment-emergent adverse event.
Source: Investigator's Brochure for CyPep-1

Additionally, CyPep-1 is currently being evaluated in a randomized, placebo-controlled, double-blind, single center Phase 1 study as topical formulation administered to subjects with cutaneous warts (Study CHDR1803).

1.2 [redacted]

[redacted]

This Phase 1b/2a study will assess the efficacy, safety, and pharmacodynamics of CyPep-1 when administered directly into measurable tumor lesions in combination with the anti-PD-1 antibody pembrolizumab. Additionally, the study will assess anti-tumor effects of CyPep-1 on injected lesions and non-injected target lesions identified at baseline, as well as local and systemic immunological effects of CyPep-1 in combination with pembrolizumab.

1.3 Risk/Benefit

1.3.1 Potential Risks

Based on preclinical experience and available clinical data from the ongoing Phase 1/2a CICILIA study, there are no specific adverse reactions to be inferred as "expected" at the 20 mg every 2 weeks (Q2W) dose level of CyPep-1.

1.3.2 Benefit

The efficacy and safety data, together with the pharmacodynamic data obtained from this study, will help design subsequent clinical studies in the target populations. Treatment of patients with CyPep-1 in combination with pembrolizumab is expected to result in improvement or stabilization of the disease state of the patients.

1.4 Coronavirus Disease 2019 Impacts

In March 2020, the Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was characterized as a pandemic by the World Health Organization. The COVID-19 pandemic has impacted clinical studies worldwide due to quarantines, study site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

The impacts of the COVID-19 pandemic on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the Clinical Study Report (CSR).

2 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are provided in Table 6.

Table 6. Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
Phase 1b	
Confirm the recommended CyPep-1 dose (20 mg Q2W) when administered by IT injection in combination with pembrolizumab	• Incidence, frequency, and seriousness of TEAEs; • Incidence of DLTs; and • Changes from baseline in vital signs, body weight, 12-lead ECG parameters, and laboratory assessments.
Phase 2a	
Assess the anti-tumor activity of CyPep-1 administered by IT injection in combination with pembrolizumab	ORR based on radiological assessment according to RECIST v1.1
Secondary Objectives	**Secondary Endpoints**
Phase 1b	
Evaluate the PK of CyPep-1 in combination with pembrolizumab	• Plasma concentration-time profile of CyPep-1 and, if detectable, the following derived PK parameters: o AUC; o C_{max}; o T_{max}; o CL; o $t_{½}$; and o VD.
Phase 2a	
Expand evaluation of efficacy CyPep-1 + pembrolizumab	• ORR according to iRECIST; • DCR according to iRECIST and RECIST v1.1; • DoR according to iRECIST and RECIST v1.1; • PFS according to iRECIST and RECIST v1.1; and • OS for up to 26 months from Cycle 1 Visit 1.
Evaluate the safety and tolerability of CyPep-1 in combination with pembrolizumab	• Incidence, frequency, and seriousness of TEAEs; and • Changes from baseline in vital signs, body weight, 12-lead ECG parameters, and laboratory assessments.

Table 6. Objectives and Endpoints (Continued)

Exploratory Objectives	Exploratory Endpoints
Analyze changes in biomarkers and tumor kinetics associated with the mode of action of CyPep-1 and pembrolizumab by tumor biopsy from injected lesions	• Number and relative change of tumor infiltrating immune cells; • Expression of selected immune cell biomarkers; • Change from baseline in target tumor lesion size over time, overall, and by injected versus non-injected lesions; • Maximum decrease from baseline in target tumor lesions, overall, and by injected versus non-injected lesions; and • Changes in new lesions treated with CyPep-1.
Expand evaluation of anti-tumor activity of CyPep-1 and pembrolizumab	ORR according to itRECIST

AUC = area under the curve; CL = systemic clearance; C_{max} = peak plasma concentration; DCR = Disease Control Rate; DLT = dose-limiting toxicity; DoR = Duration of Response; ECG = electrocardiogram; iRECIST = immune-Response Evaluation Criteria in Solid Tumors; IT = intra-tumoral; itRECIST = intratumoral-Response Evaluation Criteria in Solid Tumors; ORR = Objective Response Rate; OS = Overall Survival; PFS = Progression Free Survival; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; $t_{½}$ = elimination half-life; TEAE = treatment-emergent adverse event; T_{max} = time to reach peak plasma concentration; v = version; VD = volume of distribution.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is an open-label, multi-center, non-randomized Phase 1b/2a study. The Phase 1b portion of the study (ie, the first 6 patients enrolled) will confirm the recommended CyPep-1 dose of 20 mg Q2W in combination with pembrolizumab 400 mg Q6W (see Section 3.1.1). The patients from the Phase 1b portion will continue to the Phase 2a portion of the study (approximately 90 patients in total will be enrolled, with 30 patients per arm). The Phase 2a portion of the study will have 3 arms including patients with advanced or metastatic head and neck squamous cell carcinoma (HNSCC), melanoma, or triple-negative breast cancer (TNBC) and will assess the efficacy, safety, and pharmacodynamics of CyPep-1 (20 mg Q2W) when administered directly into measurable tumor lesions in combination with the anti-PD-1 antibody pembrolizumab (400 mg Q6W) (see Section 3.1.2).

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

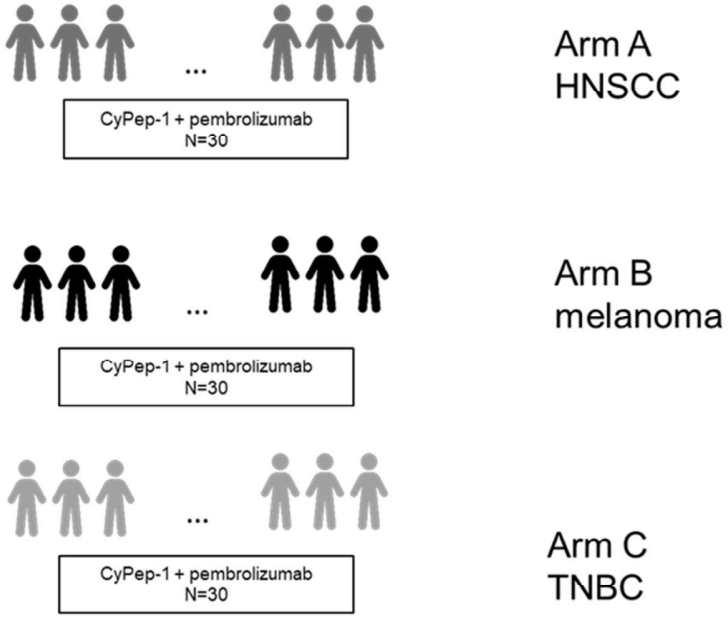
- Arm A will include patients who meet the following criteria:
  - Have histologically confirmed diagnosis of HNSCC (including nasopharyngeal squamous cell carcinoma);
  - Have advanced or metastatic HNSCC incurable by standard of care therapies; and
  - Have recurrent or metastatic HNSCC that has progressed on or failed both platinum-based chemotherapy AND an ICI (given either sequentially or concurrently).

    Note: Patients who received platinum-based chemotherapy with concurrent radiation for locally advanced HNSCC and experienced disease progression within 6 months may also be considered as having disease progression on platinum-based chemotherapy.
- Arm B will include patients who meet the following criteria:
  - Have histologically confirmed diagnosis of malignant melanoma;
  - Do not have uveal melanoma;
  - Have advanced or metastatic melanoma incurable by standard of care therapies;
  - Have received a combination of a BRAF inhibitor and a MEK inhibitor if diagnosed with a BRAF-mutated melanoma and if clinically indicated; and
  - Have failed or progressed on or after treatment with a checkpoint inhibitor administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies.
- Arm C will include patients who meet the following criteria:
  - Have histologically confirmed diagnosis of TNBC as per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines;[24]
  - Have advanced or metastatic TNBC incurable by standard of care therapies;

- Have received sacituzumab govitecan chemotherapeutic treatment if clinically indicated; and
- Have failed or progressed on or after treatment with a checkpoint inhibitor administered either as monotherapy or in combination with other therapies (if ICI eligible based on PD-L1 status) OR have received prior systemic therapy with either an anthracycline- or taxane-containing regimen (if ICI non-eligible based on PD-L1 status).

The study enrollment will follow a 1-stage design as shown in Figure 2.

Figure 2. One-Stage Study Design



HNSCC = head and neck squamous cell carcinoma; N = number of patients planned for each arm; TNBC = triple-negative breast cancer.

After signing the informed consent form (ICF), patients will be assessed for study eligibility. The Screening Visits will be completed within 28 days of the start of treatment. Screening will include the identification of measurable tumor lesions as per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1. Patients with lesions appropriate for IT injection with CyPep-1 (injected lesions) should be identified and will receive up to 4 mL of CyPep-1, after it is ensured that they meet the Inclusion Criteria (see Section 4.1) and none of the Exclusion Criteria (see Section 4.2) per the Investigator.

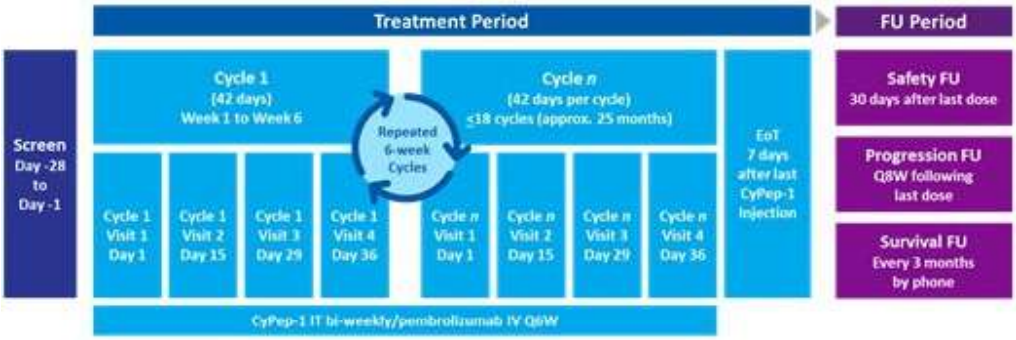
When more than 1 measurable lesion is present at screening, up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. Both injected and non-injected lesions identified at screening per RECIST v1.1 may be target lesions and will be recorded and measured at baseline and followed for response. If a patient only has 1 measurable lesion, then this lesion will be identified as an injected lesion and will be evaluated for efficacy as a target lesion. In these cases, IT therapy will not be considered a loco-regional therapy exclusionary for measurability, and single lesions may be designated as injectable target lesions per intratumoral-RECIST (itRECIST).

After each of the first 3 CyPep-1 injections, a telephone call will be conducted once daily for the first 2 days and once approximately 1 week post injection to assess patients' symptoms and temperatures.

AEs will be recorded from the time of signing the ICF until 30 days after the last dose of study treatment. All AEs that are considered serious will be monitored and recorded until 90 days (30 days if patients initiate new anti-cancer therapy) after the last dose of study treatment. Other safety assessments will be conducted as described in the Schedule of Assessments (Appendix A). The Data Monitoring Committee (DMC) will review accumulating safety data in regular intervals as per the DMC charter.

An overview of the study flow is presented in Figure 3.

Figure 3. Study Flow



The Phase 1b portion of the study will comprise of the first 6 patients enrolled in the study. After the first 6 patients have completed the DLT period (Cycle 1 [initial 6 weeks of study treatment]), the DMC and Sponsor will review safety and tolerability data prior to the enrollment of the remainder of the patients into the Phase 2a portion of the study.
DLT = dose-limiting toxicity; DMC = Data Monitoring Committee; EoT = End of Treatment; FU = follow-up; IT = intra-tumoral(ly); IV = intravenous(ly); n = number of treatment cycle; Q6W = every 6 weeks; Q8W = every 8 weeks; Screen = screening.

3.1.1 Phase 1b

The Phase 1b portion of the study will comprise of the first 6 patients enrolled in the study to confirm the recommended CyPep-1 dose (20 mg Q2W) based on safety and tolerability observations.

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

The DLT period for the Phase 1b portion of the study will be Cycle 1 (initial 6 weeks of study treatment); see Section 3.1.1.1. After the first 6 patients have completed the DLT period, the DMC and Sponsor will review safety and tolerability data prior to the enrollment of the patients into the Phase 2a portion of the study. If ≤2 DLTs are observed in the first 6 patients, then the recommended CyPep-1 dose will be confirmed and enrollment of the remainder of the patients should continue.

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

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

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

The MTD will guide confirmation, by agreement of the DMC and the Sponsor, of a recommended Phase 2 dose (RP2D). The RP2D may be equivalent to the MTD or may be a dose below the MTD and will be dependent on an acceptable tolerability profile and manageable AEs.

The patients from Phase 1b will continue to the Phase 2a portion of the study. After the DMC reviews the safety data, feedback will be provided to the Sponsor regarding the further conduct of the study, see Section 3.1.2.

3.1.1.1 Dose-limiting toxicities

All toxicities will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 based on the Investigator assessment.

The DLT window of observation will be during Cycle 1 (initial 6 weeks of study treatment).

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

1. Grade 4 non-hematologic toxicity (not laboratory);
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
    - Grade 4 thrombocytopenia of any duration; or
    - Grade 3 thrombocytopenia associated with clinically significant bleeding.
3. Any non-hematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions:
    - Grade 3 fatigue lasting ≤3 days;
    - Grade 3 diarrhea, nausea, or vomiting unless it persists for >3 days despite the use of anti-emetics or anti-diarrheals per standard of care; or
    - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
4. Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the patient;
    - The abnormality leads to hospitalization;
    - The abnormality persists for >1 week; or

- The abnormality results in a drug-induced liver injury.
- Exceptions: Clinically non-significant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc. Isolated laboratory abnormalities ≥Grade 3 (not present at baseline) that resolve to <Grade 1 in <3 days without clinical sequelae or need for therapeutic intervention.

5. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour; or
   - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour with life-threatening consequences and urgent intervention indicated.
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity;
7. Delay in administration of CyPep-1 for >7 days;
8. Any single instance of aspartate aminotransferase and/or alanine aminotransferase >3 × upper limit of normal (ULN) AND concurrent total bilirubin >2 × ULN that is not thought to be due to disease progression or other medical illness (ie, liver function abnormalities that meet the criteria of Hy's Law);
9. Any treatment-related toxicity that causes the patient to discontinue treatment during Cycle 1;
10. Missing >25% of study treatment doses as a result of drug-related AE(s) during the first cycle; or
11. Grade 5 toxicity.

3.1.2 Phase 2a

The Phase 2a portion of the study will comprise of all approximately 90 patients (including the first 6 patients assessed in the Phase 1b portion) to assess the efficacy, safety, and pharmacodynamics of CyPep-1 (20 mg Q2W) in combination with the anti-PD-1 antibody pembrolizumab (400 mg Q6W). Patients will receive IT injections of a fixed concentration of CyPep-1 Q2W beginning at Cycle 1 Visit 1. Pembrolizumab will be administered IV at a fixed dose Q6W beginning at Cycle 1 Visit 1. Each treatment cycle will be 6 weeks, and treatment will continue for a maximum of 18 cycles (108 weeks) or until the occurrence of confirmed progressive disease (PD), excessive toxicity, death, or withdrawal of consent. Patients who complete all 18 cycles, which is the Food and Drug Administration (FDA)-approved maximum duration of pembrolizumab use, may continue receiving CyPep-1 at the current dose if determined beneficial by the Investigator and following approval of the Sponsor. CyPep-1 monotherapy may proceed until the occurrence of confirmed PD, excessive toxicity, death, or withdrawal of consent.

Radiological assessments and local measurements of tumor lesion(s), according to RECIST v1.1, will be conducted and evaluated at baseline (screening) and at 8-week intervals after the first dose of CyPep-1 through the last Progression Follow-up Visit during the Follow-up Period (up to approximately 26 months after the start of treatment). Radiological assessments can be more frequent if clinically indicated. Magnetic resonance imaging (MRI) or computed tomography (CT)

are the preferred scanning procedures to be used in this study. Selection of either MRI or CT should be based on individual patient considerations and local regulations and is at the Investigator's discretion. Once selected for each patient, the same scanning procedure should be used consistently at all remaining visits. Scans will be collected and held centrally for potential central radiologic review. When radiological PD is identified by the Investigator, PD is to be confirmed by another set of scans performed approximately 4 weeks to ≤8 weeks later according to immune-RECIST (iRECIST) guidelines (Appendix D). If PD is not confirmed, study treatment will continue until progression is confirmed.

Patients who have confirmed PD or discontinue treatment for any other reason will be followed-up by phone call every 3 months for survival until the end of study (approximately 26 months after the start of treatment).

Unless death or withdrawal of consent occurs, patients who received any injection of CyPep-1 will have a Safety Follow-up Visit 30 days after the last CyPep-1 injection. If the End of Treatment (EoT) Visit occurs more than 30 days after the last dose of study treatment, the Safety Follow-up Visit will be skipped. Patients who terminate treatment prior to 18 cycles will continue to be followed for progression every 8 weeks (Q8W) from start of study treatment until the occurrence of confirmed PD as defined by iRECIST (Appendix D) or start of new anti-cancer treatment. These patients will also be followed for survival for up to approximately 26 months after the start of treatment.

3.1.3 Data Monitoring Committee

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

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

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

At the end of each DMC review meeting, the DMC will provide 1 of the following feedback to the Sponsor:

- The study is proceeding in line with the study protocol; or
- The study is not proceeding in line with the study protocol and/or there is a possible change in the benefit/risk ratio.

The observation of any Discontinuation of Enrollment Criteria (Section 4.5.3) for Phase 2a patients must trigger the immediate decision by the Sponsor to stop recruitment and organize an urgent DMC meeting, which will assess the causality of the observed AEs and the fulfillment of the criteria. The DMC will formulate a recommendation to resume recruitment, discontinue the involved cohort, or stop the study.

The Sponsor will act upon the feedback as appropriate, ie, the final decision will be made by the Sponsor. The Sponsor or designee will notify the study team (ie, the responsible project manager) of the final decision regarding the DMC feedback, including any actions to be taken. The Sponsor or designee will communicate the DMC feedback and/or final decision of the Sponsor to all

Investigators and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), if applicable.

3.1.4 Coronavirus Disease 2019 Contingency Measures

In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of patients via phone or video contact to assess the patient's well-being and assess for any AEs and collect additional clinical data as best as possible. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. Documentation of these cases and the study site's management of patients should be recorded in the Investigator study files. The impacts of the COVID-19 pandemic on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the CSR. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

3.2 Study Indications

The indications of this study are advanced or metastatic HNSCC, melanoma, or TNBC.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

No waivers for inclusion or exclusion criteria will be given.

4.1.1 General Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Are 18 years of age or older on the day of signing informed consent;
2. Provide written informed consent and are able to comply with study procedures and assessments;
3. Have measurable disease per RECIST v1.1 as assessed by the local site Investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions;
4. Have at least 1 non-ulcerated, measurable, and accessible lesion for IT injection with a maximum diameter of 5 cm;
5. Are able to provide tissue from a core or excisional biopsy at screening or have an acceptable stored tumor sample available that was collected within 90 days prior to screening;
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix C);
7. Have a life expectancy ≥3 months, as determined by the Investigator;
8. Female patients of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before screening), post-menopausal, defined as spontaneous amenorrhea for at least 2 years, or with follicle-stimulating hormone in the post-menopausal range at screening;
9. Female patients of childbearing potential (defined as <2 years after last menstruation or not surgically sterile) must have a negative serum pregnancy test at screening and agree to use a highly effective method for contraception from the time of signing the ICF until at least 120 days after the last administration of study treatment. Highly effective methods of contraception are birth control methods with a failure rate of <1% per year when used consistently and correctly, including the following:
    - Combined estrogen- and progestin-containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally; progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant; intrauterine devices; and intrauterine hormone-releasing systems;
    - Female sterilization (surgical bilateral oophorectomy with/without hysterectomy, total hysterectomy, bilateral tubal occlusion/ligation) at least 26 weeks prior to first study treatment;
    - Sterilization of male partner (at least 6 months prior to first study treatment dose); and
    - Complete sexual abstinence. Periodic abstinence (eg, calendar) and withdrawal are not acceptable. Sexual abstinence is considered a highly effective method only if defined as

refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

10. Male patients able to father children must agree to use 2 acceptable methods of contraception throughout the study (eg, condom plus spermicidal gel). Sperm donation is not recommended from the time of signing the ICF until at least 120 days after the last administration of study treatment; and
11. Have adequate organ function as defined in Table 7. Specimens must be collected within 72 hours prior to the start of study treatment at Cycle 1 Visit 1.

Table 7. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100,000/µL
Hemoglobin[1]	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Creatinine OR Measured or calculated CrCl[2] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for patients with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for patients with liver metastases)

This table includes eligibility-defining laboratory value requirements for treatment.
1. Criteria must be met without pRBC transfusion within the prior 2 weeks. Patients can be on a stable dose of erythropoietin (approximately ≥3 months).
2. CrCl should be calculated per institutional standard.

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; pRBC = packed red blood cell; ULN = upper limit of normal.

4.1.2 Inclusion Criteria for Arm A

Patients who meet all of the general Inclusion Criteria (Section 4.1.1) and the following additional criteria will be eligible for inclusion in Arm A:

1. Have histologically confirmed diagnosis of HNSCC (including nasopharyngeal squamous cell carcinoma);
2. Have advanced or metastatic HNSCC incurable by standard of care therapies; and
3. Have recurrent or metastatic HNSCC that has progressed on or failed both platinum-based chemotherapy AND an ICI (given either sequentially or concurrently).

   Note: Patients who received platinum-based chemotherapy with concurrent radiation for locally advanced HNSCC and experienced disease progression within 6 months may also be considered as having disease progression on platinum-based chemotherapy.

4.1.3 Inclusion Criteria for Arm B

Patients who meet all of the general Inclusion Criteria (Section 4.1.1) and the following additional criteria will be eligible for inclusion in Arm B:

1. Have histologically confirmed diagnosis of malignant melanoma;
2. Do not have uveal melanoma;
3. Have advanced or metastatic melanoma incurable by standard of care therapies;
4. Have received a combination of a BRAF inhibitor and a MEK inhibitor if diagnosed with a BRAF-mutated melanoma and if clinically indicated; and
5. Have failed or progressed on or after treatment with a checkpoint inhibitor administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies.

4.1.4 Inclusion Criteria for Arm C

Patients who meet all of the general Inclusion Criteria (Section 4.1.1) and the following additional criteria will be eligible for inclusion in Arm C:

1. Have histologically confirmed diagnosis of TNBC as per ASCO/CAP guidelines;[24]
2. Have advanced or metastatic TNBC incurable by standard of care therapies;
3. Have received sacituzumab govitecan chemotherapeutic treatment if clinically indicated; and
4. Have failed or progressed on or after treatment with a checkpoint inhibitor administered either as monotherapy or in combination with other therapies (if ICI eligible based on PD-L1 status) OR have received prior systemic therapy with either an anthracycline- or taxane-containing regimen (if ICI non-eligible based on PD-L1 status).

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Have only non-palpable cutaneous infiltrations (eg, breast cancer cutaneous carcinomatosis);
2. Have had anti-cancer therapy within 4 weeks prior to the first dose of study treatment (2 weeks for palliative radiotherapy);

   Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline (alopecia is an allowable exception). Upon discussion with the Sponsor, patients with ≤Grade 2 neuropathy or endocrine-related AEs requiring treatment or hormone replacement may be eligible.

   Note: If the patient had major surgery, the patient must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
3. Have participated in a clinical trial and received an investigational therapy within 30 days prior to the first dose of study treatment;

4. Have received or will receive a live or live attenuated vaccine within 30 days prior to the first dose of study treatment;

   Note: Seasonal flu vaccines that do not contain live vaccine are permitted. COVID-19 vaccines are only permitted with documentation of the date of the vaccine if the last dose of vaccine was administered >14 days prior to the first dose of study treatment. The COVID-19 booster vaccine must be administered at least 14 days prior to the first dose of study treatment and is not allowed during the first 3 months of the Treatment Period.

5. Have tested positive for SARS-CoV-2 infection within 14 days prior to the Screening Visit;

   Note: Patients who have had a known SARS-CoV-2 infection >14 days prior to the Screening Visit are permitted at Investigator discretion and must present with no symptoms.

6. Have had a major surgical procedure within 14 days prior to the first dose of study treatment;
7. Are expected to require a systemic or localized anti-neoplastic therapy during participation in this study, excluding localized palliative radiotherapy to tumors not selected for evaluation of treatment response;

   Note: Use of denosumab for patients with bone metastasis is allowed.

8. Are pregnant or breastfeeding;
9. Have clinical evidence of a secondary malignancy actively progressing or requiring active treatment other than curative therapies for early stage (carcinoma in situ or Stage 1) carcinomas or non-melanoma skin cancer;
10. Have had any autoimmune disease requiring immunosuppressive therapy (ie, use of disease modifying agents, corticosteroids, or immunosuppressive drugs) within 2 years prior to the first dose of study treatment;

    Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

11. Have a condition requiring continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive agents within 2 weeks prior to the first dose of study treatment. Inhaled, intranasal, or topical (only on areas outside the injected lesion[s]) and physiological replacement doses of up to 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease;
12. Have abnormal or clinically significant coagulation parameters as determined by the Investigator (eg, prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT]) unless patients are on anti-coagulants in which case it must be within appropriate clinical levels;

    Note: Patients who are on anti-coagulants must be able to switch to a low molecular weight heparin or equivalent prior to Cycle 1 Day 1 and continue during the Treatment Period.

13. Have a significant history or clinical manifestation of any allergic disorders and/or Quincke's edema (as determined by the Investigator) capable of significantly altering the absorption of drugs, of constituting a risk when taking CyPep-1 or pembrolizumab, or of interfering with the interpretation of the data;

14. Have a known hypersensitivity to any component of CyPep-1 or pembrolizumab;
15. Have a history of adverse reactions from treatment with ICIs, including pembrolizumab, which resulted in discontinuation of ICI or pembrolizumab or has ongoing pembrolizumab-related toxicity event(s) as per treatment-limiting toxicity definitions, except patients with ongoing endocrine disorders that are managed with replacement therapy (ie, hypothyroidism related to prior pembrolizumab treatment);
16. Have an active infection requiring systemic therapy;
17. Have a known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as Hepatitis C virus RNA [qualitative] is detected) infection;

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.
18. Have had radiotherapy within 2 weeks prior to the first dose of study treatment, are in recovery from radiation toxicity, or have had radiation pneumonitis;
19. Have a history of non-infectious pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease;
20. Have had a prior allogeneic tissue/solid organ transplant, stem cell, or bone marrow transplant;
21. Have active human immunodeficiency virus (HIV). Patients are eligible when on stable anti-retroviral therapy (no change in medication or dose) for at least 4 weeks prior to screening, have confirmed virologic suppression with HIV RNA less than 50 copies/mL or the lower limit of quantification (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks prior to screening, and have a CD4+ T cell count >350 cells/mm^3 at screening. HIV-infected patients with a history of Kaposi sarcoma and/or Multicentric Castleman Disease will be excluded;
22. Have 4 or more sites involved, including the primary cancer;

    Note: A site is defined as an organ (eg, lung, liver, or brain) or a system (eg, lymphatic or central nervous system [CNS]).
23. Have a CNS metastasis that is symptomatic, progressing, or that requires current therapy (eg, evidence of new or enlarging CNS metastasis, carcinomatous meningitis, or new neurological symptoms attributable to CNS metastasis);
24. Have a QTcF >480 ms at screening, history of long or short QT syndrome, Brugada syndrome, QTc prolongation, or Torsade de Pointes, with the exception of patients with controlled atrial fibrillation, pacemaker, or bundle branch block as the QTc will be prolonged due to the widened QRS;
25. Are an adult under legal protection, are vulnerable, or lack the capacity to give informed consent, such as:
    - Persons deprived of liberty by a judicial or administrative decision;
    - Adult persons subject to a legal protection measure (under supervision/under guardianship); or
    - Persons under a judicial protection measure; or

26. Have a history of or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or make participation in the study not in the best interest of the patient, in the opinion of the Investigator.

4.3 Retesting

If laboratory abnormalities during screening are considered by the Investigator to be transient, then the laboratory tests may be repeated once during screening. The Investigator's rationale for retesting should be documented. If the retest result is no longer exclusionary, the patient may be enrolled in the study.

4.4 Rescreening

A patient who is screened and does not meet the study eligibility criteria may be considered for rescreening upon Sponsor and/or Medical Monitor consultation and approval. Rescreened patients will keep the original patient identification. Rescreening should occur no less than 5 days after the last Screening Visit.

4.5 Withdrawal Criteria

A distinction must be made between patients who discontinue study treatment prematurely and patients who are discontinued from the study.

In all cases of impending premature study treatment discontinuation or patient requests for withdrawal from study visits, the Investigators should discuss with the patient his/her options for continuing in the study. The Investigator should ensure he/she understands the reasons for a patient's desire to discontinue study treatment or withdraw from the study prior to completion and document these reasons in the electronic case report form (eCRF).

4.5.1 Discontinuation of Study Treatment

A patient may be discontinued from study treatment before the end of the Treatment Period but remain in the study for safety follow-up for any of the following reasons:

- A confirmed complete response (CR) is attained, and the patient has been treated for at least 8 cycles (ie, at least 24 weeks), including 2 cycles of the combination treatment (including 2 doses of pembrolizumab) from the date when the initial CR was declared;
- Occurrence of a severe systemic hypersensitivity reaction that is uncontrolled with standard management or requires high dose steroids;
- Occurrence of necrosis, ulcerations, bleeding, or any other serious complication in healthy tissues surrounding the injected tumor;
- Occurrence of injected tumor ulcerations that do not show a healing trend in a 3-week period;
- Occurrence of any other medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;

- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient requests discontinuation of study treatment for any reason; and/or
- Patient failure to comply with protocol requirements or study-related procedures.

If a patient discontinues CyPep-1 but remains eligible to participate in the study after review by the Investigator and Medical Monitor, pembrolizumab treatment will be continued Q6W as per institutional guidelines until PD, unacceptable toxicity, or consent withdrawal by patient for a maximum of 18 treatment cycles. All assessments will continue to be performed according to the Schedule of Assessments (Appendix A).

If a patient discontinues pembrolizumab but remains eligible to participate in the study after review by the Investigator and Medical Monitor, CyPep-1 treatment will be continued Q2W until PD, unacceptable toxicity, or consent withdrawal by patient for a maximum of 18 treatment cycles. All assessments will continue to be performed according to the Schedule of Assessments (Appendix A).

4.5.2 Discontinuation From the Study

Participation of a patient in this study may be discontinued for any of the following reasons:

- Patient requests discontinuation or withdraws consent to participate in the study for any reason;
- Discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study;
- Demonstration of efficacy that would warrant study stopping;
- Study data are not sufficiently complete and/or evaluable;
- Determination of futility;
- The Sponsor decides to suspend or discontinue testing, evaluation, or development of the study treatment; and/or
- The regulatory authority decides to terminate the study.

4.5.3 Discontinuation of Enrollment Criteria

Discontinuation of enrollment will occur for Phase 2a patients who meet any of the following criteria:

- Any CTCAE Grade 5 toxicity attributed to CyPep-1;
- SUSAR ≥Grade 4 CTCAE attributed to any component of the treatment combination;
- Signal of increased frequency or severity of any irAEs leading to permanent discontinuation as defined in Table 10;
- Site of injection AEs ≥Grade 4 CTCAE caused by CyPep-1 that do not revert to ≤Grade 1 in a 2 week period; or
- Any CyPep-1 related toxicity resulting in liver abnormality meeting Hy's Law criteria.

The observation of any of these criteria must trigger the immediate decision by the Sponsor to stop recruitment and organize an urgent DMC meeting, which will assess the causality of the observed AEs and the fulfillment of the discontinuation of enrollment criteria (above). The DMC will formulate a recommendation to resume recruitment, discontinue the involved cohort, or stop the study.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the EoT Visit (7 [±2] days after the last CyPep-1 or pembrolizumab administration). Withdrawal from the study will not affect or prejudice the patient's further care or treatment.

In the case of a patient lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Patients who are discontinued from the study before receiving at least 1 dose of study treatment will be replaced. Patients who are discontinued from the study after receiving at least 1 dose of CyPep-1 or pembrolizumab will not be replaced. In case of pembrolizumab-related toxicity (≥Grade 2 according to the NCI CTCAE v5.0), treatment with CyPep-1 will be delayed and planned after a review by the Investigator and Medical Monitor. If CyPep-1 treatment is delayed >7 days, that dose will be omitted. After 14 days of delay, consult with the Sponsor. See Section 5.5.3.3 for management of dose toxicity.

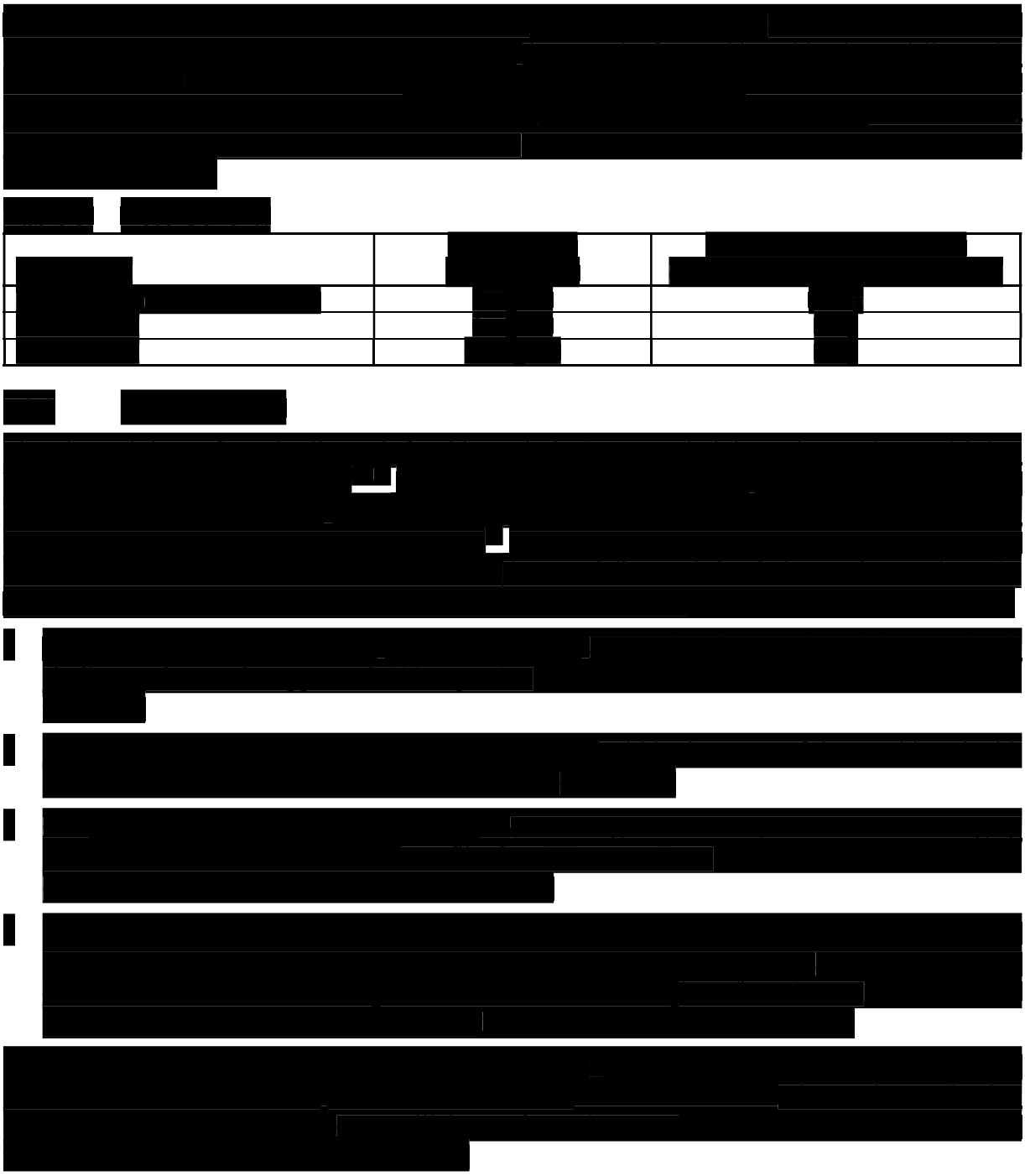
[redacted]

[redacted] Rationale for Dosing

5.2.1 [redacted]

[redacted]

[redacted]



5.3 Randomization and Blinding

This is an open-label, non-randomized study. No blinding is necessary.

5.4 Breaking the Blind

Procedures for breaking the blind are not applicable for this study.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The IT formulation of CyPep-1 is a clear and colorless aqueous solution (5 mg/mL) for subcutaneous administration supplied in single-use vials. The CyPep-1 (5 mg/mL) solution consists of the drug substance CyPep-1 dissolved in 0.9% sodium chloride solution. Each vial contains a deliverable volume of 2 mL of CyPep-1 solution that contains 10 mg of CyPep-1 and corresponding to 14 mg of acetate salt. An additional overfill is included in each vial to ensure that the labelled amount of 10 mg of CyPep-1 (corresponding to 14 mg of the acetate salt) can be delivered.

Pembrolizumab is formulated as a 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in single-dose vials.

CyPep-1 and pembrolizumab will be supplied by Cytovation ASA.

CyPep-1 and pembrolizumab will be labelled in compliance with the legal requirements of each country. The label text will also be translated and/or adjusted, to follow applicable regulatory requirements (eg, Clinical Trials Regulation EU No 536/2014 [Annex 6]), national laws in force, and in accordance with the local languages. In addition, each label will include storage conditions for the drug without the information about the study.

5.5.2 Study Drug Preparation and Handling

The study drugs must be received by a designated person at the study site, handled safely and properly, and kept in a secured location to which only the Investigator, Pharmacist, and designated assistants have access. Upon receipt of the study drugs, all supplies should be stored according to the instructions specified on the study drug labels. See Section 5.5.5 for details of storage condition.

The Pharmacy Manual contains specific instructions for the preparation of CyPep-1 and pembrolizumab administration solutions.

5.5.3 Study Drug Administration

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

5.5.3.1 CyPep-1 administration

The study Investigator will identify qualified staff who will perform IT injections and this decision will therefore be made on a site-by-site basis. The Sponsor will provide training on lesion selection and IT injection to Investigators participating in the study as part of the protocol training.

Lesions appropriate for IT injection will be determined following assessment of procedural and operational complexity and risk. While deeper lesions may be targeted, cutaneous lesions that are injectable without imaging will be prioritized. Further details regarding selection of tumor lesions as well as recommendations for IT injection procedures will be provided to Investigators and staff in the Guidance for Intra-tumoral Administration of CyPep-1 study manual.

Premedication with an antihistamine IV or oral equivalent should be administered approximately 30 to 60 minutes prior to the first IT dose of CyPep-1. Premedication should be administered prior

to subsequent CyPep-1 doses based upon clinical judgment and presence/severity of prior reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate. Patients should be well hydrated prior to CyPep-1 administration.

CyPep-1 will be administered Q2W as an IT injection. CyPep-1 will be administered through a needle, which should be redirected along multiple tracks to ensure even dispersion of CyPep-1 throughout the tumor lesion. On the visits that CyPep-1 and pembrolizumab are administered on the same day, CyPep-1 is to be administered 30 to 60 minutes **after** pembrolizumab infusion is completed. Following CyPep-1 administration, patients must be observed for 4 hours post injection at Cycle 1 Visit 1 and Cycle 2 Visit 1 and 1 hour post injection at Cycle 1 Visit 2 and Cycle 1 Visit 3 for potential immediate injection-related reactions. Refer to the Guidance for Intra-tumoral Administration of CyPep-1 study manual for more details.

[redacted]

[redacted]		[redacted]	
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[redacted]		[redacted]	
[redacted]		[redacted]	

[redacted]

5.5.3.2 Pembrolizumab administration

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

Every effort should be made to ensure the duration of infusion administration will be as close to 30 minutes as possible. However, given the variability of infusion pumps from study site to study

site, a window between -5 and +10 minutes is permitted (ie, the infusion time is 30 [-5/+10] minutes).

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

5.5.3.3 Dose modification and toxicity management

CyPep-1 dose modifications are not planned. In the event of CyPep-1-related excessive toxicity, administration of CyPep-1 may be delayed for no more than 7 days. Any delay will be per the Investigator's discretion for the management of a patient with excessive toxicity and may consider factors such as recovery from the procedure, scheduling difficulty, or recovery from toxicities. If delayed >7 days, then that dose will be omitted at the discretion of the Investigator with the approval of the Medical Monitor. After 14 days of delay, consult with the Sponsor.

CyPep-1 must be permanently discontinued if a patient experiences:

- A severe systemic hypersensitivity reaction that is uncontrolled with standard management or requires high dose steroids;
- Necrosis, ulcerations, bleeding, or any other serious complication in healthy tissues surrounding the injected tumor; or
- Injected tumor ulcerations that do not show a healing trend in a 3-week period.

In case of pembrolizumab-related toxicity (≥Grade 2 according to the NCI CTCAE v5.0), treatment with CyPep-1 will be delayed until a review is completed by the Investigator and Medical Monitor. If treatment with CyPep-1 is delayed >7 days, then that dose will be omitted. After 14 days of delay, consult with the Sponsor.

Dose modification and toxicity management for immune-related adverse events associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, pembrolizumab may be withheld or permanently discontinued, and corticosteroids may be administered. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 10.

Attribution of toxicity

When study interventions are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the Investigator may attribute a toxicity event to the combination, to CyPep-1 alone, or to pembrolizumab alone, for AEs listed in Table 10, both interventions must be held according to the criteria in Table 10.

Holding study interventions

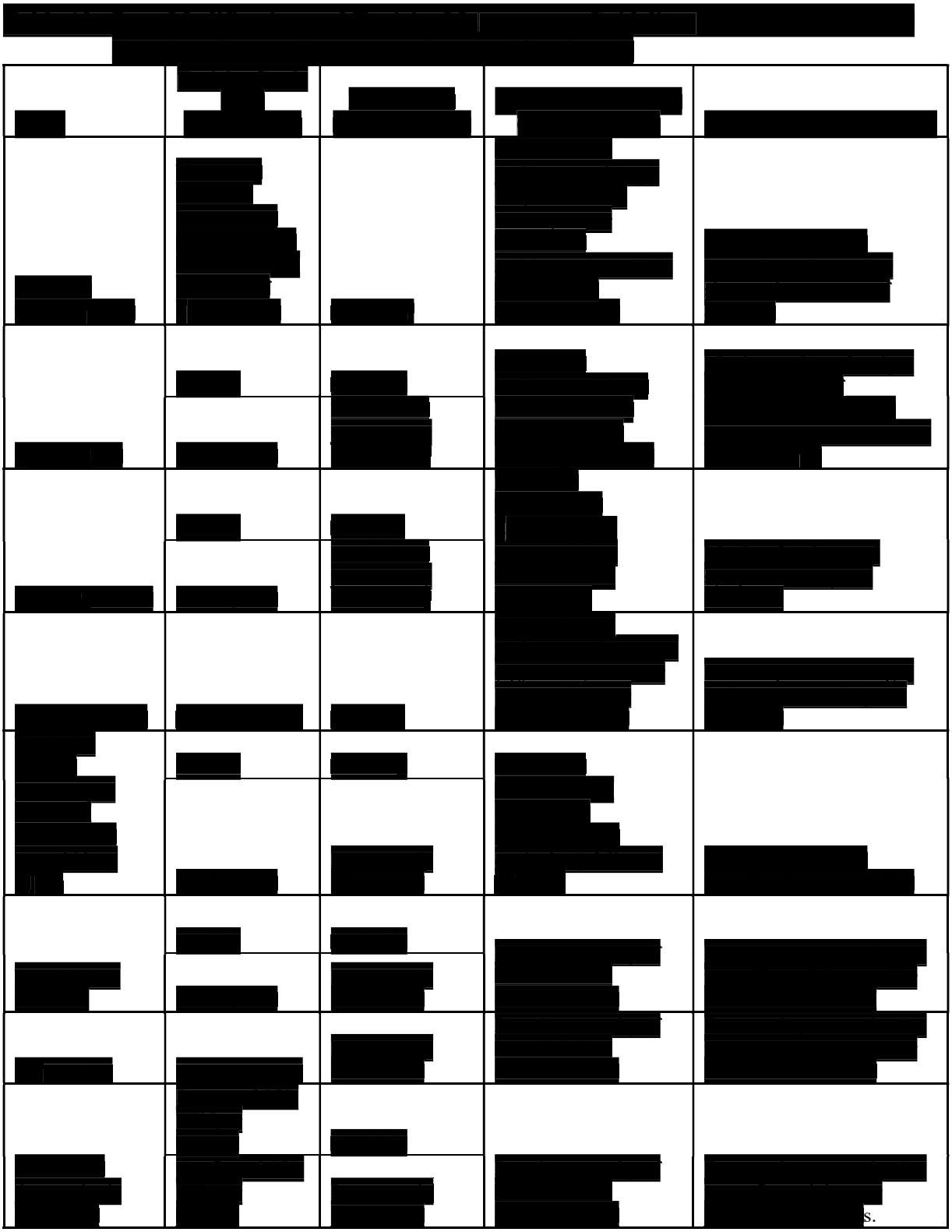
When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting study interventions

Patients may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 10.

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

If the toxicities do resolve and conditions are aligned with what is defined in Table 10, the combination of CyPep-1 and pembrolizumab may be restarted at the discretion of the Investigator. In these cases where the toxicity is attributed to the combination or to CyPep-1 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with, and agreement by, the Sponsor.



[redacted]

[redacted]

[redacted] be administered at a Q2W schedule as described in the Schedule of Assessments (Appendix A).

5.5.3.4 Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of pembrolizumab overdose. In the event of an overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

5.5.4 Treatment Compliance

Administration of IT CyPep-1 and administration of IV pembrolizumab will be done in a hospitalized environment by trained study personnel. Treatment compliance will be determined by documentation of CyPep-1 and pembrolizumab dispensation and administration, including, but not limited to, the batch numbers of CyPep-1 and pembrolizumab, the date and time of preparation, date and time of administration, and signatures of designated study site staff preparing and administering IT CyPep-1 and IV pembrolizumab.

In the event a planned CyPep-1 administration is missed, the treatment should be given as soon as possible but no less than 7 days from the next planned administration.

Any dosing deviations (eg, missed, delayed, incomplete, or interrupted doses) will be documented on the appropriate eCRF.

5.5.5 Storage and Accountability

CyPep-1 should be stored at 5 ±3°C (41 ±5.4°F), protected from light. CyPep-1 may be kept outside the storage conditions at temperatures up to 25°C (77°F) for up to 3 days to cover short-term temperature excursions (eg, during shipping, labelling, and handling).

Pembrolizumab should be used, handled, and stored in line with institutional guidelines and the IB.[23]

In accordance with regulatory requirements, the Investigator or designated study site personnel must document the amount of study drugs administered to patients, the amount received from and returned to the Sponsor (or representative) when applicable, as well as maintain a temperature log to document temperature conditions during storage. Study drug accountability records must be maintained throughout the course of the study. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study drugs will be provided in the Pharmacy Manual. The study drugs must be used only as directed in the protocol and for patients enrolled in this study only.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

The prophylactic use of systemic corticosteroids is not permitted; for exceptions, see Section 5.6.2.

Medications or vaccinations specifically prohibited in the Exclusion Criteria (Section 4.2) are not allowed during the study.

The following treatments must not be administered during the study:

- Immunotherapy not specified in this protocol, immunosuppressive drugs, or other investigational agents other than CyPep-1 or pembrolizumab within 30 days prior to the first dose of CyPep-1. Steroids are only allowed per criteria described in Section 5.6.2;
- Chronic concurrent therapy with antibiotics within 2 weeks before and during the Treatment Period. Antibiotics for new active infection (ie, AEs/SAEs) will be allowed during the Treatment Period;
- Herbal and local remedies;

  Note: Use of cannabis- or cannabidiol-containing products are only allowed if they are considered legal and used according to local regulations.
- Any other anti-neoplastic systemic chemotherapy, biological treatment, or concurrent anti-cancer treatment or chemotherapy not specified in this protocol;

  Note: Use of denosumab for patients with bone metastasis is allowed.
- Radiation therapy; and

  Note: Palliative short course, limited-field radiotherapy (ie, ≤10 fractions and ≤30% bone marrow involvement or per institutional standard) may be administered during the study only to symptomatic lesions that are not categorized as target or injected.
- Live or live attenuated COVID-19 vaccines.

Patients must not have a major surgical procedure within 14 days prior to the first dose of CyPep-1.

5.6.2 Restricted Medications and/or Procedures

COVID-19 vaccination is expected to elicit systemic post-vaccination symptoms, such as fatigue, fever, chills, headache, myalgias, and hypersensitivity in patients. The systemic side effects are dependent upon each different COVID-19 vaccine but tend to occur within 2 to 3 days of the vaccine and may be more pronounced with the second dose, where applicable. Given limited data, the possible interactions between CyPep-1, pembrolizumab, and COVID-19 vaccines are unknown at this time. Reference should be given to the summary of product characteristics/package inserts for these products, current literature, and expert consensus recommendations when considering the risk/benefit for individual patients. Therefore, COVID-19 vaccines are only permitted with documentation of the date of the vaccine if the last dose of vaccine was administered >14 days prior to the first dose of CyPep-1. The COVID-19 booster vaccine must be administered at least 14 days prior to the first dose of CyPep-1 and is not allowed during the first 3 months of the Treatment Period. Live or live attenuated COVID-19 vaccines must not be administered during the study.

Patients who are on anti-coagulants must be able to switch to a low molecular weight heparin or equivalent prior to Cycle 1 Day 1 and continue during the Treatment Period.

Administration of steroids through a route known to result in a minimal systemic exposure (topical [only on areas outside the injected lesions], intranasal, intro-ocular, or inhalation) is acceptable at the lowest possible dose.

In the absence of active autoimmune disease, systemic glucocorticoids are permitted only for the following purposes:

- To treat an AE or SAE;
- As needed for the prevention of emesis;
- As premedication for IV contrast allergies;
- For short-term oral or IV use in doses >10 mg/day prednisone equivalent for Chronic Obstructive Pulmonary Disease (COPD) exacerbations;
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent;
- For intraarticular joint use; and
- For inhalation in the management of asthma, COPD, or seasonal allergy.

5.6.3 Allowed Medications and/or Procedures

Replacement therapies (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) are allowed.

Vitamin and mineral supplements are allowed during the study.

Seasonal flu vaccines that do not contain live vaccine are permitted.

Premedication with an antihistamine IV or oral equivalent should be administered approximately 30 to 60 minutes prior to the first IT dose of CyPep-1. Premedication should be administered prior to subsequent CyPep-1 doses based upon clinical judgment and presence/severity of prior reactions. This regimen may be modified based on local treatment standards and guidelines as appropriate.

At the discretion of the Investigator, any concomitant medication or therapy deemed necessary for the welfare of the patient during the study, eg, for the treatment of AEs may be given. It is the responsibility of the Investigator to ensure that these medications or therapies are documented in the Concomitant Medication page of the eCRF.

Medications may be administered due to anticipated adverse reactions or anticipated emergency situations.

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

5.6.4 Documentation of Prior and Concomitant Medication Use

Medications and therapies taken within 28 days prior to the Screening Visit until the Safety Follow-up Visit will be recorded in the eCRF. All concomitant medications and changes in concomitant medications (including vitamins and minerals) will be recorded throughout the course

of the study in the eCRFs. Information recorded will include the medication name, dose, duration, and reason for taking each medication.

Medications and therapies taken specifically for the management of solid tumors prior to signing the ICF will be recorded on the Prior Medications and Therapies page of the eCRF.

All medications, including prescription and over-the-counter drugs; vitamins and minerals; and IV medications, fluids, and therapies used during the study, in addition to the study treatment (CyPep-1 and/or pembrolizumab), will be considered concomitant. All concomitant medications administered during SAEs or AEs of clinical interest (AECIs) are also to be recorded. The following concomitant medications or therapies are of clinical interest:

- Palliative medications;
- Medication for the treatment of infections, including prophylactic or pre-emptive use of anti-infective medication;
- Medication for the treatment of other reported AEs; and
- Prophylactic use of immunosuppressive medication.

5.6.5 Dietary Restrictions

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Assessments (Appendix A).

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to visit schedules and procedures specific to situations where COVID-19 is impacting study conduct. See Section 3.1.4 for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

7 EFFICACY ASSESSMENTS

7.1 Local Measurement of Tumor Lesions

Local tumor measurements of accessible target tumor lesion(s) will be made at screening, and then Q8W (±3 days), according to RECIST v1.1, until occurrence of confirmed PD as defined by iRECIST (Appendix D), start of a new anti-cancer treatment, pregnancy, death, withdrawal of consent, or end of study (approximately 26 months after the start of treatment).

Tumor assessment for cutaneous lesions will be made by caliper and color digital photography using a ruler held flush to the skin next to the longest diameter of the lesion to indicate the size of the lesion. As per RECIST v1.1, lesions ≥10 mm identified as target lesions require measurement by clinical exam with caliper. Lesions that cannot be accurately measured with calipers should be recorded as non-measurable. For subcutaneous lesions, itRECIST permits an ultrasound measurement if no other lesions are available for quantitative assessment. For injected lesions under ultrasound control, an ultrasound-based measurement must be performed prior to each injection. Ultrasounds and photography will be collected and held centrally for potential central radiographic review.

Lesion(s) that disappear during the Treatment Period will be evaluated during the Follow-up Period.

7.2 Radiological Assessment

A baseline radiology assessment will be performed within 4 weeks prior to Cycle 1 Visit 1 to identify injected lesions and non-injected lesions and these lesions will be assessed according to RECIST v1.1. Subsequent radiological assessments will be performed Q8W (±3 days) after the first dose of CyPep-1, according to RECIST v1.1, until the occurrence of confirmed PD as defined by iRECIST (Appendix D), start of a new anti-cancer treatment, pregnancy, death, withdrawal of consent, or end of study (approximately 26 months after the start of treatment). Tumor scans may be performed more frequently if clinically indicated. MRI or CT are the preferred scanning procedures to be used in this study. Selection of either MRI or CT should be based on individual patient considerations and local regulations and is at the Investigator's discretion. Once selected for each patient, the same scanning procedure should be used consistently at all remaining visits. Scans will be collected and held centrally for potential central radiologic review.

Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

A confirmatory radiological assessment is required 4 weeks after an initial radiological scan leading to an assessment of PD. If the PD is confirmed, the initial assessment of PD will be considered as the "first documented PD." If PD is not confirmed, the first measured PD will be disregarded and assessments should continue as per protocol (ie, the next radiological assessment will be performed after an 8-week interval).

If a patient discontinues study treatment without documented disease progression, every effort should be made to monitor disease status by continuing tumor scans Q8W from start of study treatment. Scans will be continued until occurrence of confirmed PD as defined by iRECIST (Appendix D), start of a new anti-cancer treatment, pregnancy, death, withdrawal of consent, or end of study (approximately 26 months after the start of treatment).

7.3 Tumor Biopsy

Tumor biopsy will be obtained from the identified injected and, whenever available, from the identified non-injected lesions at screening. A stored sample may be used if collected within 90 days prior to screening. At Cycle 1 Visit 4 (±3 days), the same lesion(s) will be used for post-treatment biopsy sampling.

Tumor material will be processed and sent for analysis as described in the Laboratory Manual. Tumor material of all patients will be used for analysis. No tumor sample will be obtained if a tumor is inaccessible, there is not enough tumor tissue due to shrinkage, or if the biopsy is not in the patient's best interest.

Tumor tissue staining will be performed provided there is access to sufficient tissue (formalin-fixed paraffin-embedded) post-hoc, batch-wise, during the study or at the end of the study and from the most recent available tissue. Tumor tissue will be stained at a central laboratory using immunohistochemistry/immunofluorescence in order to determine T cell infiltration and characteristics of tumor tissue. Additional staining for other factors based on emerging scientific understanding of the IT CyPep-1 therapy may also be performed.

Additional analyses (eg, tumor mutational burden) may be performed according to the Investigator's or Sponsor's decision.

7.4 Pharmacokinetic Sampling

Blood samples from the first 6 patients enrolled in the study will be collected for PK analyses. During Cycle 1 Day 15, the plasma concentration time profile of CyPep-1 will be evaluated and, if detectable plasma drug levels are identified, the derived PK parameters will be assessed including, AUC, C_{max}, T_{max}, systemic clearance, $t_{½}$, and volume of distribution.

Samples will be collected pre-dose and 15 minutes (±5 minutes), 30 minutes (±5 minutes), 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±30 minutes) post-dose on Cycle 1 Day 15.

Collection, processing, storage, and shipping of PK blood samples are described in the Laboratory Manual (including specific details for the blood collection tubes).

8 SAFETY ASSESSMENTS

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

Patients will be monitored for DLTs for confirmation of the CyPep-1 dose of 20 mg Q2W in combination with pembrolizumab 400 mg Q6W; see Section 3.1.1.1.

Safety will be monitored in conjunction with the DMC and as per DMC charter.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of signing the ICF until 30 days after the last dose of study treatment. All AEs that are considered serious, from the time of signing the ICF until 90 days (30 days if patients initiate new anti-cancer therapy) after the last dose of study treatment, will also be monitored and documented. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study treatment/procedure. Beginning at screening, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present prior to signing of the ICF should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present prior to signing the ICF and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should

not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drugs is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For CyPep-1, the reference safety information is included in Section 5.4.1 of the IB currently in force.[15] The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report. For pembrolizumab, the reference safety information is included in the IB.[23]

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE, and will also categorize each AE as to its potential relationship to study drugs using the categories of yes or no.

Assessment of severity

The severity of all AEs should be graded according to the NCI CTCAE v5.0. For those AE terms not listed in the NCI CTCAE, the following grading system should be used:

- NCI CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- NCI CTCAE Grade 2: Moderate; minimal local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- NCI CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- NCI CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated; and
- NCI CTCAE Grade 5: Death related to the AE.

Causality assessment

The relationship of an AE to the administration of the study drugs is to be assessed according to the following definitions:

- No (unrelated, not related, unlikely to be related) – The time course between the administration of study drugs and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.
- Yes (possibly, probably, or definitely related) – The time course between the administration of study drugs and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drugs. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drugs administration-

  The event should occur after the study drugs are given. The length of time from study drugs' exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drugs-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drugs-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drugs should be considered.

8.1.4 Adverse Events of Clinical Interest

Selected non-serious AEs and SAEs are also known as AECIs and must be reported to the Sponsor within 24 hours of the Investigator's awareness.

AECIs for this study include the following:

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

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

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;

  Note: Death due to tumor-related symptoms or tumor progression will not be recorded as an SAE under this criterion.

- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, elective treatment of a pre-existing condition that did not worsen from baseline, or hospitalization due to tumor-related symptoms or tumor progression. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

  Note: Events of progression of a patient's underlying cancer, as well as events clearly related to the progression of a patient's cancer (signs/symptoms of progression) should not be reported as an SAE; however, when a patient dies from the progression of underlying cancer, the event will be captured as an outcome on an eCRF for death due to disease progression. Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as an SAE.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of signing the ICF until 90 days (30 days if patients initiate new anti-cancer therapy) after the last dose of study treatment must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence.

Any SAE brought to the attention of the Investigator at any time outside of the time period specified above must be reported immediately, or within 24 hours of the knowledge of the occurrence, to Medpace Clinical Safety or the Sponsor/designee if the event is considered to be drug-related.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If

it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within 120 days (30 days if initiates new anti-cancer therapy) after the last dose of study treatment, the Investigator is to stop dosing with study drugs immediately. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/study site the Exposure In Utero (EIU) form for completion. The Investigator/study site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

All exposures during breastfeeding, during the study or within 120 days (30 days if initiates new anti-cancer therapy) after the last dose of study treatment, must be reported by the Investigator to Medpace Clinical Safety as described above.

If the female partner of a male patient becomes pregnant while the patient is receiving study drugs or within 120 days (30 days if initiates new anti-cancer therapy) after the last dose of study treatment, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities, and to the Central Ethics Committee as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Listings of cases related to pembrolizumab will be included in the Development Safety Update Report.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these special situations reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

[redacted]

8.7 Clinical Laboratory Evaluations

Clinical laboratory evaluations will include chemistry, hematology, coagulation, and urinalysis parameters from collection of blood and urine samples as indicated in the Schedule of Assessments (Appendix A). See Appendix B for a list of clinal laboratory analytes.

All blood and urine samples will be collected before dosing at dosing visits and can be collected up to 72 hours prior to each scheduled dosing visit in order to have the results (of at least chemistry, hemoglobin, white blood cell count, platelets, PT/INR, and aPTT) available on the visit day prior to dosing. If there are no normal ranges available for PT, INR may be used instead of PT.

Creatinine clearance will only be estimated at screening using the Chronic Kidney Disease Epidemiology Collaboration formula.

Urinalysis will be performed using gross (dipstick) urine examination. Midstream, clean-catch urine specimens will be collected for dipstick analysis.

Assessments completed at screening within 72 hours prior to the first CyPep-1 administration do not need to be repeated at Cycle 1 Visit 1. Unless otherwise noted, samples will be processed, analyzed, and reported locally.

If the Investigator (or qualified designee) encounters an abnormal finding, the Investigator should indicate whether the finding is clinically significant or not. Any clinical abnormalities that are considered to be clinically significant are recorded as AEs and need to be followed until resolution.

8.8 Vital Signs

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

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

All blood pressure measurements require the use of a completely automated device on the same arm at each measurement. The same type of automated device is to be used for all assessments, at least for the same patient. The automated device must be calibrated annually.

Body temperature will be measured in a consistent manner throughout the study. Continuous oxygen monitoring will be performed if the patient has respiratory problems.

8.9 Electrocardiograms

A standard single 12-lead ECG will be collected at screening, at Cycle 1 Visit 1, Cycle 1 Visit 2, and at Visit 1 of each subsequent cycle.

A computerized ECG device will be used after the patient has rested at least 10 minutes in the supine position (ie, lying horizontally with the face and torso facing up). Patient must remain supine but awake during ECG collection.

The following parameters will be automatically calculated by the ECG device: heart rate, PR/PQ interval, QRS interval, and QT interval (uncorrected).

All ECGs will be evaluated by a physician to provide immediate safety monitoring, an ECG diagnosis, and an overall assessment (including clinical relevance). Corrected QT intervals will be derived in addition for data evaluation.

ECGs should be collected prior to any invasive procedures (eg, study treatment administration and blood sample collection) and any scheduled vital signs measurements.

8.10 Height, Weight, and Physical Examinations

Height will only be recorded at the Screening Visit and will be recorded in centimeters.

Weight will be recorded in kilograms at each study site visit. At dosing visits, weight will be recorded before dosing. The same equipment should be used throughout the study, if possible. To obtain the actual body weight, patients must be weighed lightly clothed.

Physical examinations will be performed at each study site visit. At dosing visits, physical examinations will be performed before dosing. A physical examination includes, per the institutional guidelines, the evaluation of general appearance, skin, head, eyes, ears, nose, mouth, oropharynx, neck, heart, lungs, abdomen (including liver and spleen), extremities, lymph nodes, neurological and musculoskeletal systems, and genitourinary system/pelvis (at the Investigator's discretion).

If the Investigator (or qualified designee) encounters an abnormal finding, the Investigator should indicate whether the finding is clinically significant or not. Information about the physical examination must be present in the source documentation at the study site. Significant findings, except for SAEs, that are present prior to signing the ICF must be included on the Medical History eCRF. Significant findings that meet the definition of an AE, must be recorded on the AE eCRF.

8.11 Eastern Cooperative Oncology Group Performance Status

ECOG performance status assessment should be performed at each study site visit. At dosing visits, ECOG performance status will be assessed before dosing. See Appendix C for details of ECOG performance status scoring.

8.12 Pregnancy Test

Female patients of childbearing potential must have a negative serum pregnancy test at screening and before dosing (within 72 hours) at Visit 1 of Cycle 1, and a urine pregnancy test should be performed at all other visits indicated in Appendix A.

In this study, pregnancies occurring during participation (including pregnancies of partners of male patients) will not be considered as AEs or SAEs but must be reported to the Sponsor using the study Pregnancy Reporting Form. See Section 8.4 for details regarding pregnancy reporting.

8.13 Thyroid Function Testing

In clinical studies using pembrolizumab, thyroid function needs to be evaluated at regular time intervals. Blood samples for thyroid function testing will be performed locally at screening and Visit 1 of each cycle from Cycle 2 onward.

The thyroid panel should include triiodothyronine or free triiodothyronine, free thyroxine, and thyroid-stimulating hormone.

9 STATISTICS

9.1 Analysis Sets

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

The Evaluable Analysis Set (EAS) will include all patients who receive an injection of CyPep-1 on at least 2 treatment days, receive at least 1 administration of pembrolizumab, and have at least 1 post-baseline tumor response assessment after the first injection of CyPep-1 (Cycle 1 Visit 1).

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

9.2 Statistical Methods

9.2.1 Analysis of Efficacy

Analysis of efficacy will be conducted in Phase 2a. Efficacy analyses will be done using the FAS. The Objective Response Rate (ORR) will be based on the number of patients achieving a partial response (PR) or CR based on RECIST v1.1 and iRECIST (Appendix D). Best overall response will also be calculated. The Disease Control Rate will be based on the number of patients achieving a PR, CR, or stable disease ≥16 weeks based on RECIST v1.1 and iRECIST (Appendix D). Progression Free Survival (PFS) (percentage of patients alive and progression-free) at 6, 12, 18, and 24 months after the first treatment with CyPep-1 + pembrolizumab will be determined. A progression event is defined as disease relapse or progression (based on all lesions) or death due to any cause. For patients who are not known to have died or progressed as of the data cut-off date, PFS will be censored at the date of the last objective progression-free disease assessment. Patients who discontinue the study treatment without post-treatment assessments will be treated as non-responders. The detailed censoring rules will be specified in the Statistical Analysis Plan. Sensitivity analysis for primary efficacy endpoints will be provided using the EAS. An exploratory analysis of itRECIST will be applied to allow for a separate response assessment of injected and non-injected lesions.

9.2.2 Analysis of Safety

Safety analysis will be conducted in both Phase 1b and Phase 2a using the SAS. TEAE incidence rates will be described by the frequency of TEAEs and categorized by preferred term and system organ class according to the NCI CTCAE v5.0. TEAEs will be summarized by seriousness, grade, and relationship to CyPep-1 and pembrolizumab. The incidence of TEAEs will be evaluated for each study arm and for all patients combined. The following data will be summarized using descriptive statistics: treatment exposure, disposition, vital signs, body weight, 12-lead ECG parameters, and laboratory assessments. Shift tables showing changes from baseline will be generated where appropriate. Summaries will be by arm and for all patients.

The incidence of DLT events during the DLT period will be presented.

9.2.3 Analysis of Pharmacokinetics

Phase 1b patients who have received CyPep-1 and have provided 1 evaluable pre-dose and at least 1 post-dose PK blood sample will be evaluable for PK. Standard methodology will be used to estimate PK parameters. Concentration-time profiles will be derived for patients with post-dose samples.

9.2.4 [redacted]

[redacted]

[redacted]

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the study site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All study site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the study site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the study site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last patient in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at study sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient must be approved by the IRB/IEC.

No study drug will be released to the study site for dosing until written IRB/IEC authorization has been received by the Sponsor.

For European study sites, it is the responsibility of the Sponsor or their designee (ie, Medpace) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start in the respective study sites once the respective committee's written approval has been given.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Subject Card

On enrollment in the study, the patient will receive a subject card to be carried at all times. The subject card will state that the patient is participating in a clinical research study, type of treatment, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and study site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the study site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the study site by signature and date on the study-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, competent authority, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study. Details of the financial aspects of the study are addressed in the Clinical Study Agreement.

11.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

11.12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

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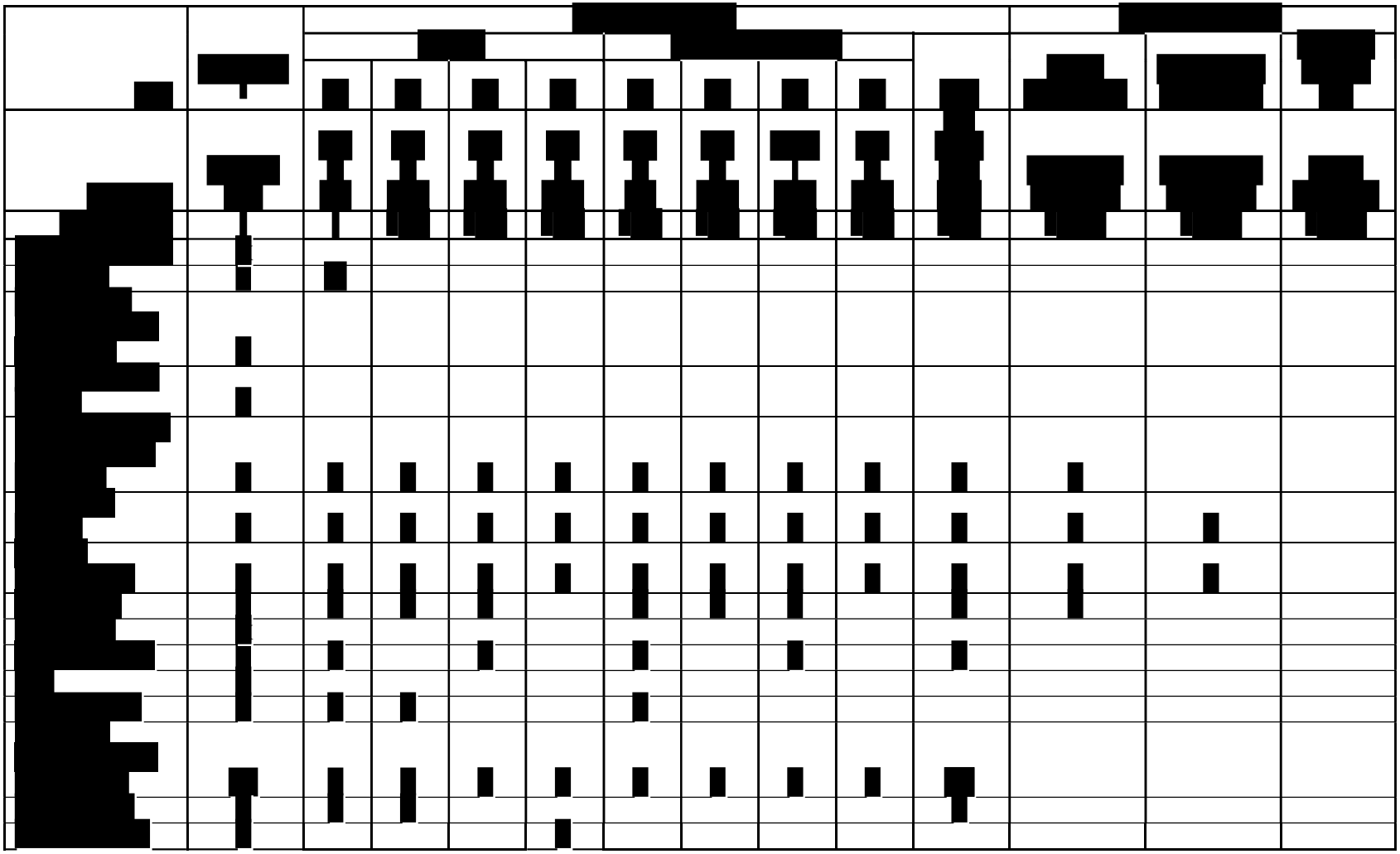

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24. [redacted]

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

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

Hematology

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

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

Coagulation

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

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

Urinalysis

Bilirubin	Blood [1]
Creatinine	Glucose
Ketones	Leukocyte esterase
Microscopy [2]	Nitrite
pH	Protein
Specific gravity	Urobilinogen

1. Including hemoglobin and erythrocytes.
2. Microscopy is performed only as needed based on positive dipstick test results.

Pregnancy Test [1]

Serum human chorionic gonadotropin	Urine human chorionic gonadotropin

1. For female patients of childbearing potential only.

Endocrinology

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

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

Serology

Human immunodeficiency virus

APPENDIX C: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCORING

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
ECOG = Eastern Cooperative Oncology Group.	

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

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

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

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

Assessment and Decision at the RECIST v1.1 Progression

For patients who show radiological progressive disease (PD) by RECIST v1.1, the Investigator will decide whether to continue a patient on study treatment until repeat scans are obtained.

Tumor flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir;

  Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST v1.1 terminology.

- Unequivocal progression of non-target lesion(s) identified at baseline; and
- Development of new lesion(s).

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

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

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

Assessment at the Confirmatory Scans

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

Confirmation of Progression

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

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

Persistent iUPD

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

- None of the progression-confirming factors identified above occurs; AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST v1.1).

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

Resolution of iUPD

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

- None of the progression-confirming factors identified above occurs; AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

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

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

Management Following the Confirmatory Scan

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

Note: If a patient has confirmed radiographic progression (iCPD), clinically meaningful study intervention may be continued after consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 7.2.

Detection of Progression at Visits After Pseudoprogression Resolves

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

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

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

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

Additional details about the iRECIST are provided in the iRECIST publication.[1]

[1] Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152.

APPENDIX E: itRECIST GUIDANCE

Intratumoral-Response Evaluation Criteria in Solid Tumors (itRECIST) is based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and immune-RECIST but adapted to account for the unique tumor response seen with intra-tumoral immunotherapeutic drugs. itRECIST will be used by the Investigator to assess tumor response.[1]

[1] Goldmacher GV, Khilnani AD, Andtbacka RHI, et al. Response Criteria for Intratumoral Immunotherapy in Solid Tumors: itRECIST. *J Clin Oncol*. 2020;38(23):2667-2676.