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)

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Primary ObjectivesPhase 1bConfirm the recommended CyPep-1 dose 20 mg every two weeks (Q2W) when administered by intratumoral (IT) injection in combination with pembrolizumab Phase 2aAssess the anti-tumor activity of CyPep-1 administered by IT...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON51302

Source
ToetsingOnline

Brief title
CYP003 - CATALYST

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

- Skin neoplasms malignant and unspecified

Synonym
breast cancer, head and neck cancer, Skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Cytovation ASA
Source(s) of monetary or material Support: Cytovation ASA

Intervention

Keyword: Advanced or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC), CyPep-1, Melanoma, Triple-Negative Breast Cancer (TNBC)

Outcome measures

Primary outcome

Phase 1b

• Incidence, frequency, and seriousness of treatment-emergent adverse events

(TEAEs);

• Incidence of dose-limiting toxicity (DLTs); and

• Changes from baseline in vital signs, body weight, 12 lead ECG parameters,

and laboratory assessments.

Phase 2a

Objective response rate (ORR) based on radiological assessment according to

Response Evaluation Criteria in Solid Tumor (RECIST) v1.1

Secondary outcome

Phase 1b

• Plasma concentration-time profile of CyPep-1 and, if detectable, the

following derived pharmacokinetics (PK) parameters:

o Area under the curve (AUC)

o Peak plasma concentration (Cmax);

o Time to reach peak plasma concentration (Tmax);

o systemic clearance (CL);

o elimination half life (t*); and

o volume of distribution (VD).

Phase 2a

• ORR according to immune-Response Evaluation Criteria in Solid Tumors

(iRECIST);

• Disease control rate (DCR) according to iRECIST and RECIST v1.1;

• Duration of response (DoR) according to iRECIST and RECIST v1.1;

• Progression free survival (PFS) according to iRECIST and RECIST v1.1; and

• OS for up to 26 months from Cycle 1 Visit 1.

• Incidence, frequency, and seriousness of TEAEs; and

• Changes from baseline in vital signs, body weight, 12 lead ECG parameters,

and laboratory assessments.

Exploratory Outcomes

• 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.

ORR according to intratumoral-Response Evaluation Criteria in Solid Tumors

(itRECIST)

Study description

Background summary

CyPep-1 is a small molecule (peptide) developed in a laboratory. CyPep-1 binds to tumor cells and changes their outer edge (membrane). Upon this change the cell starts leaking its contents and eventually dies. The leakage triggers the body*s immune system to kill more tumor cells in the same area.
Due to the small size of CyPep-1, the best way to get it close to the tumor cells is to inject it directly into the tumor. In this way, CyPep-1 does not have to travel though the entire body before it reaches the tumor and it*s anticipated to get the most effect.

CyPep-1 can be combined with a drug called pembrolizumab. Tumor cells can release signals that block the immune system. The immune system is not able to attack tumor cells anymore. pembrolizumab is a small molecule designed to interact with those blocking signals, stimulating the immune system to attack tumor cells again.
It*s anticipated that treatment of CyPep-1 and pembrolizumab together will generate an extra boost to activate the immune system and kill tumor cells.

Study objective

Primary Objectives

Phase 1b
Confirm the recommended CyPep-1 dose 20 mg every two weeks (Q2W) when administered by intratumoral (IT) injection in combination with pembrolizumab

Phase 2a
Assess the anti-tumor activity of CyPep-1 administered by IT injection in combination with pembrolizumab

Secondary Objectives

Phase 1b
Evaluate the pharmacokinetics of CyPep-1 in combination with pembrolizumab

Phase 2a
Expand evaluation of efficacy CyPep-1 + pembrolizumab
Evaluate the safety and tolerability of CyPep-1 in combination with pembrolizumab

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

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 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).

Intervention

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

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.

Study burden and risks

Taking part in the study can have pros and cons. They will be listed below

Participatation in this research, does not mean that the patient's advanced or metastatic HNSCC, advanced or metastatic melanoma, or advanced or metastatic TNBC will be cured. But taking part will help the investigators to get more insight into the treatment of advanced or metastatic HNSCC, advanced or metastatic melanoma, or advanced or metastatic TNBC.

Taking part in the study can have these cons:
- The participant may experience the side effects or adverse effects of CyPep-1 in combination with pembrolizumab.
- There may be some discomfort from the measurements during the study. For example: taking a blood sample can be a little painful. Or the participant could get a bruise as a result.
- Taking part in the study will cost the participant extra time.
- the participant has to comply with the study agreements.

What are the possible discomforts the participant may experience with checks or measurements during the study?
Risks and discomforts that the participant may experience from the study procedures include:

- Blood samples: Possible adverse effects that the participant may have from drawing blood include faintness, swelling of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection. If the participant feels faint, he/she should tell the study staff right away.
- ECG: the participant may have skin irritation, such as redness or itching. It is rare but could occur during an ECG from the electrodes or gel that is used.
- MRI: This test requires that the participant will be confined in a small, partially enclosed space. The sound of the machine may be loud. People who are claustrophobic (fear of being in small spaces) can sometimes have anxiety during an MRI. The study staff can give the participant medicine to help with those feelings. The MRI scanner does not cause any pain and does not expose the participant to x-ray radiation. If the participant has certain metals in his/her body (such as a pacemaker, joints, rods, or plates) he/she should not have this type of scan. Dental fillings are less responsive to the magnetism and are therefore allowed. The participant will be expected to notify the study doctor and study staff of any metal in his/her body, other than dental fillings.
- CT scan: CT Scan is a test that uses a small amount of radiation (x-rays) to take pictures of the inside of the participant's body. The radiation dose that is used is small. The effects of radiation exposure add up over a lifetime. It is possible that having several of these tests may add to the participant's risk of injury or cancer. The participant will be given a contrast dye. The contrast dye may cause an allergic reaction. The participant should tell the study doctor if he/she has previously had a reaction to the contract dye.
- Biopsy: Any medical procedure that involves breaking the skin carries the risk of infection, bruise or bleeding. However, as the incision is small, the risk is low. Some mild pain can be expected after needle biopsy. There is also a small risk that the participant could have an allergic reaction to the local anaesthetics.

Contacts

Public
Cytovation ASA

Solheimsgaten 11
Bergen 5058
NO
Scientific
Cytovation ASA

Solheimsgaten 11
Bergen 5058
NO

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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:
o 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;
o Female sterilization (surgical bilateral oophorectomy with/without hysterectomy, total hysterectomy, bilateral tubal occlusion/ligation) at least 26 weeks prior to first study
treatment;
o Sterilization of male partner (at least 6 months prior to first study treatment dose); and
o 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.

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

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/mm3 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:
o Persons deprived of liberty by a judicial or administrative decision;
o Adult persons subject to a legal protection measure (under supervision/under guardianship); or
o 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

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CyPep-1
Generic name:	CyPep-1
Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-07-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-08-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	20-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-01-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-006804-34-NL
ClinicalTrials.gov	NCT05383170
CCMO	NL81162.041.22