2 SYNOPSIS

Name of Sponsor/Company: Cytovation ASA

Name of Test Product: CyPep-1

Name of Active Ingredient: CyPep-1

Title of Study: 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)

Investigators and Study Centers:

This study was conducted in 5 centers in 2 countries (3 centers in France, 2 centers in Spain).

Publication (reference): No data for this study have been published.

Study Period:	**Phase of Development:**
First Patient Enrolled: 21 March 2023 **Last Patient Completed:** 23 September 2024	1b/2a

BACKGROUND AND RATIONALE

CyPep-1 is being developed for the treatment of advanced solid cancers. This Phase 1b/2a study was to 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 was to 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. Treatment of patients with CyPep-1 in combination with pembrolizumab is expected to result in improvement or stabilization of the disease state of patients with solid tumors.

Due to its unique dual-mode-of-action, CyPep-1 has the potential to treat tumors deemed resistant to immunotherapy. CyPep-1 reverses the immune excluded microenvironment by inhibiting the Wnt/β-catenin pathway and by presenting relevant antigens to the immune system. In addition, CyPep-1 offers attractive pharmacological properties such as long shelf life, easy scalability, and negligible batch-to-batch variations. As such, CyPep-1 may represent a unique "tumor-agnostic" compound bolstering the effect of established immunotherapy across a panel of cancer types. Additionally, preclinical studies show that CyPep-1 synergizes with anti-PD-1 antibody treatment in terms of decreased tumor volumes (both primary tumors directly injected with CyPep-1 and contralateral tumors) leading to tumor growth delay.

OBJECTIVES	**ENDPOINTS**
Primary	
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 • 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

Name of Sponsor/Company: Cytovation ASA	
Name of Test Product: CyPep-1	
Name of Active Ingredient: CyPep-1	
Secondary	
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 $t_{½}$ 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.
Exploratory	
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.

Name of Sponsor/Company: Cytovation ASA

Name of Test Product: CyPep-1

Name of Active Ingredient: CyPep-1

METHODS

This was an open-label, multi-center, non-randomized study. The Phase 1b portion of the study was to enroll 6 patients to 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 were to continue into the Phase 2a portion of the study and approximately 90 patients in total were to be enrolled, with 30 patients per arm: 3 arms included patients with advanced or metastatic head and neck squamous cell carcinoma (HNSCC), cutaneous melanoma, or triple-negative breast cancer (TNBC) to 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).

The Phase 2a part of the study was not initiated and the trial was stopped with 6 patients enrolled in Phase 1b and when the Phase 1b portion of the trial had been successfully completed. The decision not to proceed with the Phase 2a part of the trial was taken following a reassessment of target indications for CyPep-1.

Number of Patients:

Phase 1b	Planned: 6	Enrolled: 6	Analyzed: 6
Phase 2a	Planned: 84	Enrolled: 0	Analyzed: 0

Diagnosis and Main Criteria for Inclusion:

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

The main criteria for inclusion in Phase 1b were:

- Age ≥18 years
- Written informed consent
- Measurable disease per RECIST v1.1 as assessed by the local site Investigator/radiology; lesions situated in a previously irradiated area were considered measurable if progression had been demonstrated in such lesions.
- At least 1 non-ulcerated, measurable, and accessible lesion for IT injection with a maximum diameter of 5 cm
- Able to provide tissue from a core or excisional biopsy at screening or had an acceptable stored tumor sample available that was collected within 90 days prior to screening
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy ≥3 months, as determined by the Investigator
- Adequate organ function

Patients who met the above inclusion criteria were eligible for inclusion in a specific arm of the trial if they met the inclusion criteria as follows:

Arm A

- Had histologically confirmed diagnosis of HNSCC (including nasopharyngeal squamous cell carcinoma)
- Had advanced or metastatic HNSCC incurable by standard of care therapies; and
- Had recurrent or metastatic HNSCC that had 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 could also be considered as having disease progression on platinum-based chemotherapy

Arm B

- Had histologically confirmed diagnosis of malignant melanoma
- Did not have uveal melanoma
- Had advanced or metastatic melanoma incurable by standard of care therapies

Name of Sponsor/Company: Cytovation ASA

Name of Test Product: CyPep-1

Name of Active Ingredient: CyPep-1

- Had received a combination of a BRAF inhibitor and a MEK inhibitor if diagnosed with a BRAF mutated melanoma and if clinically indicated; and
- Had 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

- Had histologically confirmed diagnosis of triple-negative breast cancer (TNBC) as per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines
- Had advanced or metastatic TNBC incurable by standard of care therapies
- Had received sacituzumab govitecan chemotherapeutic treatment if clinically indicated; and
- Had 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 [programmed cell death ligand 1] status) OR had received prior systemic therapy with either an anthracycline- or taxane-containing regimen (if ICI non-eligible based on PD-L1 status)

Test Products, Dose/Strength/Concentration, Mode of Administration, and Batch Number:

CyPep-1 was administered in combination with pembrolizumab. CyPep-1 was administered every 2 weeks and pembrolizumab every 6 weeks.

CyPep-1

CyPep-1 was provided as a solution for intratumor (IT) injection. CyPep-1 was administered through a needle, which was to be redirected along multiple tracks to ensure even dispersion of CyPep-1 throughout the tumor lesion.

The cumulative maximal injected volume of CyPep-1 was 4 mL (cumulative maximal dose of 20 mg at the recommended 5 mg/mL concentration) per treatment day for each patient, and it could be divided for injections over 1 to 3 tumor lesions (satellitosis/grouped lesions <1 cm counted as 1 lesion) depending on tumor lesion size. The injected lesions identified at baseline were to be injected 3 times before selecting new lesions for injection, unless there was a complete response or the lesion, in the Investigator's assessment, had been adequately treated (e.g., reduced size and highly inflamed). The volume of CyPep-1 delivered to each injected lesion was determined based on the longest diameter of the lesion. Effort was to be made to administer the maximum volume of CyPep-1 as planned per lesion size, as tabulated below:

Measured Lesion Diameter (cm)	Injected Volume (mL)
≤0.79	0.1
0.80-0.99	0.2
1.00-1.24	0.5
1.25-1.50	1.5
1.51-2.49	3.0
≥2.50-5.00	4.0

On visits when CyPep-1 and pembrolizumab were administered on the same day, CyPep-1 was administered 30 to 60 minutes after pembrolizumab infusion was completed. Following CyPep-1 administration, patients were to 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 (IRRs).

Pembrolizumab

The dose of pembrolizumab was 400 mg Q6W administered via a 30-minute infusion, beginning at Cycle 1 Visit 1. Pembrolizumab could be administered up to 3 days before or after the scheduled Visit

Name of Sponsor/Company: Cytovation ASA

Name of Test Product: CyPep-1

Name of Active Ingredient: CyPep-1

1 of each cycle from Cycle 2 onward. Specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution were provided in a Pharmacy manual.

Control Products, Dose/Strength/Concentration, and Mode of Administration, and Batch Number:

Not applicable. There was no comparator group in this study.

Concomitant Therapy, Dose, and Mode of Administration:

Not applicable.

STATISTICAL METHODS

Sample Size

The sample size for the Phase 1b portion of the study was based on practical determinations. The first 6 patients of the study were planned to be enrolled in the Phase 1b portion. The Phase 2a portion of the trial was not conducted.

Statistical Analyses

The Full Analysis Set (FAS) included all patients who received an injection of CyPep-1. The FAS was used in the analysis of efficacy and exploratory endpoints. The Evaluable Analysis Set (EAS) included all patients who received an injection of CyPep-1 on at least 2 treatment days, received at least 1 administration of pembrolizumab, and had at least 1 post-baseline tumor response assessment after the first injection of CyPep-1 (Cycle 1 Visit 1). The Safety Analysis Set (SAS) included all patients who received at least 1 injection of CyPep-1 or at least 1 administration of pembrolizumab. The SAS was the basis of safety analyses.

All data were summarized using descriptive statistics. The objective response rate (ORR) was determined based on the number of patients achieving a partial response (PR) or complete response (CR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and immune RECIST (iRECIST). Safety data included frequencies of treatment-emergent adverse events (TEAEs), vital signs, body weight, 12-lead ECG parameters, and laboratory assessments. The incidence of dose-limiting toxicity (DLT) events during the DLT period was presented.

Standard methodology was used to estimate pharmacokinetic (PK) parameters. Pharmacokinetic data were analyzed and reported separately from the clinical trial report. A summary is provided.

SUMMARY AND CONCLUSIONS

Disposition

In total, 6 patients were enrolled, and all were treated with CyPep-1 and pembrolizumab. The reasons for discontinuation from treatment with CyPep-1 were progressive disease (PD) (5 patients) and withdrawal by the patient (1 patient). The reasons for discontinuation from treatment with pembrolizumab were also PD (5 patients) and withdrawal by the patient (1 patient). The reasons for discontinuation from the trial were death (3 patients) and termination of the trial by the sponsor (3 patients).

Exposure to study medication

Overall, the mean number of cycles of trial medication administered was 3.7 (standard deviation [SD] 3.27, median: 2.5; range: 1 - 10); 2 patients (33.3%) were treated for ≥4 cycles.

The mean duration of treatment with CyPep-1 was 19.33 weeks (SD 19.906; median 13.00 weeks; range: 2.0 - 58.0 weeks). One patient (16.7%) had missed doses; no patient had dose reductions. The mean cumulative dose of CyPep-1 per patient across the entire treatment period was 75.50 mg (SD 55.168; median 80.00 mg; range 13.0 - 160.0 mg). The mean dose intensity of CyPep-1 was 6.88 mg/week (SD 4.649; median 9.75 mg/week; range 0.7 - 10.0 mg/week). The mean overall relative dose intensity of CyPep-1 was 68.78% (SD 46.487; median 97.50%; range 6.5% - 100%).

Name of Sponsor/Company: Cytovation ASA

Name of Test Product: CyPep-1

Name of Active Ingredient: CyPep-1

The mean duration of treatment with pembrolizumab was 22.00 weeks (SD 19.956; median 15.00 weeks; range: 6.0 - 60.0 weeks). No patient had missed doses, dose reductions, or dose interruptions. The mean cumulative dose of pembrolizumab per patient across the entire treatment period was 1466.67 mg (SD 1306.395; median 1000.00 mg; range 400.0 – 4000.0 mg). The mean dose intensity of pembrolizumab was 66.67 mg/week (SD 0.000; median 66.67 mg/week; range 66.7 – 66.7 mg/week). The mean overall relative dose intensity of pembrolizumab was 100% (SD 0.000; median 100%; range 100% - 100%).

Demographic and baseline characteristics

In total, 2 patients (33.3%) were male and 4 patients (66.7%) were female, including 2 women of child-bearing potential. Mean age was 55.7 years (SD 10.19; median 53.5, range: 43 - 68 years), and most patients (4, 66.7%) were age <65 years. Race and ethnicity were not reported. ECOG status was 0 (5 patients, 83.3%) or 1 (1 patient, 16.7%) at baseline. Mean body mass index was 28.44 kg/m^2 (SD 6.394).

In total, 5 patients had melanoma (locally advanced or metastatic) and 1 had metastatic HNSCC. No patients with TNBC were enrolled. All 6 patients had previously been treated with systemic anti-cancer therapy. The most frequently reported types of prior systemic anti-cancer therapy were metastatic (6 patients, 100%) and adjuvant therapy (5 patients, 83.3%). In total, 4 patients (66.7%) had previously undergone cancer radiation therapy and all 6 (100%) had undergone surgery for their cancers.

Efficacy

Results were comparable for RECIST v1.1 and iRECIST assessments. The RECIST v1.1 and iRECIST objective response rates were both 16.7% overall (1 of 6 patients) and 25% for evaluable melanoma patients (1 of 4 evaluable patients). A best overall response (BOR) of PR was reported in 1 patient (16.7%; duration 12 months), stable disease in 2 patients (33.3%), and PD in 2 patients (33.3%); 1 patient (16.7%) was not evaluable.

According to RECIST, the median progression-free survival (PFS) was 3.3 months (95% CI: 1.9, 12.0), and at 6 months, the Kaplan-Meier estimated PFS rate was 20.0% (95% CI: 0.8, 58.2). According to iRECIST, the median PFS (iPFS) was 2.6 months (95% CI: 1.9, 12.0; Kaplan-Meier estimated iPFS rate at 6 months: 25.0%; 95% CI: 0.9, 66.5).

The median overall survival (OS) was 13.4 months (95% CI: 4.8, 14.9). At 6 months, the Kaplan-Meier estimated OS rate was 83.3% (95% CI: 27.3, 97.5) and at 12 months it was 83.3% (95% CI: 27.3, 97.5).

Pharmacokinetics

Plasma CyPep-1 concentrations on Cycle 1 Day 15 were quantifiable in 2 patients. Preliminary, limited PK parameters were reported due to the lack of a well-characterized terminal phase because of a truncated sampling period post-dose. The maximum concentration of CyPep-1 (C_{max}) occurred at 0.25 hours postdose, and the mean C_{max} was 89.8 ng/mL (SD ± 58.3), the time to maximum serum concentration (T_{max}) was 0.25 hours in both patients, and time of the last quantifiable concentration (T_{last}) ranged from 0.25 hours to 1 hour. The area under the concentration vs. time curve from time 0 (pre-dose) to the time of the last measurable concentration (AUC_{last}) was calculable for 1 patient with sufficient concentration-time data and was 50.7 h*ng/mL.

Safety

CyPep-1 in combination with pembrolizumab was well tolerated. All patients experienced at least 1 TEAE and 1 drug-related TEAE. All TEAEs were of CTCAE grade ≤3. The frequencies of drug-related TEAEs related to CyPep-1 or to trial medication (CyPep-1 or pembrolizumab) were comparable.

There were no TEAEs leading to treatment interruption, to treatment delay or withholding of treatment, or to permanent discontinuation of treatment. No pre-specified TEAEs of clinical interest were reported.

Name of Sponsor/Company: Cytovation ASA

Name of Test Product: CyPep-1

Name of Active Ingredient: CyPep-1

On the MedDRA preferred term (PT) level, the most frequently reported TEAEs were injection site pain (17 events reported by 2 patients), axillary pain (3 events reported by 1 patient), and asthenia (2 events reported by 2 patients). All other PTs were each reported only once by a single patient, as follows: blood glucose increased, chills, conjunctivitis, cough, cytokine release syndrome, diarrhoea, erysipelas, erythema, hyperkalaemia, hypersomnia, hypokalaemia, hyponatraemia, injection site paraesthesia, leukocytosis, malaise, myalgia, pain, perichondritis, rash, skin infection, urinary tract infection, and vitiligo.

In total, 3 patients (50.0%, 20 events) experienced TEAEs of worst severity of CTCAE grade 1, 1 patient (16.7%, 21 events) of worst severity CTCAE grade 2, and 2 patients (33.3%, 3 events) of worst severity CTCAE grade 3.

On the MedDRA PT level, the most frequently reported CyPep-1-related TEAEs were injection site pain (1 patient, 16.7%; 16 events), axillary pain (1 patient, 16.7%; 3 events) and asthenia (2 patients, 33.3%; 2 events). All other CyPep-1-related PTs were each reported once by a single patient, as follows: chills, cough, erysipelas, hyperkalaemia, hyponatraemia, injection site paraesthesia, leukocytosis, malaise, myalgia, rash, and skin infection.

Two patients (33.3%) experienced TEAEs or drug-related TEAEs of CTCAE grade 3; 3 PTs were reported: asthenia was reported by 1 patient (16.7%) and erysipelas and injection site pain were reported by 1 patient (16.7%).

In total 34 events considered to be related to trial medication (CyPep-1 or pembrolizumab) were reported. The TEAEs related to trial medication by PT were identical to those listed above as related to CyPep-1, with 2 exceptions: diarrhoea, and vitiligo were also reported as related to CyPep-1 or pembrolizumab (each reported once, by a single patient, 16.7%).

One patient (16.7%) experienced a treatment-emergent serious adverse event (TESAE) (PT: erysipelas). The event was CTCAE grade 3, was related to CyPep-1 and to CyPep-1 or pembrolizumab, and was reported as a dose-limiting toxicity event. The patient required concomitant medication and the outcome was resolved. No change in dose of CyPep-1 or pembrolizumab was required.

There were no clinically meaningful changes in hematology or clinical chemistry parameters, vital signs, or electrocardiogram parameters.

Overall conclusion

Due to the early termination of trial CYP003, only the 6 patients in the Phase 1b part of the trial were enrolled and treated. Preliminary efficacy data showed that 1 of 4 evaluable patients with metastatic melanoma achieved a durable PR (12 months), the median OS was 13.4 months, and the estimated OS rate at 12 months was 83.3%. Preliminary PK data indicated C_{max} occurred at 0.25 hours, mean C_{max} was 89.8 ng/mL (SD ± 58.3), T_{max} was 0.25 hours, T_{last} ranged from 0.25 hours to 1 hour, and AUC_{last} was 50.7 h*ng/mL. Intratumoral CyPep-1, in combination with 6-weekly cycles of pembrolizumab, was well tolerated.

Date of the Report: 13 February 2025