INITIUM Protocol

A Randomized 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)

Protocol Number, Version and Date:
UV1-202, Version 5.0 (Final), 22 Sep 2023

Study Phase:
Phase II

Sponsor Name and Legal Registered Address:
Ultimovacs ASA
Ullernchausséen 64, N-0379 Oslo, Norway

Regulatory Agency Identifying Numbers:
Investigational New Drug: 17546
EudraCT: 2019-002026-75

Sponsor:

Øivind Foss, DrSc **Head of Clinical Operations, Ultimovacs ASA**	**Date**
Kevin J. Carroll, Dr **Consultant Statistician, KJC Statistics**	**Date**
Jens Bjørheim, MD, PhD **Chief Medical Officer, Ultimovacs ASA**	**Date**

Table of Contents

List of In-text Tables and Figures

TABLES

FIGURES

1 Synopsis

INITIUM Protocol

Protocol Title:

A Randomized 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)

Protocol Number, Version:

UV1-202, Version 5.0 (Final), 22 Sep 2023

Study Phase:

Phase II

Study Sites:

The study is planned to be conducted at 40 study sites in Europe (approximately 16 sites) and the United States (approximately 24 sites).

Number of Patients:

A total of 154 patients will be randomized. It is estimated that approximately 200 patients will be screened to randomize 154 patients. In addition, 20 patients will be enrolled in a single arm UV1 cohort for exploratory purposes only. The single arm UV1 cohort is planned to start after 154 patients have been randomized in the main study.

Objectives and Endpoints

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 Tumors (RECIST) 1.1 Time from randomization to progressive disease (PD) or death from any cause
Secondary • To compare 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 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 randomization 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 tumor 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 tumor-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) • Other endpoints related to analysis conducted on biological material collected from the Extended Exploratory Cohort
* UV1 vaccination includes sargramostim, used as a vaccine adjuvant, and UV1	

Study Design and Methodology

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

This study will consist of 3 phases: Screening, Induction period, and a Follow-up period. The Follow-up period includes safety, response, and survival follow-up visits.

After a Screening period of up to 28 days, eligible patients will be randomized in a 1:1 ratio to receive induction therapy: UV1 vaccination in combination with nivolumab and ipilimumab in an experimental arm, and nivolumab and ipilimumab in a control arm. Randomization can occur after all Screening procedures have been completed (up to 3 days [from Day -3 until Day 1] prior to first dosing on Day 1) and eligibility has been confirmed.

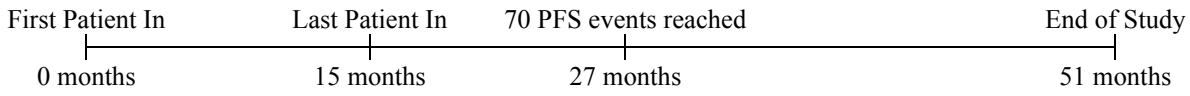
Patients in the experimental arm will receive 8 UV1 vaccinations over 4 cycles of nivolumab and ipilimumab. The UV1 vaccination will be administered alone on Days 1, 3 to 7 (2 UV1 vaccinations within Day 3 to Day 7; consecutive dosing days not allowed), and 26, and in combination with nivolumab and ipilimumab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

Patients in the control arm will receive 4 cycles of nivolumab and ipilimumab on Days 1, 22, 43, and 64.

Patients in both arms will start maintenance therapy 6 weeks after last dose of induction therapy. The maintenance therapy is nivolumab at a dose of 480 mg every 4 weeks (Q4W) according to the label. It is not allowed to use any other dose of maintenance therapy (eg, 240 mg every 2 weeks).

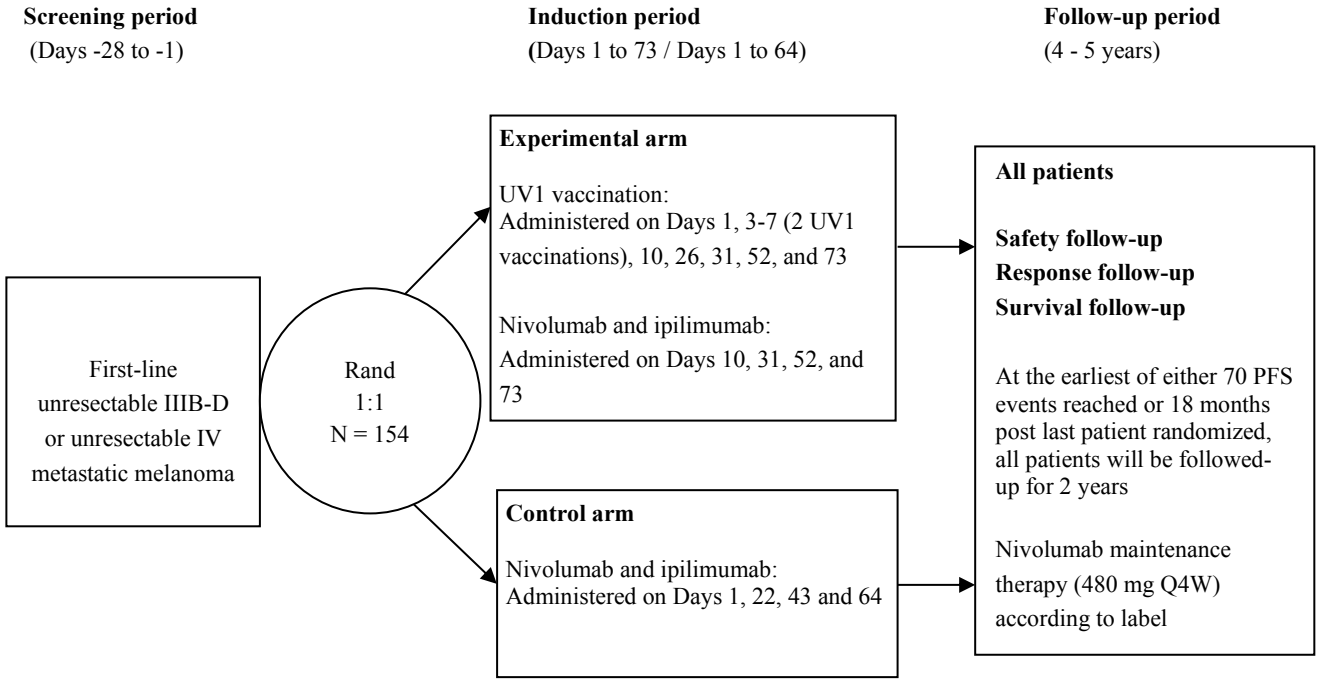
The study is event driven. The primary and secondary endpoints will be analyzed at the earliest of either (hereinafter referred to as “PFS cut-off date”) 70 PFS events reached across both treatment arms or 18 months post last patient randomized, at which time sponsor will notify the sites. From the PFS cut-off date, patients will be followed for a further 24 months for additional survival data; further analyses of OS data will be performed until defined end of study to provide evidence supportive of PFS.

All patients will be followed up until death or until the end of study (EOS), whichever comes first. Estimated timelines at start of the study are outlined below.



The estimated inclusion period is 15 months; the estimated time from last randomization to 70 PFS events reached is 12 months; the estimated time from 70 PFS events to EOS is 24 months and the total study duration is estimated to be 51 months from first patient in.

The study design and treatment are outlined below.



The UV1 vaccination includes sargramostim, used as a vaccine adjuvant, at a dose of 75 µg and UV1 at a dose of 300 µg. Sargramostim is a granulocyte-macrophage-colony-stimulating factor. Nivolumab and ipilimumab are dosed according to label in both treatment arms: induction therapy of nivolumab (1 mg/kg every 3 weeks [Q3W]) and ipilimumab (3 mg/kg every 3 weeks [Q3W]), and maintenance therapy of nivolumab (480 mg every 4 weeks [Q4W]).

Sargramostim and UV1 should 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 is administered 10 to 15 minutes prior to each UV1 treatment. Nivolumab and ipilimumab are administered intravenously, starting at least 1 hour after the administration of UV1.

Following the last dose of induction therapy, the patient will then enter the Follow-up period and perform a safety follow-up visit 30 days post last dose of induction therapy.

Tumor assessment will be done locally at the study site using RECIST 1.1 and immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria. Tumor imaging will be performed within 14 days prior to randomization and then on Week 12 and Week 19 post randomization. Subsequent response follow-up imaging will be performed every 8 weeks for 32 weeks and then every 12 weeks.

Patients with PD per RECIST 1.1 will have a new scan 4 to 8 weeks later to confirm PD per iRECIST. Patients with immune unconfirmed PD per iRECIST (iUPD), will continue at the

Investigator's discretion, with tumor imaging and treatment per protocol until immune confirmed PD per iRECIST (iCPD), until 70 PFS events are reached or until 18 months post last patient randomized (whatever comes first). Patients with iCPD per iRECIST will be discontinued from treatment and will proceed into the survival follow-up phase and be contacted per phone (or, at the investigator's discretion visit the hospital) every 12 weeks until the earliest of either 70 PFS events reached or 18 months post last patient randomized. From the PFS cut-off date, the survival follow-up will continue in all patients every 6 months for 2 years.

To reduce bias in evaluation of the efficacy endpoints, tumor evaluation for the statistical analysis of the efficacy endpoints will be done by Blinded Independent Central Review (BICR) according to the RECIST 1.1 criteria. All images must be submitted to the central imaging vendor, but the results from the BICR will not be provided to the study site. Two independent radiologists will perform the central imaging review without knowledge of treatment assignments. If there are discrepancies between the 2 readers, a standardized procedure involving a third reviewer for adjudication will take place.

From signing of the Informed Consent Form (ICF) until the first dose of induction therapy, only AEs/serious AEs (SAEs) caused by study-specific procedures should be reported. Non-serious AEs should be reported from the first dose of induction therapy until 30 days after the last dose of induction therapy, or until new anticancer treatment is initiated (whichever comes first). All SAEs should be reported from the first dose of induction therapy until 70 PFS events are reached, until 18 months post last patient randomized or until new anticancer treatment is initiated (whichever comes first). Adverse events and SAEs that are ongoing beyond the required reporting timelines shall be followed up locally per institutional practice until resolution or stabilization or the patient is lost to follow up.

During the study, an Independent Data Monitoring Committee will monitor safety information to ensure patient safety.

Patients at selected sites will have the option to be Included in the Extended Exploratory Cohort of the study. This cohort of approximately 40 patients, randomized in a 1:1 ratio to either of the 2 treatment arms, will have additional sampling of blood, tissue, and feces for exploratory purposes. A biobank will be established for current and future analysis of the samples collected.

To support the Extended Exploratory Cohort of the study, an additional 20 patients will be enrolled in a single arm UV1 cohort for collection of additional biological material (Appendix 7 Single Arm UV1 Cohort). These patients will receive the same study treatment as patients in the experimental arm.

Study Population

Inclusion Criteria

Patients are eligible for randomization if all of the following criteria are met:

1. Male or female patients at least 18 years of age at the time of signing the ICF.

2. Histologically confirmed diagnosis of unresectable stage IIIB-D, or unresectable stage IV malignant melanoma. Patient must have at least 1 measurable lesion at Screening according to the RECIST 1.1 criteria.
   Note that lesions not measurable on computed tomography or magnetic resonance imaging (MRI) will be considered as non-measurable lesions.
3. Eligible for combination treatment with nivolumab and ipilimumab.
4. An ECOG performance status of 0 or 1.
5. Adequate organ function as indicated by the following laboratory values:

   Hematological

   a. Absolute neutrophil count ≥1,500/µL
   b. Platelet count ≥100 x 10^3/µL
   c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L

   Renal

   d. Creatinine ≤1.5 x upper limit of normal (ULN)

   Hepatic

   e. Total bilirubin ≤1.5 x ULN or

      direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 ULN

   f. Aspartate aminotransferase/glutamic-oxaloacetic transaminase and alanine aminotransferase/glutamic-pyruvic transaminase ≤2.5 x ULN for patients without liver metastasis or ≤5 x ULN for patients with liver metastasis.
6. Male patients who are sexually active with a female of childbearing potential must agree to use an adequate method of contraception prior to the first dose through 5 months after the last dose of UV1 vaccination, nivolumab, or ipilimumab, whichever is administered last. The recommended method is using a male condom.
7. Women of childbearing potential (WOCBP) must have a negative urine or serum/plasma pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum/plasma pregnancy test will be performed. The serum/plasma pregnancy test must be negative for the patient to be eligible.
8. WOCBP must use adequate contraception. Adequate contraception must be maintained throughout the study, starting with the first dose through 5 months after the last dose of UV1 vaccination, nivolumab, or ipilimumab, whichever is administered last. The acceptable contraceptive methods for WOCBP included in the study are:
   Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), Intrauterine device (IUD), Intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical

assessment of the surgical success), or sexual abstinence (if this is the preferred and usual lifestyle of the subject)

9. Written informed consent prior to any study-specific procedures.

Exclusion Criteria

Patients are not eligible for randomization if any of the following criteria are met:

1. Previous non-melanoma malignancies unless curatively-treated and complete remission was achieved at least 2 years prior to randomization. Patients with prior curatively-treated basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or carcinoma in situ of the breast, or other in situ cancers are allowed irrespective of time passed since curative treatment. Patients with prior completely resected malignant melanoma are also allowed.
2. Known brain metastases or leptomeningeal metastases. If a patient experiences neurological symptoms indicative of brain metastases, a brain MRI should be performed.
3. Diagnosis of uveal or ocular melanoma.
4. Known history or any evidence of active, non-infectious pneumonitis.
5. History of New York Heart Association class 3-4 congestive heart failure or history of myocardial infarction within 6 months of starting induction therapy.
6. Active infection requiring systemic treatment.
7. Diagnosis of immunodeficiency.
8. Known history of severe hypersensitivity reactions to nivolumab, ipilimumab, sargramostim, or their excipients.
9. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies). No HIV testing is required unless mandated by local health authority.
10. History of or active hepatitis B (hepatitis B surface antigen reactive) or active hepatitis C (hepatitis C virus antibody). Testing must be performed to determine eligibility.
11. Women who are breastfeeding.
12. Prior systemic treatment for unresectable stage IIIB-D or unresectable stage IV malignant melanoma. Prior systemic BRAF/MEK inhibitors or immunotherapy as neoadjuvant or adjuvant or other setting treatment of stage I-IIIA, resectable IIIB-D, or resectable IV if patient progressed earlier than 6 months after last dose of such treatment.
13. 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. Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) are allowed. Physiologic replacement doses of systemic corticosteroids, a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions is permitted even with >10 mg/day prednisone equivalents.

14. Receipt of a live vaccine within 30 days prior to start of induction therapy.
15. Receipt of any other investigational treatment within 4 weeks of the first dose of induction therapy.
16. Any medical, psychological, or social condition that would make it difficult for the patient to participate in the study and comply with the study procedures, restrictions, and requirements.

Statistical Methods

Statistical Hypothesis

The primary endpoint is PFS. Under the null hypothesis, the PFS hazard ratio (HR) for UV1 vaccination in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab is assumed to be unity. Under the alternative hypothesis, the PFS HR is assumed to be 0.60 or better, representing a beneficial effect on PFS for UV1 vaccination in combination with nivolumab and ipilimumab compared to nivolumab and ipilimumab.

Sample Size Determination

To test the PFS null hypothesis with 80% power and a 1-sided alpha level of 0.10, a total of 70 PFS events are required. To generate the required 70 PFS events, 154 patients will be randomized over a 15-month period and followed thereafter for a minimum of 12 months. This will give a mean follow-up of PFS events of approximately 20 months.

As of 19 September 2023, blinded event accrual stood at 63 PFS events. A blinded examination of the overall PFS Kaplan Meier curve made as of 23 July 2023, and then repeated as of 19 September 2023, showed strong evidence for a plateau at 54 to 55% of subjects alive and without progression. Such a PFS curve plateau is not uncommon for IO therapies. In CheckMate 67, nivolumab plus ipilimumab, nivolumab alone and ipilimumab alone were evaluated in advanced melanoma (Hodi 2018). This study formed the basis of the sample size calculations for the current study and showed a prolonged PFS tail for nivolumab plus ipilimumab plateauing at approximately 40% subjects alive and without progression. However, the blinded data realized thus far, has shown a higher plateau at 54 to 55% subjects alive and without progression.

Specifically, there seems to be very little contribution to PFS events after 18 months in the study, with the PFS curve nearing asymptote. The plateau in the current study commences at approximately 21 months post first subject randomized with an estimated 56.02% of subjects alive and without progression and persists thereafter for 15 months, out to 36 months at which time 54.32% subjects are alive and without progression, i.e. an increase in the progression rate of only 1.7% over 15 months. Based on the projected PFS curve, 70 PFS events are not expected to be reached until late 2028 at which time 69.3 events, 90% CI of (69.2, 72.3), are expected.

Given the observed plateau in the accrual of PFS events, it has been decided to execute the primary analysis of PFS at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized.

Timing of Analyses

It should be noted that this study is event driven so that the timing of the primary endpoint analysis is dependent upon the attainment of 70 PFS events and is not calendar based. Based on the assumptions supporting the sample size calculation (Hodi, 2018), it is expected that 70 PFS events will have accrued at around 27 months after the first patient is randomized.

However, as of 19 September 2023, blinded event accrual stood at 63 PFS events. A blinded examination of the overall PFS Kaplan Meier curve made as of 23 July 2023, and then repeated as of 19 September 2023, showed strong evidence for a plateau at 55% of subjects alive and without progression. Given the observed plateau in the accrual of PFS events, it has been decided to execute the primary analysis of PFS at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized.

The secondary endpoints will also be analyzed at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized. Follow-up for survival will continue for an additional 24 months after the PFS cut-off date at which time 60 deaths are expected to have accrued.

Primary Efficacy Analyses

A Cox proportional hazards regression model will be used to analyze PFS. The HR will be estimated from the model along with the associated 2-sided confidence interval (CI) and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and median PFS times will be estimated. The PFS at 12 months will be estimated from the Kaplan-Meier curves along with the associated 80% and 95% CIs.

Note, patients who withdraw consent to follow-up may have missing PFS data. The impact of such patients on the analysis will be explored via imputation and possibly tipping point analyses. Full details will be provided in the Statistical Analysis Plan (SAP).

Secondary Efficacy Analyses

Overall Survival will be analyzed in a fashion similar to that described for PFS at the time of the PFS analysis. Patients who withdraw consent to follow-up may have missing OS data. The impact of such patients on the analysis will be explored via imputation and possibly tipping point analyses. Full details will be provided in the SAP. Additionally, follow-up for survival will continue for a further 24 months after the PFS analysis at which time 60 deaths are expected to have accrued.

Objective Response Rate will be analyzed by exact logistic regression. Patients who have missing tumor assessment data leading to missing objective response data will be included in the analysis as non-responders.

Duration of Response will be analyzed via Cox regression modelling.

Safety Analyses

Adverse events will be summarized descriptively by treatment group, in terms of body system and Medical Dictionary for Regulatory Activities preferred term. Adverse events will be summarized in terms of the number of patients and percentage of patients experiencing related AEs, SAEs, AEs leading to dose interruption, AEs leading to withdrawal from randomized treatment, and AEs leading to death.

Laboratory values, ECOG performance status, and vital signs will be summarized.

Planned Timelines

First patient in:	Q2 2020
Last patient in:	H1 2022
Primary endpoint read out:	H1 2024
End of study:	H1 2026

The First Patient In is defined as the timepoint when the first patient is randomized.

2 Introduction

2.1 Malignant Melanoma

Worldwide over 280,000 new cases of malignant melanoma were diagnosed in 2018, and it is estimated that more than 60,000 persons died from the disease.[1]

There are 4 main subtypes of cutaneous melanomas: superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma. These can be clinically and histologically defined based on overall appearance, location, and histologic features of the melanocytes. The most common risk factors are of phenotypic (fair skin), genetic (inheriting melanocortin-1 receptor variant; presence of high numbers of common naevi, large congenital naevi, multiple, and/or dysplastic naevi), and external (exposure to ultraviolet irradiation) types.

Melanoma is categorized into 5 stages: Stage 0 is in situ (intraepithelial) melanoma, Stages I and II are localized invasive cutaneous disease, Stage III is regional spread disease, and Stage IV is disease with distant metastasis. Over 90% of new cases are diagnosed as primary tumors 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. Targeted therapy is approved for patients with gene encoding B-Raf protein (BRAF) mutations and includes BRAF/mitogen-activated protein kinase (MEK) inhibitor combinations. Approved immune therapies include the anti-cytotoxic T-lymphocyte-associated protein-4 antibody ipilimumab and anti-programmed cell death 1 (PD-1) antibodies pembrolizumab and nivolumab.

In September 2015, the Food and Drug Administration (FDA) granted accelerated approval of nivolumab in combination with ipilimumab in patients with BRAF V^{600} wild-type, unresectable, or metastatic melanoma. Positive opinion from the Committee for Medicinal Products for Human Use for the combination recommending a change to the terms of the marketing authorization for nivolumab was received in April 2016.

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-time survivors. Further therapeutic advances exploring additional immunotherapy combinations are therefore warranted.

2.2 Checkpoint Inhibitors for Advanced Malignant Melanoma

2.2.1 Checkpoint Inhibitors Monotherapy

Ipilimumab monotherapy for advanced malignant melanoma gives a median progression free survival (PFS) of 3 to 4 months and a median overall survival (OS) of 6 to 20 months.[2,3,4,5,6,7,8,9,10]

In the CheckMate-066 study, nivolumab monotherapy showed a median PFS of 5.1 months and a 1-year OS rate of 72.9%. The median OS was not reached; however, the study demonstrated a statistically significant improvement in OS for the nivolumab arm compared with the dacarbazine arm in an interim analysis based on 47% of the total planned events for OS (hazard ratio [HR] for death, 0.42; 99.79% confidence interval [CI], 0.25 to 0.73; p<0.001).[11] Pembrolizumab demonstrated a median PFS of 3 to 6 months, median OS of 13 to 15 months, and a 2-year survival of 36% to 55%.[11,12]

2.2.2 Combination of Nivolumab and Ipilimumab

The combination of nivolumab and ipilimumab was approved based on study CheckMate-067 (NCT01844505), a multicenter, double-blind study in which 945 patients with previously untreated, unresectable, or metastatic melanoma were randomized 1:1:1 into one of the following arms: nivolumab and ipilimumab, nivolumab, or ipilimumab. Patients received either nivolumab 1 mg/kg with ipilimumab 3 mg/kg intravenously every 3 weeks (Q3W) for 4 doses, followed by nivolumab as a single agent at a dose of 3 mg/kg by intravenous infusion every 2 weeks (Q2W) (nivolumab plus ipilimumab arm); nivolumab 3 mg/kg by intravenous infusion Q2W (nivolumab arm); or ipilimumab 3 mg/kg intravenously Q3W for 4 doses, followed by placebo Q2W (ipilimumab arm). Randomization was stratified by PD-L1 expression (≥5% versus <5% tumor cell membrane expression) as determined by a clinical study assay, BRAF V^{600} mutation status, and M stage per the American Joint Committee on Cancer staging system, 8^{th} edition (M0, M1a, M1b versus M1c). Tumor assessments were conducted 12 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter. The major efficacy outcome measures were Investigator assessed PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and OS. Additional efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR).

The median PFS was 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab plus ipilimumab group, 6.9 months (95% CI, 4.3 to 9.5) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. A significant improvement in PFS was observed in the nivolumab plus ipilimumab group as compared with the ipilimumab group (HR, 0.42; 95% CI, 0.31 to 0.57; p<0.0001). A significant improvement in PFS was also observed in the nivolumab group as compared with the ipilimumab group (HR, 0.57; 95% CI, 0.43 to 0.76; p<0.0001). The HR for the comparison between nivolumab plus ipilimumab and nivolumab groups was 0.74 (95% CI, 0.60 to 0.92).[6]

The analysis results at 4 years of follow-up confirmed the improvement in PFS from the combination treatment over ipilimumab alone and showed a survival benefit of nivolumab plus ipilimumab or nivolumab alone over ipilimumab. At a minimum follow-up of 48 months from the date that the final patient was enrolled and randomized, median OS was not reached (95% CI, 38.2 to not reached) in the nivolumab plus ipilimumab group, 36.9 months (28.3 to not reached) in the nivolumab group, and 19.9 months (16.9 to 24.6) in the ipilimumab group. The HR for death for the combination versus ipilimumab was 0.54 (95% CI, 0.44 to 0.67; p<0.0001) and for nivolumab versus ipilimumab was 0.65 (0.53 to 0.79; p<0.0001). Median PFS was 11.5 months (95% CI, 8.7 to 19.3) in the nivolumab plus ipilimumab group, 6.9 months (5.1 to 10.2) in the nivolumab group, and 2.9 months (2.8 to 3.2) in the ipilimumab group. The HR for PFS for the combination versus ipilimumab was 0.42 (95% CI, 0.35 to 0.51; p<0.0001) and for nivolumab

versus ipilimumab was 0.53 (0.44 to 0.64; p<0.0001).[6] At 5 years, the OS was 52% in the nivolumab plus ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group.[13,14,15] Five-year PFS was 36%, 29%, and 8% in the nivolumab plus ipilimumab, nivolumab, and ipilimumab groups, respectively. Among patients with tumors with BRAF mutations and those with tumors without BRAF mutations, OS at 5 years was 60% and 48%, respectively, in the nivolumab plus ipilimumab group, 46% and 43% in the nivolumab group, and 30% and 25% in the ipilimumab group.

Despite advances in the development of new treatment options, advanced malignant melanoma remains a condition with a large unmet medical need.

2.3 The UV1 Vaccine

UV1 is a therapeutic cancer vaccine consisting of 3 synthetically-produced peptides covering an epitope rich sequence within the active site of the human telomerase reverse transcriptase (hTERT).

Role of Telomerase in Cancer Cell Pathogenesis

Human telomerase reverse transcriptase is one of 2 major components of the enzyme telomerase which catalyses the synthesis and extension of telomeric deoxyribonucleic acid (DNA) in order to maintain telomere length.[16]

Telomerase activity is associated with stem cell proliferation, and telomerase is highly active in embryonal cells and less active in stem cells and germinal cells. During embryonic development, telomerase activity decreases as cells differentiate[17] and telomerase activity and hTERT messenger ribonucleic acid (RNA) are not detectable in the majority of normal adult tissues, including cardiac/skeletal muscle, liver, prostate, breast, pancreas, brain, lung, and kidney.[18]

Telomerase activation is the major mechanism implicated in human cell immortalization and cancer cell pathogenesis.[16] In the absence of functional telomeres, chromosomes become highly unstable, and this can ultimately be lethal to the cell. Tumor cells avoid this situation by turning on the expression of telomerase activity. Thus, immortalization involves the arrest of the process of telomere shortening, and telomerase is the key enzyme in this process. Telomerase activity is present in approximately 100% of immortal cell lines and in >85% of human tumors of various histological types.[17,18,19] Telomerase is expressed in cancer cells at every stage of tumor evolution, from the cancer stem cell to circulating tumor cells. Due to its essential role for the immortality of tumor cells and its universal expression by most human tumors, telomerase represents a unique cancer antigen as a basis for immunotherapy.[20] Telomerase activity is reflected in the up-regulated expression of hTERT.[21]

The UV1 Peptides

The hTERT peptides composing the UV1 vaccine have been selected based on analyses of clinical and immunological response data from long-term cancer survivors responding immunologically to an unrelated first-generation hTERT vaccine. It was shown that epitope

spreading within hTERT and T-helper type 1 (Th1) reactivity (ie, secretion of interferon gamma, tumor necrosis factor alpha, and interleukin-2) were associated with prolonged survival. Based on these analyses, 3 long novel hTERT peptides associated with clinical benefit, shown to elicit strong CD4 T cell responses in blood from patients across several cancer types and predicted to contain multiple human leukocyte antigen epitopes, were selected for the next-generation hTERT vaccine UV1.[22,23]

The UV1 Vaccine

The mode of action of UV1 is to activate the immune system to induce T cells that recognize hTERT. The efficacy of the vaccine is thought to be mediated through these T cells.

Expression of telomerase is essential for unlimited growth and immortality of cancer cells (ie, the antigen is present throughout the tumorigenesis and the tumor cannot escape from dependence on telomerase). [21] Due to the temporo-spatial presence of the target, the CD4 T cells induced by UV1 can provide a pro-immunological environment in the tumor and tumor-draining lymph node, continuously over time, regardless of the genetic makeup of the individual tumor cell. The vaccine mediated the CD4 immune response to optimize for priming of de novo immune responses (epitope spreading) and tumor cell killing in an otherwise highly dynamic tumor.

UV1 is administered together with granulocyte-macrophage colony-stimulating factor (GM-CSF) as vaccine adjuvant. The GM-CSF used is sargramostim. Peptide-based vaccines generally are poorly immunogenetic due to their small size. Adjuvants provide “danger signals” for cells of the innate immune system to present vaccine epitopes in the context of major histocompatibility complex molecules, surface adherence molecules, and costimulatory molecules which are required for induction of a robust adaptive immune response. Sargramostim is selected as adjuvant for UV1 since it is documented to favor induction of peptide-specific Th11 immune responses after intradermal injections with peptides.[24,25,26] UV1 vaccination refers to administration of both sargramostim and UV1.

2.4 Clinical Data on UV1 Vaccination

UV1 was brought into clinical development in 2013. Two dose-evaluation studies including 40 patients with prostate cancer[27] and non-small cell lung cancer (NSCLC)[28] have completed treatment and patients are in follow-up for survival. One safety study combining UV1 vaccination with ipilimumab in patients with melanoma has completed treatment of 12 patients. One safety study combining UV1 vaccination and pembrolizumab in patients with melanoma is ongoing for safety follow-up, with 30 patients enrolled and treated. A tabulated summary of completed, ongoing, and planned clinical studies is provided in Table 1.

Table 1 Summary of Completed, Ongoing, and Planned Clinical Studies for UV1 Vaccination

Protocol no. (EudraCT) /country	Study design	Study population	Enrolled/ planned	Dose and dosage regimen
Completed studies[a)]				
UV1/hTERT-2012-L (2012-001852-20)/ Norway	Phase I/IIa open-label, single-center dose-evaluation study of UV1 Up to 10-year follow-up	Locally advanced and/or metastatic NSCLC with stable disease after radiation and/or chemotherapy	18	Dose: UV1 100/300/700 µg, sargramostim 75 µg (intradermal injection) Week 1: Three UV1 vaccinations (D1, 3, 5) Weeks 2, 3, 4, 6, 8, 10, 14, 18, 22, 26: One UV1 vaccination From Week 39: UV1 vaccination every 3 months up to Week 91
UV1/hTERT-2012-P (2012-002411-26)/ Norway	Phase I/IIa open-label, single-center dose-evaluation study of UV1 Up to 10-year follow-up	Hormone-sensitive metastatic prostate cancer	22	Dose: UV1 100/300/700 µg, sargramostim 75 µg (intradermal injection) Week 1: Three UV1 vaccinations (D1, 3, 5) Weeks 2, 3, 4, 6, 8, 10, 14, 18, 22, 26: One UV1 vaccination From Week 52: UV1 vaccination every 3 months up to Week 104
UV1/hTERT-MM (2013-005582-39)/ Norway	Phase I/IIa, open-label, single-center study of UV1 and ipilimumab Up to 10-year follow-up	Unresectable or metastatic melanoma	12	Dose: UV1 300 µg, sargramostim 75 µg (intradermal injection) Ipilimumab according to label Week 1[b)]: Three UV1 vaccinations (D1, 3, 5) Weeks 3, 4, 7, 10, 13, 17, 21: One UV1 vaccination Weeks 2, 5, 8, 11: Ipilimumab
Ongoing studies				
UV1/hTERT-MM-103/ US	Phase I open-label, multicenter study of UV1 and pembrolizumab 2-year follow-up	Unresectable or metastatic melanoma	30/ 30	Dose: UV1 300 µg, sargramostim 37.5/75 µg (intradermal injection) Pembrolizumab according to label Week 1: Three UV1 vaccinations (D1, 3, 5) Weeks 2, 5, 8, 11, 14: One UV1 vaccination and pembrolizumab After Week 14: Pembrolizumab continued according to label

a) Enrollment and UV1 treatment is completed and patients are in follow-up
b) In the clinical study report, the first week of UV1 vaccination is referred to as "introduction week" and the week of first ipilimumab administration is "Week 1"

As of November 2019, 72 patients have received UV1 vaccinations in the context of clinical trials, and of these 68 patients have completed the UV1 vaccination therapy. The completed studies have shown that UV1 is generally safe and well tolerated. Common adverse events (AEs) related to UV1 include pruritus, erythema, fatigue, diarrhoea, pain, and rash. Serious AEs were reported in 18% of the patients, and related SAEs in 10%. A few patients (7%) have reported serious allergic reactions to the UV1 vaccination. Four prostate cancer patients and 1 patient with metastatic malignant melanoma experienced serious allergic reactions occurring within 3 to 30 minutes after injection of 9 or more doses of UV1 and sargramostim. All events resolved without sequelae.

Across the three Phase I/IIa studies conducted with UV1 vaccination, vaccine-specific T cells were induced in 78% (range 67% to 91%) of the patients. This supports the universal utility of the vaccine across different individuals and cancer types, and thus pre-screening of patients for human leukocyte antigen-type or other biomarkers before treatment with UV1 is not needed.

In the study investigating the use of the UV1 vaccine in combination with ipilimumab in metastatic malignant melanoma patients, UV1-specific immune responses were induced in 91% of the patients. The vaccine-specific T cells appeared more frequently and rapidly in this study than in the studies investigating patients with prostate cancer and late-stage NSCLC, suggesting a synergistic effect of blocking of CTLA-4 and vaccination with UV1. Nine patients were evaluable for tumor response according to RECIST 1.1. Of these, 3 patients obtained a partial response (PR) as best overall response, 3 achieved stable disease (SD), and 3 experienced progressive disease (PD). The median PFS was 6.5 months and the 3-year survival rate was 67% (8/12).

The ongoing study combining UV1 and pembrolizumab in treatment of melanoma (UV1/hTERT-MM-103) has currently enrolled and treated 30 patients who are now in follow-up. Serious AEs and AEs of special interest (AESIs) are reported expedited to the sponsor and are the basis for the continuous safety assessment in this study. The collection of non-serious adverse is ongoing and will be reported when the study is completed, and all data have been finally verified. A thorough assessment of the safety profile of UV1 vaccination used in combination with pembrolizumab will include an evaluation of possible increase in frequency and severity of adverse reactions to pembrolizumab, the proportion of patients who have to terminate pembrolizumab treatment due to adverse reactions, and if the combination treatment enhances the UV1 related side effects.

Up to the date of this protocol, the safety information available from study UV1/hTERT-MM-103 include nine serious adverse events (SAEs) for 7 patients (23.3%) in the study, the majority of which were considered unrelated to study treatment. One SAE of grade 3 arthritis was assessed as possibly related to administration of UV1 vaccine and pembrolizumab, but the patient continued with treatment after resolution of the SAE. No AESIs (anaphylactic reaction, anaphylactic shock or hypersensitivity) have been reported among the patients. The number of UV1 vaccinations in this study is reduced to 8 compared to 12 to 18 in the completed Phase I studies as a measure to reduce the risk for serious allergic reactions following UV1 vaccination treatment.

Based on the currently available safety information, study UV1/hTERT-MM-103 has not revealed any immediate safety hazard for the use of UV1 vaccination as add-on to treatment to pembrolizumab for patients with malignant melanoma.

Conclusion on the safety of UV1 vaccination in combination with checkpoint inhibitors

With the safe treatment of 42 patients with UV1 vaccination in combination with either ipilimumab or pembrolizumab the safety of the product does not preclude continued clinical development of UV1 vaccination in combination with CTLA-4 inhibitors or PD-1/PD-L1 inhibitors.

2.5 Rationale for Combination of UV1 with Checkpoint Inhibitors

Checkpoint inhibition has become one of the main pillars in immune-based cancer therapies and involves inhibition of regulatory signalling pathways which normally reduces or modulates T cell activation in order to promote immune tolerance and suppress autoimmunity.[29] Central to these processes are the CTLA-4 and PD-1 immune checkpoint pathways. These 2 pathways operate on different stages of an immune response. CTLA-4 mainly regulate activation of naïve T cells in the lymph nodes, and PD-1 regulates previously activated T cells at the later stages of an immune response, primarily in the peripheral tissue.[30]

The mode of action of checkpoint inhibitors is to block the interaction between PD-1 and CTLA-4 expressed on T cells with their respective ligands, reducing negative effects on T cell activation and T effector mechanisms, and hence to promote T-cell-mediated immune activity.

The immune checkpoint inhibitor ipilimumab is a monoclonal antibody specific for CTLA-4. The proposed mechanism of action for ipilimumab is the disruption of the interaction of CTLA-4 which is expressed in the cell surface of naïve T cells following stimulatory signals, with B7 co-stimulatory molecules (CD80 or CD86) expressed on antigen presenting cells.[31] The result is inhibition of the down-modulatory function of CTLA-4, and hence potentiation of a T-cell-mediated immune response.[32] Ipilimumab also interferes with the negative action of regulatory T-cells. The combined effect is a release of pre-existing immune responses and generation of a subsequent wave of secondary immune responses.

Nivolumab is a monoclonal antibody specific for PD-1 which is expressed by T cells after persistent antigen exposure. PD-1 interacts with its ligands, PD-L1 and PD-L2, which is normally expressed on a range of different types of leucocytes, such as natural killer cells and macrophages and plays a role in modulation of immune system response. This interaction leads to inhibition of kinase-mediated signaling pathways, and thus, inhibition of T-cell activation and response. PD-L1 can be expressed on the surface of tumor cells as well and interaction between PD-1 on T cells and PD-L1 on tumor cells inhibits immune response against malignant cell. Blocking of the PD-1 receptor interaction with PD-L1 or PD-L2 reverses this immune suppression and releases T-cell effector function.

Blockade of both CTLA-4 and PD-1 aims to induce proliferation of a higher number of T cells early in an immune response, and to restore immune responses of previously activated T cells that have become exhausted by chronic antigen stimulation. Combination therapy with nivolumab and ipilimumab in clinical studies has been shown to provide enhanced clinical benefit compared to single-agent therapy with either nivolumab or ipilimumab.

Efficacy of the combined treatment of ipilimumab and nivolumab depends on the presence of a spontaneously induced T cell response against relevant tumor antigens. Patients who lack or have few tumor-specific T cells in their tumor are less likely to obtain durable benefit from combination therapy with nivolumab plus ipilimumab. UV1 vaccination has the potential to increase the efficacy of the combination therapy in patients where the immune response spontaneously primed by tumor antigens is insufficient for induction of long-term clinical benefit. Vaccination with UV1 amplifies the pool of hTERT specific tumor-reactive CD4 T cells from the naïve repertoire and has the potential to increase the breadth and diversity of the

tumor-reactive T cell response (epitope spread). Reciprocally, the efficacy of UV1 vaccination may be enhanced since the checkpoint inhibitors can augment the clonal expansion and effector activity of UV1-induced T cells that is otherwise restricted by intrinsic immune regulatory and tumor induced suppressor mechanisms. The addition of UV1 vaccination to checkpoint inhibitors thus have the potential to produce synergistic immunological activity which may transfer into increased clinical benefit compared to dual CTLA-4 and PD-1 checkpoint inhibitor therapy.

2.6 Rationale for Dose and Administration Regimen

Three Phase I/II studies investigating the use of UV1 vaccinations have been completed (n=52). One study in NSCLC and one study in prostate cancer were dose-finding studies comparing the safety of 100, 300, and 700 µg UV1 using 75 µg sargramostim per vaccination for up to 18 vaccinations. No dose-limiting toxicities were observed in doses up to 700 µg. Signals of efficacy have been observed in all 3 studies in the form of vaccine-specific immune responses and PFS and OS which compares favorably to historical controls.

Across the 3 completed Phase I/II studies with UV1 vaccination, 78% (40/51) of the patients with samples available for analysis had detectable vaccine-specific immune response. A higher proportion of patients with vaccine-specific immune response was seen in the group of patients receiving the 300 µg UV1 dose; 88% compared to 69% and 71% in the 100 and 700 µg groups, respectively. In the study where 300 µg UV1 was used in combination with ipilimumab in patients with melanoma, 91% of the patients showed an immune response to UV1.

No clear dose relationship was observed in the proportion of patients experiencing AEs, although a tendency towards a lower frequency of related AEs, injection site events, and Grade 3 events was observed in the 300-µg dose group. Across the 3 studies, a total of 17 SAEs were reported, and 9 patients (17%) had related SAEs. Three patients had events that were related to ipilimumab, and 6 patients (12%) experienced 6 SAEs that were related to UV1 vaccination. Of these, 5 events in 5 patients (10%) were serious allergic reactions: anaphylactic reaction, anaphylactic shock, and hypersensitivity. Three events of serious allergic reactions occurred in the 700 µg UV1 dose group, 2 in the 300 µg UV1 dose group, and none in the 100 µg UV1 dose group.

Taken together, the data on efficacy in terms of vaccine-specific immune response and safety related to dose of UV1 from the completed Phase I/II studies with UV1 support the use of the 300 µg UV1 dose for further clinical development of UV1.

Across the 3 completed Phase I/II studies, UV1 was administered with 75 µg of the adjuvant sargramostim per vaccination for up to 18 vaccinations. Localized dermal injection site reactions indicative of an inflammatory reaction to sargramostim and hence recruitment of dendritic cells to the injection site were seen in 63% of patients and 78% developed a vaccine-specific immune response. This supports the use of 75 µg sargramostim per UV1 vaccination for the further clinical development of UV1.

To reduce the risk for serious allergic reactions to UV1 and/or sargramostim, the number of vaccinations with UV1 and sargramostim have been limited to 8 vaccinations over a period of 73 days in the current protocol. The serious allergic reactions observed in 5 patients (10%)

occurred within 3 to 30 minutes after administration of the 9th or more vaccinations (>20 weeks of exposure). The immune response data from the completed study investigating the use of UV1 with ipilimumab in patients with malignant melanoma support that 8 UV1 doses sufficed to generate a vaccine-specific immune response. The patients in that study received an average of 5.5 UV1 vaccinations (range 3 to 9), and 91% of the evaluable patients had immune response within 12 weeks after first vaccination.

In the current study, a dose of 75 µg sargramostim will be injected intradermally 10 to 15 minutes prior to intradermal injection of UV1 at the same site.

The 75 µg sargramostim dose is the same dose that has been used in the 3 completed Phase I/II studies with UV1 and in 10 out of 30 patients in the UV1/hTERT-MM-103 study.

Patients in the experimental arm will receive 8 UV1 vaccinations over 4 cycles of nivolumab and ipilimumab. UV1 vaccination will be administered alone on Days 1, 3-7 (2 UV1 vaccinations within Day 3 to Day 7, consecutive dosing days not allowed) and 26, and in combination with nivolumab and ipilimumab on Days 10, 31, 52 and 73. The administration regimen for UV1 vaccination during Days 1-10 is optimized for synergy with ipilimumab leading to effective priming and expansion of naïve hTERT specific T cells in the local lymph node draining the vaccine injection site. At Days 26 and 73, the UV1 vaccinations are optimized for re-activation and effector activity of the vaccine induced T cells in the tumor micro-environment in synergy with nivolumab and ipilimumab.

The proposed vaccine administration regimen for study UV1 202 is similar to the vaccination regimen used in the Phase I studies UV1-hTERT-L (NSCLC), UV1-hTERT-P (prostate cancer) and UV1-hTER-MM (malignant melanoma) respectively. The Phase I administration regimen was based on animal studies of immune responses to peptide vaccines using sargramostim as adjuvant.[24,25] It was documented that an intradermal co-administration regimen with 3 injections of the UV1 peptides with sargramostim during Week 1, followed by regular vaccinations is effective for induction of a vaccine-specific immune responses. This regimen aims to provide a gradient of sargramostim over time to attract Langerhans cells in the dermis to the vaccine injection site, allowing them to take up intact peptides while maturing into proper antigen presenting cells, migrate to the local lymph node and present the vaccine epitopes to naïve T cell, thereby priming vaccine-specific T cells.

Since CTLA-4 is expressed on the cell surface of T cells within 72 hours of activation and will limit clonal expansion and induce G1 arrest of proliferating T cells.[32,33] The first ipilimumab dose was administered subsequent to three initial UV1 vaccinations in study UV1-hTERT-MM. The following UV1 vaccinations were administered intermittent to the ipilimumab doses. UV1 vaccination and ipilimumab administration was spaced in time to allow for CTLA-4 to be expressed in the cell membrane of clonally expanded T cells primed and activated by UV1 vaccinations before blocking of the signaling through CTLA-4 with ipilimumab. The vaccine-specific immune response in study UV1-hTERT-MM appeared more frequently and rapidly than in the studies investigating the use of UV1 vaccination as monotherapy,[27] supporting that ipilimumab act synergistically with UV1 to induce a vaccine-specific immune response. A similar regimen with spacing between UV1 vaccinations and administration of the first and second ipilimumab doses is proposed for the present study.

Nivolumab is administered every third week and will block signaling through PD-1 on tumor-specific T cells, thus releasing the effector activity of T cells activated by UV1 vaccination and T cells spontaneously activated by antigens in the tumor. The UV1 vaccinations at Days 52 and 73 are administered concurrent with nivolumab and ipilimumab to optimize for boosting of an ongoing vaccine-specific immune response and release of effector activity of T cells in the tumor and draining lymph nodes.

2.7 Rationale for Study Design

Study UV1-202 is a randomized, multicenter, open-label, active-controlled clinical study to document the efficacy and safety of adding UV1 vaccination to dual checkpoint blockade therapy with nivolumab plus ipilimumab.

Primary Endpoint

Progression free survival is the primary endpoint of the study. In line with European Medicines Agency and FDA anticancer guidance, PFS is an acceptable primary endpoint in first-line metastatic disease, being reflective of clinical benefit. Progression free survival is considered an appropriate choice of endpoint especially when effective second-line therapies are available that would serve to confound subsequent OS outcome, as is the case in advanced malignant melanoma.

Median PFS with nivolumab plus ipilimumab in unresectable or metastatic melanoma has been reported to be 11.5 months (95% CI, 8.9 to 16.5) in the nivolumab plus ipilimumab group.[14] Upon progression to more advanced melanoma, patients will likely receive subsequent effective anticancer treatment, including checkpoint monotherapy, chemotherapy, and targeted therapy, thus ruling out OS as a viable primary endpoint due to the diluting effect of these additional therapies.

Progression free survival is appropriate for evaluating the effect of a therapeutic cancer vaccine. The expected mode of action for a therapeutic peptide cancer vaccine is to induce proliferation of T cells recognizing epitopes within the vaccine peptides. The secondary effects of these T cells will depend on the individual patient's genetic, biochemical, and immunological status and may include increased frequency of tumor responses (increased ORR), prolonged DOR[34], and increased frequency and duration of SD. Progression free survival, unlike DOR or ORR, as primary endpoints is suited to capture all tentative efficacy attributes of the vaccine. The study is therefore formally powered for analysis of PFS. Overall survival will be analyzed as supportive evidence.

Treatment Arms

UV1-202 is a randomized study with 2 arms, with the objective of documenting the add-on effect of UV1 vaccination to nivolumab and ipilimumab:

- Experimental arm: UV1 vaccination in combination with nivolumab and ipilimumab
- Control arm: nivolumab and ipilimumab

A 2-armed study will provide data on the efficacy and safety of UV1 vaccination as add-on to nivolumab and ipilimumab in patients with unresectable stage IIIB-D or unresectable metastatic melanoma which will suffice for hypothesis generation.

In addition to the 2-armed part of the study, 20 patients will be enrolled in a single arm UV1 cohort for collection of additional biological material to support the Extended Exploratory Cohort of the study. The single arm UV1 cohort is intended for exploratory purposes only (Appendix 7 Single Arm UV1 Cohort).

2.8 Benefit/Risk Assessment

The clinical studies completed to date (n=52) have demonstrated that UV1 vaccination is generally well tolerated, both as monotherapy and in combination with ipilimumab. There were no dose-limiting toxicities observed in the 2 dose-finding studies completed, and no apparent dose relationships in the rate of patients experiencing the most common related AEs (injection site related AEs). Anaphylactic reaction, anaphylactic shock, and hypersensitivity have been identified as AESIs for UV1 vaccination based on 5 events in 5 patients included in the completed studies.

Study UV1/hTERT-MM-103, investigating the use of UV1 in combination with the anti-PD-1 monoclonal antibody pembrolizumab, is currently ongoing for follow-up. 30 patients have been included and treated with UV1 and pembrolizumab. The combination of pembrolizumab and UV1 appears to be generally well tolerated. Nine serious adverse events (SAEs) for 7 patients (23.3%) in the study, the majority of which were considered unrelated to study treatment.

To reduce the risk for AESIs, a maximum of 8 UV1 vaccinations will be administered to the patients under the current protocol. Patients will remain at the study site for observation for at least 4 hours after each UV1 vaccination. Patients who develop serious allergic reactions during treatment with UV1 vaccinations will be discontinued from further UV1 vaccinations.

No information on the effects of UV1 vaccination on fertility and reproduction is available, and patients of childbearing potential must agree to use an adequate method of contraception prior, during, and after completion of treatment with UV1 vaccination.

Nivolumab and ipilimumab are approved for the patient population suggested in the current study, and the toxicity profile of the combination is well characterized. The toxicities reported in the studies investigating the use of UV1 vaccination in combination with single agent ipilimumab and single agent pembrolizumab in malignant melanoma have so far been modest. Since the use of UV1 vaccination combined with nivolumab and ipilimumab has not been investigated previously, the protocol specifies specific safety monitoring for the study.

The UV1 vaccine induces vaccine-specific CD4 T cell response in the majority of patients across indications. The immunogenicity of the peptides in UV1 is further supported by data from several long-term surviving patients with pancreatic cancer, lung cancer, and malignant melanoma treated with an earlier hTERT vaccine.[28,29] The available clinical data on efficacy and reported AEs versus exposure from the completed and ongoing studies with UV1 indicates a favorable risk/benefit profile for UV1 vaccination. The underlying scientific rationale for

expected immunological synergy the use of UV1 vaccination in combination with nivolumab and ipilimumab justifies the present clinical study.

3 Objectives and Endpoints

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 Tumors (RECIST) 1.1 Time from randomization to progressive disease (PD) or death from any cause
Secondary • To compare 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 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 randomization 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 tumor 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 tumor-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). Other endpoints related to analysis conducted on biological material collected from the Extended Exploratory Cohort (refer to Appendix 2).
*UV1 vaccination includes sargramostim, used as a vaccine adjuvant, and UV1	

4 Study Design

4.1 Overall Design

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

The study is planned to be conducted at 40 study sites in Europe (approximately 16 sites) and the United States (approximately 24 sites).

This study will consist of 3 phases: Screening, Induction period, and Follow-up period. The Follow-up period includes safety, response, and survival follow-up visits.

After a Screening period of up to 28 days, eligible patients will be randomized in a 1:1 ratio to receive induction therapy: UV1 vaccination in combination with nivolumab and ipilimumab in an experimental arm, or nivolumab and ipilimumab in a control arm. Randomization can occur after all Screening procedures have been completed (up to 3 days [from Day -3 until Day 1] prior to first dosing on Day 1) and eligibility has been confirmed. It is estimated that approximately 200 patients will need to be screened in order to randomize the required 154 patients.

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

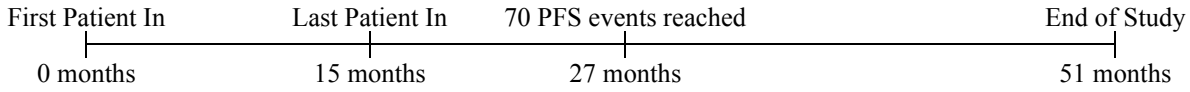
Patients in the control arm will receive 4 cycles of nivolumab and ipilimumab on Days 1, 22, 43, and 64.

Patients in both arms will start maintenance therapy 6 weeks after the last dose of induction therapy. The maintenance therapy is nivolumab at a dose of 480 mg every 4 weeks (Q4W) according to the label. It is not allowed to use any other dose of maintenance therapy (eg, 240 mg Q2W).

The study is event driven. The primary and secondary endpoints will be analyzed at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized, at which time the sponsor will notify the sites. From the PFS cut-off date, patients will be followed for a further 24 months for additional survival data; further analyses of OS data will be performed until defined end of study to provide evidence supportive of PFS.

All patients will be followed up until death or until the end of the study (EOS), whichever comes first. Estimated timelines at start of the study are outlined in Figure 1.

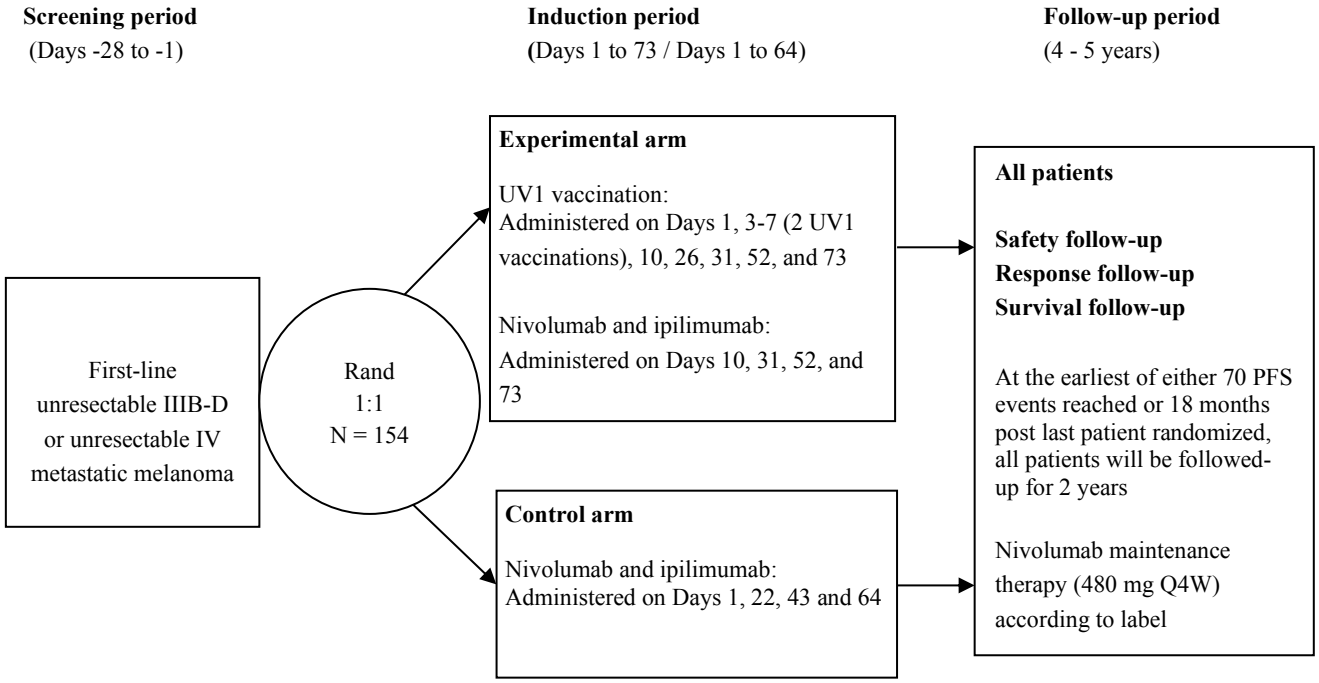
Figure 1 Estimated Timelines



The estimated enrollment period is 15 months; the estimated time from last randomization to 70 PFS events reached is 12 months; the estimated time from 70 PFS events to EOS is 24 months and the total study duration is estimated to be 51 months from first patient in.

The study design and treatment are outlined in Figure 2.

Figure 2 Study Design



The UV1 vaccination includes sargramostim, used as a vaccine adjuvant, at a dose of 75 µg and UV1 at a dose of 300 µg. Nivolumab and ipilimumab are dosed according to label in both treatment arms: induction therapy of nivolumab (1 mg/kg Q3W) and ipilimumab (3 mg/kg Q3W), and maintenance therapy of nivolumab (480 mg Q4W).

Sargramostim and UV1 should 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 is administered 10 to 15 minutes prior to each UV1 injection. Nivolumab and ipilimumab are administered intravenously, starting at least 1 hour after the administration of UV1.

Following the last dose of induction therapy, the patient will then enter the Follow-up period and perform a safety follow-up visit 30 days post last dose of induction therapy.

Tumor assessment will be done locally at the study site using RECIST 1.1 and immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria. Tumor imaging will be performed within 14 days prior to randomization and then on Week 12 and Week 19 post randomization. Subsequent response follow-up imaging will be performed every 8 weeks for 32 weeks and then every 12 weeks. Patients with PD per RECIST 1.1 will have a new scan 4 to 8 weeks later to confirm PD per iRECIST. Patients with immune unconfirmed PD per iRECIST (iUPD) will continue at the Investigator's discretion, with tumor imaging and treatment per protocol until immune confirmed PD per iRECIST (iCPD), until 70 PFS events are reached or until 18 months post last patient randomized (whatever comes first). Patients with iCPD per iRECIST will be discontinued from treatment and will proceed into the survival follow-up phase and be contacted per phone (or, at the investigator's discretion visit the hospital) every 12 weeks until the earliest of either 70 PFS events reached or 18 months post last patient randomized. From the PFS cut-off date, the survival follow-up will continue in all patients every 6 months for 2 years.

To reduce bias in evaluation of the efficacy endpoints, tumor evaluation for the statistical analysis of the efficacy endpoints will be done by blinded independent central review (BICR) according to the RECIST 1.1 criteria. All images must be submitted to the central imaging vendor, but the results from the BICR will not be provided to the study site. Two independent radiologists will perform the central imaging review without knowledge of treatment assignments. If there are discrepancies between the 2 readers, a standardized procedure involving a third reviewer for adjudication will take place.

From signing of the Informed Consent Form (ICF) until the first dose of induction therapy, only AEs/SAEs caused by study-specific procedures should be reported. Non-serious AEs should be reported from the first dose of induction therapy until 30 days after the last dose of induction therapy, or until new anticancer treatment is initiated (whichever comes first). All SAEs should be reported from the first dose of induction therapy until 70 PFS events are reached, until 18 months post last patient randomized or until new anticancer treatment is initiated (whichever comes first). Adverse events and SAEs that are ongoing beyond the required reporting timelines shall be followed up locally per institutional practice until resolution or stabilization or the patient is lost to follow up.

During the study, an Independent Data Monitoring Committee (IDMC) will monitor safety information to ensure patient safety (refer Section 8.2.1).

Patients at selected sites will have the option to be included in the Extended Exploratory Cohort of the study (Appendix 2) provided that the cohort is still open for inclusion. This cohort of approximately 40 patients, randomized in a 1:1 ratio to either of the 2 treatment arms, will have additional sampling of blood, tissue, and feces for exploratory purposes (see Table 9 and Table 10). The biologic sampling will be in addition to blood samples planned for all patients in the study. Fecal samples will be collected in the Screening period while tumor biopsies (snap-frozen tissue and formalin fixated paraffin embedded tissue) will be harvested in the Screening period and at the safety follow-up visit. In the experimental arm, delayed-type hypersensitivity (DTH) response will be assessed at 5 timepoints during the study. A biobank will be established for current and future analysis of the samples collected.

In addition to the 2-armed part of the study, 20 patients will be enrolled in a single arm UV1 cohort for collection of additional biological material to support the Extended Exploratory Cohort of the study. The single arm UV1 cohort is intended for exploratory purposes only (Appendix 7 Single Arm UV1 Cohort).

Planned Timelines

First patient in:	Q2 2020
Last patient in:	H1 2022
Primary endpoint read out:	H1 2024
End of study:	H1 2026

The First Patient In is defined as the timepoint when the first patient is randomized.

4.2 Measures to Minimize Bias: Randomization and Blinding

Patients who satisfy all eligibility criteria will be randomly assigned by the central interactive web response system (IWRS; or equivalent) to receive induction therapy as either UV1 vaccination in combination with nivolumab and ipilimumab in the experimental arm, or nivolumab and ipilimumab in the control arm. Randomization will be at a 1:1 ratio between the 2 treatment arms.

Randomization will be done by the IWRS provider using a validated software. Randomization can occur after all Screening procedures have been completed (up to 3 days [from Day -3 until Day 1] prior to first dosing on Day 1) and eligibility has been confirmed, to prevent the Investigator's knowledge of treatment allocation influencing the decision to include the patient.

Given the study design, with visits occurring at different timepoints in the 2 treatment arms, neither patients nor Investigators will be blinded to the study treatment arms. To limit bias in evaluation of the efficacy endpoints, the statistical efficacy analyses will be based on tumor assessments by BICR.

Patients in the single arm UV1 cohort will not be randomized and will therefore not be included in the data used for analysis of primary and secondary endpoints.

5 Study Population

The study population will consist of male and female patients at least 18 years of age with a histologically confirmed diagnosis of unresectable stage IIIB-D or unresectable stage IV metastatic melanoma. Patients must provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

Prospective approval of protocol deviations to the inclusion criteria, also known as protocol waivers or exemptions, will not be given.

5.1 Inclusion Criteria

To be eligible for randomization all of the following criteria must be met:

Age and Sex

1. Male or female patient at least 18 years of age at the time of signing the ICF.

Type of Patient and Disease Characteristics

2. Histologically confirmed diagnosis of unresectable stage IIIB-D or unresectable stage IV malignant melanoma. Patient must have at least 1 measurable lesion at Screening according to the RECIST 1.1 criteria.
   Note that lesions not measurable on a computed tomography (CT) scan or a magnetic resonance imaging (MRI) will be considered as non-measurable lesions.
3. Eligible for combination treatment with nivolumab and ipilimumab.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
5. Adequate organ function as indicated by the following laboratory values:

   Hematological

   a. Absolute neutrophil count (ANC) ≥1,500/µL
   b. Platelet count ≥100 x 10^3/µL
   c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L

   Renal

   d. Creatinine ≤1.5 x upper limit of normal (ULN)

   Hepatic

   e. Total bilirubin ≤1.5 x ULN or

      direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 ULN

   f. Aspartate aminotransferase/glutamic-oxaloacetic transaminase and alanine aminotransferase/glutamic-pyruvic transaminase ≤2.5 x ULN for patients without liver metastasis or ≤5 x ULN for patients with liver metastasis.

Male Patients:

6. Male patients who are sexually active with a female of childbearing potential must agree to use an adequate method of contraception prior to the first dose through 5 months after the last dose of UV1 vaccination, nivolumab, or ipilimumab, whichever is administered last. The recommended method is using a male condom.

Female Patients:

7. Women of childbearing potential (WOCBP) must have a negative urine or serum/plasma pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum/plasma pregnancy test will be performed. The serum/plasma pregnancy test must be negative for the patient to be eligible.
8. WOCBP (refer to Section 8.3.6) must use adequate contraception Adequate contraception must be maintained throughout the study, starting with the first dose through 5 months after the last dose of UV1 vaccination, nivolumab, or ipilimumab, whichever is administered last. The acceptable contraceptive methods for WOCBP included in the study are:
   Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), Intrauterine device (IUD), Intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success), or sexual abstinence (if this is the preferred and usual lifestyle of the subject)

Informed Consent

9. Written informed consent prior to any study-specific procedures.

5.2 Exclusion Criteria

Patients are not eligible for randomization if any of the following criteria are met:

Medical Conditions

1. Previous non-melanoma malignancies unless curatively treated and complete remission was achieved at least 2 years prior to randomization. Patients with prior curatively-treated basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or carcinoma in situ of the breast, or other in situ cancers are allowed irrespective of time passed since curative treatment. Patients with prior completely resected malignant melanoma are also allowed.
2. Known brain metastases or leptomeningeal metastases. If a patient experiences neurological symptoms indicative of brain metastases, a brain MRI should be performed.
3. Diagnosis of uveal or ocular melanoma.

4. Known history or any evidence of active, non-infectious pneumonitis.
5. History of New York Heart Association class 3-4 congestive heart failure or history of myocardial infarction within 6 months of starting study treatment.
6. Active infection requiring systemic treatment.
7. Diagnosis of immunodeficiency.
8. Known history of severe hypersensitivity reactions to nivolumab, ipilimumab, sargramostim, or their excipients.
9. Known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies). No HIV testing is required unless mandated by local health authority.
10. History of or active hepatitis B (hepatitis B surface antigen reactive) or active hepatitis C (hepatitis C virus antibody). Testing must be performed to determine eligibility.
11. Women who are breastfeeding.

Prior/Concomitant Therapy – Also Prohibited During the Induction Therapy

12. Prior systemic treatment for unresectable stage IIIB-D or unresectable stage IV malignant melanoma. Prior systemic BRAF/MEK inhibitors or immunotherapy as neoadjuvant or adjuvant or other setting treatment of stage I-IIIA, resectable IIIB-D, or resectable IV if patient progressed earlier than 6 months after last dose of such treatment.
13. 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. Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) are allowed. Physiologic replacement doses of systemic corticosteroids, a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions is permitted even with >10 mg/day prednisone equivalents.
14. Receipt of a live vaccine within 30 days prior to the start of induction therapy.

Prior/Concurrent Clinical Study Experience

15. Receipt of any other investigational therapy within 4 weeks of the first dose of study treatment.

Other Exclusions

16. Any medical, psychological, or social condition that would make it difficult for the patient to participate in the study and comply with the study procedures, restrictions, and requirements.

6 Treatments

6.1 Study Drugs

Table 2 Study Drugs (Induction Period)

	Investigational Medicinal Products		**Non-Investigational Medicinal Products**	
Study drug name:	Sargramostim	UV1	Nivolumab	Ipilimumab
Dosage Formulation:	Reconstituted for injection	Reconstituted for injection	Reconstituted according to the prescribing information	Reconstituted according to the prescribing information
Dose Strengths/ Dosage Levels:	75 µg	300 µg	1 mg/kg	3 mg/kg
Route of Administration:	Intradermal injection	Intradermal injection	Intravenous infusion	Intravenous infusion
Dosing Instructions:	75 µg administrated in a volume of 150 µL	300 µg administered in a volume of 100 µL	1 mg/kg according to the prescribing information	3 mg/kg according to the prescribing information
Packaging and Labeling:	Lyophilized sargramostim provided in a glass vial. Labelled according to GCP/GMP and local regulations	Lyophilized UV1 provided in a glass vial. Labelled according to GCP/GMP and local regulations	According to the prescribing information	According to the prescribing information
Storage conditions:	Lyophilized: 2ºC to 8ºC Reconstituted: 2ºC to 8ºC (maximum 6 hours) Do not freeze or shake	Lyophilized: 2ºC to 8ºC Reconstituted: 2ºC to 8ºC (maximum 6 hours)	According to the prescribing information	According to the prescribing information
Manufacturer:	Partner Therapeutics, Inc.	Corden Pharma SpA	Bristol-Myers Squibb	Bristol-Myers Squibb

Abbreviations: GCP = Good Clinical Practice; GMP = Good Manufacturing Practice; N/A = not applicable.

6.1.1 Sargramostim

Sargramostim will be used as an adjuvant to UV1 in this study.

Lyophilized sargramostim vials must be stored refrigerated (2°C to 8°C) and protected from light.

Lyophilized sargramostim (250 µg) should be reconstituted with 0.5 mL water for injection to a concentration equal to 500 µg/mL giving a clear liquid ready for use. The volume to be administered is 150 µL, giving a dose of 75 µg. See also Table 3.

Reconstituted sargramostim must be stored at 2ºC to 8ºC for a maximum of 6 hours prior to administration. Discard unused portion of reconstituted sargramostim.

Table 3 Instructions for Preparation of Sargramostim

Dose of Sargramostim per injection	Package Format	Content	Water	Concentration	Volume injected
75 µg	Lyophilized sargramostim glass vial	250 µg	0.5 mL	500 µg/mL	150 µL

Sargramostim is not approved as a vaccine adjuvant to UV1 and is considered an investigational medicinal product (IMP) in this study.

6.1.2 UV1

UV1 is produced by lyophilization of a sterile aqueous solution of drug substances. No additional excipients are present in the UV1 product.

Lyophilized UV1 vials must be stored refrigerated (2°C to 8°C) and protected from light. The vials may also be stored at room temperature (≤27ºC) for a maximum of 3 days to cover short-term excursions.

Lyophilized UV1 (0.9 mg) should be reconstituted with 0.3 mL water for injection to a concentration equal to 3.0 mg/mL giving a clear liquid ready for use. The volume to be administered is 100 µL, giving a dose of 300 µg. See also Table 4.

Reconstituted UV1 must be stored at 2°C to 8ºC for a maximum of 6 hours prior to administration. Excursions up to room temperature (≤27ºC) are allowed for a maximum of 1 hour in total. Unused portion of reconstituted UV1 should be discarded.

Table 4 Instructions for Preparation of UV1

Dose of UV1 per injection	Package Format	Content	Water	Concentration	Volume injected
300 µg	Lyophilized UV1 glass vial	0.9 mg	0.30 mL	3.0 mg/mL	100 µL

UV1 is not approved as a therapeutic cancer vaccine and is considered an IMP in this study.

6.1.2.1 UV1 Used for Delayed-type Hypersensitivity Testing

For patients who are participating in the Extended Exploratory Cohort, and who are randomized to the experimental arm, a DTH skin test will be performed as described in Appendix 2 and at timepoints described in Table 9.

For the DTH testing, 20 µL of the reconstituted UV1 solution should be injected (intradermally) without sargramostim in the skin of the anterior forearm. For the visits where both UV1 vaccination and DTH testing are performed, the UV1 solution prepared for the vaccination

should also be used for the DTH testing. The injection for the DTH testing should be done prior to the UV1 vaccination.

6.1.3 Nivolumab

Nivolumab will be reconstituted according to the prescribing information/product characteristic. Patients will receive an induction therapy dose of 1 mg/kg, administered intravenously.

Six weeks following the last dose of induction therapy, patients will receive maintenance therapy at a dose of 480 mg Q4W according to the label. It is not allowed to use any other dose of maintenance therapy (eg, 240 mg Q2W).

Nivolumab is to be used according to the prescribing information and is a non-investigational medicinal product (NIMP) in this study.

6.1.4 Ipilimumab

Ipilimumab will be reconstituted according to the prescribing information. Patients will receive an induction therapy dose of 3 mg/kg, administered intravenously.

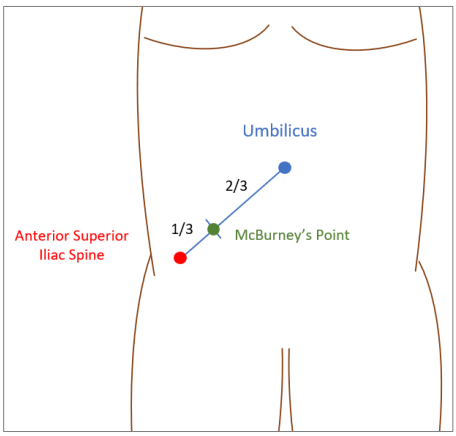
Ipilimumab is to be used according to the prescribing information and is a NIMP in this study.

6.1.5 Administration of Study Drugs

The administration of study drugs should be done as the last procedure at each applicable study visit per the schedule of activities (Table 5 and Table 6).

Sargramostim and UV1 should be administered **intradermally** in an area corresponding to McBurney's point (Figure 3) on the right side of the abdomen (or corresponding spot on the left side in case of appendectomy scar). It is important that both injections are strictly intradermal. The utmost care must be taken so no material is administered subcutaneously. When done correctly, a small bleb should appear following the injection. An injection too superficial will result in loss of volume from the injection site during injection or after withdrawal of the needle. All 16 injections (8 sargramostim and 8 UV1) should be injected at the **exact same site**. Permanent marker-pens may be used to ensure that the same site is utilized each time.

Figure 3 McBurney's Point



Administration of UV1 should be done **10 to 15 minutes *after*** the administration of sargramostim. The UV1 is to be administrated at the exact same site as the sargramostim.

Allergic reactions may occur after sargramostim and UV1 injections. Therefore, patients should remain at the site for observation for at least 4 hours after each UV1 injection.

Nivolumab and ipilimumab are administered intravenously according to the label and administration is to be started at least 1 hour after the injection of UV1.

Patients in the experimental arm will receive 8 UV1 vaccinations over 4 cycles of nivolumab and ipilimumab. The UV1 vaccination will be administered alone on Days 1, 3 to 7 (2 UV1 vaccinations), and 26, and in combination with nivolumab and ipilimumab on Days 10, 31, 52, and 73.

Patients in the control arm will receive 4 cycles of nivolumab and ipilimumab, on Days 1, 22, 43, and 64.

The administration of sargramostim, UV1, nivolumab, and ipilimumab must be recorded in the patients' medical files and the appropriate section of the electronic Case Report Form (eCRF). The reason for dose interruption, reduction, or omission will also be recorded in the medical files of patient and later in the eCRF. This information will be used to assess compliance with treatment.

Following the induction therapy, patients in both treatment arms will start maintenance therapy and receive nivolumab at a dose of 480 mg Q4W according to the label. It is not allowed to use any other dose of maintenance therapy (eg, 240 mg Q2W). Nivolumab is the standard of care and should be monitored according to the institutional practice (including routine blood sampling).

6.1.6 Preparation/Handling/Storage/Accountability

Unless stated otherwise, sargramostim, nivolumab, and ipilimumab should be stored and handled according to the prescribing information. All handling of study drug should be compliant with normal handling of sterile products for injection.

UV1 and sargramostim will be supplied to the study sites by the Sponsor. Nivolumab and ipilimumab will be sourced locally by the study sites.

The Investigator or designee must maintain accurate records of study drugs received from the Sponsor, and documentation of preparation and administration of sargramostim, UV1, nivolumab, and ipilimumab. Drug name, dose, and batch number/study treatment ID (if required) will be documented for all study drugs administered.

Only patients randomized in the study may receive study drug and only site staff authorized by the Investigator may supply or administer the study drug(s). All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area with access limited to the Investigator and authorized site staff.

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during storage for all study drugs received by the Sponsor and any discrepancies must be reported and resolved before use of the study drug.

The Investigator or designee is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Where appropriate facilities and procedures for drug destruction exist and prior approval from the site monitor has been received, site personnel will account for appropriate destruction.

6.1.7 Treatment of Allergic Reactions to UV1 Vaccination

Investigators are advised to follow the standard treatment of anaphylaxis and allergies per local guidelines.

6.1.8 Dose Modification

Dose modification of sargramostim or UV1 is not allowed in this study. Nivolumab and ipilimumab should be dosed according to the label.

6.1.9 Overdose

There is no information on overdose of UV1 vaccination, but the distribution route and degradation of the UV1 vaccination suggests that there would be few consequences, if any. Therefore, in the event of an overdose, the patient should be observed for any reactions and treated symptomatically.

There is no information on overdose with ipilimumab and nivolumab, given either as monotherapies or concomitantly. In case of overdosage, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

6.2 Concomitant Medication

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of randomization or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All ongoing and new medications will be recorded from 28 days prior to randomization, until 30 days after the last dose of induction, or until new anticancer treatment is initiated (whichever comes first). Ongoing and new medications shall also be recorded in connection with any SAEs.

6.2.1 Prohibited Medications During Induction Period

The following medications and vaccinations are not allowed during the Induction period:

- Immunosuppressive agents
- Systemic corticosteroids >10 mg daily prednisone equivalent (except as stated in Section 6.2.2)
- Any concurrent anticancer therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy, or investigational agents for treatment of cancer). Radiation therapy to a symptomatic lesion may be allowed after consultation with the sponsor. Supportive care for disease-related symptoms, including bisphosphonates and denosumab, may be offered to all patients in the study.
- Live vaccines within 30 days prior to the first dose of induction therapy and while participating in the study. Examples of live vaccines include, but are not limited to, measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.
- Other investigational agents.

6.2.2 Permitted Medications During Induction Period

Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids, a brief course of corticosteroids for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions is permitted even with >10 mg/day prednisone equivalents.

6.2.3 New Anticancer Treatment

Details of any new anticancer treatments, from the time of the last dose of induction therapy until the earliest of either 70 PFS events reached or 18 months post last patient randomized, must be recorded in the eCRF. The reason for end of treatment for IMP and NIMP (nivolumab and ipilimumab) must be recorded.

6.3 Treatment After Progressive Disease

Clinical evidence indicates that some patients treated with immune system-stimulating agents may develop PD by conventional response criteria (ie, pseudo-progression per iRECIST), before demonstrating clinical overall responses and/or SD. This may be explained by:

- Enhanced inflammation within tumors leading to increased tumor size which would appear as an enlarged index lesion and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement.
- Initially, the kinetics of tumor growth may outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent.

For patients who have initial radiological evidence of PD by RECIST 1.1 or iUPD (per iRECIST), it is at the discretion of the Investigator to keep the patient on induction/maintenance therapy (in the absence of clinical deterioration) until repeat imaging is obtained 4 to 8 weeks afterwards (iRECIST-based management). The decision to continue induction/maintenance therapy should only be made if the patient is assessed to be clinically stable, deriving clinical benefit, and tolerating the treatment.

At a minimum, patients must meet the following criteria for continuing induction/maintenance therapy after PD per RECIST 1.1/iUPD is identified:

- Absence of worsening symptoms and signs (including worsening of laboratory values)
- No decline in ECOG performance status
- Absence of rapid PD or of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.

If repeat imaging fails to demonstrate iCPD (by iRECIST) and the patient continues to be clinically stable, induction/maintenance therapy should continue per protocol.

If repeat imaging demonstrates iCPD, induction/maintenance therapy should be discontinued.

The continuation/discontinuation of nivolumab as maintenance therapy will be recorded in the patients' medical file and in the eCRF.

7 Study Duration and Schedule of Activities

This study will consist of 3 phases: Screening, an Induction period, and a Follow-up period. The Follow-up period includes safety, response, and survival follow-up visits.

Table 5 Schedule of Activities – Experimental Arm

	Screening	Induction period								Follow-up period			
Visit/Cycle		**V1**	**V2 + 3**		**V4 C1**	**V5**	**V6 C2**	**V7 C3**	**V8 C4**	**Safety follow-up**	**Response follow-up**	**Survival follow-up[a]**	**Survival follow-up[a]**
Visit window		**0**	**0**		**± 2d**	**± 2d**	**± 2d**	**± 2d**	**± 2d**	**+7d**	**±1w**	**±1w**	**+2w**
Days/Weeks	D -28 to -1	D1	D3-7 UV1 vaccinations Consecutive dosing days not allowed		D10	D26	D31	D52	D73	30 days post last dose of induction therapy	10w post last dose of induction therapy then every 8w for 32w. Subsequent visits every 12w until iCPD per iRECIST or PFS cut-off date reached	Every 12w from iCPD per iRECIST until PFS cut-off date reached	From time of the PFS cut-off date reached: Every 6 months for 2 years
Signed consent	X												
Eligibility criteria	X												
Medical history	X												
Vital signs & ECOG	X	X			X		X	X	X	X			
Physical examination	X									X			
Local lab analysis (all patients)[b]													
• Hematology & chemistry[m]	X	X			X	X	X	X	X	X			
• Hepatitis B & C virus	X												
• Pregnancy test[c]	X				X		X	X	X	X			
Central lab sampling (all patients)[d]		X					X	X		X	X (2nd visit only)		
Randomization[e]		X											
Treatment:													
• UV1 vaccination		X	X	X	X	X	X	X	X				
• Nivolumab					X		X	X	X	Nivolumab 480 mg Q4W according to label (maintenance therapy)[f]			
• Ipilimumab					X		X	X	X				
Adverse Events[g]	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication[h]	X	X	X	X	X	X	X	X	X	X			
Subsequent anticancer treatment										X	X	X	
Survival status												X	X
Tumor imaging[i]	FIRST tumor imaging during Screening at Day -14 to -1 SECOND tumor imaging at Week 12 and THIRD tumor imaging at Week 19 post randomization SUBSEQUENT tumor imaging every 8 weeks for 32 weeks and then every 12 weeks until PD per iRECIST or until PFS cut-off date is reached (whichever comes first) ADDITIONAL tumor imaging if premature treatment discontinuation due to any cause												
Extended Exploratory Cohort (40 patients)[j]													
Signed consent (exploratory	X												
Fecal sample	X												
Tumor biopsy (FFPE &	X									X			
DNA & SNP		X											
PBMC		X					X			X	X (2nd visit only)		
DTH[l]		X					X	X		X	X (2nd visit only)		

Abbreviations: AE = adverse event; C = cycle; D/d = day; DNA = deoxyribonucleic acid; DTH = delayed-type hypersensitivity; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin fixed, paraffin embedded; ICF = Informed Consent Form; iCPD = immune confirmed progressive disease; iRECIST = immune Response Evaluation Criteria in Solid Tumors; PFS = Progression Free Survival; PBMC = peripheral blood mononuclear cell; Q4W = every 4 weeks; SAE = serious adverse event; SNP = single nucleotide polymorphisms; V = visit; w = week.

[a] Patients with iCPD per iRECIST will be discontinued from treatment and will proceed into the survival follow-up phase and be contacted per phone (or, at the Investigator's discretion visit the hospital) every 12 weeks until PFS cut-off date is reached (earliest of either 70 PFS events or 18 months post last patient randomized). From the PFS cut-off date, the survival follow-up visits will continue every 6 months for 2 years.

[b] Local lab analysis for verification of eligibility criteria is required during Screening at Day -14 to -1. See Table 7 for protocol-required safety laboratory assessments.

[c] WOCBP require negative pregnancy test within 72 hours prior to randomization, at Days 10, 31,52, 73 and at the safety follow-up visit. Additional pregnancy tests according to local regulations for treatment of nivolumab and ipilimumab, if required.

[d] See Table 8 for collection of samples for exploratory analysis.

[e] Patients can be randomized up to 3 days (from Day -3 until Day 1) prior to first dosing on Day 1 but only after all Screening assessments are completed.

[f] Patients will start maintenance therapy 6 weeks after last dose of induction therapy.

[g] From signing of the ICF until the first dose of induction therapy only AEs/SAEs caused by study-specific procedures should be reported. All non-serious AEs should be reported from the first dose of induction therapy until 30 days after the last dose of induction therapy, or until new anticancer treatment is initiated (whichever comes first). All SAEs should be reported from the first dose of induction therapy until the PFS cut-off date is reached or until new anticancer treatment is initiated (whichever comes first).

[h] All ongoing and new medications will be recorded from 28 days prior to randomization, until 30 days after the last dose of induction, or until new anticancer treatment is initiated (whichever comes first). Ongoing and new medications shall also be recorded in connection with any SAEs.

[i] Tumor imaging should be performed regardless of treatment stop or delays and within a visit window of ± 7 days. Tumor imaging will be performed using CT/MRI scans of the chest, abdomen, and pelvis. CT scans are the required modality for measurable disease unless a patient has a clinical condition (e.g. severe contrast allergy) or the lesions are better visualized through the use of MRI. The same imaging technique has to be used in a patient throughout the study. If an unscheduled CT/MRI is performed during the study, subsequent protocol planned CTs/MRIs should be performed unless the time interval between the CTs/MRIs is $\leq$4 weeks.

[j] A cohort of approximately 40 patients at selected sites will be asked to volunteer for additional biological sampling and analysis. See Table 9 and Table 10 for collection of samples and DTH for the Extended Exploratory Cohort.

[k] If the patient has only one target lesion, the biopsy should be taken either subsequent or at least 7 days prior to the screening imaging scan.

[l] UV1 without sargramostim injected intradermally in the skin of the anterior forearm. Patient will measure and record the skin reaction 48±4 hours after the injection.

[m] It is recommended to have blood sampling on day of treatment. If the sampling was not done on the day of treatment and the most current Liver Function Test (LFT) results warrant a safety concern, the site must repeat the LFT panel on the day of treatment and review the results prior to study drug administration.

Table 6 Schedule of Activities – Control Arm

	Screening	Induction therapy				Follow-up period			
Visit/Cycle		**V1 C1**	**V2 C2**	**V3 C3**	**V4 C4**	**Safety follow-up**	**Response follow-up**	**Survival follow- up[a]**	**Survival follow- up[a]**
Visit window		**0**	**± 2d**	**± 2d**	**± 2d**	**+7d**	**±1w**	**±1w**	**+2w**
Days/Weeks	D -28 to -1	D1	D22	D43	D64	30 days post last dose of induction therapy	10w post last dose of induction therapy then every 8w for 32w. Subsequent visits every 12w until iCPD per iRECIST or PFS cut-off date reached	Every 12w from iCPD per iRECIST until PFS cut-off date reached	From time of thePFS cut-off date reached: Every 6 months for 2 years
Signed consent	X								
Eligibility criteria	X								
Medical history	X								
Vital signs & ECOG	X	X	X	X	X	X			
Physical examination	X					X			
Local lab analysis (all patients)[b]									
• Hematology & chemistry[l)]	X	X	X	X	X	X			
• Hepatitis B & C virus	X								
• Pregnancy test[c]	X	X	X	X	X	X			
Central lab sampling (all patients)[d]		X		X	X	X	X (2nd visit only)		
Randomization[e]		X							
Treatment:									
• Nivolumab		X	X	X	X	Nivolumab 480 mg Q4W according to label (maintenance therapy)[f]			
• Ipilimumab		X	X	X	X				
Adverse Events[g]	X	X	X	X	X	X	X	X	
Concomitant medication[h]	X	X	X	X	X	X			
Subsequent anticancer treatment						X	X	X	
Survival status								X	X
Tumor imaging[i]	FIRST tumor imaging during Screening at Days -14 to -1 SECOND tumor imaging at Week 12 and THIRD tumor imaging at Week 19 post randomization SUBSEQUENT tumor imaging every 8 weeks for 32 weeks and then every 12 weeks until PD per iRECIST or until the PFS cut-off date is reached (whichever comes first)								
Extended Exploratory Cohort (40 patients)[j]									
Signed consent (exploratory cohort)	X								
Fecal sample	X								
Tumor biopsy (FFPE & snap-frozen)[k]	X					X			
DNA & SNP		X							
PBMC		X		X		X	X (2nd visit only)		

Abbreviations: AE = adverse event; C = cycle; D/d = day; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin fixed, paraffin embedded; ICF = Informed Consent Form; iCPD = immune confirmed progressive disease; iRECIST = immune Response Evaluation Criteria in Solid Tumors; PFS = Progression Free Survival; PBMC = peripheral blood mononuclear cell; Q4W = every 4 weeks; SAE = serious adverse event; SNP = single nucleotide polymorphisms; V = visit; w = week.

[a] Patients with iCPD per iRECIST will be discontinued from treatment and will proceed into the survival follow-up phase and be contacted per phone (or, at the Investigator's discretion visit the hospital) every 12 weeks until PFS cut-off date is reached (earliest of either 70 PFS events or 18 months post last patient randomized). From the PFS cut-off date, the survival follow-up visits will continue every 6 months for 2 years.

[b] Local lab analysis for verification of eligibility criteria is required during Screening at Day -14 to -1. See Table 7 for protocol-required safety laboratory assessments.

[c] WOCBP require negative pregnancy test within 72 hours prior to randomization, at Days 1, 22, 43, 64 and at the safety follow-up visit. Additional pregnancy tests according to local regulations for treatment of nivolumab and ipilimumab, if required.

[d] See Table 8 for collection of samples for exploratory analysis.

[e] Patients can be randomized up to 3 days (from Day -3 until Day 1) prior to first dosing on Day 1 but only after all Screening assessments are completed.

[f] Patients will start maintenance therapy 6 weeks after last dose of induction therapy.

[g] From signing of the ICF until the first dose of induction therapy only AEs/SAEs caused by study-specific procedures should be reported. All non-serious AEs should be reported from the first dose of induction therapy until 30 days after the last dose of induction therapy, or until new anticancer treatment is initiated (whichever comes first). All SAEs should be reported from the first dose of induction therapy until the PFS cut-off date is reached or until new anticancer treatment is initiated (whichever comes first).

[h] All ongoing and new medications will be recorded from 28 days prior to randomization, until 30 days after the last dose of induction, or until new anticancer treatment is initiated (whichever comes first). Ongoing and new medications shall also be recorded in connection with any SAEs.

[i] Tumor imaging should be performed regardless of treatment stop or delays and within a visit window of ± 7 days. Tumor imaging will be performed using CT/MRI scans of the chest, abdomen, and pelvis. CT scans are the required modality for measurable disease unless a patient has a clinical condition (e.g. severe contrast allergy) or the lesions are better visualized through the use of MRI. The same imaging technique has to be used in a patient throughout the study. If an unscheduled CT/MRI is performed during the study, subsequent protocol planned CTs/MRIs should be performed unless the time interval between the CTs/MRIs is ≤4 weeks.

[j] A cohort of approximately 40 patients at selected sites will be asked to volunteer for additional biological sampling and analysis. A separate ICF will be used for the Extended Exploratory Cohort and will be different than the main study. See Table 9 and Table 10 for collection of samples for the Extended Exploratory Cohort.

[k] If the patient has only one target lesion, the biopsy should be taken either subsequent or at least 7 days prior to the screening imaging scan.

[l] It is recommended to have blood sampling on day of treatment. If the sampling was not done on the day of treatment and the most current Liver Function Test (LFT) results warrant a safety concern, the site must repeat the LFT panel on the day of treatment and review the results prior to study drug administration.

7.1 Screening

Within 28 days prior to randomization, potential patients will be evaluated to determine if they fulfill the eligibility criteria described in Section 5.1 and Section 5.2. Procedures conducted as part of the patient's routine clinical management (eg, blood count) obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the schedule of activities (Table 5 and Table 6).

7.1.1 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but who are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the consolidated standards of reporting trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any AEs caused by study-specific procedures.

Individuals who do not meet the criteria for randomization (screen failures) may be re-screened once. Re-screened patients should be assigned a new screening number and be re-consented.

The Investigator must account for all patients screened and randomized. A patient participation log is to be completed with the patient's screening number, randomization number (if patient is randomized), date of consent, and date of the initial administration of induction therapy. If a patient is not randomized, the reason for exclusion from the study will be documented in the eCRF.

7.2 Induction Period

Patients who satisfy all eligibility criteria will be randomized in a 1:1 ratio between the 2 treatment arms and start treatment with induction therapy:

- Experimental arm: UV1 vaccination in combination with nivolumab and ipilimumab
- Control arm: nivolumab and ipilimumab.

The combination of nivolumab and ipilimumab as induction therapy is administered Q3W for 4 doses. Patients randomized to the experimental arm will undergo 4 additional visits to receive single doses with UV1 vaccination.

7.2.1 Discontinuation of Induction Therapy

If, during the Induction period, both nivolumab and ipilimumab are temporarily discontinued for patients randomized to the experimental arm, study visits and treatment with UV1 vaccination should also be temporarily discontinued. However, UV1 vaccination at visit 5 (monotherapy) can be administered if the patient would have been considered eligible to receive nivolumab and ipilimumab at that time point.

If, during the Induction period, nivolumab and ipilimumab are permanently discontinued, study visits and treatment with UV1 vaccination should be permanently discontinued. If the decision to permanently discontinue induction therapy is done during a scheduled study visit, the procedures and assessments applicable for that visit should be performed. However, if it's been > 30 days since last induction dose, the safety follow-up visit should be performed instead. If the decision to permanently discontinue induction therapy is done between two scheduled study visits, the next visit will be the safety follow-up visit which shall be performed 30-37 days after the last induction dose. If it's been > 37 days since last induction dose, the safety follow-up visit should be performed as soon as possible.

If the UV1 vaccination is discontinued, nivolumab and ipilimumab induction therapy may continue as scheduled in the protocol. With the exception of the DTH testing, all study procedures and assessments described in the schedule of activities will be performed.

Discontinuation of induction therapy does not represent withdrawal from the study. All patients that permanently discontinue all induction therapies prior to completion of the Induction period (Days 1 to 73 in the experimental arm and Days 1 to 64 in the control arm) will attend the safety follow-up visit and continue in the study for the determination of PD and survival.

UV1 vaccination will be discontinued if any of the following situations occur:

1. Patient requests to stop UV1 vaccination, nivolumab and ipilimumab
2. Any clinical AE, laboratory abnormality, intercurrent illness which, in the opinion of the Investigator, indicates that continuation with UV1 vaccination is not in the best interest of the patient
3. Patient starts another anticancer treatment while receiving UV1 vaccination, nivolumab, and ipilimumab
4. Pregnancy
5. At the discretion of the Investigator
6. Termination of the study by the Sponsor.

Adverse events associated with nivolumab and/or ipilimumab and/or UV1 vaccine exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab and/or ipilimumab must be withheld for moderate or severe drug-related toxicities and severe or life-threatening AEs.

Patients who develop serious allergic reactions during treatment with sargramostim and/or UV1 will be discontinued from further vaccinations independently of the deemed relatedness to sargramostim or UV1. Treatment with nivolumab and ipilimumab may continue at the Investigator's discretion.

Permanent Discontinuation of Induction Therapy Due to Safety Reasons

If due to safety reasons, all induction therapies are discontinued, the patient will complete the safety follow-up visit 30 to 37 days after the last dose of induction therapy. Thereafter, the

patient will continue with the response follow-up visits (10 weeks post last dose of induction therapy).

Permanent Discontinuation of Induction Therapy Due to Progressive Disease

If, during the Induction period, a patient has PD confirmed by a repeat CT/MRI scan according to iRECIST (iCPD), all induction therapy will be discontinued and the patient will complete the safety follow-up visit 30 to 37 days after the last dose of induction therapy. Further anticancer treatment will be given at the Investigator's discretion. If anticancer treatments other than nivolumab are planned to start prior to 30 days after the last dose of induction therapy, the safety follow-up visit will be performed as soon as possible following the confirmed PD. The patient will thereafter continue into the survival follow-up.

Permanent Discontinuation of Induction Therapy Due or Patient Decision or Investigator's Discretion

Patients taking part in the study can request to stop treatment with all induction therapies or decision to stop can be done at the Investigator's discretion. If either occurs, the patient will be asked to complete the safety follow-up visit 30 to 37 days after the last dose of induction therapy. The patient should be encouraged to continue the study as scheduled thereafter. If this is not accepted by the patient, he/she should be asked for acceptance to continue in the survival follow-up and be contacted by phone (or, at the investigator's discretion visit the hospital).

7.3 Follow-up Period

Six weeks after last dose of induction therapy, patients in both treatment arms will start maintenance therapy and receive nivolumab at a dose of 480 mg Q4W according to the label. It is not allowed to use any other dose of maintenance therapy (e.g. 240 mg Q2W).

The Follow-up period includes a safety follow-up visit, response follow-up visits, and survival follow-up visits as described below. All patients should be followed for the intended duration of the study on an intent-to-treat basis for confirmation of PD and OS, regardless of the receipt of any new anticancer treatment.

7.3.1 Safety Follow-up Visit

The safety follow-up visit should be conducted 30 to 37 days after the last dose of induction therapy. If anticancer treatments other than nivolumab are planned to start prior to 30 days after the last dose of induction therapy, the safety follow-up visit will be performed before the initiation of new anticancer treatment if possible.

7.3.2 Response Follow-up Visits

Patients who complete the Induction period and/or who discontinue the Induction period for other reasons than confirmed PD will continue with response follow-up visits (after the completion of the safety follow-up visit) and should be assessed with imaging and assessments according to the schedule of activities for monitoring of disease status.

The first response follow-up visit should occur 10 weeks post last dose of induction therapy. Subsequent response follow-up visits will be performed every 8 weeks for 32 weeks and then every 12 weeks thereafter. Every effort should be made to collect information regarding disease status until confirmed PD (iCPD) per iRECIST, until 70 PFS events are reached or until 18 months post last patient randomized (whichever comes first). If required, images may be requested by BICR also after local iRECIST progression.

Handling Progressive Disease During the Response Follow-up Period

If, during the response Follow-up period a patient has iCPD confirmed by 2 scans, 4 to 8 weeks apart according to iRECIST criteria, the patient will continue with survival follow-up visits and will be contacted by phone (or, at the investigator's discretion visit the hospital) every 12 weeks until the earliest of either 70 PFS events reached or 18 months post last patient randomized. From the PFS cut-off date is reached, survival follow-up visits will continue every 6 months for 2 years.

If PD is not confirmed according to iRECIST criteria, patient should continue with the response follow-up visits and imaging schedule according to Table 5 and Table 6.

Handling Complete Response During the Response Follow-up Period

If, during the response Follow-up period a patient has complete response (CR) according to RECIST 1.1, the patient will be treated according to the Investigator's discretion. Patients who stop anticancer treatment while in CR will continue to undergo tumor imaging as scheduled in the study protocol. In the event of disease recurrence, any anticancer treatment including nivolumab may be resumed at the Investigator's discretion.

7.3.3 Survival Follow-up Visits

Patients who have confirmed iCPD according to iRECIST will continue with survival follow-up visits and be contacted per phone (or, at the investigator's discretion visit the hospital) every 12 weeks for survival status, assessment of SAEs and new anticancer treatments until the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized.

From the PFS cut-off date is reached, the survival follow-up visits will continue every 6 months for 2 years and only survival status will be collected. Detailed visit instructions will be provided by the sponsor at this time.

The Sponsor may request survival status to be collected at additional timepoints during the study. For example, updated survival status may be requested prior to an IDMC review.

7.4 Withdrawal of Consent

- A patient may withdraw consent from the study at any time at his/her own request. Although a patient is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. Survival status post withdrawal of consent can still be obtained from publicly available sources such as national cancer registries.
- If a patient withdraws consent from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the medical records.

If Withdrawal of Consent Occurs During the Induction Period

If possible, the procedures for the safety follow-up visit should be performed at the time of withdrawal. If the withdrawal takes place between 2 study visits, the patient should be asked to attend the safety follow-up visit as soon as possible. Any DTH registration card should be returned. The patient will no longer receive induction therapy or be followed at scheduled protocol visits.

If Withdrawal of Consent Occurs During the Follow-up Period

If possible, the procedures for the applicable visit where withdrawal takes place should be performed. If withdrawal takes place between 2 study visits, the patient should be asked to attend the next visit as soon as possible. Any DTH registration card should be returned. The patient will no longer be followed at scheduled protocol visits.

7.5 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A patient is not considered lost to follow-up until the study is declared stopped.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study or not.

- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- For lost to follow-up patients, survival status can still be obtained from publicly available sources such as national cancer registries.

7.6 End of Study

The primary and secondary endpoint analysis will be conducted at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized. From the PFS cut-off date is reached, all patients will have survival follow-up visits every 6 months for 2 years. The EOS is defined as the date of the last survival follow-up visit of the last patient undergoing the study.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the schedule of activities (Table 5 and Table 6). Adherence to the study design requirements is essential and required for study conduct.
- Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. These should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- All screening evaluations must be completed and reviewed prior to randomization to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, is estimated to be 30 mL for local analysis and 95 mL for exploratory analysis. Patients who volunteer to take part in the extended exploratory sampling (Section 8.5) will have approximately 326 mL extra volume of blood collected.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Assessment of Tumor Response

8.1.1.1 Tumor Imaging

Tumor imaging will be performed as detailed in the schedule of activities (Table 5 and Table 6) and should not be adjusted for dosing delays. It is important that patients are assessed according to the intended scanning schedule to prevent bias in analysis that may occur if one treatment arm is assessed differently compared to the other. If an unscheduled CT/MRI is performed during the study, subsequent protocol planned CTs/MRIs should be performed unless the time interval between the CTs/MRIs is <4 weeks.

Mandatory tumor imaging consists of:

- Contrast enhanced CT or MRI of chest, abdomen, and pelvis and all other known sites of disease. The CT scans are the preferred modality for measurable disease unless a patient has a severe iodine contrast allergy or other clinical condition that precludes optimal CT imaging, or the lesions are better visualized through the use of MRI. An MRI is the preferred modality for central nervous system (CNS) imaging in the case of suspected new CNS involvement. For a given patient, the same imaging modality should be used throughout the entire study to allow for comparability of lesions over time

- A CT or MRI of other body regions where lesions are present or suspected and can be visualized on CT or MRI (does not apply to superficial skin lesions). Once a lesion has been identified and documented with CT/MRI scanning, follow-up CT/MRI scans must be consistently repeated at all subsequent tumor assessment timepoints
- Digital photography and documentation with label and ruler of all skin lesions

All scheduled tumor images will be submitted for BICR. In addition, images that are obtained at an unscheduled timepoint and which relate to tumor assessment should also be submitted for BICR. Further details on tumor imaging and data transfer will be provided in a separate Imaging Guidance document.

8.1.1.2 Tumor Assessments

Tumor assessments will be performed by the local Investigator/site and by BICR according to RECIST 1.1. In addition, the Investigator will evaluate new lesions and any potential PD by iRECIST (Appendix 4). For this protocol, target skin lesions are considered measurable only if measurable on CT or MRI. Measurable lesions that have previously been irradiated will not be considered target lesions unless size increase has been observed following completion of radiation treatment.

As a clarification to RECIST 1.1, the following applies if a lesion is resected or receives any form of treatment or local therapy during the study:

- The procedure itself, the pathology result (positive, negative, non-evaluable [NE]), and all post-procedure lesion assessments should always be recorded in the eCRF
- Subsequent assessments for such patients will be NE until PD has been determined from the nadir

Patients with PD per RECIST 1.1 and unconfirmed PD (iUPD) per iRECIST will have a new scan 4 to 8 weeks later to confirm PD per iRECIST (iCPD). A detailed description of response criteria is given in Appendix 4.

If confirmatory scan performed 4 to 8 weeks after iUPD does not confirm progression, further scans continue as originally planned.

Patient treatment will be determined by the Investigator. The BICR will perform assessments for statistical endpoint analysis only and will not interfere with Investigator assessments or treatment decisions. Treatment should continue until iCPD has been confirmed.

8.2 Safety Plan and Assessments

The administration of study treatment will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Eligibility criteria were selected to guard the safety of patients in this study. During the study, patients will be closely monitored for the development of any AEs, including signs or symptoms of

autoimmune conditions. Patients receiving UV1 injections will be observed in study site for 4 hours following each treatment with UV1 and sargramostim.

Planned timepoints for all safety assessments are provided in the schedule of activities. Adverse events will be reported throughout the study as described in Section 8.3. Any clinically significant abnormalities persisting at the PFS cut-off date reached will be followed by the Investigator until resolution or until a stable clinical status is reached but will not be recorded in the eCRF; however, clinically significant abnormalities should be noted in the patient's medical file.

8.2.1 Independent Data Monitoring Committee

During the course of the study, an IDMC will monitor safety information to ensure patient safety. The primary responsibility of the IDMC is to safeguard the interests of patients in the study. The IDMC will provide recommendations regarding stopping, modifying, or continuing the trial. The IDMC will consist of medical and statistical experts and provide their recommendations to the Sponsor. The safety and well-being of the study patients are the most important considerations.

An organizational IDMC meeting will be held and an IDMC charter developed prior to the first patient screened in the study. The first operational IDMC meeting will take place approximately three weeks after the first 6 patients (3 in experimental and 3 in control arm) have completed the first treatment cycle (defined as until planned start of C2 dosing) of ipilimumab and nivolumab +/- UV1 and will include a safety review of all the included patients. The second IDMC meeting will take place approximately three weeks after the first 6 (3+3) patients have finished or discontinued the second cycle (defined as until planned start of C3 dosing), and the third meeting will take place approximately seven weeks after the 6 (3+3) patients have finished or discontinued planned cycle 4.

The safety data of all included patients will be reviewed at each meeting. Subsequent meetings will be held every 3 months until the PFS cut-off date is reached or until last dose of induction therapy in the single arm UV1 cohort, whichever comes later.

The IDMC's assessment will be based on accumulated listings of the safety data collected in the study (ie, AEs, SAEs, hematology and chemistry data, withdrawals due to AEs, and treatment termination caused by AEs, etc).

8.2.1.1 Study Stopping Rules

A decision to stop the study on the basis of safety findings will be done in accordance with the IDMC Charter for the study. Conditions that may warrant halting of the study include, but are not limited to the following:

- The discovery of an unexpected, significant, or unacceptable risk to the patients
- Subsequent discovery of a detrimental impact on efficacy of UV1 resulting in a negative risk/benefit balance
- Cancellation of drug development

8.2.2 Physical Examinations

- Height will be measured at Screening only.
- Weight should be measured using the same scale for a patient.
- A physical examination of the skin, cardiac, pulmonary, abdomen, and peripheral lymph node status will be conducted.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Clinically significant findings observed by the Investigator or symptoms reported spontaneously by the patient during the physical examination will be reported as AEs and in accordance with Section 8.3.3.

8.2.3 Vital Signs

- Temperature, pulse rate and blood pressure will be assessed.
- Blood pressure will be assessed in the seated position (after 5 minutes of rest) with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.4 Eastern Cooperative Oncology Group

The ECOG performance status will be measured as indicated in the schedule of activities. See Appendix 3 for the ECOG performance status scale.

8.2.5 Clinical Safety Laboratory Assessments

Refer to Appendix 1 Clinical Laboratory Tests for the list of clinical laboratory tests to be performed and to the schedule of activities for the timing and frequency.

The Investigator must review the laboratory report, document this review, and report any clinically relevant changes in the AE section of the eCRF. Abnormal laboratory findings should be reported as AEs if they are clinically significant (ie, medical intervention or corrective action, such as transfusions, initiation of antibiotics, other treatment regimens, or hydration, is required) or the abnormality is deemed clinically significant by the treating physician due to any other reason. The laboratory reports must be filed with the source documents. Laboratory values must be graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

All abnormal laboratory tests with values considered clinically significant should be followed up per institutional practice. Every attempt should be made to perform repeat assessment until the values return to normal or baseline or if a new baseline is established, as determined by the Investigator.

8.2.6 Toxicity of the Study Drugs

There are no data on the toxicity of the combined therapy with all 4 study drugs in the present study. The combined toxicity of ipilimumab and nivolumab is known through several studies and is mentioned in the respective prescribing information. If a patient receiving ipilimumab and/or nivolumab develops suspected immune AEs, this must be handled according to the label/prescribing information for the relevant study drug(s). Further, both the IMPs and NIMPs may give general symptoms like fatigue. Please refer to the Investigator's Brochure (IB)/label for the IMP/study drug for further information.

8.3 Adverse Events

8.3.1 Definitions

8.3.1.1 Definition of AE

An AE is any untoward medical occurrence in a subject or clinical study patient, temporally associated with the use of a study treatment, whether or not considered related to the medicinal product.

Examples of events meeting the AE definition:

- Any unfavorable laboratory test abnormality (hematology, clinical chemistry, or urinalysis) or other unfavorable safety assessment abnormality (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from Baseline, will be considered an AE. An unfavorable laboratory test abnormality may be one which requires medical intervention, requires action on the study drug(s) or is considered one at the discretion of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se should not be reported as an AE unless it is an intentional overdose taken with possible suicidal/self-harming intent. In that case, the overdose should be reported as an AE regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se should not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy should be reported as an AE if they fulfill the definition of an AE.

8.3.1.2 Events Not Meeting the AE Definition

The following are examples of events that do not meet the definition of an AE. These events should not be reported as AEs, **unless** there is evidence suggesting a causal relationship between the study treatment and the event:

- The disease being studied. This includes signs, symptoms, clinically significant abnormal laboratory findings, or other abnormal safety assessments that are associated with the underlying disease, **unless** more severe than expected for the patient's condition.
- Progression from the disease being studied. This includes AEs definitely related to disease progression.
- Death from the disease being studied.
- Elective medical or surgical procedure (eg, endoscopy, appendectomy). Note: The condition that leads to the procedure is the AE (or part of medical history).
- Situations in which an untoward medical occurrence did not occur, but the patient was hospitalized (social and/or convenience admission to a hospital).
- Minor laboratory deviations outside of normal ranges and anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pregnancy, unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. All pregnancies must be reported in a pregnancy report form and should follow the procedures outlined in Section 8.3.4.
- Elective abortions without complications.
- Hospitalization for normal delivery of a healthy newborn. All pregnancy outcomes must be reported in a pregnancy outcomes form and should follow the procedures outlined in Section 8.3.4.

8.3.1.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if seriousness conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

1. Results in death
2. Is life-threatening

   The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

4. Results in persistent disability/incapacity

   The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions.

   This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption

5. Is a congenital anomaly/birth defect

6. Other situations

   Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

   Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.3.1.4 Potential Drug Induced Liver Injury (DILI)

All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

7. ALT or AST elevation > 3 times upper limit of normal (ULN), AND
8. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated alkaline phosphatase), AND
9. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.3.1.5 Definition of Adverse Event of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the safety of UV1 vaccination. An AESI may be serious or non-serious. For all AESIs, the Investigator should provide a description of the event, including but not limited to time of onset, treatment given, and outcome. Events falling under the AESI definition is an AESI regardless of the investigator's assessment of relatedness to a study drug, and regardless of which treatment arm the patient is randomized to.

Adverse events of special interest include any of the following events occurring on the same day of sargramostim, UV1, nivolumab or ipilimumab administration:

- **Anaphylactic shock**
- **Anaphylactic reaction**
- **Hypersensitivity** (allergic reactions except local injection site reactions).

8.3.1.6 Definition of Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is not expected, and for which there is a reasonable possibility that the study treatment caused the event.

For UV1 and sargramostim, the reference safety information section in the UV1 IB is the reference document for what is considered to be expected SAEs. All clinical data in the IB are for use of the UV1 vaccination (ie, the combination of UV1 and sargramostim). An event that is expected for the UV1 vaccination is considered as expected for both UV1 and sargramostim.

The causality assessment for SUSARs is the same as for other events, as described in Section 8.3.2.2.

8.3.2 Classification of Adverse Events

8.3.2.1 Severity and Grade

The National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 criteria will be used to grade AEs.

The Investigator will assess severity for each AE and assign it to one of the following categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Activities of Daily Living:

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.3.2.2 Causality

The Investigator is obligated to assess the causal relationship between each study treatment and an AE. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality must be reported as one of the following:

1. Definitely: The AE is definitely related to the study treatment.
2. Probably: There is high degree of certainty that the AE is related to the study treatment.
3. Possibly: The AE could be related to either the study treatment or to concurrent disease/medication.
4. Unlikely: There is high degree of certainty that the AE is NOT related to the study treatment.
5. Not related: The AE is clearly due to other causes (eg, concurrent medication, underlying disease, etc.).

If causality is assessed as definitely, probably, or possibly related, the event will be considered as related for regulatory reporting purposes.

The Investigator will use clinical judgment to determine the relationship between an event and the study drugs. For an event to be assessed as related there should be a reasonable possibility that the drug caused the event. 'Reasonable possibility' means that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to study treatment administration must be considered and investigated.

The Investigator should also consult the IB and/or product information in their assessment.

For each AE, the Investigator must document in the medical records or other source data that he/she has reviewed each AE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event, with the currently available information,

before the initial transmission of the SAE data to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.3.3 Adverse Event Reporting and Follow-up

8.3.3.1 Reporting

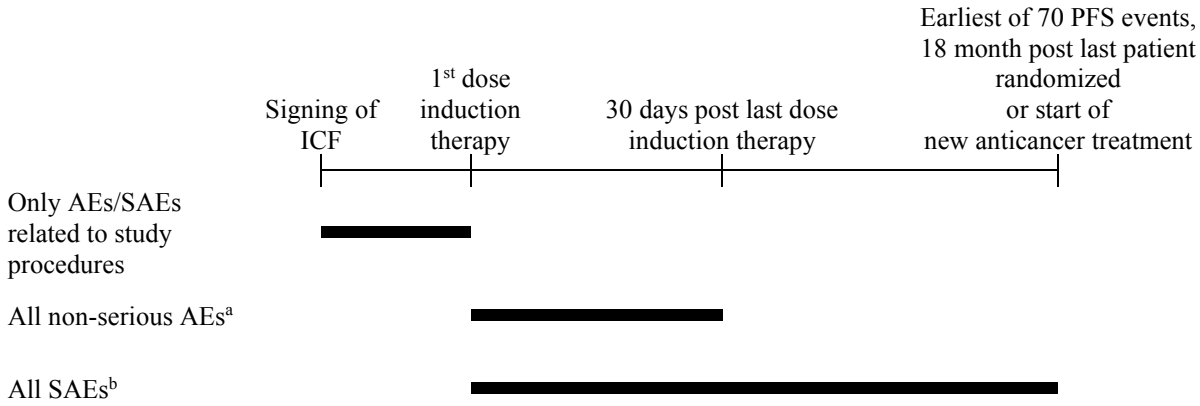
Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative). Care will be taken not to introduce bias when detecting AEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrence (for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?").

From signing of the ICF until the first dose of induction therapy, only AEs/SAEs caused by study-specific procedures should be reported. All non-serious AEs should be reported from the first dose of induction therapy until 30 days after the last dose of induction therapy, or until new anticancer treatment is initiated (whichever comes first).

All SAEs should be reported from the first dose of induction therapy until 70 PFS events are reached, until 18 months post last patient randomized or until new anticancer treatment is initiated (whichever comes first).

The time periods for reporting of AEs and SAEs are outlined in Figure 4.

Figure 4 Time Periods for Reporting Adverse Events, Serious Adverse Events



[a] All non-serious AEs should be reported until 30 days after the last dose of induction therapy, or until new anticancer treatment is initiated (whichever comes first)
[b] All SAEs should be reported until 70 PFS events are reached, until 18 months post last patient randomized or until new anticancer treatment is initiated (whichever comes first)

When an AE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE information in the eCRF.

It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the site monitor/Contract Research Organization (CRO)/Sponsor in lieu of completion of the AE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the site monitor/CRO/Sponsor. In this case, all patient identifiers, with the exception of the screening and/or randomization number, will be blinded on the copies of the medical records before submission.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE.

Investigators are not obliged to actively inquire about AEs after the patient has been withdrawn from the study. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and considers the event to be related to the induction therapy or study participation, the Investigator must promptly report to the Sponsor.

Medical history will include all active conditions and any condition considered to be clinically significant by the Investigator. Medical history including demographic information (birth date, race, gender, etc.), current and historical medical conditions, cancer history (malignant melanoma, melanoma mutations, and other cancer types), and relevant surgical procedures must be collected at the Screening visit. Medical history will be recorded up until the first dose of induction therapy; however, AEs that occur between the time of signature of the ICF and the first dose of induction therapy that are believed to be at least possibly caused by study-specific procedures (ie, blood draws, imaging, biopsies, or other study procedures) will be reported as AEs as indicated.

8.3.3.2 Follow-up

After the initial detection of an AE, the Investigator is required to proactively follow each patient at subsequent visits/contacts. Adverse events and SAEs that are ongoing beyond the required reporting timelines shall be followed up locally per institutional practice until resolution or stabilization or the patient is lost to follow up.

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. E.g. if an Adverse Event is classified as an AESI CTCAE grade ≥ 3, a plasma sample (from ≥ 5 mL whole blood) should be collected the same day as the event and stored for shipment to sponsor upon request.

New or updated information will be reported in the eCRF until 70 PFS events are reached or until 18 months post last patient randomized (whichever comes first).

8.3.4 Expedited Reporting

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following events must be reported by the Investigator to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious AEs
- Pregnancies

If only limited information is initially available, follow-up reporting is required.

The minimum *information required for an initial report is:*

- Name of person sending the report (ie, name, address of Investigator)
- Participant identification (screening/randomization number, initials, NOT participant name)
- Protocol number
- Description of SAE
- Causality assessment; please refer to Section 8.3.2.2.

However, as far as possible all information on the SAE form should be covered in the initial report.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, follow-up SAE reporting should be sent to the Sponsor within 24 hours.

8.3.5 Regulatory Reporting Requirements for Investigator and Sponsor

Prompt notification of SAEs (within 24 hours) by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators. This includes annual safety updates.

Suspected unexpected serious adverse reactions have additional reporting requirements. The Sponsor will report SUSARs as described below.

- If the SUSAR is fatal or life-threatening, regulatory authorities and IRBs/IECs will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up (cause of death, autopsy report, and hospital report) information will be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious, regulatory authorities and IRBs/IECs will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will prepare Investigator safety reports for SUSARs according to local regulatory requirements and forward to Investigators as necessary.

Only SUSARs related to the IMPs (UV1 and sargramostim) will be expeditiously reported by the Sponsor.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor must file it along with the IB and notify the IRB/IEC, if appropriate according to local requirements.

8.3.6 Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of induction therapy and until 5 months after the last dose of UV1 vaccination, nivolumab, or ipilimumab (whichever comes last). For male patients, this still applies if their partners become pregnant within 5 months after the last dose of UV1 vaccination, nivolumab, or ipilimumab (whichever is administered last.) The pregnancy and outcome of pregnancy should be monitored.

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug.

All pregnancies must be reported by the Investigator to the Sponsor in a pregnancy report form within 24 hours after becoming aware of the pregnancy and should follow the procedures outlined in Section 8.3.4. The Investigator must follow-up and document the course and outcome of all pregnancies even if the patient was discontinued from the study or if the study has ended.

All pregnancy outcomes must be reported by the Investigator to the Sponsor in a pregnancy outcome report form within 30 days after he or she has gained knowledge of the outcome. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication.

Any pregnancy complication should be reported as an AE. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy and abnormal pregnancy outcomes (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) should be reported even if they occur outside the normal SAE reporting period. These events must be reported within 24 hours in accordance with the procedure for reporting SAEs.

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

NOTE: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

Post-menopausal female

- *A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).* However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective con*traception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study randomization.*

8.4 Exploratory Assessments

Blood samples for exploratory analysis of immune-related gene profiling and immune- and tumor-related protein and gene profiles will be collected from all patients. In the experimental arm, collection will be done on Days 1, 31, and 52; and in the control arm on Days 1, 43, and 64. Collection will also be done in both treatment arms on the safety follow-up visit and 18 weeks post last dose of induction therapy (2nd response follow-up visit). Assessments related to these samples are described in Table 8.

8.4.1 Biomarkers

Blood samples for DNA and RNA isolation will be collected from all patients. Analysis of DNA and RNA isolated from blood will include, but is not limited to, analysis of the T cell receptor repertoire, analysis of circulating tumor DNA, and analysis of microRNAs. Blood samples may be also used to isolate and analyze circulating tumor cells.

Blood samples will be stored, and analysis may be performed on biomarker variants thought to underlie the interplay between immune activation provoked by vaccination with UV1 and inhibition of tumor resistance mechanisms and peripheral immune tolerance induced by checkpoint blockade. Analyses may include but are not limited to levels of antibodies specific for vaccine peptides, tumor-specific antigens, cytokines, chemokines, and inflammatory factors. Assessments of potential biomarkers may be used to evaluate their association with observed clinical responses to UV1 vaccination in combination with nivolumab and ipilimumab, or nivolumab and ipilimumab alone.

The final disposition of samples will be conducted per local regulations.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last patient's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses.

8.5 Extended Exploratory Cohort

A cohort of approximately 40 patients at selected sites will be asked to volunteer for additional biological sampling and analysis. Extended blood sampling, tumor biopsy collection, fecal sampling, and DTH testing (only for experimental arm) will be conducted on patients in the Extended Exploratory Cohort. Exploratory assessments related to the biological samples collected from this cohort of patients with rationale and objectives are described in Appendix 2. The samples collected in the Extended Exploratory Cohort will be in addition to those required elsewhere per protocol for all patients.

8.6 Single Arm UV1 Cohort

To support the Extended Exploratory Cohort of the study, an additional 20 patients at selected sites will be enrolled in a single arm UV1 cohort for collection of additional biological material. (Appendix 7).

9 Statistical Methods

The statistical considerations summarized in this section outline the plan for data analysis of this study. Any deviations from the planned analyses will be described in the Statistical Analysis Plan and justified in the final integrated study report.

9.1 Statistical Hypothesis

The primary endpoint is PFS. Under the null hypothesis, the PFS HR for UV1 vaccination in combination with nivolumab and ipilimumab versus nivolumab and ipilimumab is assumed to be unity. Under the alternative hypothesis, the PFS HR is assumed to be 0.60 or better, representing a beneficial effect on PFS for UV1 vaccination in combination with nivolumab and ipilimumab compared to nivolumab and ipilimumab.

9.2 Sample Size Determination

To test the PFS null hypothesis with 80% power and a 1-sided alpha level of 0.10, a total of 70 PFS events are required. Hodi et al (2018) [14] provides data on PFS with nivolumab and ipilimumab in patients with advanced melanoma. Assuming a similar shape of the PFS curve for nivolumab and ipilimumab is observed in the current study, 154 patients randomized over a 15-month period and followed thereafter for a minimum of 12 months will give a mean follow-up of PFS events of approximately 20 months. Follow-up for survival will continue for an additional 24 months after the PFS analysis at which time 60 deaths are expected to have accrued; this many deaths, an observed OS HR of 0.60 would reach $p<0.025$ 1-sided.

As of 19 September 2023, blinded event accrual stood at 63 PFS events. A blinded examination of the overall PFS Kaplan Meier curve made as of 23 July 2023, and then repeated as of 19 September 2023, showed strong evidence for a plateau at 54 to 55% of subjects alive and without progression. Such a PFS curve plateau is not uncommon for IO therapies. In CheckMate 67, nivolumab plus ipilimumab, nivolumab alone and ipilimumab alone were evaluated in advanced melanoma (Hodi 2018). This study formed the basis of the sample size calculations for the current study and showed a prolonged PFS tail for nivolumab plus ipilimumab plateauing at approximately 40% for subjects alive and without progression. However, the blinded data realized thus far has shown a higher plateau at 54 to 55% for subjects alive and without progression.

Specifically, there seems to be very little contribution to PFS events after 18 months in the study, with the PFS curve nearing asymptote. The plateau in the current study commences at approximately 21 months post first subject randomized with an estimated 56.02% of subjects alive and without progression and persists thereafter for 15 months, out to 36 months at which time 54.32% subjects are alive and without progression, i.e. an increase in the progression rate of only 1.7% over 15 months. Based on the projected PFS curve, 70 PFS events are not expected to be reached by late 2028 at which time 69.3 events, 90% CI of (69.2, 72.3), are expected.

Given the observed plateau in the accrual of PFS events, it has been decided to execute the primary analysis of PFS at the earliest of either 70 PFS events reached across both treatment

arms or 18 months post last patient randomized. An analysis with slightly fewer PFS events has negligible impact on the observed HR to reach a given level of statistical significance.

9.3 Analysis Populations

For purposes of analysis, the following analysis populations are defined:

Analysis populations	Description
Intention-to-treat (ITT) population	All randomized patients. Efficacy data in this population will be summarized by randomized treatment. The primary PFS and secondary OS analysis will be assessed in the ITT population. Patients will be analyzed by the treatment arm to which they are randomized.
Response evaluable population	All randomized patients with measurable disease by RECIST 1.1. The secondary endpoint analyses of ORR and DOR will be assessed using the response evaluable population. Patients will be analyzed by the treatment arm to which they are randomized.
Safety population	All randomized patients who receive at least one dose (or partial dose) of induction therapy. Patients will be assessed by the treatment received, based on the first dose of study drug.

9.4 Statistical Analysis

9.4.1 General Considerations

Demographic data and disease-related baseline characteristics will be summarized using descriptive statistics (count and percent, mean, median, standard deviation, minimum, and maximum). All patient, efficacy, and safety data will be summarized. In addition to the summarized analysis plan outlined below, a Statistical Analysis Plan (SAP) will be written and finalized prior to the first planned data analysis. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will also be described in the SAP.

9.4.2 Efficacy Analyses

9.4.2.1 Primary Efficacy Analyses

Progression Free Survival

Progression free survival is defined as time from randomization to progression (by BICR) or death from any cause, whichever occurs first. A Cox proportional hazards regression model will be used to analyze PFS on an ITT basis. Patients who have not progressed or died will be censored at their last follow-up tumor assessment. The model will include a single covariate for randomized treatment and covariates for baseline ECOG (0 versus 1) score. The HR will be estimated from the model along with the associated 2-sided CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and median PFS times will be estimated. The PFS

at 12 months will be estimated from the Kaplan-Meier curves along with the associated 80% and 95% Cis.

Sensitivity Analyses of the Progression Free Survival

Several sensitivity analyses will be performed on the primary endpoint:

i. As per FDA guidance, a sensitivity analysis will be performed in patients who started any subsequent anticancer treatment without a prior reported progression. Patients will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anticancer treatment; and
ii. A log rank test on PFS as determined by BICR. The 2-sided p-value will be extracted and presented alongside the results of the Cox analysis; and
iii. A Cox regression analysis on PFS as determined by the local Investigator's review; and
iv. A log rank test on PFS as determined by the local Investigator's review. The 2-sided p-value will be extracted and presented alongside the results of the Cox analysis.

Additional sensitivity analyses may be specified in the SAP.

9.4.2.2 Secondary Efficacy Analyses

Overall Survival

Overall survival is defined as the time from randomization to death from any cause. Overall survival will be analyzed in a fashion similar to that described for PFS. Overall survival data at the time of the PFS analysis and with an additional follow-up thereafter will be analyzed until defined end of study to provide evidence supportive of PFS.

Objective Response Rate

Objective response rate is defined as the proportion of patients with a best response of CR or PR (by BICR). The ORR will be analyzed by exact logistic regression. The model will include a single covariate for randomized treatment and covariates for baseline ECOG (0 versus 1) score. The exact odds ratio will be estimated from the model along with the associated 80% and 95% Cis and 2-sided p-value. Exact Clopper-Pearson 2-sided 80% and 95% confidence limits will be calculated for the proportion of patients with ORR in each arm.

Duration of Response

Duration of response is defined as the time from first CR or PR (by BICR), whichever is recorded first, to progression (by BICR) or death from any cause, whichever occurs first. The DOR will be analyzed via Cox regression modelling with a fixed effect term for randomized treatment. The HR will be estimated from the model along with the associated 80% and 95% CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves; median DOR and the 80% and 95% Cis will be estimated from the Kaplan-Meier curve by treatment arm. Since DOR is assessed in responding patients only, a supportive analysis will be performed

based on the expected duration of response as per Ellis et al (2008)[32] as this analysis includes all randomized patients, including those who did not respond.

9.4.3 Safety Analyses

Adverse events will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system. Treatment-emergent AEs (TEAEs) will be summarized. A TEAE is defined as an AE that was not present prior to first study treatment but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). For simplicity, TEAEs will be referred to as AEs in this protocol. Adverse events will be summarized descriptively by treatment arm, in terms of body system and MedDRA preferred term. Patients with multiple occurrences of the same AE will only be counted once at the maximum severity/grade for each preferred term, system organ class, and overall. Adverse events will be summarized in terms of the number and percentages of patients experiencing related AEs, SAEs, AEs leading to dose interruption, AEs leading to withdrawal from randomized treatment, and AEs leading to death. In the event that a patient experiences repeated episodes of the same AE, the patient will be counted once within each system organ class and similarly counted once within each preferred term and the event with the highest severity grade and/or strongest causal relationship to each treatment will be used for incidence tabulations.

Laboratory values and change from Baseline will be summarized using descriptive statistics at scheduled visits by treatment. Shift tables of the worst on-study laboratory toxicity relative to Baseline will be presented by treatment arm. Patient listings of Grades ≥3 laboratory toxicities will be provided.

Vital signs and ECOG performance status (observed and change from Baseline) will be summarized using descriptive statistics by timepoint and treatment.

9.4.4 Exploratory Analyses

Biomarkers and parameters for immunological mode of action (eg, T-cell response) will be summarized per timepoint with descriptive statistics. The potential relationship between exploratory biomarkers and treatment response/immune response will be summarized using cross-tabulation (biomarker measured as present Yes/No) and level of biomarker (mean, standard deviation, median, minimum, and maximum) for each response group (biomarkers measured on continuous scales).

9.5 Timing of the Analyses

This study is event driven so that the timing of the primary endpoint analysis is dependent upon the attainment of 70 PFS events and is not calendar based. Based on the assumptions supporting the sample size calculation (Hodi, 2018), it is expected that 70 PFS events will have accrued at around 27 months after the first patient is randomized.

However, as of 19 September 2023, blinded event accrual stood at 63 PFS events. A blinded examination of the overall PFS Kaplan Meier curve made as of 23 July 2023, and then repeated as of 19 September 2023, showed strong evidence for a plateau at 54-55% of subjects alive and without progression. Given the observed plateau in the accrual of PFS events, it has been decided to execute the primary analysis of PFS at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized. Follow-up for survival will continue for an additional 24 months after the PFS cut-off date, at which time 60 deaths are expected to have accrued.

The secondary endpoints will also be analyzed at the earliest of either 70 PFS events reached across both treatment arms or 18 months post last patient randomized.

In addition, overall survival will be analyzed until defined end of study.

10 Regulatory, Ethical, and Study Oversight Considerations

10.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference of Harmonisation (ICH), ethical principles derived from the Declaration of Helsinki, the General Data Protection Regulation, the United States Code of Federal Regulations (CFR) Title 21, European regulation No 536/2014, and other applicable laws and regulations.
- The study will be conducted in compliance with the protocol and amendments, as applicable.
- The protocol, protocol amendments, ICF, and other relevant documents (eg, advertisements) will receive required regulatory authority approval and IRB/IEC approval/favorable opinion before the study is initiated.
- Any substantial amendments to the protocol will require regulatory authority approval and IEC/IRB approval/favorable opinion before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will ensure that:
    - Written and dated approval/favorable opinion from the IRB/IEC for the protocol, ICF, and other relevant documents have been obtained before study initiation
    - The IRB/IEC has been provided with a copy of the IB
    - Written summaries of the status of the study are provided to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - The IRB/IEC is notified of SAEs and other significant safety findings as required by IRB/IEC procedures
    - Overall conduct of the study at the site and adherence to national and international regulations, IRB/IEC requirements, and all other applicable local regulations are followed.

10.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, the European Union General Data Protection Regulation, IRB/IEC requirements, and applicable laws regulations.
- The medical record must include a statement that written informed consent was obtained before the patient was randomized in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.
- Prior to any study-specific procedures being performed, all patients must sign the ICF. Patients that decide to take part in the extended exploratory analyses need to sign a separate ICF (Appendix 2).
- After the patient has signed the ICF, the site will enter information into the IWRS, or equivalent, which will assign a unique screening number. Once assigned, a screening number cannot be re-used for any reason.

Patients who are rescreened are required to sign a new ICF and will receive a new screening number.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently screened in the study as well as those currently randomized in the study.

10.4 Data Protection

- Participants will be assigned a unique identifier by interactive web response system. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with relevant data protection laws. The level of disclosure must also be explained to the patient.

- The patient must be informed that his/her medical records may be examined by study monitors, quality assurance auditors, and other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Dissemination of Clinical Study Data

When the Clinical Study Report is completed, the Sponsor will provide the major findings of the study to the Investigator. A summary of the study results will also be posted in a publicly accessible database (eg, www.ClinTrials.gov). The results may also be submitted for publication.

10.6 Data Quality Assurance

- All patient data relating to the study will be recorded in an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Once the eCRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change and the name of the person who performed the change, together with the time and date, will be logged to provide an audit trail.
- If additional corrections are needed, the responsible monitor or data manager will raise a query in the eCRF. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail.
- The specific procedures to be used for data entry and query resolution using the eCRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the eCRF.

10.7 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The study site will maintain an Investigator site file containing, at a minimum, the IB, protocol and any amendments, drug accountability records, correspondence with the IEC/IRB, the identification of all participating patients, study-specific source documents, source worksheets, all original signed and dated ICF forms, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the Sponsor or its designees.

The Investigator will retain the Investigator site file to be maintained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

No data should be destroyed without the agreement of the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

10.8 Study and Site Closure

For reasonable cause, the Sponsor may terminate a study site or the entire study prematurely. When feasible, a 30-day written notification will be given. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients
- Difficulties in the screening and/or randomization of patients – individual sites or entire study may be closed/terminated based on this criterion
- Insufficient adherence to protocol requirements (non-compliance) – individual sites may be closed based on this criterion
- Cancellation of drug development.

Should this be necessary, the Sponsor will arrange discontinuation procedures. In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. In terminating the study, the Investigator will ensure that adequate consideration is given to the protection of the patients' interests.

10.9 Publication Policy

- The results of this study may be published and/or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- All data generated from this study are the property of the Sponsor and will be held in strict confidence along with all information furnished by the Sponsor. Independent analysis and/or publication of these data by the Investigator(s) or any member of their staff is not permitted without the prior, written consent of the Sponsor. Written permission to the Investigator will be contingent on the review by the Sponsor of the manuscript and will provide for nondisclosure of Sponsor confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

10.10 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be reviewed and/or approved by the IRB/IEC, and of regulatory authorities in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient performs any study-specific procedures.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/regulatory authority approval prior to implementation (if appropriate). In the United States: The protocol amendment(s) will be submitted to the Investigational New Drug under which the study is being conducted.

Administrative changes may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.11 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him or her, and the study site, practice, or institute in which they are employed and the liability of the

Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.12 Access to Source Data

On behalf of the Sponsor, a study monitor will contact and visit the Investigator at the study center prior to entry of the first patient and at appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, the Investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The Investigator will make all source data (ie, the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification). It is the monitor’s responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the Investigator agrees to cooperate with the monitor and to ensure that any problems detected in the course of the monitoring visits are resolved. Representatives from the Sponsor may also contact and visit the Investigators and monitor data during the study.

Appendix 1 Clinical Laboratory Tests

- Local laboratory analysis (all patients) are detailed in Table 7.
- Central laboratory sampling for exploratory analysis (all patients) are detailed in Table 8.
- Extended Exploratory Cohort assessments (approximately 40 patients) are detailed in Appendix 2, Table 9, and Table 10.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Blood samples must be collected prior to administration of treatment.

Table 7 Local Laboratory Analysis (all patients, N=154)

Laboratory Assessments	Parameters		
Hematology	Red blood cell (RBC) Count Hemoglobin Hematocrit White blood cell (WBC) Count Platelet Count Absolute neutrophil count	<u>RBC Indices:</u> Mean corpuscular volume Mean corpuscular hemoglobin	<u>WBC count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry from serum or plasma[1]	Blood urea nitrogen (BUN)/Urea* Potassium Total and direct bilirubin Creatinine Sodium Albumin Chloride	Glucose (non-fasting) Calcium Alkaline phosphatase Aspartate aminotransferase (AST/GOT) Alanine aminotransferase (ALT/GPT) Lactate dehydrogenase Uric acid Thyroid panel (TSH and fT4)	
Other Screening Tests	• Hepatitis B surface antigen and hepatitis C virus antibody • Human chorionic gonadotropin pregnancy test (for women of childbearing potential)[2]		

NOTES:
[1] All events of ALT or AST ≥3 × upper limit of normal (ULN) AND bilirubin ≥2 × ULN, which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event.
[2] Local urine testing will be standard for the protocol unless serum or plasma testing is required by local regulation or Institutional Review Board/Independent Ethics Committee. If the urine test is positive or cannot be confirmed as negative, a serum or plasma pregnancy test will be required.
*Assessment of urea to be performed by sites where laboratories are not using BUN.
Total amount of blood for local analysis will be approximately 30 mL per patient.

Investigators must document their review of each laboratory safety report.

Table 8 Central Laboratory Sampling for Exploratory Analyses (all patients, N=154)

Treatment arm	**Visits**	**Laboratory assessments**	**Volume of blood collected**
Experimental arm	• Day 1 • Day 31 • Day 52 • Safety Follow-up • 18 weeks post last dose of induction therapy (2nd response follow-up visit)	• Blood for immune-related gene profiling based on cell-free plasma DNA and cellular genomic DNA • Blood for generation of plasma	95 mL blood over 5 visits
Control arm	• Day 1 • Day 43 • Day 64 • Safety Follow-up • 18 weeks post last dose of induction therapy (2nd response follow-up visit)	• Blood for immune-related gene profiling based on cell-free plasma DNA and cellular genomic DNA • Blood for generation of plasma	95 mL blood over 5 visits
	Total blood volume		**95 mL blood / patient**

Appendix 2 Extended Exploratory Cohort (N= approximately 40 patients)

Background

As part of the development and evaluation of the UV1 vaccine, a cohort of approximately 40 patients at selected sites will be asked to volunteer for additional biological sampling and analysis. The patients will have to sign a separate Informed Consent Form (ICF) to enroll in this part of the study. The analysis of the samples will aim to reveal how changes in biological markers, including tumor mutational burden (TMB), and T-cell receptor (TCR) repertoire diversity reflect the efficacy of the treatments. The goal is to further elucidate and characterize the immunological mechanisms induced with UV1 in combination with nivolumab and ipilimumab in blood and tumor.

Research Objectives and Assessments

A biobank will be established for current and future analysis of the samples collected. The specific research objectives include, but are not restricted to investigate if:

- UV1 vaccination in addition to ipilimumab and nivolumab: induce a broader repertoire of TCR specificities including epitopes not included in the UV1 vaccine compared to ipilimumab and nivolumab.
- UV1 vaccination in addition to ipilimumab and nivolumab: induces changes in the post-treatment TMB from the pre-treatment TMB compared to ipilimumab and nivolumab.
- UV1 vaccination in addition to ipilimumab and nivolumab: induces changes in the post-treatment immune cell infiltrate of the tumor from the pre-treatment immune cell infiltrate compared to ipilimumab and nivolumab.
- UV1 vaccination in addition to ipilimumab and nivolumab: induces vaccine-specific immune responses in blood.
- The microbial composition in feces pre-treatment affects response to treatment with UV1 vaccination in addition to ipilimumab and nivolumab compared to ipilimumab and nivolumab.
- UV1 vaccination in addition to ipilimumab and nivolumab: induces delayed-type hypersensitivity (DTH) responses.

Exploratory Endpoints

- Correlation in the change in TCR repertoire in blood over time to clinical response in both treatment arms.
- Correlation between vaccine-specific immune response in blood and clinical response in the UV1 in addition to ipilimumab and nivolumab arm.
- Correlation between DTH and clinical response in the UV1 in addition to ipilimumab and nivolumab arm.

- Change in the post-treatment TMB from pre-treatment TMB in both treatment arms.
- Change in composition of the immune cell infiltrate of the tumor post-treatment compared to pre-treatment in both treatment arms.
- Correlation of microbiologic composition of fecal samples to response to treatment in both treatment arms.

Target Population

Selected study sites that have the necessary laboratory facilities to collect and handle the requested lab samples can take part in the extended laboratory cohort part of the study. Patients eligible for the study will be offered to take part in the Extended Exploratory Cohort until the needed number of patients in the cohort is reached.

Discontinuation from Extended Exploratory Cohort

Patients can withdraw their extended exploratory cohort consent at any time without this affecting their care and treatment. These patients can continue in the main part of the study. In case of withdrawal of extended exploratory cohort consent, the patient can request all samples collected under this consent to be destroyed. Results from samples already analyzed will not be deleted.

Sample Collection and Assessments

The sample collection and assessments in the Extended Exploratory Cohort will be done in addition to those requested elsewhere per protocol. In the experimental arm these will be done during the Screening period, and at Days 1, 31, and 52. In the control arm these will be done during the Screening period, and at Days 1 and 43. In both treatment arms sample collection and assessment will also be done at the safety follow-up visit and 18 weeks post last dose of induction therapy. Sample type and assessments are described in Table 9 and Table 10 below.

Table 9 Extended Exploratory Cohort Assessments – Experimental Arm

Visit	Assessment	Volume of tissue collected
Screening	Fecal sample Tumor biopsy (FFPE biopsy) Tumor biopsy (Snap-frozen biopsy)	Dedicated sample card At the pathologist's decision (one biopsy) At the pathologist's decision (two snap-frozen)
Day 1	Whole blood for DNA SNP sample Whole blood for PBMC DTH[a]	3 mL blood 3 mL blood 80 mL blood Not applicable
Day 31	Whole blood for PBMC DTH[a]	80 mL blood Not applicable
Day 52	DTH[a]	Not applicable
Safety follow-up	Whole blood for PBMC Tumor biopsy (FFPE biopsy) Tumor biopsy (Snap-frozen biopsy) DTH[a]	80 mL blood At the pathologist's decision (one biopsy) At the pathologist's decision (two snap-frozen) Not applicable
18 weeks post last dose of induction therapy (2nd response follow-up visit)	Whole blood for PBMC DTH[a]	80 mL blood Not applicable
Total blood volume		**326 mL blood / patient**

Abbreviations: DNA = deoxyribonucleic acid; DTH = delayed-type hypersensitivity; FFPE = formalin fixed, paraffin embedded; PBMC = peripheral blood mononuclear cell; SNP = single nucleotide polymorphisms.
[a] UV1 without sargramostim intradermally in the skin of the anterior forearm. Patient will measure and record the skin reaction 48±4 hours after the injection.

Table 10 Extended Exploratory Cohort Assessments – Control Arm

Visit	Assessment	Volume of tissue collected
Screening	Fecal sample Tumor biopsy (FFPE biopsy) Tumor biopsy (Snap-frozen biopsy)	Dedicated sample card At the pathologist's decision (one biopsy) At the pathologist's decision (two snap-frozen)
Day 1	Whole blood for DNA SNP sample Whole blood for PBMC	3 mL blood 3 mL blood 80 mL blood
Day 43	Whole blood for PBMC	80 mL blood
Safety follow-up	Whole blood for PBMC Tumor biopsy (FFPE biopsy) Tumor biopsy (Snap-frozen biopsy)	80 mL blood At the pathologist's decision (one biopsy) At the pathologist's decision (two snap-frozen)
18 weeks post last dose of induction therapy (2nd response follow-up visit)	Whole blood for PBMC	80 mL blood
Total blood volume		**326 mL blood / patient**

Abbreviations: DNA = deoxyribonucleic acid; FFPE = formalin fixed; paraffin embedded; PBMC = peripheral blood mononuclear cell; SNP = single nucleotide polymorphisms.

Sample Processing, Shipping, and Storage

The study sites will receive a sampling kit and laboratory manual with instructions on sample collection and processing. Details on storage conditions will be provided in the laboratory manual.

Assessments

In the future, additional genes, biomarkers, and analysis methods of interest will most likely be identified. It is therefore important not to restrict the utilization of this biologic material to current knowledge and retain the possibility of conducting other investigations as well. However, based on current knowledge, it is planned to utilize the material in the manner described in the following sections.

Whole Blood for DNA

Exome sequencing of deoxyribonucleic acid (DNA) will be performed on blood samples collected before initiation of UV1 vaccination. The DNA from normal cells will serve as a basis for comparison to DNA sequence from tumor tissue, allowing to detect tumor-specific DNA alterations.

Use/Analysis of DNA

- Genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Board/Independent Ethics Committee allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to sargramostim and/or UV1 or metastatic malignant melanoma. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome in relation to sargramostim and/or UV1.
- DNA samples will be analyzed as described in Section 8.4.1. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data or help resolve issues with the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to sargramostim and/or UV1 or study treatment of this class to understand study disease or related conditions.
- The results of genetic analyses will be reported in a separate study addendum.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained while research on sargramostim and/or UV1 or study treatments of this class or indication continues but no longer than 5 years or other period as per local requirements.

Whole Blood for Analyses of Single Nucleotide Polymorphisms (SNPs)

Whole blood for analyses of SNPs will be taken prior to initiation of study treatment. Genomic DNA will be extracted and subsequently assessed for SNPs and other genetic variations in candidate genes that may predispose patients to benefit from the addition of UV1 vaccination to nivolumab and ipilimumab), or adverse events. Such genes include, but are not limited to hTERT, PD-1, PD-L1, PD-L2 and CTLA-4. Additional use of these data may include correlative analysis aimed at identifying genotypic associations with clinically relevant biomarkers identified by other methodologies.

Whole Blood for Peripheral Blood Mononuclear Cells (PBMCs)

Whole blood samples will be taken prior to initiation of study treatment and at designated timepoints for PBMC preparation. These samples may be used for immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T-cells, B cells, natural killer cells, myeloid-derived suppressor cells, or subpopulations of the aforementioned immune cell types. Additionally, these samples may be used for human leukocyte antigen typing, cytokine-release analyses, for functional immune cell tests, and characterization of the immune reactivity against tumor antigen.

Tumor Tissue Specimens

Tumor biopsies (formalin fixed, paraffin embedded [FFPE]) will form the basis for in situ characterization of the tumor and the tumor-microenvironment, including the tumor-infiltrating immune cells. The FFPE biopsies and snap-frozen biopsies will be used for DNA/RNA extraction and sequencing aiming at characterizing the immune contexture of the tumor, and to identify tumor-specific somatic mutations.

The biopsies should be collected from the *same lesion* at each timepoint of sampling (ie, it should be taken into consideration when selecting the lesion for tissue sampling that the lesion may shrink in response to therapy). Since heterogeneity within tumors is an issue, it should be aimed at sampling within the same area of the lesion at each sampling timepoint. If a previous biopsy site is noted in the specimen to be sampled, the biopsies should be taken from near that site, but not from the exact site, as biopsies may alter the biology of adjacent tissue. If the patient has only one target lesion, the biopsy should be taken either subsequent or at least 7 days prior to the screening imaging scan.

Biopsy samples should be excisional, incisional, or core needle. Punch biopsies are allowed as well. Fine needle aspirates or other cytology samples are only allowed after discussion with the Sponsor’s biomarker expert. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed.

Detailed instructions of the obtaining, processing, labeling, handling, storage, and shipment of specimens will be provided in a separate Laboratory Manual.

Fecal Samples

Fecal samples will be collected prior to treatment to evaluate the gut microbiome by use of PCR amplification of candidate gene sequences. Planned exploratory analyses are subject to changes in line with scientific understanding and technical development.

Delayed-type Hypersensitivity

Patients in the experimental arm will be asked to measure area of skin irritation on the skin of the anterior forearm and record it on a patient diary card (details to be explained to patient). This will be done 48 ±4 hours after each DTH test injection according to timepoints described in Table 9. A positive DTH test is defined as an erythema and/or induration ≥5 mm. The DTH patient diary card should be delivered to the study personnel at the next visit at the study site.

If a patient prematurely discontinues induction therapy, no more DTH testing will be performed for that patient.

Appendix 3 Eastern Cooperative Oncology Group Performance Status Scale

Eastern Cooperative Oncology Group Performance Status	
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 or 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.

Appendix 4 Response Evaluation Criteria in Solid Tumors and Immune Response Evaluation Criteria in Solid Tumors

RECIST 1.1 Response and Evaluation Endpoints

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with computed tomography (CT) scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-measurable Disease. All other lesions (or sites of disease), including small lesions, are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin, and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor lesion is present at Baseline, all lesions 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 and will be recorded and measured at Baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At Baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After Baseline, a value should be provided on the Case Report Form for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at Baseline and should be followed as “present” or “absent.”

Response. All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-progressive disease (PD). Confirmation of response is only required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression.

iRECIST Response Assessment

Overall response will be assessed using immune Response Evaluation Criteria in Solid Tumors (iRECIST). Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below.

Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1: **Comparison of RECIST 1.1 and iRECIST**

All responses defined using iRECIST criteria are designated with a prefix. The iRECIST timepoint and best overall responses will be recorded separately.

Confirming progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met in target, non-target disease, or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.

- RECIST 1.1 criteria are met in lesions types (target, non-target, or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or immune stable disease [iSD], immune partial response [iPR], or immune complete response [iCR] if those criteria are met compared to Baseline). Prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent timepoint assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD.

New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site), at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from Baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at Baseline. Rather, these measurements will be collected on a separate table in the Case Report Form.

Progressive disease is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD, confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Appendix 5 Abbreviations

AE	adverse event
AESI	adverse events of special interest
ADL	Activities of Daily Living
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BRAF	Gene encoding B-Raf protein
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
CTLA-4	anti-cytotoxic T-lymphocyte-associated protein-4
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DOR	duration of response
DTH	delayed-type hypersensitivity
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOS	end of study
FDA	Food and Drug Administration
FFPE	formalin fixed, paraffin embedded
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
hTERT	human telomerase reverse transcriptase
GOT	glutamic-oxaloacetic transaminase
GPT	glutamic-pyruvic transaminase
HIV	human immunodeficiency virus
HR	hazard ratio

HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intention-to-treat
iCPD	immune confirmed progressive disease
iCR	immune complete response
iPR	immune partial response
iRECIST	immune RECIST
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
NE	non-evaluable
NIMP	non-investigational medicinal product
NLNT	New Lesion-Non-Target
NLT	New Lesions-Target
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	anti-programmed cell death
PFS	progression free survival
PR	partial response
RBC	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
Q2W	every 2 weeks
Q3W	every 3 weeks

Q4W	every 4 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SNPs	single nucleotide polymorphisms
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
Th1	T-helper type 1
TMB	tumor mutational burden
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cells
WOCBP	women of childbearing potential

Appendix 6 References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394-424.
2. Ascierto PA, Simeone E, Sileni VC, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. *J Transl Med*. 2014 May 7;12:116.
3. Ahmad SS, Qian W, Ellis S, et al. Ipilimumab in the real world: the UK expanded access programme experience in previously treated advanced melanoma patients. *Melanoma Res*. 2015;25(5):432-442.
4. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2015 Jun 25;372(26):2521-2532.
5. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet*. 2017;390(10105):1853-1862.
6. Hamid O, Puzanov I, Dummer R, et al. Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma. *Eur J Cancer*. 2017;86:37-45.
7. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
8. Hersh EM, O'Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. *Invest New Drugs*. 2011;29(3):489-498.
9. Wilgenhof S, Du Four S, Vandenbroucke F, et al. Single-center experience with ipilimumab in an expanded access program for patients with pretreated advanced melanoma. *J Immunother*. 2013;36(3):215-222.
10. Ascierto PA, Del Vecchio M, Robert C, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2017;18(5):611-622.
11. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015 Jan 22;372(4):320-330.
12. Hamid O, Puzanov I, Dummer R, et al. Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma. *Eur J Cancer*. 2017;86:37-45.
13. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med*. 2015 Jul 2;373(1):23-34.
14. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018 Nov;19(11):1480-1492. doi: 10.1016/S1470-2045(18)30700-9. Epub 2018 Oct 22.

15. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019 Oct 17;381(16):1535-1546.

16. Vasef MA, Ross JS, Cohen MB. Telomerase activity in human solid tumors. Diagnostic utility and clinical applications. *Am J Clin Pathol*. 1999;112(1 Suppl 1): S68-75.

17. Mattson MP, Zhang P, Fu W. Roles for TERT and telomerase in cell differentiation and apoptosis. *Madame Curie Bioscience Database* [Internet]. 2000-2013.

18. Hiyama E, Hiyama K, Yokoyama T, Shay JW. Immunohistochemical detection of telomerase (hTERT) protein in human cancer tissues and a subset of cells in normal tissues. *Neoplasia*. 2001;3(1):17-26.

19. Kim NW, Piatyszek MA, Prowse KR, et al. Specific association of human telomerase activity with immortal cells and cancer. *Science*. 1994;266(5193):2011-2015.

20. Zanetti M. A second chance for telomerase reverse transcriptase in anticancer immunotherapy. *Nat Rev Clin Oncol*. 2017;14(2):115-128.

21. de Kok JB, Ruers TJ, van Muijen GN, et al. Real-time quantification of human telomerase reverse transcriptase mRNA in tumors and healthy tissues. *Clin Chem*. 2000;46(3):313-318.

22. Inderberg-Suso EM, Trachsel S, Lislerud K, Rasmussen AM, Gaudernack G. Widespread CD4+ T-cell reactivity to novel hTERT epitopes following vaccination of cancer patients with a single hTERT peptide GV1001. *Oncoimmunology*. 2012;1(5):670-686.

23. Suso EM, Dueland S, Rasmussen AM, et al. hTERT mRNA dendritic cell vaccination: complete response in a pancreatic cancer patient associated with response against several hTERT epitopes. *Cancer Immunol Immunother*. 2011 Jun;60(6):809-818.

24. Disis ML, Bernhard H, Shiota FM, et al. Granulocyte-macrophage colony-stimulating factor: an effective adjuvant for protein and peptide-based vaccines. *Blood*. 1996;88(1): 202-210.

25. Kaplan G, Walsh G, Guido LS, et al. Novel responses of human skin to intradermal recombinant granulocyte/macrophage-colony-stimulating factor: Langerhans cell recruitment, keratinocyte growth, and enhanced wound healing. *J Exp Med*. 1992;175(6): 1717-1728.

26. Kremer IB, Stevens SR, Gould JW, DiCarlo J, Quinby GE, Cooper KD. Intradermal granulocyte-macrophage colony-stimulating factor alters cutaneous antigen-presenting cells and differentially affects local versus distant immunization in humans. *Clin Immunol*. 2000;96(1):29-37.

27. Lilleby W, Gaudernack G, Brunsvig PF, et al. Phase I/IIa clinical trial of a novel hTERT peptide vaccine in men with metastatic hormone-naive prostate cancer. *Cancer Immunol Immunother*. 2017 Jul;66(7):891-901.

28. Brunsvig PF, Aamdal S, Gjertsen MK, et al. Telomerase peptide vaccination: a phase I/II study in patients with non-small cell lung cancer. *Cancer Immunol Immunother*. 2006;55(12):1553-1564.

29. Kyte JA, Trachsel S, Risberg B, thor Straten P, Lislerud K, Gaudernack G. Unconventional cytokine profiles and development of T cell memory in long-term survivors after cancer vaccination. *Cancer Immunol Immunother*. 2009;58(10):1609-1626.

30. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol*. 2016 Feb;39(1):98-106.

31. Wei SC, Levine JH, Cogdill AP, et al., Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell*. 2017;170(6):1120-1133.

32. Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials*. 2008;29(4):456-465.

33. Perez-Garcia A, Osca G, Bosch-Vizcaya A, et al. Kinetics of the CTLA-4 isoforms expression after T-lymphocyte activation and role of the promoter polymorphisms on CTLA-4 gene transcription. *Hum Immunol*. 2013;74(9):1219-1224.

34. Doyle AM, Mullen AC, Villarino AV, Hutchins AS, High FA, Lee HW, et al. Induction of cytotoxic T lymphocyte antigen 4 (CTLA-4) restricts clonal expansion of helper T cells. *J Exp Med*. 2001 Oct 1;194(7):893–902.

Appendix 7 Single Arm UV1 Cohort

Background and Rationale

Patients participating in the Extended Exploratory cohort of the study (Appendix 2) provide biological sample material including PBMCs and tumor tissue to answer the exploratory objectives of the INITIUM study. The material is used to test for immune response in blood and to characterize changes in the tumor and the tumor microenvironment. The PBMCs and tumor tissue from patients in the experimental arm of the extended exploratory cohort is needed for these analyses, as this material is used to identify changes in the tumor and tumor environment that are unique for the vaccine responders.

As an immunological response to the vaccine is not expected in all patients in the experimental arm of the extended exploratory cohort, and as all patients in this arm will not be able to provide a complete set of biological sample material, 20 additional patients will be enrolled in a single arm UV1 cohort and provide additional biological material to support the extended exploratory cohort. This will be done to secure that sufficient material is available to identify anti-tumor activity unique for the vaccine responders and thereby to strengthen the support from the mechanistical data to the clinical outcome data derived from all patients in the study.

Design and Methodology

20 patients at selected sites will be included in a single arm UV1 cohort. The inclusion of patients in this cohort will start after the 154 patients have been enrolled in the 2-armed randomized part of the study. All patients in this single arm UV1 cohort will receive UV1 vaccination in combination with nivolumab and ipilimumab.

If not described otherwise in Appendix 7, the patients will follow the same treatment schedule, visits and procedures as in the experimental arm described elsewhere in this study protocol. In addition, all patients in the single arm UV1 cohort will perform the biological sampling and procedures as described for the Extended Exploratory Cohort (Appendix 2). The patients will have to sign a separate Informed Consent Form (ICF) to enroll in this part of the study.

As in the randomized part of the study, this single arm UV1 cohort will consist of 3 phases: Screening, Induction period and a Follow-up period. The Follow-up period includes safety, response, and survival follow-up visits. The Response Follow-up visits will be performed until iCPD per iRECIST or until the end of study (whichever comes first). The Survival Follow-visits will be performed every 12 weeks from iCPD per iRECIST until the end of study.

Patients in the single arm UV1 cohort will not be randomized and will therefore not be included in the data used for analysis of primary and secondary endpoints.

Planned Timelines for the Single Arm UV1 Cohort:

First patient in:	H1 2022
Last patient in:	H1 2023

End of study: H1 2026

The first patient in is defined as the timepoint when the first patient is enrolled.

The estimated inclusion period is 9 months. All patients in the single arm UV1 cohort will be followed up until death or until the end of study (EOS), whichever comes first.

Target Population

Patients in the single arm UV1 cohort must meet all the inclusion criteria and none of the exclusion criteria as described in Sections 5.1 and 5.2. Only selected study sites that have the necessary laboratory facilities to collect and handle the requested lab samples can take part in this cohort.

After the patient has signed the ICF, the site will enter information into the IWRS which will assign a unique screening number. Once assigned, a screening number cannot be re-used for any reason. After a screening period of up to 28 days, eligible patients will be enrolled in the study using IWRS. Individuals who do not meet the criteria for enrollment (screen failures) may be re-screened once. Re-screened patients should be assigned a new screening number and re-consent.

Discontinuation from the Single Arm UV1 Cohort

Patients can withdraw their single arm UV1 cohort consent at any time without this affecting their care and treatment. The patient can request all samples collected under this consent to be destroyed. Results from samples already analyzed will not be deleted.

Sample Processing, Shipping, and Storage

The study sites will use the same laboratory manual and sampling kits as applicable for Extended Exploratory cohort. Details regarding sample collection, processing and storage conditions will be provided in the laboratory manual.

Adverse Event Reporting

The time periods for reporting of AEs and SAEs are outlined in Figure 4.

In the single arm UV1 cohort all SAEs should be reported from the first dose of induction therapy until the end of study or until new anticancer treatment is initiated (whichever comes first).

Appendix 8 Protocol Version Log

Protocol version 5.0 22 September 2023	**Changes**
Substantial amendment: Yes	Amended the protocol to modify the timing of reading the primary endpoint at 70 PFS events reached, to the earliest of either 70 PFS events reached or 18 months post last patient randomized. Updated sections: 1 Synopsis 4.1 Overall Design 6.2.3 New Anticancer Treatment Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 7.3.2 Response Follow-up Visits 7.3.3 Survival Follow-up Visits 7.6 End of Study 8.2 Safety Plan and Assessments 8.2.1 Independent Data Monitoring Committee 8.3.3 Adverse Event Reporting and Follow-up 9 Statistical Methods
	Amended the protocol to include updated information about the UV1/hTERT-MM-103 study (Ultimovacs is the sponsor) <u>Updated sections:</u> 2.4 Clinical Data on UV1 Vaccination 2.6 Rationale for Dose and Administration Regimen 2.8 Benefit/Risk Assessment
	Amended the protocol to include non-substantial amendment version 3.0, dated 14 December 2022: an amendment to ensure that the blinded independent central review (BICR) receives the required images needed for determination of progression per RECIST 1.1. Updated section: 7.3.2 Response Follow-up Visits
Protocol version 4.0 21 January 2022	**Changes**

Substantial amendment: Yes	Amended the protocol to include non-substantial protocol amendment version 1.0, dated 24 February 2021: a clarification of the measurements that are expected per protocol in the case of severe allergic reactions (Adverse Events of Special Interests). Updated sections: 8.3.3.2 Follow-up
	Amended the protocol to include non-substantial protocol amendment version 2.0, dated 07 September 2021: a clarification of prohibited medications during the induction period and which measurements that are expected in the case of discontinuation of induction therapy. Updated sections: 6.2.1 Prohibited Medications During Induction Period 7.2.1 Discontinuation of Induction Therapy
	Amended the protocol to mitigate the risk of hepatotoxicity in the study. Updated sections: Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 8.2.1 Independent Data Monitoring Committee
	Amended the protocol to include the single arm UV1 cohort where 20 patients will be enrolled for collection of additional biological material to support the Extended Exploratory Cohort of the study. Updated sections: 1 Synopsis 2.7 Rationale for Study Design 4.1 Overall Design 4.2 Measures to Minimize Bias: Randomization and Blinding 8.2.1 Independent Data Monitoring Committee Appendix 7 Single arm UV1 cohort - NEW
	Name of International Coordinating Investigator updated due to change Updated section: Page 2

	Updated planned timelines <u>Updated sections:</u> 1 Synopsis 4.1 Overall Design
	Table numbers corrected <u>Updated section:</u> 6.1.5 Administration of Study Drug
Protocol version 3.0 **02 November 2020**	**Changes**
Substantial amendment: Yes	Amended the protocol to reflect that from the time of 70 PFS events reached across both treatment arms, patients will be followed for a further 24 months for additional survival data; further analyses of OS data will be performed at 12 and 24 months to provide evidence supportive of PFS. <u>Updated sections:</u> 1 Synopsis 4.1 Overall Design 6.2.3 New anticancer treatment Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 7.2.1 Discontinuation of Induction Therapy 7.3.2 Response Follow-up visits 7.3.3 Survival Follow-up visits 7.6 End of study 8.2 Safety plan and assessments 8.3.3 Adverse event reporting and follow-up 9 Statistical methods
	Signature for International Coordinating Investigator added
	Amended planned number of patients in the extended exploratory cohort from N = 60 to N = approximately 40 <u>Updated sections:</u> 1 Synopsis 4.1 Overall Design

	Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 8.5 Extended exploratory cohort Appendix 1 Clinical Laboratory Tests Appendix 2 Extended exploratory cohort
	Text updated to clarify that Adverse Events of Special Interest should be reported regardless of which treatment arm the patient is randomized to. Text revised to clarify that events falling under the AESI definition must occur on the same day as sargramostim, UV1, nivolumab or ipilimumab administration. Updated section: 8.3.1.5 Definition of adverse event of special interest
	Text revised to allow sites to use either plasma or serum for the biochemistry analyses and pregnancy test. Updated sections: 1 Synopsis (Inclusion Criteria) 5.1 Inclusion Criteria 8.3.1.4 Potential Drug Induced Liver Injury (DILI) Appendix 1 Clinical Laboratory Tests
	Text updated to reflect the planned number of study sites in Europe and the United States Updated section: 1 Synopsis 4.1 Overall Design
	Text updated to clarify that unused portions of reconstituted sargramostim should be discarded. Updated section: 6.1.1 Sargramostim
	Text updated to clarify the visit scenario if a decision to discontinue induction therapy is done between two scheduled study visits. Clarification made on when to discontinue UV1 vaccination.

	Updated section: 7.2.1 Discontinuation of induction therapy
	Text updated to clarify the definition of the "end of study" Updated section: 7.6 End of study
	Text updated to clarify that a brief course of corticosteroids can be allowed even with doses >10 mg/day prednisone equivalents Updated section: 1 Synopsis (Exclusion Criteria) 5.2 Exclusion Criteria 6.2.2 Permitted medications during induction period
	Text updated to clarify what is defined as "completed treatment cycle" Updated section: 8.2.1 Independent Data Monitoring Committee
	Typing error corrected from "will be stratified" to "covariates" Updated section: 9.4.2.2 Secondary efficacy analyses
Protocol version 2.1 20 February 2020	**Changes**
Substantial amendment: No	Text revised to clarify that all SAEs should be reported until end of study or until new anticancer treatment is initiated (whichever comes first) Updated sections: 1 Synopsis 4.1 Overall Design 7 Study Duration and Schedule of Activities: Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 7.2.1 Discontinuation of Induction Therapy 8.3.3.1 Reporting and Figure 3

	Clarification of when a vasectomized partner is an acceptable highly effective contraception method Updated sections: 1 Synopsis (*Inclusion Criteria*) 5.1 Inclusion Criteria
	Typing error corrected from "iPD" to "iCPD" Updated section: 7.3.3 Survival Follow-up Visits
	Minor typing errors corrected Updated section: Appendix 7 Protocol Version Log
Protocol version 2.0 27 January 2020	**Changes**
Substantial amendment: Yes	Amended safety data collection. Revised to include collection of all serious AESIs until the end of the study, in both treatment arms, and regardless of the investigator's causality assessment Updated sections: 1 Synopsis 4.1 Overall design 7 Study Duration and Schedule of Activities: Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 7.2.1 Discontinuation of Induction Therapy 8.3.1.5 Definition of Adverse Event of Special Interest 8.3.3.1 Reporting and Figure 3
	Amended to accurately describe what is highly effective contraceptive methods Updated sections: 1 Synopsis (*Inclusion Criteria*) 5.1 Inclusion Criteria

	The IDMC meeting schedule has been amended with an additional third meeting and to allow for review of patients in both treatment arms. The primary responsibility of the IDMC has been more clearly described. Updated section: 8.2.1 Independent Data Monitoring Committee
	Text revised to align with the wording used for BRAF/MEK inhibitors in section 5.2 exclusion criteria Updated section: 1 Synopsis (*the exclusion criteria*)
	Text revised to clarify that Overall Survival will be analyzed at the end of the study, which is defined by having reached 70 PFS endpoints across both study arms. Updated sections: 1 Synopsis 9.5 Timing of Analyses *(new section)*
	Clarification that the UV1 vaccination will be permanently discontinued if nivolumab and/or ipilimumab is temporarily or permanently discontinued. Updated section: 7.2.1 Discontinuation of Induction Therapy
	Text revised to clarify that patients who continue with survival follow-up visits will be contacted per phone (or, at the Investigator's discretion visit the hospital) Updated sections: 1 Synopsis *(study design and methodology)* 4.1 Overall design 7 Study Duration and Schedule of Activities: Table 5 Schedule of Activities – Experimental arm Table 6 Schedule of Activities – Control arm 7.3.3 Survival Follow-up visits
	Text revised to clarify the timing of the biopsy sampling at screening Updated sections: 7 Study Duration and Schedule of Activities: Table 5 Schedule of Activities – Experimental arm

	Table 6 Schedule of Activities – Control arm Appendix 2, Tumor Tissue Specimen
	Text revised to reflect that the patient may continue with maintenance therapy if withdrawing the informed consent form Updated section: 7.4 Withdrawal of Consent
	Deleted collection of respiratory rate. Updated section: 8.2.3 Vital Signs
	Clarification of what is considered a clinically significant laboratory abnormality. Updated sections: 8.3.1.1 Definition of AE 8.3.1.2 Events Not Meeting the AE Definition
	Deleted and revised Clinical Study Protocol signature/declaration pages to reflect the signature roles required

Declaration of the National Coordinating Investigator

Title: A Randomized 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)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in October 2013 and the guidelines on Good Clinical Practice.

National Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Principal Investigator

Title: A Randomized 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)

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, electronic Case Report Form, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the participants.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Responsible Principal Investigator of the local study center

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number