2. SYNOPSIS

Sponsor: Ultimovacs ASA

Investigational product: UV1

Title of study: A Randomised Phase II, Open-label, Active-controlled, Multicenter Study Investigating the Efficacy and Safety of UV1 Vaccination in Combination with Nivolumab and Ipilimumab as First-line Treatment of Patients with Unresectable or Metastatic Melanoma (UV1-202)

Investigators: This study was planned to be conducted at a total of 40 sites in 4 countries (4 in Belgium, 7 in Norway, 8 in the UK, and 21 in the US); out of those, 36 sites screened patients, and 35 sites enrolled/randomised.

Publications: None at the time of this report.

Period of study: 27 May 2020 (date of first informed consent) to 11 January 2024 (cut-off date for primary analysis).

Phase of development: Clinical Phase II

Background and rationale for the study: Worldwide, over 331,000 new cases of malignant melanoma were diagnosed in 2022, and it is estimated that more than 58,000 persons died from the disease. Over 90% of new cases are diagnosed as primary tumours without any evidence of metastasis, and surgical excision can be curative. The preferred treatment options for later stages of malignant melanoma include targeted therapy and immunotherapy. Approved immune therapies include the anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody ipilimumab and anti-programmed cell death 1 (PD-1) antibodies pembrolizumab and nivolumab. In September 2015, the Food and Drug Administration granted accelerated approval of nivolumab in combination with ipilimumab in patients with gene encoding B-Raf protein (BRAF) V^{600} wild-type, unresectable, or metastatic melanoma. Many patients with unresectable or metastatic melanoma benefit from monotherapy or combination therapy with immune checkpoint inhibitors, but still many patients do not respond or become long-term survivors. Further therapeutic advances exploring the addition of other immunotherapies, such as UV1, were therefore warranted. The addition of UV1 vaccination to checkpoint inhibitors had the potential to produce additive immunological activity which could transfer into increased clinical benefit compared to dual CTLA-4 and PD-1 checkpoint inhibitor therapy.

Objectives:

Objectives	Endpoints
Primary • To compare progression free survival (PFS) of UV1 vaccination* in combination with nivolumab and ipilimumab to that of nivolumab and ipilimumab	**Primary** • PFS per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 Time from randomisation to progressive

Objectives	Endpoints
	disease (PD) or death from any cause
Secondary • To compare the overall survival (OS) of UV1 vaccination in combination with nivolumab and ipilimumab to that of nivolumab and ipilimumab • To compare the objective response rate (ORR) of UV1 vaccination in combination with nivolumab and ipilimumab to that of nivolumab and ipilimumab • To compare the duration of response (DOR) of UV1 vaccination in combination with nivolumab and ipilimumab to that of nivolumab and ipilimumab • To compare the safety of UV1 vaccination in combination with nivolumab and ipilimumab to that of nivolumab and ipilimumab	**Secondary** • OS Time from randomisation to death from any cause • ORR per RECIST 1.1 Proportion of patients with a best response of complete response (CR) or partial response (PR) • DOR per RECIST 1.1 Time from first CR or PR to PD or death from any cause • Adverse events (AEs), deaths, vital signs, laboratory assessments, and Eastern Cooperative Oncology Group (ECOG) performance status
Exploratory • To elucidate the immunological mechanisms underlying the interplay between immune activation provoked by UV1 vaccination and inhibition of tumour resistance mechanisms and peripheral immune tolerance induced by checkpoint blockade, and how biological factors affect the efficacy of the combination therapy	**Exploratory** • Change in immune- and tumour-related gene, cell, and protein profiles in blood over time in both treatment arms (analysis of plasma proteins, cell-free plasma deoxyribonucleic acid [DNA], and cellular genomic DNA). Other endpoints related to analysis conducted on biological material collected from the Extended Exploratory Cohort (refer to Appendix 2 of the Clinical Study Protocol in Appendix 16.1.1).
*UV1 vaccination includes sargramostim, used as a vaccine adjuvant, and UV1	

Methodology:

This was a randomised, open-label, active-controlled, multicenter study to investigate the efficacy and safety of UV1 vaccination in combination with nivolumab and ipilimumab as first-line treatment of adult patients (≥18 years) with unresectable histologically confirmed metastatic melanoma.

Number of patients (planned and analyzed):

An estimated total of approximately 200 patients were to be screened. In the main study, a total of 177 patients were screened, and a total of 156 patients were randomised. In addition, 21 patients were enrolled in a single-arm UV1 cohort for exploratory purposes only. The single-arm UV1 cohort was planned to start after 154 patients were randomised in the main study, and the results of the single-arm UV1 cohort will be presented in an addendum to the clinical study report (CSR) together with the exploratory outcome of the randomised part of INITIUM.

Diagnosis and main criteria for inclusion and exclusion:

The following are the main inclusion criteria for patients in this study:

- At least 18 years of age at the time of signing the informed consent form, with histologically confirmed diagnosis of unresectable stage IIIB-D or unresectable stage IV malignant melanoma. Patient was required to have at least 1 measurable lesion at screening according to the RECIST 1.1 criteria.
- Eligible for combination treatment with nivolumab and ipilimumab, with an ECOG performance status of 0 or 1 and adequate organ function as indicated by laboratory values.

The following are the main exclusion criteria for patients in this study:

- Previous non-melanoma malignancies unless curatively treated, and complete remission was achieved at least 2 years prior to randomisation (with exceptions).
- Known brain metastases or leptomeningeal metastases.
- Known history of severe hypersensitivity reactions to nivolumab, ipilimumab, sargramostim, or their excipients.
- Diagnosis of uveal or ocular melanoma.
- Known history or any evidence of active, non-infectious pneumonitis history of New York Heart Association classes 3 to 4 congestive heart failure or history of myocardial infarction within 6 months of starting study treatment.
- Prior systemic treatment for unresectable stage IIIB-D or unresectable stage IV malignant melanoma; prior systemic BRAF/mitogen-activated protein kinase inhibitors or immunotherapy as neoadjuvant or adjuvant or other setting treatment of stage I-IIIA, resectable IIIB-D, or resectable IV if the patient progressed earlier than 6 months after last dose of such treatment.
- Systemic corticosteroid treatment (doses exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive treatment within 7 days prior to the first dose of induction therapy (with exceptions).

Investigational product, dose and mode of administration, batch number:

The investigational medicinal product (IMP) included UV1 (300 µg; lot numbers L121007, L119003, L120002, and L121007) administered with sargramostim (75 µg; lot numbers

B23986A, B24468A, B25199A, and E8023E) as an adjuvant. Sargramostim and UV1 were to be administered intradermally and injected at the same injection site (McBurney's point) each time, located 1/3 of the distance from the anterior superior iliac spine to the umbilicus on the right side of the abdomen (or corresponding spot on the left side in case of appendectomy scar). Sargramostim was to be administered 10 to 15 minutes prior to each UV1 injection.

Non-investigational product, dose and mode of administration:

Nivolumab and ipilimumab (lot numbers not available; standard of care provided by sites) were administered during the Induction period, and nivolumab alone was administered during the Follow-up period. Nivolumab and ipilimumab were administered according to the label in both treatment arms: induction therapy of nivolumab (1 mg/kg every 3 weeks [Q3W]) and ipilimumab (3 mg/kg Q3W), and maintenance therapy of nivolumab (480 mg every 4 weeks [Q4W]).

Duration of treatment:

Patients in the Experimental Arm (EA) were to receive 8 UV1 vaccinations over 4 cycles of nivolumab and ipilimumab. UV1 vaccination was to be administered alone on Days 1, 3 to 7 (2 UV1 vaccinations within Day 3 to Day 7; consecutive dosing days were not to be allowed), and Day 26, and in combination with nivolumab and ipilimumab on Days 10, 31, 52, and 73.

Patients in the Control Arm (CA) were to receive 4 cycles of nivolumab and ipilimumab on Days 1, 22, 43, and 64.

Patients in both arms were to start maintenance therapy 6 weeks after the last dose of induction therapy. The maintenance therapy was to be nivolumab at a dose of 480 mg Q4W, according to the label. No other dose of maintenance therapy (ie, 240 mg every 2 weeks) was to be allowed.

Endpoints:

Efficacy:

- PFS per RECIST 1.1. - time from randomisation to PD or death from any cause (primary)
- OS - time from randomisation to death from any cause (secondary)
- ORR per RECIST 1.1. - proportion of patients with a best response of CR or PR (secondary)
- DOR per RECIST 1.1. - time from first CR or PR to PD or death from any cause (secondary)
- Change in immune- and tumour-related gene, cell, and protein profiles in blood over time in both treatment arms - analysis of plasma proteins, cell-free plasma DNA, and cellular genomic DNA (exploratory)

- Other endpoints related to analysis conducted on biological material collected from the Extended Exploratory Cohort (exploratory)

Safety:

- AEs, deaths, vital signs, laboratory assessments, ECOG performance status (secondary)

Statistical methods:

All data processing, summarisation, and analyses were performed using Fortrea's SAS Environment / Version 9.4 (or later) of the SAS statistical software package. All data collected in this study were documented using summary tables, figures, and patient data listings.

As a general rule, the baseline value of the study assessment (eg, weight) was defined as last available value collected prior to the first dose of treatment. For all patients randomised without any treatment intake, last available data before randomisation was considered as baseline value.

Analysis populations were:

- The Intent-To-Treat population consisted of all randomised patients. The ITT patients were analysed according to their randomised treatment.

- The Response Evaluable (RE) population consisted of all randomised patients with at least 1 post-baseline assessment with measurable disease (response assessment post-baseline not missing) by RECIST 1.1 according to blinded independent central review (BICR). The RE patients were analysed according to their randomised treatment.

- The Safety population consisted of all randomised patients treated with at least 1 dose (or partial dose) of induction therapy (any administered treatment from the EA or CA). Safety patients were analysed according to their actual treatment received, based on the first dose of induction therapy.

A Cox proportional hazards regression model was used to analyse PFS and OS. The model included a single covariate for randomised treatment and covariates for baseline ECOG (0 versus 1) score. The hazard ratio (HR) was estimated from the model along with the associated 2-sided 80% and 95% 2-sided confident intervals (CIs) and 2-sided p-value. The PFS was summarised by treatment group using Kaplan-Meier estimates (median with associated 80% and 95% 2-sided CIs and survival rate at 12 months) and illustrated graphically using a Kaplan-Meier plot. The PFS at 12 months was estimated from the Kaplan-Meier curves. The OS was analysed at the time of the PFS analysis and subsequently, with additional follow-ups at 6, 12, 18, and 24 months, to provide data supportive of PFS. However, with the early termination of the study, no patients were followed for survival for 2 years from the PFS cut-off date. The PFS and OS were analysed on the ITT population.

The ORR was summarised by treatment group, with 80% and 95% exact Clopper-Pearson 2-sided CI for binomial proportions. The ORR was analysed using exact logistic regression. The model included a single covariate for randomised treatment and covariates for baseline ECOG (0 versus 1) score. The exact odds ratio was estimated from the model along with the associated 80% and 95% CIs and 2-sided p-value. The ORR was analysed on the RE population.

The DOR was summarised by treatment group using Kaplan-Meier estimates (median with associated 80% and 95% CIs, and survival rate at 12 months) and illustrated graphically using a Kaplan-Meier plot (globally first and then by type of best overall response). The DOR was analysed via Cox proportional hazards regression model. The model included a single covariate for randomised treatment. The HR were estimated from the model along with the associated 80% and 95% CIs and 2-sided p-value. The DOR was analysed on the RE population.

Additionally, several sensitivity analyses were performed on the primary and secondary endpoints.

Safety data included AEs, deaths, laboratory values (haematology and chemistry), physical examinations, vital signs, and ECOG. All safety analyses were presented by treatment group in patients from the Safety population. The following descriptions of AEs were also provided with number and percentage of patients with at least 1 event and the number of events:

- treatment-emergent AEs (TEAEs) by system organ class (SOC) and preferred term (PT)
- treatment related TEAEs by SOC and PT
- treatment related TEAEs by National Cancer Institute - Common Terminology Criteria (NCI-CTC) grade, SOC, and PT
- serious TEAEs by SOC and PT
- TEAEs of special interest by SOC and PT
- TEAEs leading to dose interruption by SOC and PT
- TEAEs leading to withdrawal from summarised treatment by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs by associated NCI-CTC worst grade, SOC, and PT.

No statistical comparisons of AEs between treatment groups were performed.

Summary - Conclusions: Patient disposition:

The first patient for study UV1-202 was randomised on 12 June 2020; the data cut-off date for the primary analysis was 11 Jan 2024. A total of 40 sites in 4 countries (4 in Belgium, 7 in Norway, 8 in the UK and 21 in the US) were initiated for the study; out of those, 36 sites

screened patients, and 35 sites enrolled/randomised. A total of 177 patients were screened for the study.

A total of 154 patients were included in the safety population, 156 patients were included in the ITT, and 153 patients were included in the RE. Two patients were randomised to the EA but withdrew from the study before receiving any study medication; these patients were excluded from the safety population.

At the time of the PFS cut-off, there were 112/156 (71.79%) patients remaining on study, with 53/78 (67.95%) remaining in the EA, and 59/78 (75.64%) in the CA. Overall, the primary reason for study discontinuation in both arms was death.

Demography and baseline characteristics:

Overall, there were no notable differences between the treatment arms. The mean age of patients was 59.6 years (range: 27 to 88 years). The majority of patients were male (102/156 [65.38%] patients), White (151/156 [96.79%] patients), and from the United States (63/156 [40.38%] patients), with a baseline ECOG performance status of 0 (120/156 [76.92%] patients) or 1 (34/156 [21.79%] patients). Mean heights, weights, and body mass indexes were approximately equal between the treatment arms.

Efficacy results:

- There were no notable differences between the treatment arms in PFS as assessed by BICR, with 12-month PFS rates of 0.57 in the EA and 0.57 in the CA, and PFS HR of 0.95. The PFS as assessed locally differed from the BICR results, with 12-month PFS rates of 0.46 in the EA and 0.58 in the CA, and PFS HR of 1.23, indicating a non-significant result in favour of the CA.
- The OS rates at 12 months were nearly identical between the treatment arms (0.87 in the EA versus 0.88 in the CA), but rates began to diverge between the arms at 24 months (0.74 versus 0.80, respectively), and continued into 36 months (0.65 versus 0.75, respectively). The OS HR was 1.15, indicating a non-significant result slightly in favour of the CA. Sensitivity analyses were mostly consistent with the primary analysis, with the exception of the ‘LDH level >2 times the upper limits of normal’ subgroup, for which the result was significant (approximately 8 times higher risk of OS events in the EA compared to CA); however, this subgroup had a comparatively small sample size.
- The ORR and best overall response (BOR) results were comparable between the 2 treatment arms, as assessed by BICR. The ORR odds ratio (EA versus CA) model was 1.12, indicating that the odds were non-significantly in favour of a BOR of CR or PR in the EA. Results from the sensitivity analyses of ORR considering local assessment were consistent with the primary analysis.
- As assessed by BICR, the 12-month KM estimate was 0.81 for the EA and 0.84 for the CA. The DOR HR was 1.43, indicating a non-significant result in favour of the CA. However, in the DOR sensitivity analysis, by local assessment the 12-month KM estimate was 0.71 for the EA and 0.88 for the CA, and the DOR HR was 2.30, indicating a result strongly, but not significantly, in favour of the CA.

- Exploratory endpoints will be reported in a CSR addendum.

Safety results:

- Frequency and severity of TEAEs were similar between the treatment arms. All patients in both arms experienced at least 1 TEAE, and almost all experienced a TEAE related to treatment with UV1 and/or nivolumab/ipilimumab. TEAEs were most frequently moderate or severe in intensity. Over half of the patients in each treatment arm experienced at least 1 serious adverse event (SAE).
- The most frequently reported TEAEs in both treatment arms were fatigue, nausea, diarrhoea, rash, and pruritis. There were no notable differences in number/percentage of patients with TEAEs between the treatment arms. However, there were more individual TEAEs in the EA as compared with the CA (725 events versus 600 events, respectively); this difference was likely driven by the presence of injection site reactions in the EA from administration of UV1.
- Incidence of any related TEAEs was well-balanced between the treatment arms, and closely mirrored the distribution observed for TEAEs overall. The most common SOCs for related TEAEs were skin and subcutaneous tissue disorders, general disorders and administration site conditions, and gastrointestinal disorders. As expected, there were notably more patients in the EA who experienced TEAEs related to administration site conditions, due to the injection of UV1.
    - A substantial percentage of the patients in the EA arm reported TEAEs related to UV1 and/or sargramostim, most frequently fatigue, injection site erythema, and injection site reaction. Based on previous studies, these events are not unexpected for patients treated with UV1 and sargramostim.
    - Almost all patients in both treatment arms reported TEAEs related to nivolumab and/or ipilimumab, most frequently rash and pruritis. Based on previous studies, these events are not unexpected for patients treated with nivolumab and ipilimumab.
- Treatment-emergent AEs of special interest (AESIs) occurred infrequently in both treatment arms. All AESIs were in the SOC of immune system disorders.
- Adverse reactions of any grade, and of Grades 3 to 4, occurred approximately equally across both treatment arms. Fatigue, nausea, diarrhoea, pyrexia, and rash were the most frequently reported adverse reactions; however, reactions in those categories rarely presented as Grade 3 or 4. Colitis, diarrhoea, alanine aminotransferase and aspartate aminotransferase increased, and immune-mediated hepatitis were the most frequently reported Grades 3 to 4 reactions.
- One patient in the CA died during the study due to cerebral haemorrhage; the death was judged to be unrelated to IMP.
- There was no appreciable difference in occurrence of SAEs between the treatment arms, and no trends emerged. In both treatment arms, the most common SOCs for SAEs were gastrointestinal disorders, and infections and infestations.

- While numerically more patients in the EA experienced TEAEs resulting in infusion interruption than in the CA, this was not an unexpected result, due to concurrent administration with UV1 in this treatment arm.
- The TEAEs leading to withdrawal from nivolumab and/or ipilimumab occurred in almost half of patients in the EA arm, and more than half in the CA arm. There were no notable differences between the treatment arms in frequency or types of these TEAEs, and no unexpected trends emerged.
- Haematology and clinical chemistry results were unremarkable for the majority of patients, and there were no notable differences between treatment arms. Two patients in each treatment group experienced changes in haematology parameters that qualified as NCI-CTC Grade ≥ 3 toxicities. Vital signs were unremarkable, and there were no differences between the treatment arms.
- ECOG results were generally stable, with the majority of patients in both treatment arms starting and remaining at Grades 0 or 1 from baseline through the EOS, and few patients starting at or moving to Grade 2. Rarely, patients within each treatment had shifts from Grade 0 to Grade 3, and from Grade 1 to Grade 4.

Conclusions:

- UV1 vaccination in combination with nivolumab and ipilimumab did not demonstrate efficacy or an improvement in PFS (time from randomisation to PD or death from any cause), OS (time from randomisation to death from any cause), ORR (proportion of patients with a best response of CR or partial response PR), or DOR (time from first CR or PR to PD or death from any cause) over SOC treatment with nivolumab and ipilimumab.

- There were no notable differences in safety between UV1 vaccination in combination with nivolumab and ipilimumab compared to SOC treatment with nivolumab and ipilimumab, as evaluated by AEs, deaths, vital signs, laboratory assessments, and ECOG status.

- Exploratory endpoints from the Single-arm cohort and the Extended Exploratory Cohort will be reported in a future CSR addendum.

- The study was terminated as of 10 April 2024 (3 months after the PFS cut-off). No patients were followed for survival for 2 years from the PFS cut-off.