CLINICAL STUDY PROTOCOL

Protocol Name:	**ONCOS C824**
Title:	**A Pilot Study of Sequential ONCOS-102, an Engineered Oncolytic Adenovirus Expressing GM-CSF, and Pembrolizumab in Patients with Advanced or Unresectable Melanoma Progressing after PD1 Blockade**
Clinical Phase:	**I**
Version:	**6.0 Final**
Date:	**12Nov 2018**
Sponsor:	**Targovax Oy**

Statement about proper study conduct

This study will be conducted in compliance with Good Clinical Practices, according to ICH Harmonized Tripartite Guideline.

Confidentiality Statement

The information in this document is provided to you as an investigator, potential investigator, consultant, or contractor, for review by you, your staff, and the appropriate Institutional Review Board or Ethics Committee. By accepting this document, you agree that the information contained herein will not be disclosed to others without written authorization from the lead site/sponsor, except to the extent necessary to initiate the study or conduct study-related activities.

CLINICAL STUDY PROTOCOL APPROVAL

PROTOCOL TITLE:	**A Pilot Study of Sequential ONCOS-102, an Engineered Oncolytic Adenovirus Expressing GM-CSF, and Pembrolizumab in Patients with Advanced or Unresectable Melanoma Progressing after PD1 Blockade**
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This protocol has been approved by:

_____ _____

Magnus Jäderberg **Date**
Chief Medical Officer

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Alexander Shoushtari **Date**
Coordinating/Principal Investigator

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This protocol has been approved by:

[redacted] **Date**

Biostatistician

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1 ADMINISTRATIVE STRUCTURE AND CONTACT INFORMATION

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Contract Research Organization (CRO) for study management:
[redacted]

Biostatistician: [redacted]

2 ABBREVIATIONS

List of Abbreviations and definitions of terms:

AE	Adverse event
AST, SGOT	Aspartate aminotransferase
ALT, SGPT	Alanine aminotransferase
ATAP	Advanced Therapy Access Program
BB-IND	Biological-Based Investigational New Drug
BSL	Biosafety level
BUN	Blood urea nitrogen
CI	Confidence interval
CPI	Checkpoint inhibitor
CPO	Cyclophosphamide
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony stimulating factor
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalised ratio
irAE	Immune-related adverse events
IRB	Institutional Review Board
irRECIST	Modified immunologically relevant RECIST
i.t.	intratumoral
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MHC-1	Major histocompatibility complex 1
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
PB	Privacy board
PBMC	Peripheral blood mononuclear cells

PD1	Programmed cell death protein 1
PPR	Protocol Participant Registration
RA	Research authorization
RECIST	Response Evaluation Criteria In Solid Tumors
RR	Response rate
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocytes
TSH	Thyroid stimulating hormone
TVEC	Talimogene laherparepvec
ULN	Upper Limit of Normal
VP	Viral particles
WHO	World Health Organization

3 PROTOCOL SYNOPSIS

Name of sponsor/company: Targovax Oy
Study identification code: ONCOS C824
Title of the study: A Pilot Study of Sequential ONCOS-102, an Engineered Oncolytic Adenovirus Expressing GM-CSF, and Pembrolizumab in Patients with Advanced or Unresectable Melanoma Progressing after PD1 Blockade
Investigational product: ONCOS-102 (Ad5/3-D24-GMCSF)
Study duration: The study duration includes a recruitment phase of [redacted] and a treatment phase of [redacted]
Phase of development: I
Participating countries and number of sites: Patients enrolled in the study will be recruited at 2-4 sites in the United States and Europe.
Number of patients: In total, up to a maximum of 24 patients will be enrolled. The study will be divided in two parts; Part 1 and Part 2. Part 1: approximately 6-12 patients will receive sequential treatment with ONCOS-102 followed by pembrolizumab. Part 2: approximately 6-12 patients will receive an initial treatment phase with ONCOS-102 followed by a treatment phase with ONCOS-102 in combination with pembrolizumab. The patients will be divided into two cohorts: • patients with prior anti-Programmed cell death protein 1 (anti-PD1) monotherapy • patients with prior anti-PD1 and ipilimumab therapy given sequentially or concomitantly.
Study objectives: **Primary Objective** **Part 1:** • To determine the safety of sequential treatment with ONCOS-102 followed by pembrolizumab. **Part 2:** • To determine the safety of an initial treatment phase with ONCOS-102 followed by a treatment phase with ONCOS-102 in combination with pembrolizumab.

Secondary Objectives

- To estimate the objective response rates (ORR) by RECIST 1.1 and irRECIST.
- To investigate changes in immune cell subsets in tumor tissue and peripheral blood before, during and after treatment.
- To estimate correlation of Tumor Infiltrating Lymphocytes (TILs) and ORR.
- To estimate PFS by RECIST 1.1 and irRECIST.
- To estimate the clinical benefit rate at 27 weeks, defined as any confirmed objective response by RECIST 1.1 or stable disease lasting at least until week 27.
- To estimate the clinical benefit rate at 27 weeks, defined as any objective response by irRECIST criteria or immune-related stable disease lasting at least until week 27.
- To estimate the change in size in individual lesions.

Exploratory Objectives

- To investigate somatic mutational rate and neoepitope burden in tumors and explore relationship to response.
- To investigate changes in T-cell receptor clonality in infiltrating and circulating T-cells.
- To investigate gene expression changes in the tumor microenvironment and peripheral blood.

Study design:
This is a Phase 1 study exploring the safety and immune activation of sequential treatment with ONCOS-102, an engineered oncolytic adenovirus expressing granulocyte-macrophage colony stimulating factor (GM-CSF), primed with cyclophosphamide (CPO) bolus, and followed by pembrolizumab (**Part 1**) in patients with advanced melanoma who have progressed despite prior pembrolizumab or nivolumab with or without ipilimumab.
A second study part (**Part 2**) will explore safety and immune activation after an initial treatment phase with ONCOS-102, primed with cyclophosphamide (CPO) bolus, followed by a treatment phase with ONCOS-102 in combination with pembrolizumab.

Part 1: Patients will receive 3 doses of intratumoral (i.t.) injection of ONCOS-102 (days 1, 4, and 8) at $3x10^{11}$ viral particles (VP), preceded by intravenous (i.v.) cyclophosphamide priming 1-3 days prior to day 1. They will then receive pembrolizumab according to institutional practice (2mg/kg or 200mg flat dose) on day 22 (Week 3) and every 3 weeks thereafter until the end of treatment visit on day 169 (Week 24) or until unacceptable toxicity or clinically relevant disease progression, whichever occurs first. Safety of the sequential treatment with ONCOS-102 and pembrolizumab will be evaluated starting at baseline and continuing for a 9 week dose limiting toxicity (DLT) monitoring period. Possible DLTs will be assessed by a safety review committee. Imaging will be done at baseline, Weeks 9, 18 and 27. Tumor biopsies and blood are collected to analyze immune activation. Tumor biopsies

will be performed at baseline, Week 3 (day 22), and Week 9 (day 64) and blood will be collected regularly throughout the study. Swabs of the injection site will be analyzed for viral shedding at baseline and at 4 consecutive time points. The study will be deemed complete when the patient returns for end of study assessments at Week 27 (day 190).

Part 2: Patients will first receive intravenous (i.v.) CPO priming 1-3 days prior to Day 1. Subsequently 4 doses of intratumoral (i.t.) injections of ONCOS-102 (Days 1, 4, 8 and 15) at $3x10^{11}$ viral particles (VP) will be given followed by ONCOS-102 in combination with Pembrolizumab starting on Day 22/Week 3 and every three weeks thereafter until Day 169/Week 24 or until unacceptable toxicity or clinically relevant disease progression, whichever occurs first. Pembrolizumab will be given according to institutional practice (2mg/kg or 200mg flat dose) until Day 190/Week 27. Safety of the initial treatment phase with ONCOS-102 followed by a treatment phase with ONCOS-102 and pembrolizumab will be evaluated starting at baseline and continuing for a 9 week dose limiting toxicity (DLT) monitoring period. Possible DLTs will be assessed by a Safety Review Committee. Imaging will be done at baseline, Week 9, 18 and 27. Tumor biopsies and blood are collected to analyze immune activation. Tumor biopsies will be performed at Week 1 (day 1), Week 3 (day 22), and Week 9 (day 64) and blood will be collected regularly throughout the study. Swabs of the injection site will be analyzed for viral shedding at Week 1 (day 1) and at another four time points. The patient's study period will be deemed complete when the patient returns for End of Study assessments at Week 27 (day 190).

Subject population:

Criteria for inclusion:

- Adults 18 years of age or older.
- Histopathologically confirmed melanoma with an injectable cutaneous or lymph node metastasis that has progressed in the opinion of the treating investigator despite administering a Food and Drug Administration (FDA) approved anti-PD1 agent, with or without ipilimumab.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
- Measurable disease according to RECIST 1.1.
- Acceptable coagulation status: international normalised ratio (INR) of blood clotting, prothrombin time and activated partial thromboplastin time within ≤1.5 x upper limit of normal (ULN).
- Completion of local therapy, such as radiation, surgical resection, injectable immune-based therapy, or topical pro-inflammatory agent, 21 days prior to first dose of protocol therapy.
- Adverse events from previous cancer therapies (excluding alopecia) must have recovered to grade 1 (CTCAE, most recent version). Stable grade 2 AEs such as endocrine conditions are allowed, and other chronic stable AEs may be considered on a case by case basis by the Principal Investigator.

- Clinical stability of brain metastases for at least 4 weeks prior to first day of study therapy.
- Acceptable liver and renal functions defined as:
  - Total bilirubin ≤1.5 x ULN (does not include patients with Gilbert's Disease)
  - Aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT) ≤3.0 x ULN
  - Serum creatinine ≤1.5 x ULN
- Acceptable haematological function defined as (Patients can be transfused to meet the haemoglobin entry criteria):
  - Haemoglobin ≥ 9g/dL
  - Neutrophils ≥1.5 x 10^9/L
  - Platelet count ≥75 x 10^9/L
- Able to provide valid written informed consent.
- All women of childbearing potential must have a negative urine or serum pregnancy test at screening.
- All patients must agree to use barrier contraception (i.e. condom) during study treatment and for 2 months after the last virus treatment and 4 months after the last dose of chemotherapy and pembrolizumab.

Criteria for exclusion:

- A concomitant medical condition requiring receipt of a therapeutic anticoagulant that in the opinion of the treating physician cannot safely allow for therapeutic injection of ONCOS-102 and tumor biopsies. Local clinical practice can be followed with regard to holding a therapeutic anticoagulant during invasive procedures such as biopsies.
- A concomitant medical condition that in the opinion of the treating physician would pose unreasonable additional risk to therapeutic injection of ONCOS-102.
- Receipt of Investigational agents within 28 days prior to first dose of protocol therapy.
- Any symptomatic autoimmune disease (such as lupus, scleroderma, Crohn's disease, ulcerative colitis) that requires administration of >10mg of prednisone equivalent. Lower dose steroids for conditions such as hypophysitis are allowed.
- Any prior severe adverse event attributed to prior anti-PD1 therapy that, in the principal investigator's opinion, would contraindicate pembrolizumab administration such as:
  - Grade 2 or higher pneumonitis
  - Grade 4 AST or ALT elevation
  - Grade 3 or higher colitis attributable to PD1 blockade; note that colitis attributable to ipilimumab is not excluded

- Note: in the absence of clinical symptoms of pancreatitis, elevations of amylase or lipase are not contraindications to therapy on this trial
- Known active infection with Hepatitis B Virus, Hepatitis C Virus, or HIV. Cleared HBV/HCV infection is not an exclusion, nor is HIV infection with CD4 counts >500 and an undetectable viral load.
- Active bacterial, viral, or fungal infections, requiring systemic therapy apart from anti-viral maintenance therapy for HIV.
- History of organ transplant.
- Patients requiring chronic systemic immunosuppressants, including steroids (prednisone daily equivalent of >10 mg).
- Brain metastases that are clinically unstable (e.g. showing unequivocal growth on imaging, requiring radiation therapy, or steroids >10mg of prednisone equivalent) within 4 weeks of first dose of study drug.
- Known severe congenital or acquired cellular or humoral immunodeficiency such as common variable immunodeficiency.
- Women who are pregnant or breast-feeding currently or are planning to conceive during or up to 4 months after the end of protocol therapy.

Investigational medicinal product, dose and form of administration: Patients will receive ONCOS102 (Ad5/3-D24-GMCSF) at $3x10^{11}$ virus particles (VP) [redacted]

Patients will also be administered CPO as an i.v. bolus of 300 mg/m^2, 1 to 3 days before the day 1 administration of ONCOS-102.

Reference therapy, dose and mode of administration:
Patients will receive pembrolizumab i.v. according to institutional practice (2mg/kg or 200mg flat dose) on day 22 (Week 3) and every 3 weeks thereafter.

Duration of treatment:
In the first part of the study (Part 1), the patients will receive 3 doses of ONCOS-102 (days 1, 4 and 8). Pembrolizumab will be given in 21-day cycles starting on Day 22. Patients will continue treatment until emergence of unacceptable toxicity related to any of the drugs given, other side effects, clinically relevant disease progression requiring alternative therapy as assessed by the patient's Investigator, or until the patient reaches the End of Treatment visit at Week 24 (day 169).

In the second part of the study (Part 2), the patients will receive 4 doses of ONCOS-102 (day 1, 4, 8 and 15) during the initial treatment phase. Subsequently, ONCOS-102 will be given in combination with Pembrolizumab on Day 22, Day 43, Day 64, Day 85, Day 106, Day 127, Day 148 and Day 169. Patients will continue treatment until emergence of unacceptable

toxicity related to any of the drugs given, other side effects, clinically relevant disease progression requiring alternative therapy as assessed by the patient's Investigator, or until the patient reaches the End of Study visit at day 190/Week 27.
Baseline and screening assessments: Demography, medical and medication history, physical examination, vital signs (blood pressure, pulse, body temperature, weight), Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO) performance status, routine laboratory testing (haematology, clinical chemistry, urinalysis), computed tomography (CT) or magnetic resonance imaging (MRI), digital photographs of tumors, tumor biopsy, collection of blood (Peripheral blood mononuclear cells (PBMCs), serum and whole blood) as well as assessment of viral shedding (injection site).
Efficacy assessments: Tumor response assessed by diagnostic CT or MRI, Objective response rate (ORR), Progression-free survival (PFS), clinical benefit rate at 27 weeks, size of lesions. Tumor size may be followed by digital photographs. Immune activation in tumor biopsies and peripheral blood mononuclear cells.
Safety assessments: Adverse events, physical examination, vital signs, routine laboratory safety variables, ECOG/WHO performance status.
Statistics: The results from this study will be presented using descriptive statistical methods. Data will be presented by time of measurement, dosing regimen and cohort. Continuous variables will be described using standard summary statistics such as number of observations, mean value, standard deviation, minimum and maximum value and median. Categorical variables will be summarized in frequency tables as counts and percentages. All individual data collected will be presented in data listings.

4 BACKGROUND AND STUDY RATIONALE

4.1 Efficacy of Standard Immune Checkpoint Inhibitors in Metastatic Melanoma

Research into the immune system and its influence on tumor growth has led to significant clinical advancements in the treatment of advanced malignant melanoma. With the clinical introductions of checkpoint inhibitors (CPIs) such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade (ipilimumab) and PD-1 blockade (pembrolizumab, nivolumab), both response rates (RR) and OS have been improved. Hodi et al. (NEJM 2010) reported a RR of 11% and a 1 year OS of 46% for ipilimumab. Further improvements have been seen with nivolumab and pembrolizumab. Topalian et al. (JCO 2014) reported a RR of 31% for nivolumab with a 1 year OS of 62% while Kefford et al. (ASCO 2014) presented data on pembrolizumab showing a RR of 34% and a 1 year OS of 69%. Further increases in efficacy have been seen with combined ipilimumab plus nivolumab, with a RR of 61% and a 1year OS rate of >80% (Sznol et al. 2014). However, despite significant clinical advancements, at least 40% of patients with advanced malignant melanoma do not respond to CPIs, and a higher percentage are likely to require further systemic therapy following CPIs. Furthermore, even those who respond to CPIs may have eventual progression.

4.2 Mechanisms of response to CPIs

Research into tumor resistance to CPI are focused on either tumor-intrinsic factors such as mutational burden (Snyder et al. 2014; Rizvi et al. 2015) or the tumor microenvironment, specifically lymphocyte infiltration and expression of PD-L1 (Tumeh et al. 2014). In the latter report, pre-existing intratumoral CD8+ lymphocyte density was the best predictive marker for response to pembrolizumab in a study of 46 patients with metastatic melanoma. A larger study of 277 patients with a variety of incurable cancers including malignant melanoma showed that pre-existing anti-tumor immunity and PD-L1 expressing tumors were associated with the best efficacy in response to treatment with MPDL3280A, a PD-L1 blocker (Herbst et al. 2014).

These data suggest that a mechanism that can boost infiltration of activated CD4+ and CD8+ T cells and reduce immune-tolerant M2 macrophages and regulatory T cells (Tregs) may increase the efficacy of these interventions. As the median duration of clinical follow-up increases, we are also noting the development of isolated or multifocal progression of disease following initial response to PD1 blockade. These mechanisms of tumor 'escape' from immune-mediated surveillance have yet to be elucidated in great detail, although recently, investigators have suggested mechanisms such as active T-cell exclusion via beta-catenin signaling (Spranger et al. 2015). Again, this suggests that a rational approach to overcoming some cases of resistance to CPI would be to utilize a local therapy, such as an oncolytic virus, to enhance local immune infiltration with cytotoxic T cells in CPI-resistant or 'escape' lesions.

4.3 Oncolytic Viruses as therapy in Metastatic Melanoma

The most advanced studies of oncolytic viruses in metastatic melanoma have occurred with talimogene laherparepvec (TVEC). This is a modified type-1 herpes simplex virus engineered to express granulocyte monocyte colony stimulating factor (GM-CSF) that is injected into lesions to stimulate an immune response. A phase I trial of TVEC in 30 patients with

cutaneous or subcutaneous metastases from a variety of malignancies (breast, head and neck, melanoma, gastrointestinal) who had failed prior therapy demonstrated the safety of this approach (Hu et al. 2006). A subsequent phase II study of 50 patients with cutaneous metastases from melanoma demonstrated an overall response rate of 26% and revealed responses of metastases that were not injected (Senzer et al. 2009). Correlative analyses suggested that response in metastases that were not injected were due to immunologic effects of TVEC (Kaufman et al. 2010).

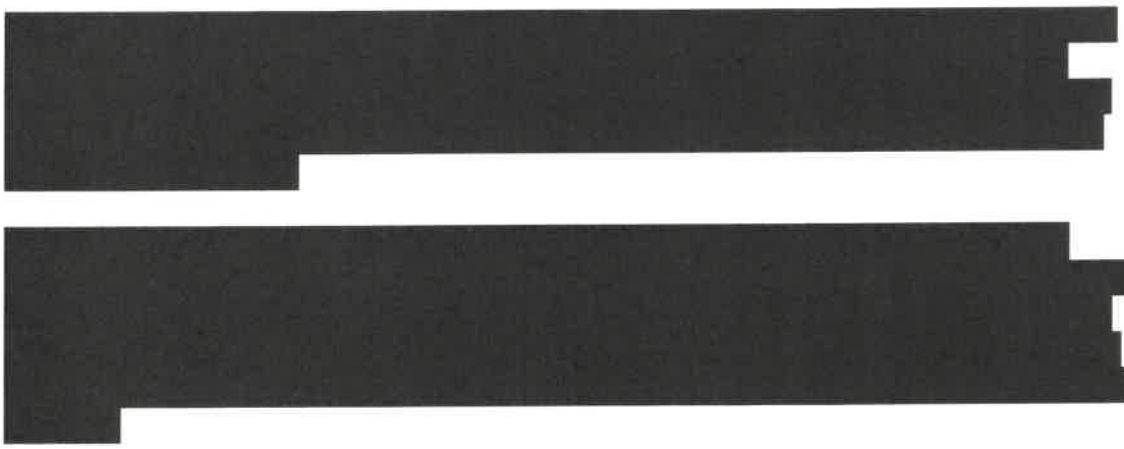
Results of a phase III study of TVEC versus GM-CSF for patients with unresectable stage IIIB-IV melanoma have recently been published, and demonstrated a durable response rate (systemic objective response lasting 6 months or more within the first 12 months) of 16.3% (95% CI 12.1 - 20.9%), with a trend toward improved overall survival, HR 0.79 (95% CI 0.62 – 1.00, p = 0.051) (Andtbacka et al. 2015). Responses were seen most often at the site of the injected cutaneous metastasis (64.3%), but also in non-injected cutaneous metastases (33.7%), and non-injected visceral metastases (15.2%). Based on these data, in October 2015, TVEC was approved by the FDA for treatment of metastatic melanoma, providing a proof of concept that oncolytic therapy is efficacious in metastatic melanoma. TVEC is now marketed under the name Imlygic.

4.4 Rationale for Using Adenoviral Intratumoral Injection of GM-CSF

Adenoviruses are excellent immunotherapeutic agents with a unique ability to prime and boost immune responses. Recombinant adenoviruses cause immunogenic cancer cell death and subsequent release of tumor antigens for antigen presenting cells, resulting in the priming of potent tumor-specific immunity (Ranki et al. 2014; Vassilev et al. 2015). This effect may be further enhanced by immune-stimulating transgenes expressed by the virus. ONCOS-102 is a granulocyte-macrophage colony stimulating factor (GM-CSF)-expressing oncolytic adenovirus, Ad5/3-D24-GMCSF.

[redacted]

- [redacted]
- [redacted]



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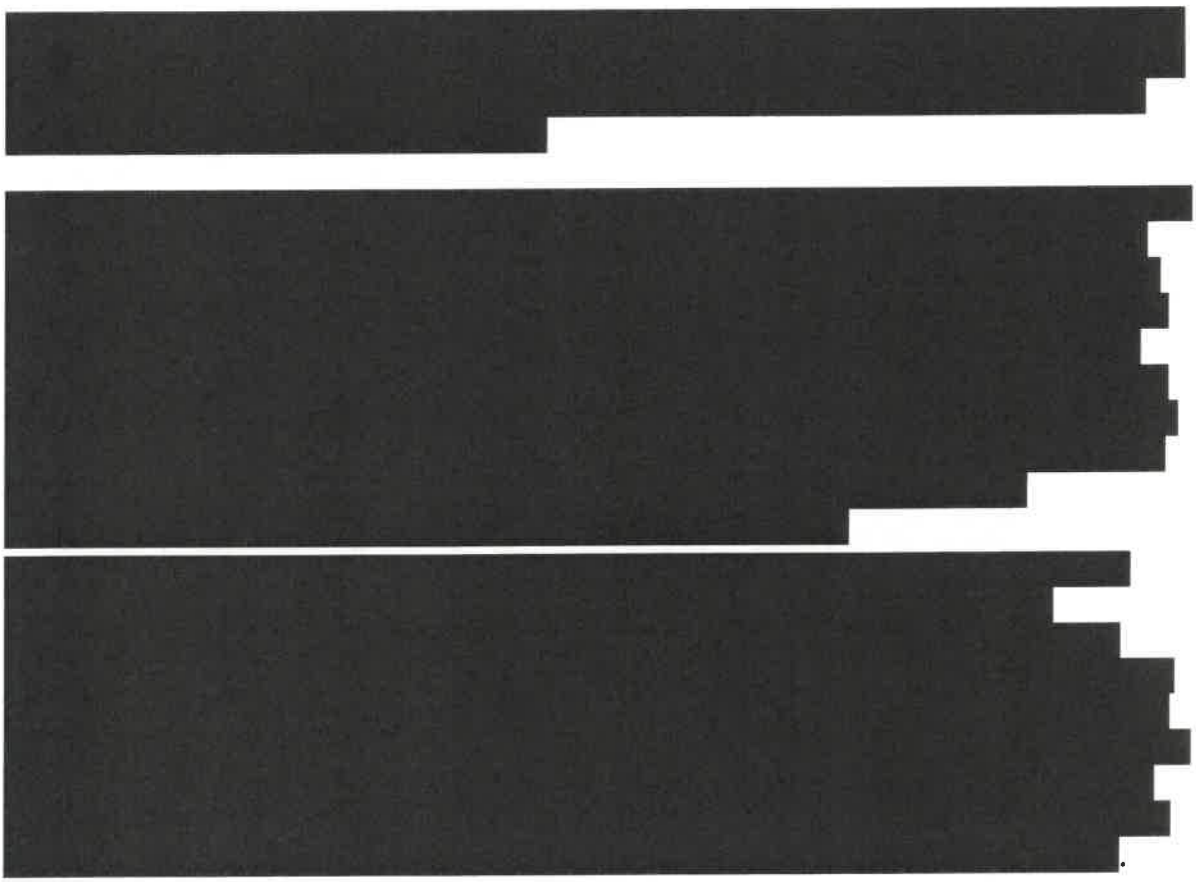
4.5 Previous experience with ONCOS-102

Antitumor activity of ONCOS-102 has been demonstrated in numerous melanoma cell lines in vitro as well as in human xenograft mouse model alone and in combination with cyclophosphamide (Bramante et al. 2015).



4.6 Justification of the Dosing Regimen

[redacted]

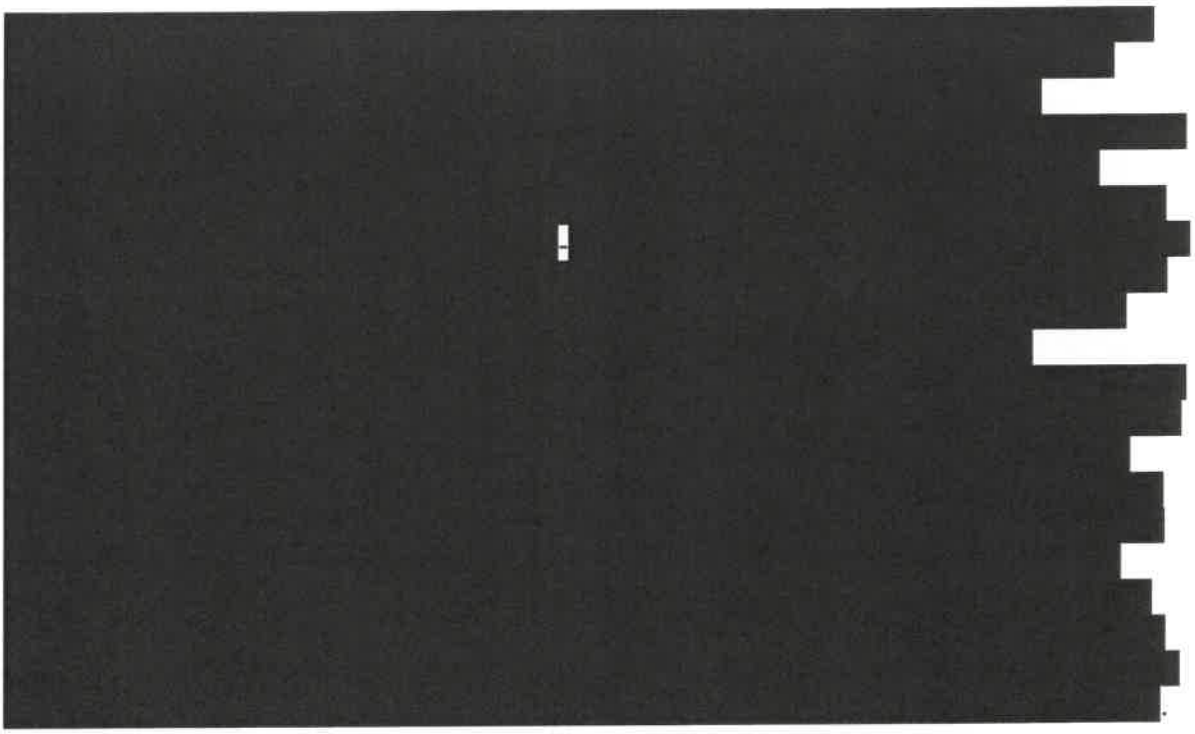
4.7 Rationale for the Study

In the Phase 1 study of 12 patients with late stage progressive solid tumors, where ONCOS-102 was administered mono-therapeutically 9 times, 10 out of 12 had post baseline imaging, and 40% had stable disease at 3 months and the treatment resulted in infiltration of CD8+ lymphocytes to tumor lesions in 11 of 12 patients. Concomitant systemic induction of a variety of tumor-specific CD8+ T-cell populations was seen in two patients while an increased expression level of lesional PD-L1 was seen in 10 out of 12 patients post ONCOS-102 (Pesonen et al. 2014).

[redacted]

In summary, first-line therapy for many patients with advanced melanoma consists of either PD1 blockade as monotherapy or combined with CTLA-4 blockade, and objective response rates range from 25-61% (Ribas et al. 2015, Hamid et al. 2013, Larkin et al. 2015, Postow et al. 2015, Weber et al. 2015). These responses are generally durable, lasting 1.5 to 2 years. Once relapse has occurred, there are no standard immune-based therapies. For the majority of tumors that do not harbour a BRAF V600 mutation, there are no standard therapies that have demonstrated any survival benefit, even in the front-line setting. For this reason, novel clinical trial options for these patients are sorely needed. Select patients may have isolated regions of resistance to immune CPI therapy that may be overcome with co-administration of an oncolytic virus and continued CPI.

[redacted]



5 STUDY OBJECTIVES

Primary Objective

Part 1

- To determine the safety of sequential treatment with ONCOS-102 followed by pembrolizumab.

Part 2

- To determine the safety of an initial treatment phase with ONCOS-102 followed by a treatment phase with ONCOS-102 in combination with pembrolizumab

Secondary Objectives

- To estimate the objective response rates (ORR) by RECIST 1.1 and irRECIST.
- To investigate changes in immune cell subsets in tumor tissue and peripheral blood before, during and after treatment.
- To estimate correlation of TILs and ORR.
- To estimate PFS by RECIST 1.1 and irRECIST.
- To estimate the clinical benefit rate at 27 weeks, defined as any confirmed objective response by RECIST 1.1 or stable disease lasting at least until week 27.
- To estimate the clinical benefit rate at 27 weeks, defined as any objective response by irRECIST criteria or immune-related stable disease lasting at least until week 27.
- To estimate the change in size in individual lesions.

Exploratory Objectives

- To investigate somatic mutational rate and neoepitope burden in tumors and explore relationship to response.
- To investigate changes in T cell receptor clonality in tumor infiltrating and circulating T cells.
- To investigate gene expression changes in the tumor microenvironment and peripheral blood.

6 STUDY DESIGN AND DESCRIPTION OF THE STUDY

6.1 Endpoints

Primary Endpoint:

- Safety for the duration of the therapy.

Secondary Endpoints:

- Objective responses by RECIST 1.1 and irRECIST criteria.
- [redacted]
- [redacted]
- PFS by RECIST 1.1 and irRECIST criteria
- Clinical benefit rate, defined as subjects who are not in progression by RECIST 1.1 at 27 weeks.
- Clinical benefit rate, defined as subjects who are not in progression by irRECIST at 27 weeks.
- Change in size in individual lesions.

Exploratory Endpoints:

- Analysis of somatic mutational rate and neoepitope burden in relation to response.
- Changes in T-cell receptor clonality in tumor infiltrating and circulating T-cells.
- Gene expression analysis on biopsied tumor tissue and peripheral blood at baseline and subsequent collection time points.

6.2 Study Design

Part 1 of this study is a prospective, open-label, pilot safety study of sequential ONCOS-102 injection with cyclophosphamide priming followed by pembrolizumab.
Part 2 of this study is a prospective, open-label, pilot safety study of an initial treatment phase with ONCOS-102 injection primed with CPO, followed by a treatment phase with ONCOS-102 and pembrolizumab.

The study will include patients with advanced or unresectable melanoma who have had progression following PD1 blockade as monotherapy or in combination with ipilimumab with at least 1 cutaneous or lymph node amenable to injection with ONCOS-102.

In Part 1 of the study: The primary objective is to determine the safety of the sequential treatment with ONCOS-102 and pembrolizumab starting at baseline and continuing for a 9 week DLT monitoring period.
In Part 2 of the study: The primary objective is to determine safety of initial treatment phase with ONCOS-102 followed by a treatment phase with ONCOS-102 and pembrolizumab. The

DLT monitoring period starts at baseline and continues for 9 weeks. [redacted] Suspected DLTs will be assessed continuously by a safety review committee.

In Part 1 of the study:

Patients will undergo standard radiologic and clinical screening. Following screening, eligible patients will receive a 300 mg/m^2 i.v. bolus of cyclophosphamide 1-3 days prior to the first of 3 injections of ONCOS-102. 2.5mL of ONCOS-102 will be injected into accessible tumor(s) a[redacted] on days 1, 4, and 8. The dose at each timepoint will be 3x10^{11} VP. Pembrolizumab will be administered according to institutional practice (either 2mg/kg or flat dosing at 200mg) starting at Week 3 (day 22) and continue every 3 weeks. [redacted]. Photographs will be taken to document location, size and possible changes to tumors at baseline and as applicable throughout the study. The study will be deemed complete when the patient returns for end of study assessments at Week 27 (day 190). Following week 27, the patient may continue receiving pembrolizumab outside of the context of the protocol. Safety Laboratory Variables and Vital signs will be evaluated and Physical examination performed regularly throughout the study. [redacted]. Please see Figure 1 for a schematic of the study.

Figure 1. Schematic of study interventions – Part 1
BL=Baseline, CPO=Cyclophosphamide, DLT=Dose Limiting Toxicity, Yellow circle indicating Imaging

In Part 2 of the study:

Patients will undergo standard radiologic and clinical screening. Following screening, eligible patients will receive a 300 mg/m^2 i.v. bolus of CPO 1-3 days prior to the first of 4 injections of ONCOS-102. [redacted] of ONCOS-102 [redacted] on days 1, 4, 8 and 15. The dose at each timepoint will be 3x10^{11} VP.

Subsequently, ONCOS-102 ($3x10^{11}$ VP) will be given in combination with pembrolizumab on Day 22/Week 3 and every three weeks thereafter until Day 169/Week 24. Pembrolizumab will be given according to institutional practice (2mg/kg or 200mg flat dose) until Day 190/Week 27. [redacted]. Photographs will be taken to document location, size and possible changes to tumors at baseline and as applicable throughout the study. The patient's study will be deemed complete when the patient returns for the End of Study assessment at Week 27 (day 190). At week 27 onwards, the patient may continue receiving pembrolizumab outside of the context of the protocol. Safety Laboratory Variables and Vital signs will be evaluated and Physical examination performed regularly throughout the study. PBMCs will be collected at Baseline, day 1 (Week 1), day 22 (Week 3), day 64 (Week 9), day 127 (Week 18) and day 190 (Week 27). [redacted] Please see Figure 2 for a schematic of the study.

Figure 2. Schematic of study interventions – Part 2
BL=Baseline, CPO=Cyclophosphamide, DLT=Dose Limiting Toxicity

6.3 Study Duration

The planned duration of participation in the study is 27 weeks in total for the patients.

6.4 Study Visit Schedule

The study includes a screening period, a pre-treatment period and a treatment period.

6.5 Study Visit Schedule Part 1

6.5.1 Screening Period, Visit 1 (Day -28 to -1) - Part 1

Each patient will be given detailed information about the study, including timelines, description of each planned visit, possible side-effects and potential benefits. The information given to each patient will be both oral and written. Patients who are willing to participate will sign the informed consent form. Patients will then be given a study number before the screening evaluation procedures are performed.

- Standard assessment of disease burden with cross-sectional imaging by CT and/or MRI. This will serve as a baseline measure for the study. The method of scan (CT or MRI) will be determined by the investigator after the disease stage has been determined, and must be used consistently throughout the trial for the individual patient.
- Assessment of pregnancy status for women of childbearing age using a urine or blood pregnancy test
- Physical examination
- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded
- Demography (sex, date of birth, race).
- Medical history, including history of cancer and Tumor Node Metastasis staging at the time of diagnosis and at screening.
- Medication and treatment history, including full details of all previous therapies for cancer, and medications taken at the time of the screening visit.
- Concomitant medications, including natural products and other drug-like substances.
- Clinical assessment that includes ECOG performance status, vital signs blood pressure, pulse, temperature) and weight, and physical examination
- Blood and urine samples for routine haematology, clinical chemistry, Thyroid Stimulating Hormone (TSH) and urine dipstick test. Laboratory assessments must be done no greater than 4 days before treatment administration. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken within the visit window.
- Digital photography will be performed to document the location and size of cutaneous metastases and to follow possible changes of tumors. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. This will serve as a baseline measure for the study.

An ultrasound scan may be performed, if required, to determine that the patient has at least one injectable tumor that is suitable for biopsy.

Potentially eligible patients will be notified when the results of all of the screening assessments are available.

6.5.2 Pre-treatment with CPO, Visit 2 (Day -3 to -1) - Part 1

Eligible patients who will receive ONCOS-102 will be pre-treated with a 300 mg/m^2 dose of CPO by i.v. bolus, during the screening period, 1 to 3 days before the Day 1 administration of ONCOS-102.

Before administration of CPO the following assessments will be performed:

- [redacted]

6.5.3 Treatment Period, Visit 3 (Day 1), Visit 4 (Day 4 ± 1) and Visit 5 (Day 8 ± 1) - Part 1

The following assessments will be performed:

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.5.4 Treatment Period, Visit 6 (Day 22 ± 3), Visit 7 (Day 43 ± 4), Visit 8 (Day 64 ± 4), Visit 9 (Day 85 ± 4), Visit 10 (Day 106 ± 7), Visit 11 (Day 127 ± 7), Visit 12 (Day 148 ± 7) and Visit 13 (Day 169 ± 7) - Part 1

Starting on Day 22 ± 3 days, standard i.v. pembrolizumab will be scheduled every 21 days (see visit specific time frame windows) through week 24 while on study. Standard institutional guidelines for dosing pembrolizumab will be followed. While the schedule is written assuming doses will be given within the pre-specified time frame windows, dose delays for adverse events or other clinical developments are allowed per the treating physician. Any delays of pembrolizumab outside the pre-specified time frame windows for the study visits should be documented in the electronic case report form (eCRF) and patient's records. Please note, any other study specific interventions (e.g., imaging and sample collection) should be done within the pre-specified time frame window, although the dosing of pembrolizumab is delayed.

The following assessments will be performed:

- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded.
- Physical examination, changes since the screening visit.
- ECOG/WHO performance status.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.
- Diagnostic CT scan (Visit 8 and 11 only).

- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Patients will be dosed with pembrolizumab.
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.

6.5.5 End of Study Visit 14 (Day 190 ± 7) - Part 1

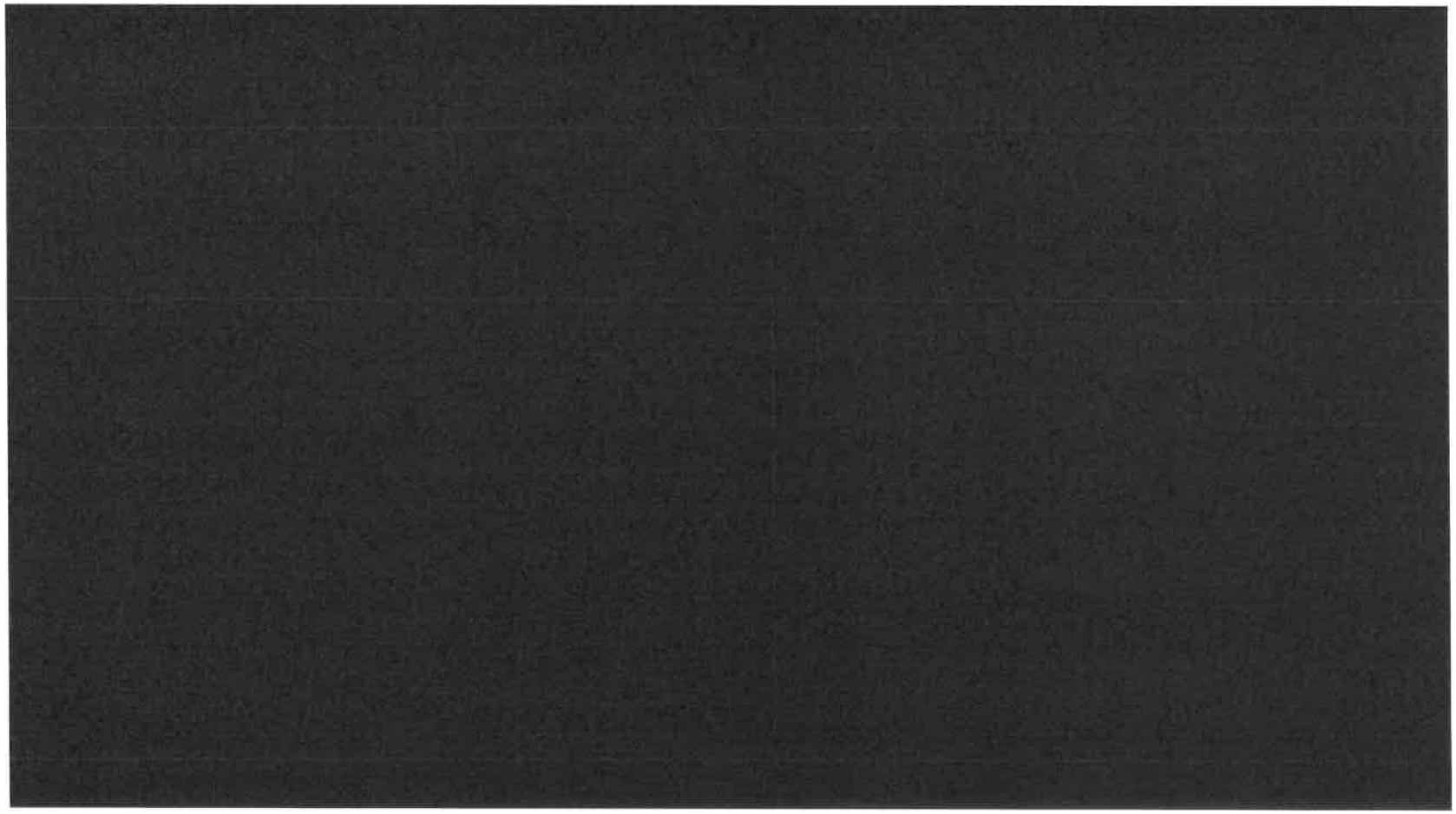
The following assessments will be performed:

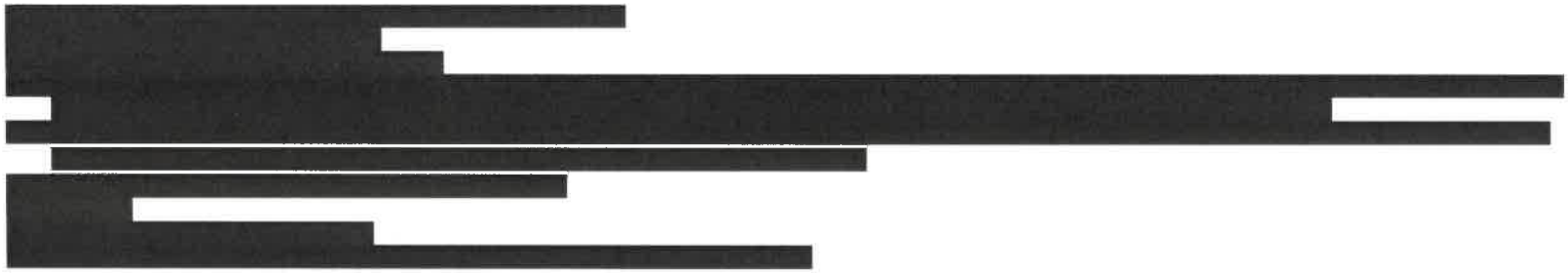
- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded.
- Physical examination, changes since the screening visit.
- ECOG/WHO performance status.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing.
- Diagnostic CT scan.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale.
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Patients may continue treatment with pembrolizumab at investigators decision/SoC, - further administration is outside of this study protocol will occur only after all end of study samples have been collected and assessments have been performed.

6.5.6 Study Flow Chart – Part 1

A summary of the assessments that are to be performed at screening and at each visit is provided in Table 1, Schedule of Assessments Part 1.

Table 1: Schedule of assessments Part 1





6.6 Study Visit Schedule Part 2

6.6.1 Screening Period; Day -28 to -1 (Visit no. 1) - Part 2

Each patient will be given detailed information about the study, including timelines, description of each planned visit, possible side-effects and potential benefits. The information given to each patient will be both oral and written. Patients who are willing to participate will sign the informed consent form. Once Informed Consent is obtained the patients will immediately be registered in the [redacted] system and will receive a subject ID number before the screening evaluation procedures are performed.

The following tests and procedures are required:

- Standard assessment of disease burden with cross-sectional imaging by CT and/or MRI. This will serve as a baseline measure for the study. The method of scan (CT or MRI) will be determined by the investigator after the disease stage has been determined, and must be used consistently throughout the trial for the individual patient.
- Assessment of pregnancy status for women of childbearing age using a urine or blood pregnancy test
- Demography (sex, date of birth, race).
- Medical history, including history of cancer and Tumor Node Metastasis staging at the time of diagnosis and at screening.
- Medication and treatment history, including full details of all previous therapies for cancer, and medications taken at the time of the screening visit.
- Concomitant medications, including natural products and other drug-like substances.
- Clinical assessment that includes ECOG performance status, vital signs blood pressure, pulse, temperature) and weight, and physical examination
- Blood and urine samples for routine haematology, clinical chemistry, Thyroid Stimulating Hormone (TSH) and urine dipstick test. Laboratory assessments must be done no greater than 4 days before treatment administration. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken within the visit window.
- Digital photography will be performed to document the location and size of cutaneous metastases and to follow possible changes of tumors. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. This will serve as a baseline measure for the study.

[redacted]

Potentially eligible patients will be notified when the results of all of the screening assessments are available.

6.6.2 Pre-treatment with CPO; Day -3 to -1 (Visit no. 2) - Part 2

Eligible patients who will receive ONCOS-102 will be pre-treated with a 300 mg/m^2 dose of CPO by i.v. bolus, during the screening period, 1 to 3 days before the Day 1 administration of ONCOS-102.

Before administration of CPO the following assessments will be performed:

- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded.
- Physical examination, changes since the screening visit.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing.
- [redacted]
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. Please note, if a tumor was photographed at screening, the same tumor will be photographed throughout the study.

6.6.3 Treatment Phase with ONCOS-102 only - Part 2

ONCOS-102 as monotherapy will be given at the following days:

Day 1 / Week 1 (Visit no. 3)
Day 4 ± 1 / Week 1 (Visit no. 4)
Day 8 ± 1 / Week 1 (Visit no. 5)
Day 15 ± 1/ Week 2 (Visit no. 6)

The following assessments will be performed:

Day 1 / Week 1 (Visit no. 3) - *Part 2*

- Check that patient has received CPO 1 to 3 days previously
- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded before ONCOS-102 injection. After injection, blood pressure, pulse, and temperature will be monitored 1 hour ± 15 min and before the patient is discharged from the clinic, approximately 2-4 hours after dosing. Additional monitoring may be performed if clinically indicated.

- Physical examination, changes since the screening visit.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. Please note, if a tumor was photographed at screening, the same tumor will be photographed throughout the study.

Day 4 ± 1 / Week 1 (Visit no. 4) - *Part 2*

- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded before injection. After injection, blood pressure, pulse, and temperature will be monitored 1 hour ± 15 min and before the patient is discharged from the clinic, approximately 2-4 hours after dosing. Additional monitoring may be performed if clinically indicated.
- Physical examination, changes since the screening visit.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.

- [redacted]
- [redacted]
- [redacted]

- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. Please note, if a tumor was photographed at screening, the same tumor will be photographed throughout the study.

Day 8 ± 1 / Week 1 (Visit no. 5) - *Part 2*

- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded before injection. After injection, blood pressure, pulse, and temperature will be monitored 1 hour ± 15 min and before the patient is discharged from the clinic, approximately 2-4 hours after dosing. Additional monitoring may be performed if clinically indicated.
- Physical examination, changes since the screening visit.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.

- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. Please note, if a tumor was photographed at screening, the same tumor will be photographed throughout the study.

Day 15 ± 1 / Week 1 (Visit no. 6) - *Part 2*

- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded before injection. After injection, blood pressure, pulse, and temperature will be monitored 1 hour ± 15 min and before the patient is discharged from the clinic, approximately 2-4 hours after dosing. Additional monitoring may be performed if clinically indicated.
- Physical examination, changes since the screening visit.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.
- [redacted]
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. Please note, if a tumor was photographed at screening, the same tumor will be photographed throughout the study.

6.6.4 Treatment Phase with ONCOS-102 and Pembrolizumab - Part 2

[redacted] Pembrolizumab will be administered by standard i.v.. Standard institutional guidelines for dosing pembrolizumab will be followed.

[redacted] Any delays of pembrolizumab and/or ONCOS-102 outside the pre-specified time frame windows for the study visits should be documented in the electronic case report form (eCRF) and patient's records. Please note, any other study specific interventions (e.g.

imaging and sample collection) should be done within the pre-specified time frame window, although the dosing of pembrolizumab and/or ONCOS-102 is delayed.

ONCOS-102 + pembrolizumab visits – Part 2

ONCOS-102 and pembrolizumab will be given at the following days:

Day 22 ± 3 / Week 3 (Visit no. 7)
Day 43 ± 4 / Week 6 (Visit no. 8)
Day 64 ± 4 / Week 9 (Visit no. 9)
Day 85 ± 4 / Week 12 (Visit no. 10)
Day 106 ± 7/ Week 15 (Visit no. 11)
Day 127 ± 7/ Week 18 (Visit no. 12)
Day 148 ± 7 / Week 21 (Visit no. 13)
Day 169 ± 7 / Week 24 (Visit no. 14)

The following assessments will be performed:

- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded prior to dosing. Blood pressure, pulse, and temperature will be monitored at 10 ± 5 min, 30 ± 10 min, 1 hour ± 15 min and before the patient is discharged from the clinic, approximately 2 - 4 hours after ONCOS-102 injection. Additional monitoring may be performed if clinically relevant.
- Physical examination, changes since the screening visit.
- ECOG/WHO performance status.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing. If any laboratory values are outside the range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.
- Patients will be administered ONCOS-102 and pembrolizumab.
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale.

[redacted]

- [redacted]
- [redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Diagnostic CT scan

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.6.5 End of Study; Day 190 ± 7 / Week 27 (Visit no. 15) – Part 2

The following assessments will be performed:

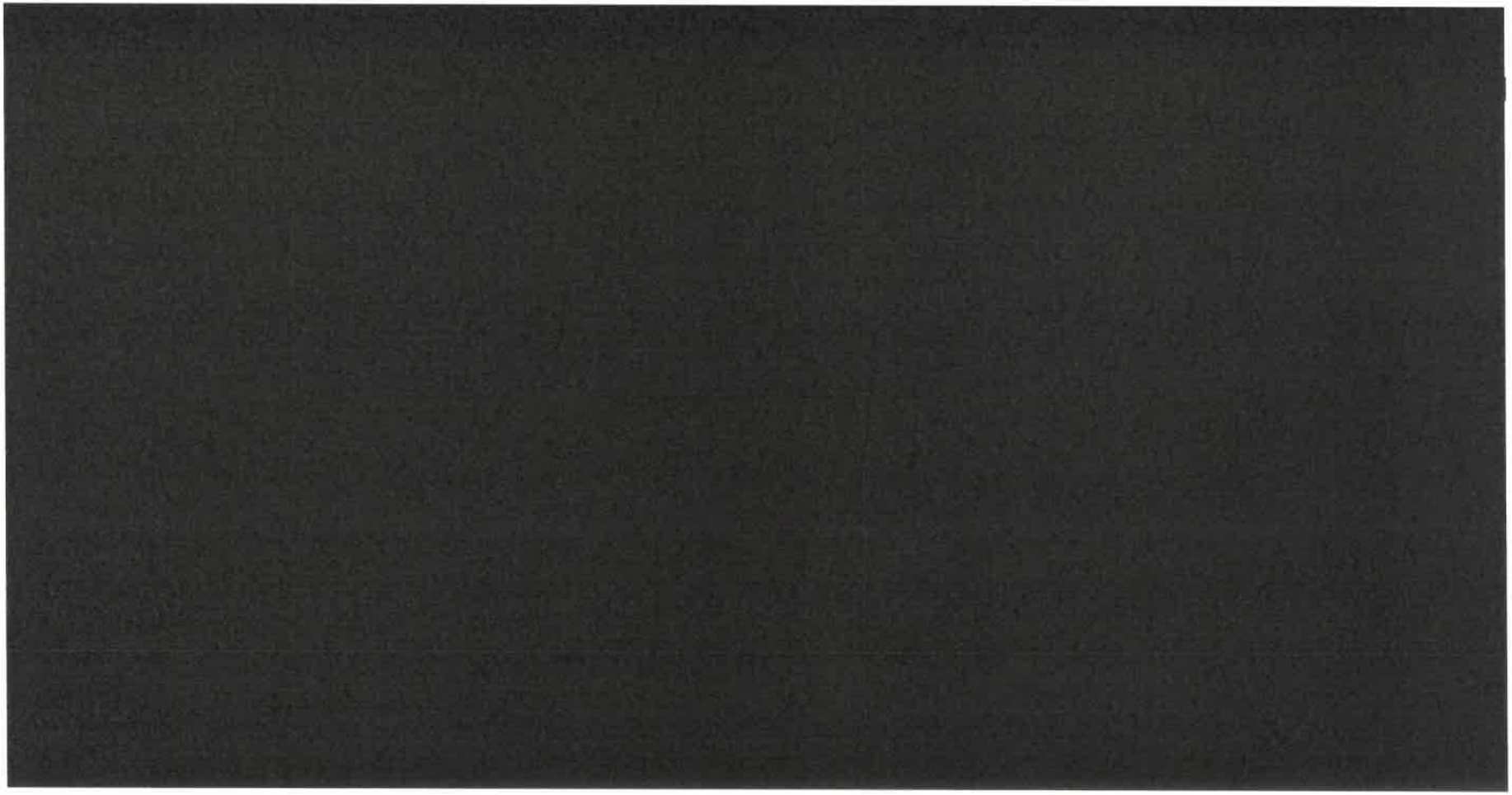
- Vital signs (blood pressure, pulse, temperature) and weight will be measured and recorded.
- Physical examination, changes since the screening visit.
- ECOG/WHO performance status.
- Blood and urine samples for routine haematology, clinical chemistry, TSH and urine dipstick test will be taken before dosing.
- [redacted]
- [redacted]
- [redacted]
- [redacted]

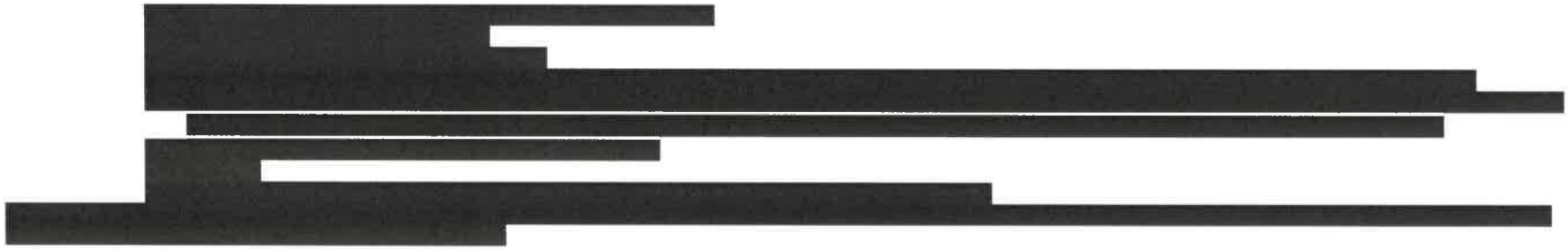
- Diagnostic CT scan.
- Digital photographs will be taken as applicable. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale.
- AEs will be elicited and recorded, and any changes in concomitant medications will be recorded.
- Patients may continue treatment with pembrolizumab at investigators decision/SoC, but further administration is outside of this study protocol will occur only after all End of Study samples have been collected and assessments have been performed.

6.6.6 Study Flow Chart – Part 2

A summary of the assessments in Part 2 that are to be performed at screening and at each visit is provided in Table 2 Schedule of Assessments Part 2.

Table 2: Schedule of assessments Part 2





6.7 Safety Review Committee

Adverse events, safety laboratory variables and vital signs are followed by the Safety Review Committee. The Safety Review Committee consists of the investigators, the sponsor and the medical monitor.

The Safety Review Committee and pertinent site personnel will meet via teleconference to review the current patient screening and enrollment status, status of patients receiving study treatment, and any ongoing safety concerns. Schedule and frequency of these reviews will be adjusted based on the enrollment rate and/or occurrence of a significant toxicity (e.g., SAEs, DLTs) requiring timely assessment, and take place approximately when every three patients have been dosed or as otherwise agreed. Minutes of the meetings will be written by the medical monitor to document the safety conclusions.

Any suspicion of a DLT will be discussed and assessed by the safety review committee within one week. If there is already one confirmed DLT and a second DLT is being assessed, the recruitment will be stopped until the second DLT has been assessed by the safety review committee. If there are two DLTs to be assessed, the recruitment will be stopped until the open DLTs have been assessed. In case there are two confirmed DLTs, no further patients will be enrolled. DLTs will be assessed in each cohort separately.

7 SUBJECT SELECTION

7.1 Description of Patient Population

Eligible patients are adults with advanced or unresectable melanoma who have had progression following PD1 blockade as monotherapy or in combination with ipilimumab [redacted]

7.2 Number and Source of Subjects

Up to a maximum of 24 patients will be enrolled in the study, 6-12 in Part 1 and 6-12 in Part 2. [redacted]

Investigators and their research teams will serve as the primary recruiters for this study. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team. If the investigator is a member of the treatment team, he/she will screen the patient's records for suitable research study criteria and discuss the study and the potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Women and minorities will be identified in this same manner.

During the initial contact between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of the patient's medical records to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient is ineligible for enrollment in the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

The study will not be advertised. Subjects will not be reimbursed for participation. However, reasonable travel expenses (e.g., second class train tickets and bus fares) may be reimbursed against receipts.

7.3 Patient Registration

Confirm eligibility as defined in the Inclusion and Exclusion Criteria.

Obtain informed consent, by following procedures defined in section entitled Subject Information and Consent.

Once Informed Consent is obtained the patients will immediately be registered in the [redacted] system and will receive a subject ID number.

7.4 Inclusion Criteria

- Adults 18 years of age or older.
- Histopathologically confirmed melanoma with an injectable cutaneous or lymph node metastasis that has progressed in the opinion of the treating investigator despite administering an FDA approved anti-PD1 agent, with or without ipilimumab.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
- Measurable disease according to RECIST 1.1.
- Acceptable coagulation status: INR of blood clotting, prothrombin time and activated partial thromboplastin time within ≤1.5 x ULN.
- Completion of local therapy, such as radiation, surgical resection, injectable immune-based therapy, or topical pro-inflammatory agent, 21 days prior to first dose of protocol therapy.
- Adverse events from previous cancer therapies (excluding alopecia) must have recovered to Grade 1 (CTCAE, most recent version). Stable Grade 2 AEs such as endocrine conditions are allowed, and other chronic stable AEs may be considered on a case by case basis by the Principal Investigator.
- Clinical stability of brain metastases for at least 4 weeks prior to first day of study therapy.
- Acceptable liver and renal functions defined as:
    - Total bilirubin ≤1.5 x ULN (does not include patients with Gilbert's Disease)
    - Aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT) ≤3.0 x ULN
    - Serum creatinine ≤1.5 x ULN
- Acceptable haematological function defined as (Patients can be transfused to meet the haemoglobin entry criteria):
    - Haemoglobin ≥ 9 g/dL
    - Neutrophils ≥1.5 x 10^9/L
    - Platelet count ≥75 x 10^9/L
- Able to provide valid written informed consent.
- All women of childbearing potential must have a negative urine or serum pregnancy test at screening.
- All patients must agree to use barrier contraception (i.e. condom) during study treatment and for 2 months after the last virus treatment and 4 months after the last dose of chemotherapy and pembrolizumab.

7.5 Exclusion Criteria

- A concomitant medical condition requiring receipt of a therapeutic anticoagulant that in the opinion of the treating physician cannot safely allow for therapeutic injection of ONCOS-102 and tumor biopsies. Local clinical practice can be followed with regard to holding a therapeutic anticoagulant during invasive procedures such as biopsies.
- A concomitant medical condition that in the opinion of the treating physician would pose unreasonable additional risk to therapeutic injection of ONCOS-102.
- Receipt of Investigational agents within 28 days prior to first dose of protocol therapy.
- Any symptomatic autoimmune disease (such as lupus, scleroderma, Crohn's disease, ulcerative colitis) that requires administration of >10mg of prednisone equivalent. Lower dose steroids for conditions such as hypophysitis are allowed.
- Any prior severe adverse event attributed to prior anti-PD1 therapy that, in the principal investigator's opinion, would contraindicate pembrolizumab administration such as:
    - Grade 2 or higher pneumonitis
    - Grade 4 AST or ALT elevation
    - Grade 3 or higher colitis attributable to PD1 blockade; note that colitis attributable to ipilimumab is not excluded
    - Note: in the absence of clinical symptoms of pancreatitis, elevations of amylase or lipase are not contraindications to therapy on this trial
- Known active infection with Hepatitis B Virus, Hepatitis C Virus, or HIV. Cleared HBV/HCV infection is not an exclusion, nor is HIV infection with CD4 counts >500 and an undetectable viral load.
- Active bacterial, viral, or fungal infections, requiring systemic therapy apart from anti-viral maintenance therapy for HIV.
- History of organ transplant.
- Patients requiring chronic systemic immunosuppressants, including steroids (prednisone daily equivalent of >10 mg).
- Brain metastases that are clinically unstable (e.g. showing unequivocal growth on imaging, requiring radiation therapy, or steroids >10mg of prednisone equivalent) within 4 weeks of first dose of study drug.
- Known severe congenital or acquired cellular or humoral immunodeficiency such as common variable immunodeficiency.
- Women who are pregnant or breast-feeding currently or are planning to conceive during or up to 4 months after the end of protocol therapy.

7.6 Discontinuation Criteria and or Removal from study

Patients will be removed from the study for any of the following reasons:

- Loss of Clinical Benefit: Either symptomatic progression necessitating a change in systemic therapy in the opinion of the treating physician or confirmed radiologic progression as defined by cross-sectional imaging utilizing immune-related Response Criteria when the treating physician concurs that further therapy is not in the patient's best interest. Patients may continue treatment past the point of radiographic progression if they feel the patient is still obtaining clinical benefit.
- Treatment cessation: Due to severe or unexpected toxicity felt to necessitate cessation by the treating physician; patient or treating physician preference; or inability to undergo the assessments in a timely manner to ensure patient safety.
- Treatment change: Addition of any systemic therapy agent to pembrolizumab. Local therapy (i.e. local radiation or resection) is allowed.
- Screening failure: If, at any point after enrollment, the principal investigator determines that the patient does not meet all inclusion criteria or meets any exclusion criteria.
- Withdrawal of consent: Patient may withdraw consent at any time
- Non-adherence to Study Protocol: If the patient deviates from outlined protocol to the extent that the principle investigator deems that experimental therapy can no longer be safely administered.
- Pregnancy
- Death

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the patient's medical records. If possible, patients who withdraw from the trial should have all procedures required for the end of study visit completed. As a minimum, all AEs should be followed until they are fully and permanently resolved or stabilised (if resolution is not anticipated).

Patients considering withdrawing consent should be encouraged to provide the reason and information so that the Investigator may ascertain whether there is an underlying serious or significant safety issue.

7.7 [redacted]

8 TRIAL TREATMENT(S) AND REGIMEN OF INVESTIGATIONAL PRODUCTS

8.1 Identity of Investigational Product(s)

Part 1: In Part 1 of the study, patients will be administered ONCOS-102, primed with cyclophosphamide and followed by pembrolizumab.

Part 2: In Part 2 of the study, patients will be primed with CPO, followed by an initial treatment phase of four ONCOS-102 injections followed by a treatment phase with ONCOS-102 and pembrolizumab.

8.1.1 ONCOS-102

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

8.1.2 Cyclophosphamide

In addition to ONCOS-102, each patient will be administered low dose i.v. cyclophosphamide (CPO) at 300mg/m^2. This is an investigational use of a standard cytotoxic agent. CPO is administered as it is known to enhance the effect of GM-CSF-induced natural killer and cytotoxic T-cells by reducing regulatory T-cells.

CPO 500 mg powder for solution for injection or infusion can be stored in an unopened, properly sealed vial at controlled room temperature (≤25°C) for up to 3 years. The CPO solution will be administered within 24 hours after dilution.

CPO will be sourced from commercial stock and will be administered according to the manufacturer's instructions. Please see the Summary of Product Characteristics for further details. An accountability log will be kept tracking the use of CPO.

8.1.3 Pembrolizumab

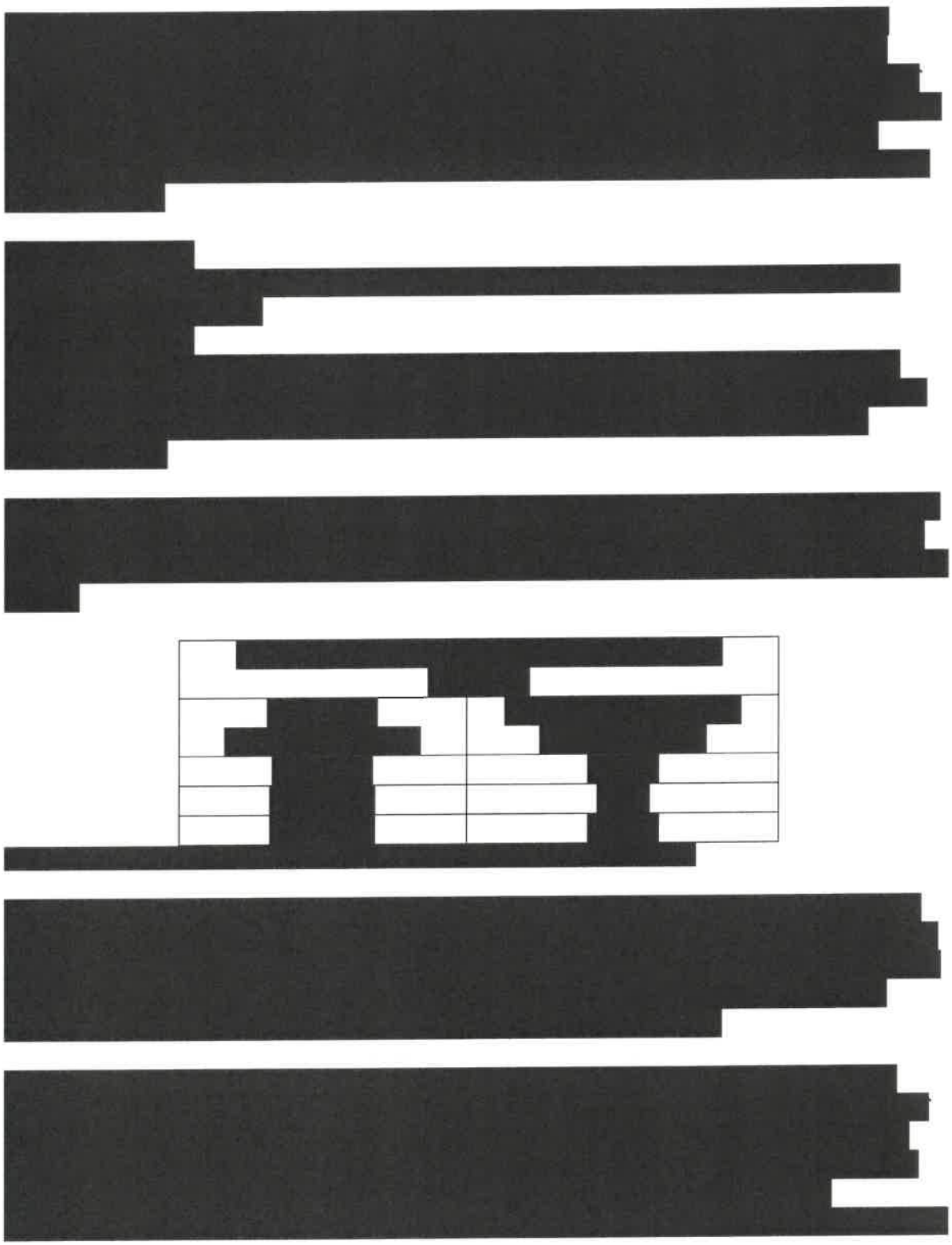
Pembrolizumab is a standard agent used in metastatic melanoma and will be sourced from commercial stock and administered according to manufacturer's instructions. Please see the Summary of Product Characteristics for further details. An accountability log will be kept tracking the use of pembrolizumab.

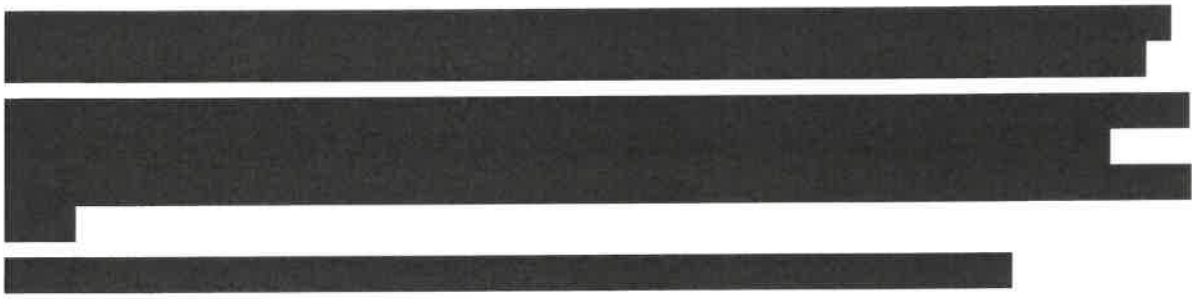
8.2 Dosing, Mode of Administration, Duration of Treatment

8.2.1 ONCOS-102

The planned total dose of ONCOS102 on each dosing day is 3x10^{11} VP administered i.t.

[redacted]





8.2.2 Cyclophosphamide

Patients will be pre-treated with a 300 mg/m^2 dose of CPO by i.v. bolus, during the screening period, 1 to 3 days before the Day 1 administration of ONCOS-102.

The doses of CPO may be reduced for an individual patient if deemed necessary by the Investigator, and in accordance with the manufacturer's prescribing instructions and/or local medical practice.

8.2.3 Pembrolizumab

Starting on Day 22 ± 3 days, standard i.v. pembrolizumab according to institutional practice (either 2mg/kg or flat dosing at 200mg) will be scheduled every 21 days ± 4 days up until week 12 and thereafter every 21 days ± 7 days while on study. Standard institutional guidelines for dosing pembrolizumab will be followed. While the schedule is written assuming doses will be given within the pre-specified time frame windows, dose delays for adverse events or other clinical developments are allowed per the treating physician. Any delays outside the pre-specified time frame windows for the study visits should be documented in the eCRF and patient's records.

The doses of pembrolizumab may be reduced for an individual patient if deemed necessary by the Investigator, and in accordance with the manufacturer's prescribing instructions and/or local medical practice.

8.3 Definition of Dose Limiting Toxicity and Maximum Tolerated Dose

Please see the Summary of Product Characteristics (SPC) for the safety data regarding CPO and pembrolizumab.

8.4 Adenoviral-Related Events

AEs will be evaluated for toxicity according to most recent version of CTCAE. AEs will be followed by the Safety Review Committee.

The DLT period for this study starts at baseline and continues for 9 weeks.

[redacted]

- [redacted]
- [redacted]

8.5 Clinically Significant Immune-related Adverse Events (irAE)

- General Guidelines for Classifying irAEs as DLTs
  - Any irAE that requires two classes of systemic immunosuppression, i.e. corticosteroids plus mycophenolate mofetil or infliximab
  - Any Grade 3 irAE unless qualified below
  - Any irAE that requires a hospitalization for 24 hours or longer
  - Any AEs judged to be likely related to adenovirus (i.e. fevers, nausea/emesis temporally related to injection, preceding pembrolizumab administration) should be classified as DLTs as above
- Rash: Grade 3 lasting >7 days from initiation of systemic steroid
- Diarrhea: Grade 3 or higher diarrhea lasting more than 48 hours from time of systemically absorbed steroid initiation
- Pneumonitis: Any Grade 2 or higher pneumonitis
- Peripheral Neuropathy: Any Grade 2 or higher peripheral neuropathy
- Amylase and Lipase
  - When otherwise asymptomatic from a gastrointestinal standpoint, not considered DLTs regardless of value
  - Any Grade 4 or higher when accompanied by clinical signs of pancreatitis in the judgment of the treating physician (radiographic evidence of pancreatic inflammation, clinical signs of abdominal pain, anorexia, nausea, emesis)
- Fatigue: Grade 3 >24 hours

8.6 Packaging and Labeling

[redacted]

Pembrolizumab and CPO will be supplied from commercial stock.

8.7 Storage, Handling and Dispensing of Investigational Product(s)

[redacted]

CPO will be stored according to the manufacturer's instructions (not more than 25°C). After reconstitution, the solutions of CPO can be stored for up to 24 hours at 2 to 8°C. CPO should be protected from light.

Pembrolizumab will be stored according to the manufacturer's instructions. After reconstitution, the solution of pembrolizumab can be stored at room temperature and at 2°C to 8°C/36°F to 46°C as described on the local label for the product.

8.8 Blinding Procedures

[redacted]

8.9 Randomization and Subject Allocation

[redacted]

8.10 Treatment Compliance

ONCOS-102 will be administered to the patients by the physician(s) assigned as Investigator(s) for the study. Chemotherapy and other medications can be administered by qualified personnel assigned to the study. Therefore, no special steps to assure compliance are deemed necessary.

8.11 Prior and Concomitant Medications

[redacted]

9 STUDY ASSESSMENTS

9.1 Assessment of Efficacy and biological activity

A summary of sample analysis and collection is presented below. More details can be found in a separate Laboratory Manual.

9.1.1 Analysis of Clinical Response

Imaging will be done at baseline, week 9, 18 and 27 regardless of the timing and number of doses of pembrolizumab given.

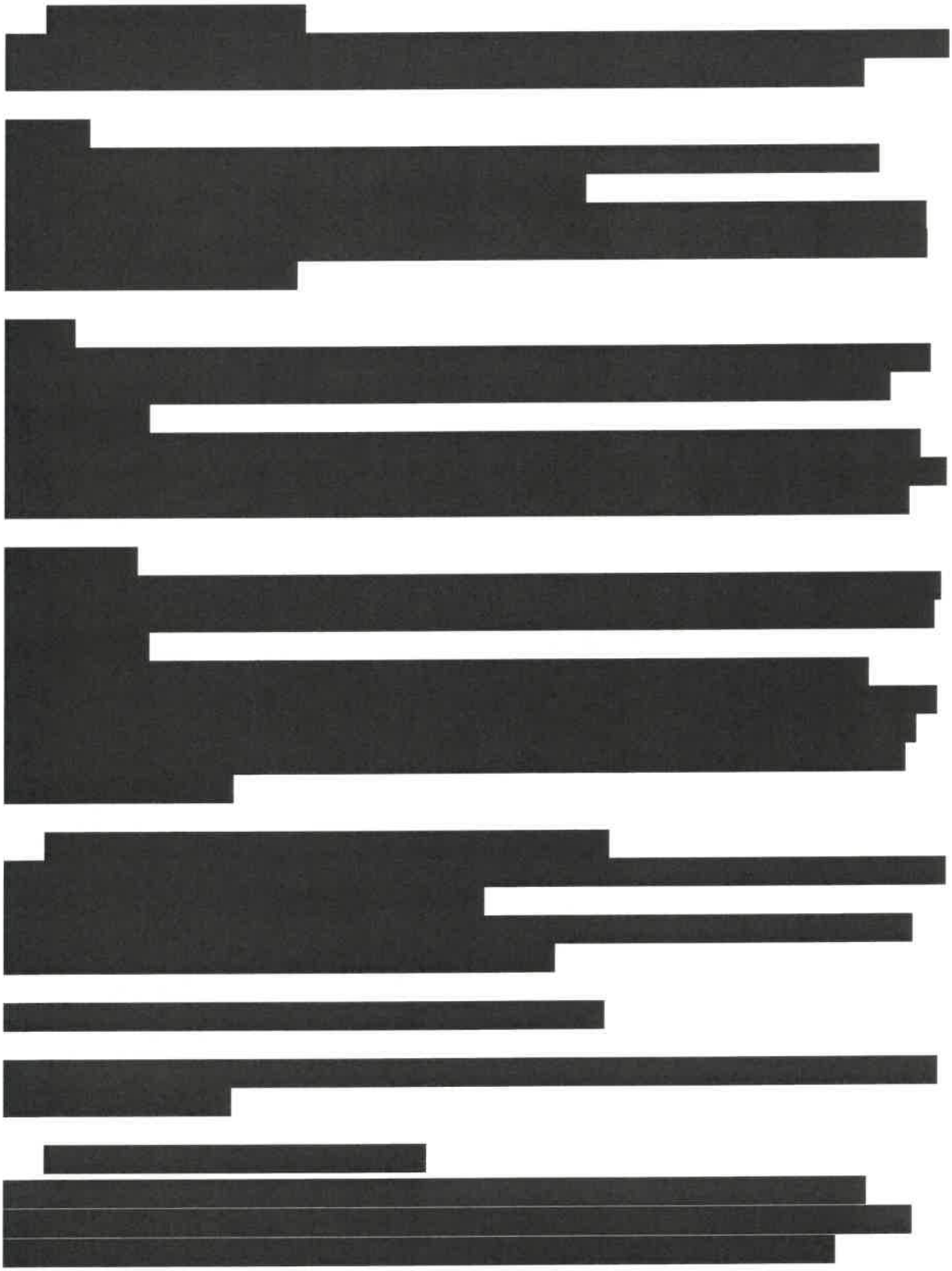
Two sets of criteria will be applied for assessment of clinical response:

a) standard RECIST1.1 (Eisenhauer *et al*, 2009)
b) immune related RECIST criteria (irRECIST) to allow for the immunological nature of the therapy (Bohnsack et al. 2014).

Digital photography will be performed to document the location and size of cutaneous metastases and to follow possible changes of tumors. Photographs will be taken at baseline and as applicable thereafter. The photograph should preferably be taken with a standard ruler or calipers present to allow for accurate assessment of scale. RECIST and irRECIST assessment should take into account the most up-to-date measurement of skin lesions done at the separate study visits.

9.1.2 A

[redacted]



9.2 Assessment of Safety

9.2.1 Adverse Events

All adverse events (AEs) will be reported. AEs will be recorded from first dose of IMP up to 30 days following the last dose. The report will include information on onset/stop, nature, severity, duration, interventions and medications required. Possible serious adverse events (SAEs) will be reported to the regulatory authorities and Independent Ethics Committee (IEC) according to local regulations and followed-up until the resolution of the event.

9.2.1.1 Definitions

AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship to this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the treatment administered. AEs will be coded by use of an internationally recognized dictionary.

SAE is defined as any untoward medical occurrence that at any dose: results in death, or is life-threatening, i.e. the patient was at immediate risk of death at the time of the event, or requires in-patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect is an important medical event, i.e. may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Examples of such events are bronchospasms requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; development of cancer; drug dependency or drug abuse.

9.2.1.2 Adverse Event Reporting

Adverse events will be collected with a non-leading question at each clinic visit: "Have you had any new or worsening health problems since the last visit?" as well as by reporting those events directly observed and spontaneously reported by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome whenever possible. **Intensity** (mild, moderate or severe) and **relationship to study treatment** (none, unlikely, possible, probable, definite) as well as **action taken**, **seriousness** and **outcome** should be recorded in the adverse event page of CRF. **Start and end date and time** of the event will also be recorded as exactly as possible.

Intensity
Intensity is the accumulated degree of discomfort since the last AE recording and should be assessed according to the following definitions:
Mild: awareness of sign or symptom, but easily tolerated (acceptable)
Moderate: discomfort to interfere with usual activities (disturbing)

Severe: incapacity to work or to perform usual activities (unacceptable). A distinction should be drawn between serious and severe adverse events. The term severe is used to describe the intensity of the event and does not necessarily need to be considered serious. The term "serious" is based on the subject/event outcome or action and serves as a guide for defining regulatory reporting obligations.

Relationship to Study Treatment.
Assessment of causality is based on the following considerations: associative connections (time and/or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations.

The investigator will be asked to assess causal relationship to the study treatment of each IMP (i.e. CPO, ONCOS-102, and pembrolizumab) according to following classifications:
Unrelated: The time course between administration of the study product and occurrence or worsening of the AE rules out causal relationship; and/or another cause is confirmed and no indication for involvement of the study product in the occurrence/worsening of the A E exists
Unlikely: The time course between study product administration and occurrence/worsening of the AE makes causal relationship unlikely; and/or the known effects of the study product or substance class provide no indication for involvement of the study product in the occurrence/worsening of the AE; and/or although it is conceivable based on previous knowledge that study product may have causal relationship to occurrence/worsening of the AE, another cause is much more probable; and/or another cause is confirmed and involvement of the study product in the occurrence/worsening of the AE is unlikely
Possible: It is conceivable based on previous knowledge that study product may have causal relationship to the occurrence/worsening of the AE but other factors exist that are equally likely to be causative factors; or although the previous knowledge on study product does not provide any support for causal relationship, no other possible causative factors exist.
Probable: Time relationship exists; and previous knowledge on study product supports causal relationship although another cause cannot be ruled out; and/or improvement on dechallenge or dose reduction has occurred (if performed); and/or recurrence of symptoms on rechallenge has occurred (if performed); and/or a specific laboratory test has confirmed supports causal relationship.
Definite: The criteria for probable relationship are fulfilled and no other possible causative factors exist.

Action taken
The investigator will be asked to record action taken in relation to study/study treatment and to other treatments. The categories in relation to study or study treatment are:

No action taken
Study medication discontinued temporarily
Study medication discontinued permanently
Withdrawn from the study
Other, specify

The categories in relation to other treatments are:

No action
Medication given (must be specified in the concomitant medication page) Non-medication treatment given (must be specified)
Hospitalization
Other, specify

Outcome

The investigator will be asked to record the outcome by choosing one of the following alternatives:

Recovered
Recovering
Not recovered
Recovered with sequelae
Death
Unknown

Reporting of Serious Adverse Events

Adverse events classified as serious require expeditious handling and reporting to [redacted] to comply with regulatory requirements.

For any serious adverse event (SAE) that occurs while a patient is on-study; within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug; or if any SAE that the Investigator feels is related to the study drug occurs later than 30 days after the last study drug administration, the [redacted] Safety Desk must be notified immediately (within 24 hours of becoming aware of the event) by fax, email or telephone. Notification by email is preferred. The fax and telephone numbers and the email address listed below may be used during both business and non-business hours. During non-business hours a recorded message will provide the telephone caller with the contact information for the on-call monitor.

All SAEs require that a Serious Adverse Event Report Form be completed and forwarded either via facsimile or as a PDF via email to [redacted] at the fax number or email listed below within 24 hours of becoming aware of the event.

SAEs will be reported to [redacted]

The SAE will also be reported to the FDA through Targovax Oy's US Agent, and the report must include the FDA assigned BB-IND number and name. A copy of this report will also be provided to Targovax Oy.

The Sponsor must report to the regulatory authorities all serious unexpected adverse reactions, which are fatal or life-threatening within seven days of the Sponsor being informed of such an adverse reaction. Any additional relevant information on such an adverse reaction must be reported within 8 days of submission of the first notification.

Serious unexpected adverse reactions which are not life-threatening or fatal must be reported to the regulatory authority within 15 days of the Sponsor first being informed thereof.

Pregnancy

Any pregnancy diagnosed during the study, or that occurs within 4 months after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form and emailing it or faxing it to the [redacted] Safety Desk.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described.

9.2.2 Safety Laboratory Variables

Blood and urine samples for analysis of routine laboratory safety variables will be taken from all patients throughout the study as summarized in the flowchart (see section 6.4.5).

If the screening sample is taken less than 4 days before Day 1, it does not need to be repeated. If any laboratory values are outside the normal range permitted in the protocol, repeat samples may be taken for reassessment within the allowed time window for the visit.

Blood samples will be analysed for the following:

Haematology: complete blood count (red blood cells, haemoglobin, haematocrit), white blood cells, and differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

Clinical chemistry: sodium, potassium, creatinine, ALT (SGPT), AST (SGOT), alkaline phosphatase, albumin, total bilirubin, BUN (blood urea nitrogen), Calcium, Chloride, HCO^3 (Bicarbonate), glucose and total protein.

INR, Prothrombin and activated partial thromboplastin time test [PT&APTT] should be assessed at screening. Further monitoring is not necessary, but may continue after screening if considered applicable.

TSH should be assessed at screening and monitored per local standards during therapy (TSH does not have to result prior to therapy)

Urine samples will be tested by dipstick for pH, blood, ketones, protein, and glucose. Further analysis will be performed if considered clinically indicated by the Investigator.

Women of childbearing potential will have a urine or serum pregnancy test at the screening visit.

Clinically significant laboratory values or changes in values will be reported as adverse events.

9.2.3 Other Safety Variables

Vital signs:
Part 1 - Vital signs (blood pressure, pulse, body temperature) and weight will be measured as summarized in summarized in the flowchart (see section 6.5.6). Additional monitoring may be performed if clinically indicated. Vital signs will be checked 1 hour ± 15 min, 2 hours ± 30 min, and 5 hours ± 60 min after injection on Days 1, 4, and 8.
Part 2 - Vital signs (blood pressure, pulse, body temperature) and weight will be measured as summarized in Section 6.6. Additional monitoring may be performed if clinically indicated.

Physical examination: Patients will have a physical examination, including review of the major body systems at screening, and at intervals as summarized in the flowchart (see section 6.5.6 and 6.6.6). All patients will have a physical examination at the end of study visit. Height will be measured at screening only.

10 DATA MANAGEMENT.

10.1 Case Report Forms

Electronic CRFs will be used to capture study results and data. The study coordinator or other authorised study personnel will transcribe data from source documents to the eCRFs. All eCRFs will be reviewed and source-verified by the study monitor during periodic site visits, and the study monitor will ensure that all data in the eCRF are correct and completed. Once the eCRF are completed and source-verified, the investigator must electronically sign and date all required pages, verifying the accuracy of all data in the eCRF. Specific instructions for completing and submitting eCRFs will be provided.

All data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data.

10.2 Data Management Plan and Database Design

The data management plan will be a live document detailing the processes used by the Sponsor's representatives handling the data management. Any updates to the processes employed during the course of the study will be reflected in the data management plan. The system is completed within a fully validated clinical database data management system. The system is built in a development environment before being moved to the testing environment. All testing must be completed prior to the release of the live system

10.3 Data Entry and Validation

All computerized data processing will be performed by Sponsor's representative. All eCRFs will be entered electronically by staff into a validated database. Data entry will be source data verified by a sponsor representative. Comprehensive edit checks will be used to clean data. Patient data will be entered continuously. All changes to the data and the database structure will be recorded in an automatic audit trail.
Data queries will be generated at data entry or if questions arise during the data validation or detected during a manual review (safety data). The queries are entered into the eCRF and resolved according to the electronic data capture user manual.

AEs and SAEs will be handled in the same way as the other data reported in the eCRF. However, in addition the initial notification of SAEs will be entered into the safety database for coding, medical assessment and for reporting to authorities according to national regulatory requirements. Before the study database is locked, reconciliation of the data will be performed between the two databases.

10.4 Handling of External Data

Data entry of the immunomonitoring data is done by of the laboratory responsible of the analysis. Sponsor and the laboratory agrees the format of the database. Any external data will be reconciled against the clinical database, and transferred to SAS®-datasets by the Sponsor or Sponsor's representative. The process will be fully documented.

10.5 Medical Coding

Medical coding of AEs and medical history will be performed according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and coding of concomitant medication, prior anti-cancer therapy and further therapy will be performed according to World Health Organization (WHO) drug dictionary.

10.6 Database Lock

A final database will be declared when all data has been entered, the data verified, the data validated and the database defined clean by the Responsible Data Manager. After declaration of a final database the data will be exported from the database to SAS datasets and both the database and the SAS datasets will locked and protected from changes. Statistical analyses for the final analysis will be performed on the locked datasets. Data management will be carried out as described in the Sponsor's representative's Standard operating procedures (SOPs) for clinical studies.

11 STATISTICAL ANALYSES

11.1 Power Considerations and Determination of Sample Size

[redacted]

11.2 Statistical Hypothesis

[redacted]

11.3 Datasets to be Analyzed

All patients who enroll and receive cyclophosphamide and a minimum of one dose of ONCOS-102 will be included in the *Safety Analysis Set.*

All patients with a repeat assessment of tumor burden, including a photograph or cross-sectional imaging, will be included in the *Efficacy Analysis Set.*

[redacted]

11.4 General Statistical Considerations

A[redacted]

11.5 Demographic and Baseline Characteristics

Demographic data, medical and cancer history, all other relevant background data will be summarized in terms of descriptive statistics in Safety Analysis Set.

11.6 Analysis of Efficacy

Imaging data

Imaging data will be summarized in the Efficacy Analysis Set.
Imaging data will be assessed using RECIST 1.1 and irRECIST criteria.
Objective response rate (ORR) is defined according to RECIST 1.1 or irRECIST, separately.
ORR will be calculated for Efficacy Analysis set for all patients and each cohort.

Clinical benefit rate, is defined as subjects who are not in progression according to RECIST 1.1/irRECIST at 27 weeks. Patients who discontinue before week 27 are considered to have progressive disease.

For each patient, the mean absolute and relative change in size in uninjected and injected lesions will be calculated. This data will be presented in terms of descriptive statistics by time point.

Progression Free Survival (PFS) will be calculated separately for progression per RECIST 1.1 and irRECIST. It is defined as time from start of IMP until progression or death from any cause. If a patient had not had an event (progression or death) before end of trial, then PFS will be censored at the last date known of non-progression.

The tumor size measured from digital photographs will be listed.

[redacted]

11.7 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

11.8 Analysis of Safety

Adverse events

All adverse events will be classified by MedDRA, version 15 or higher.

A treatment-emergent adverse event (TEAE) is defined as an AE with start date/time on or after the first administration of investigational medicinal product, in this case ONCOS-102. A pre-treatment AE is defined as an AE with start date/time prior to the first administration of ONCOS-102.

Further, the primary end point of the study is the TEAEs after two cycles of pembrolizumab (day 64).

Following summary tables will be created, reporting number of events and number of patients with events by MedDRA System Organ Class and Preferred Term for the TEAEs after two cycles of pembrolizumab and separately for all TEAEs:

- total TEAEs
- total serious TEAEs

- total ONCOS-102 related serious TEAEs
- TEAEs leading to ONCOS-102 withdrawal
- TEAEs leading to study withdrawal
- TEAEs leading to death
- TEAEs by severity
- Related TEAEs by each IMP (ONCOS-102, pembrolizumab) separately
- Related TEAEs by severity

Other Safety Variables

All other safety variables will be presented in terms of descriptive statistics, and details will be elaborated in Statistical Analysis Plan.

11.9 Hardware and Software

All statistical analyses, including descriptive tables and listings, will be produced using SAS software.

12 QUALITY CONTROL AND ASSURANCE

12.1 Monitoring

The study will be monitored regularly, according to a monitoring plan that will be written specifically for this study. The monitoring plan will define the monitoring frequency and detailed procedures. In general, during monitoring visits the monitor will ensure that the study is being conducted according to the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines and other applicable regulations, and will compare the electronic Case Report Form (eCRF) entries to original source data. He or she will make sure the informed consent procedure has been appropriately carried out and will ensure that all Serious Adverse Events (SAEs) have been reported within applicable timeframes. He or she will also ensure that Investigational Medicinal Product (IMP) accountability has been maintained and will, after completion of the study, perform final accountability and arrange for the return or destruction of IMP.

12.2 Audits and Inspections

The Sponsor has the right to perform an audit of the study site and the Contract Research Organisation (CRO). Such an audit will be conducted according to a specific audit plan.

The regulatory (competent) authorities, both national and foreign, may inspect the study site at any time. The Investigator is responsible for notifying the Sponsor of such an inspection immediately after gaining knowledge of it.

During the audit or inspection, the Investigator will permit the auditor, IEC or Institutional Review Board (IRB) reviewer, and regulatory inspector(s) direct access to all relevant medical records and other source data, study related files and eCRFs.

12.3 Record Keeping and Archiving

The study specific essential documents must be retained until at least 15 years after the completion of the study. The investigator must not destroy any study specific documentation before receiving written permission for this from the sponsor. Hospital record will be archived according to local regulations.

13 ETHICS

13.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study will not commence until favorable opinion has been obtained from the appropriate IEC/IRB.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued and submitted to relevant IEC/IRB for approval. The amendment will not be implemented until IEC/IRB approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the subjects.

13.2 Guidelines and Regulations

The trial will be conducted in compliance with the protocol, ICH GCP, the applicable regulatory requirement(s) and the Declaration of Helsinki.

13.3 Subject Information and Consent

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an Institutional Review Board/Privacy Board (IRB/PB)-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the IRB/PB of this Center.

The consent form will include the following:

- The nature and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
- The name of the investigator(s) responsible for the protocol.
- The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.
- A request for HLA typing

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

If new information becomes available that potentially affects the subject's safety or willingness to continue in the study, or if a protocol amendment is issued that affects subject's safety, study procedures or any aspects of the study that may influence the subject's willingness to continue in the study, subject information and informed consent form will be revised. After the new documents have received approval by IEC/IRB and regulatory authorities, the subject will be asked to sign the new consent form to confirm his/her continuation in the study.

13.4 Subject Confidentiality

The investigator(s) will respect and protect the confidentiality of the subject in all possible ways. Subject identification, other than subject number and initials, will not appear in any Case Report Form (CRF) pages or other documents given to the Sponsor. Only the investigator and the persons authorized to verify the quality and integrity of the study will have access to subject records where the subject can be identified.

For MSK site only:
MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB/PB).

14 FINANCING AND INSURANCE

14.1 Financial Issues

Financial contracts will be signed between the Sponsor (or its legal representative) and the Investigator (or a representative of the hospital or clinic) before commencement of the study.

All the investigators who are directly involved in the study will be asked to sign Financial Disclosures, according to FDA regulations.

14.2 Insurance

The Sponsor is responsible for insuring all study subjects against any harm caused by study procedures or investigational product.
Other sources of insurance will be added as appropriate in case new countries are enrolled in the study. The source of insurance may be altered without issuing a formal protocol amendment provided that the insurance coverage remains appropriate.

15 STUDY REPORT AND PUBLICATIONS

The Sponsor is responsible for generating a Clinical Study Report of the study after completion of it. This report or parts of it must be submitted to relevant authorities if applicable.

Details of the study will be registered on www.ClinicalTrials.gov. The publication of study results will be agreed between the Sponsor and the Investigator(s). The Sponsor has the right to prevent publication of any confidential information and retains the right to review all publications and presentations before they are made public.

16 REFERENCES