MOFFITT CANCER CENTER

Protocol MCC 16545, IRB #11.05.0007

TITLE	**A Randomized Phase II Study to Assess the Safety and Immunogenicity of recMAGE-A3+AS15 ASCI with or without Poly IC:LC in Patients with Resected MAGE-A3 Positive, Stage IV Melanoma**
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Recombinant MAGE-A3 protein combined with the AS15 adjuvant (recMAGE-A3 + AS15) ASCI provided by GSK Biologicals, SA. (IND 13253)

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SYNOPSIS

This is an open, randomized, two-arm, Phase II study in MAGE-A3 positive patients with completely resected stage IV melanoma to assess the safety, tolerability, immunogenicity and clinical activity (RFS and OS) of recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC as adjuvant therapy compared to recMAGE-A3 + AS15 ASCI alone.

The study will be conducted solely at the Moffitt Cancer Center in Tampa, Florida.

Adjuvant treatment for patients with resectable stage IV melanoma:

Many patients will relapse after surgery for stage IV resectable disease. Surgery of stage IV melanoma is generally not curative and approximately 90% of the patients will ultimately die of metastatic disease by 5 years from diagnosis. There is thus a need for adjuvant therapy to prevent disease relapse after surgical resection of isolated metastases. The role of chemotherapy or high dose interferon alpha-2b as adjuvant treatment remains unclear with no documented tangible benefit in terms of prolonged overall survival.

Non-specific immunotherapy with high-dose interferon has shown activity in disease-free survival in resected stage III disease, but its impact on overall survival in that setting, and in stage IV resected melanoma is less clear. A recent Phase III trial with pegylated interferon in stage III resected disease showed a significant long-term impact of this treatment on relapse-free survival, but not on overall survival. Subgroup analyses further showed that patients with macroscopic lymph node involvement did not derive a significant clinical benefit from this treatment, clouding the outcome for higher risk patients with stage IV resected disease and warranting the development of new treatment options for these patients. Active specific immunization against tumor antigens is certainly one such possible approach.

The recMAGE-A3 Antigen-Specific Cancer Imunotherapeutics (ASCI) has shown promising results in Phase II studies in stage IV melanoma. In a recent Phase II proof-of-concept trial of two different formulations of recMAGE-A3 ASCI in melanoma patients with early metastatic disease (GSK study 249553/008), a strong and robust immunological response was seen, and the safety of the treatments was considered acceptable, raising no specific safety concerns. Objective clinical response was observed for 5 of the 75 patients treated and another 7 patients showed disease stabilization (over periods varying between 5 and 12 months, some still ongoing). These preliminary findings support the development of recMAGE-A3 ASCI as adjuvant therapy for stage IV resected melanoma. A double-blind, randomized, placebo-controlled Phase III trial is currently evaluating the efficacy of recMAGE-A3 + AS15 ASCI versus placebo in patients with resected stage IIIB/C melanoma with macroscopic lymph node involvement (DERMA Study).

Additional support for developing recMAGE-A3 ASCI in the adjuvant melanoma setting may be found in a recent Phase II proof-of-concept trial of MAGE-A3 ASCI as adjuvant therapy for patients with resectable stage IB and II NSCLC. This study (GSK 249553/004) showed a relative reduction of the risk of disease recurrence of 27% in the group receiving the ASCI compared to the placebo group. The immunological responses observed in melanoma patients and NSCLC

patients in the adjuvant and metastatic settings, respectively, are very similar, so it is reasonable to expect that an equivalent tumor response might be seen in the adjuvant melanoma setting.

Taking into account the tumor-specificity of recMAGE-A3, the MAGE-A3 antigen expression levels in stage IV melanoma tumors, the acceptable tolerability of the recMAGE-A3 + AS15 ASCI and the promising results from Phase II proof-of-concept trials (GSK 249553/008 and 249553/004), this Phase II trial will evaluate the immunogenicity of the recMAGE-A3 + AS15 ASCI with or without the toll-like receptor (TLR) agonist Poly IC:LC (Hiltonol) as adjuvant therapy for MAGEA3-positive patients with resected stage IV melanoma that have been rendered free of disease but are at very high risk of relapse.

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC in patients with resected stage IV melanoma.

- To evaluate the immunogenicity of recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC as measured by humoral response (antibodies serum titers) in patients with resected stage IV melanoma.

Secondary Objectives:

- To evaluate the clinical activity of the recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC in terms of relapse-free survival (RFS) and overall survival (OS) in the overall study population.

- To evaluate the immunogenicity of the recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC measured by T cell responses against MAGE-A3 antigen.

- To assess the gene profile of tumor tissue in the two study arms and evaluate the activity of the recMAGE-A3 + AS15 ASCI +/- Poly IC:LC in terms of RFS in the sub-population of patients presenting a potentially favorable gene signature (see Section 6.4.4), and in the sub-population of patients without this gene signature.

Translational Research Objectives:

- Translational research includes assessment of MAGE-A3 expression of tumor tissue from recurrent lesions, and gene profiling of recurrent or new lesions.

Study design:

- Experimental design: Two-arm, open, randomized single center study.
- Treatment allocation: Patients will be randomized (1:1 ratio) to receive either recMAGE-A3 + AS15 ASCI or recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC.
- Blinding: None, open label.
- Treatment groups: Two groups, recMAGE-A3 + AS15 ASCI and recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC.
- Treatment schedule: The study treatment will consist of an Induction phase and a Maintenance phase. During the Induction phase, recMAGE-A3 + AS15 ASCI +/- Poly IC:LC will be administered 5 times at 3-week intervals. During the Maintenance phase, recMAGE-A3 + AS15 ASCI +/- Poly IC:LC will be administered 8 times at 3-month intervals. A total of 13 doses of recMAGE-A3 + AS15 ASCI +/- Poly IC:LC will be administered over a period of 27 months.
- Control: recMAGE-A3 + AS15 ASCI.
- Data collection: Case report form (CRF).
- Duration of the study: The total duration of the study treatment phase (including concluding visit) is 30 months per patient. The duration of active follow-up for survival, recurrence and serious adverse events (SAEs) related to the study participation will be 5 years from the first administration of study treatment.

Main inclusion criteria:

- Patients with histologically proven resected stage IV cutaneous or mucosal melanoma rendered free of disease.
- The patient's tumor expresses MAGE-A3, as determined by RT-PCR analysis on formalin-fixed paraffin-embedded (FFPE) tumor tissue sample obtained during the screening phase.
- ECOG performance status 0 or 1.
- Adequate bone marrow reserve with Hg >10, platelets > 100,000, and WBC >3000 per mm^3.

Number of patients:

The study will enroll up to 44 patients to end up with 40 evaluable patients in two cohorts of 20 patients each.

Endpoints:

Primary endpoints:

- Toxicity and tolerability in the two study arms (recMAGE-A3 + AS15 ASCI and recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC) defined by the adverse events and serious adverse events.

- Immunogenicity in the two study arms (recMAGE-A3 + AS15 ASCI and recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC) defined by antibodies serum titer (such as anti-MAGE-A3).

Secondary endpoints:

- Immunogenicity as measured by T cell responses directed against MAGE-A3 antigen.

- Relapse-Free Survival (RFS), defined as the time from randomization to the date of first relapse of melanoma or of death, whichever comes first.

- Overall Survival (OS), defined as the time from randomization to the date of death.

- A potential correlation between gene expression profile and treatment clinical activity (RFS) in both study arms (recMAGE-A3 + AS15 ASCI and recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC).

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AE	Adverse event
AJCC	American Joint Committee on Cancer
AS	Adjuvant System
ASCI	Antigen-Specific Cancer Immunotherapeutic
ATP	According to protocol
CI	Confidence interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Co-operative Oncology Group
ELISA	Enzyme-linked Immunosorbent assay
FDA	Food and Drug Administration, United States
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GMT	Geometric Mean Titre
GSK Bio	GlaxoSmithKline Biologicals SA
HR	Hazard Ratio
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IND	Investigational New Drug
IRB	Institutional Review Board
MAGE-A3	Melanoma AntiGEn-A3
MCC	MOFFITT CANCER CENTER
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocomptability Complex
PBMC	Peripheral blood mononuclear cell
q	Indicates time interval between administrations of study medication
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAS®	Statistical Analysis System
TNM	Tumor, nodes and metastases

GLOSARY OF TERMS

Adverse event: Any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Adequate contraception: defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly (when applicable, as mentioned in the product label) for example abstinence, combined or progestogen oral contraceptives, injectable progestogen, implants of levonorgestrel, oestrogenic vaginal ring, percutaneous contraceptive patches or intrauterine device (IUD) or intrauterine system (IUS), vasectomy with documented azoospermia of the sole male partner or double barrier method (condom or occlusive cap plus spermicidal agent).

Eligible: Qualified for enrolment into the study based upon strict adherence to inclusion/ exclusion criteria.

Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Study Coordinator: An individual medically qualified to assume the responsibilities of the sponsor, Moffitt Cancer Center, especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.

Patient: Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.

Patient number: A unique number identifying a patient, assigned to each patient as soon as they sign their first informed consent.

ICH defines a protocol amendment as: “A written description of a change(s) to or formal clarification of a protocol.”

Protocol administrative change: A protocol administrative change addresses changes to change: only logistical or administrative aspects of the study.

N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of patients, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.

Randomization: Process of random attribution of treatment to patients in order to reduce bias of selection

Treatment: Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a patient, identified by a unique number, according to the study randomization or treatment allocation.

Treatment number: A unique number identifying a treatment to a patient, according to the study randomization or treatment allocation.

1. INTRODUCTION

1.1. Background

Cutaneous melanoma is the most aggressive form of all skin cancers. Although it represents only 4% of all cancers, its incidence is continuing to rise in the world at a rate exceeding all other cancers [Jemal, 2007]. Worldwide, it is expected that approximately 132,000 people will be diagnosed with melanoma each year and approximately 37,000 people are expected to die of the disease annually.

Surgical resection is the treatment of choice for localized melanoma and results in a large number of cures with a 90% long term survival rate for stage I disease [Van Akkooi et al 2007]. But, patients with resected stage IIB-C (T4N0M0), stage III (T1-4N1-3M0) and stage IV (T1-4, N1-3,M1a-c) disease are at high risk of relapse after definitive surgery [Kirkwood, 2001]. The risk of recurrence after surgery for the stage IV patients is reported to be 90% at five years. [Kirkwood, 2000].

The role of chemotherapy as adjuvant treatment remains unclear with no tangible benefit in terms of prolonged overall survival [Nathan, 1995]. High dose interferon remains the most active adjuvant agent evaluated to date for high risk stage III, but not stage IV melanoma. It has been shown to prolong relapse free survival, while its impact on overall survival in stage III resected disease is less clear [Garbe, 2001]. Recently, the results of a Phase III trial showed that pegylated interferon (PEG-IFN) in resected stage III melanoma patients had a significant and sustained effect on Relapse-Free Survival (RFS) but with no significant effect on Overall Survival [Eggermont, 2007]. The significant long-term effect on RFS was only found in melanoma patients with microscopic nodal involvement. The trial showed no improvement in the safety profile of PEG-IFN as compared to non-pegylated IFN-a [Eggermont, 2007].

Immunity to melanoma appears to be central to disease control. Spontaneous regression has been reported in melanoma, suggesting a role for host immunity, indirectly supported by the presence of lymphoid infiltrate associated with the primary tumor [Balch, 2001]. It has also been shown that patients with melanoma do have tumor rejection antigen recognized by CD4 and CD8 cells [Kadison, 2003].

1.2. recMAGE-A3 + AS15 Antigen-Specific Cancer Immunotherapeutics

1.2.1. Properties of the study investigational products

The primary study investigational product in this trial is an Antigen-Specific Cancer Immunotherapeutic (ASCI) comprising the recombinant protein ProtD-MAGE-A3/His (abbreviated as recMAGE-A3 in the rest of this document) and the GSK proprietary immunological Adjuvant System AS15. The recMAGE-A3 antigen is a 432-amino acid fusion protein containing 109 residues of Protein D, a lipoprotein present on the surface of Haemophilus influenzae B (ProtD), the MAGE-A3 protein, and a polyhistidine tail (His).

MAGE-A3 is a human gene that encodes a tumor-specific antigen (the MAGE-A3 protein) [Van Den Eynde, 1997]. The MAGE-A3 gene is silent in all normal human tissues with the exception of testis and placenta [De Plaen, 1994; Jungbluth, 2007] and is under epigenetic control [Sigalotti, 2002, Jones et al 2005, Baylin et al 2006]. However, the MAGE-A3 antigen is believed to be strictly tumor specific, as the cells, where it is expressed (spermatogonia in testis and trophoblasts in placenta), do not bear Major Histocompatibility Complex (MHC) molecules on their surface and therefore do not present any MAGE-A3 antigen [Boël, 1995; Jungbluth, 2007].

Because of this high tumor specificity, targeting MAGE-A3 with a cancer immunotherapeutic is expected to show a favorable safety profile. The aim of the ASCI approach is to immunize the patients against the antigens that are expressed by their tumor cells and thereby to eradicate these tumors.

The interest in MAGE-A3 is caused by its expression in various tumor types (**Table 1**), and its expression in both early and more advanced disease stages [Brasseur, 1995; Patard, 1995]. Detection of MAGE-A3 expression on tumor samples is easy and can be performed by RT-PCR.

Tumor	MAGE-A3 expression
NSCLC	35-50 %
Melanoma	65 %
Bladder	62 %
Esophagus	47 %
Head & Neck	65 %
Leukemia	29 %
Liver	48 %
Ovary	30 %
Prostate	18 %

Table 1. MAGE-A3 expression in various types of cancer. Adapted from Gure 2005 and GSK Bio data.

The expression of MAGE-A3 may also be associated with poor prognosis. Indeed, Gure et al. observed that survival of patients with Non-Small Cell Lung Cancer (NSCLC) was shorter when MAGE-A3 was highly expressed [Gure, 2005] in comparison to survival of NSCLC patients with low MAGE-A3 expression.

To efficiently elicit a strong and enduring immune response upon injection of recMAGEA3 it is necessary to combine the MAGE-A3 protein with an immunological Adjuvant System. This need was first demonstrated in preclinical studies [Krieg, 2001; Meidenbauer, 2004; Ren, 2004; Speiser, 2005], but was soon after demonstrated in humans. In an early clinical trial evaluating the administration of recMAGE-A3 either alone or in combination with an immunological Adjuvant System, it was shown that combining MAGE-A3 with an immunological Adjuvant System was required to efficiently elicit both humoral and cellular immune responses [Atanackovic, 2004, Brichard et al 2007].

The AS15 Adjuvant System consists of the liquid immunological adjuvant AS01B and the immunostimulatory nucleotide CpG 7909 (which is co-lyophilized with the recMAGE-A3 antigen).

Per dose, the liquid immunological adjuvant AS01B contains 50 µg of QS21 and 50 µg of Monophosphoryl lipid A (MPL) [Moore et al, 1999], made up to 500 µL with a suspension of liposomes. The liposomes are composed of 1000 µg of dioleylphosphatidylcholine (DOPC) and 250 µg of cholesterol, in phosphate-buffered saline (PBS).

There is 420 µg of immunostimulatory nucleotide CpG 7909 per dose. CpG 7909 is a single-stranded oligodeoxynucleotiode of 24 bases in length and containing 4 CpG dinucleotides.

For details of the pre-clinical safety and toxicology of the AS15 Adjuvant System and its components, please refer to the Investigator's Brochure.

In this trial, we will determine whether the addition of another adjuvant, poly IC:LC, a Toll-like receptor agonist [Pulendran 2004, Seya 2006], will improve the immunogenicity of the recMAGE-A3 product with adjuvant AS-15.

1.2.2. Preclinical safety and toxicology tests of recMAGE-A3+AS15

For details of preclinical safety and toxicology tests of recMAGE-A3 and AS15, either separately or in combination, see the Investigator's Brochure.

1.2.3. Previous clinical experience with recMAGE-A3 protein

1.2.3.1. First clinical studies with recMAGE-A3 protein

Several clinical Phase I/II studies with the recMAGE-A3 protein to be used in this study have been performed or are currently in progress. These studies have included mainly melanoma and NSCLC patients, and evaluated recMAGE-A3 either alone or combined with various Adjuvant Systems. Clinical responses to the treatment with recMAGE-A3 have been observed mainly in patients with metastatic melanoma, including partial responses and some complete responses, in certain cases of significant long-term duration. An immunological response could be measured in the group of patients administered the adjuvanted recMAGE-A3 [Marchand, 2003; Atanackovic, 2004; Vantomme, 2004; Kruit, 2005]. These early studies also demonstrated that the recMAGE-A3 administrations are well tolerated.

1.2.3.2. Phase II proof-of-concept study in NSCLC

A study of particular interest for the development of the MAGE-A3 ASCI in the adjuvant melanoma setting is a Phase II proof-of-concept study in the NSCLC adjuvant setting.

This double-blind, randomized, placebo-controlled trial was testing recMAGE-A3 + AS02B as adjuvant therapy in 182 MAGE-A3-positive stage IB and II NSCLC patients after complete surgical resection of the tumor. The treatment phase of the study is finished, but follow-up is still ongoing. The results described here are based on the main analysis performed in November 2006 after a median follow-up of 28 months.

A total of 1214 ASCI injections have been administered to 122 patients and 60 patients have received 561 placebo administrations. The injections were overall well tolerated, with only 3 Grade 3 events (2 cases of pain in extremity and 1 exacerbation of chronic obstructive pulmonary disease (COPD)) considered as possibly related to the ASCI treatment. Only 2 SAEs were considered as possibly related to the treatment with the MAGE-A3 ASCI: one injection site reaction and one exacerbation of COPD.

The primary objective of the trial was to estimate the clinical activity of the treatment in terms of the time-to-recurrence or the disease-free interval. At the time of the main analysis, a Cox regression analysis performed to determine the relative improvement of the disease-free interval showed a 27% relative reduction in the MAGE-A3 ASCI group compared to the placebo group of the risk of cancer recurrence (hazard ratio = 0.73; p = 0.213) [Vansteenkiste, 2007].

1.2.3.3. Phase II proof-of-concept study in metastatic melanoma

The encouraging early clinical data, the high proportion of metastatic melanoma patients with MAGE-A3-positive tumors and the important unmet medical need for these patients prompted the initiation of a Phase II trial in this disease (GSK study 249553/008), conducted in collaboration with the EORTC (EORTC study 16032-18031). In this randomized, open label study, the recMAGE-A3 protein is being administered as first-line treatment for metastatic disease to patients who have progressive metastatic melanoma with regional or distant skin and/or lymph-node lesions (unresectable stage III and stage IV M1a) but without visceral disease. The recMAGE-A3 protein is combined with 2 different Adjuvant Systems, AS02B (38 patients) or AS15 (37 patients). The trial is currently ongoing, with 12 patients still on treatment. The results described here are based on interim analyses performed in October 2007 on the total cohort of 75 patients.

Almost all adverse events observed were of Grade 1 or 2 and injection site reactions, fever and fatigue were by far the most common. In each of the groups, 2 grade 3 events possibly related to the treatment were observed: fatigue and muscle pain in the AS15 group, injection site reaction and tumor flare in the AS02B group. SAEs were reported for 6 patients in the AS02B arm and for 8 patients in the AS15 arm, and all of these except one were assessed to be unrelated to the study treatment. For one SAE, a case of disseminated intravascular coagulation occurring in a patient in the AS15 arm, the investigator assessed that it could not be excluded that this SAE was possibly related to the study treatment.

The clinical activity of the treatments was assessed by the rate of objective clinical response. Of the 37 patients enrolled in the AS15 arm, 3 showed a complete response and 1 developed a partial response. Two of the complete responses are still ongoing, both with a duration of more

than 30 months. One of the 38 patients in the AS02B arm showed a partial response. Another 7 of the patients in the trial experienced disease stabilization for about 6 months or more.

All the patients developed a specific anti-MAGE-A3 antibody response and some of the tested patients also developed a cell-mediated immune response. The observation of the immune responses suggests that the ASCI combining recMAGE-A3 with the AS15 Adjuvant System induces a more robust immunological response, both humoral and cell-mediated.

The preliminary results of this trial showed an acceptable safety profile for the AS15 Adjuvant System and a potential for this ASCI formulation to induce a stronger immune response and lead to higher clinical activity. These findings confirm preclinical and clinical findings suggesting that AS15 is able to induce stronger immune and anti-tumor responses [Krieg, 2001; Meidenbauer, 2004; Ren, 2004; Speiser, 2005]. For this reason, GSK Biologicals has chosen recMAGE-A3 combined with AS15 as the preferred ASCI for development in melanoma and other cancers.

1.2.3.4. Summary of the safety data from previous clinical trials with recMAGE-A3 ASCI

The immunotherapy with recMAGE-A3 appears to be well tolerated. As of February 2008, more than 320 patients have received a total of more than 2,600 doses of recMAGE-A3 combined with 3 different Adjuvant Systems or alone; approximately 500 doses of the MAGE-A3 + AS15 ASCI have been administered to some 60 patients. The AS15 Adjuvant System has also been investigated combined with other antigens in the treatment of patients with prostate cancer or breast cancer.

Most of the adverse events observed in all these studies were to be anticipated and consist of local and systemic symptoms, such as injection site reactions, myalgia and fatigue. These adverse events have mainly been of Grade 1 or 2, but systemic Grade 3 events have occasionally been reported. Except for fatigue, these Grade 3 symptoms have rarely been assessed to be possibly related to the ASCI treatment. Almost all serious adverse events observed in the studies were assessed by the investigators as being unrelated to the study treatment.

Please refer to the Investigator's Brochure for a detailed description of all the clinical studies of the recMAGE-A3 protein and the results in terms of safety, clinical activity and immunological response.

1.2.3.5. Identification of a gene signature being associated with clinical benefit in response to MAGE-A3 ASCI treatment

Microarray gene profiling has been shown to be a powerful technique predicting treatment response or disease relapse in cancer patients, and a number of large scale clinical trials are currently in progress to validate the gene profiles potentially associated with different prognoses [Vantomme, 2004; Weigelt, 2005]. Also in the Phase II melanoma trial (GSK 249553/008), an attempt was made to identify from a tumor biopsy a gene signature that may predict a favorable clinical outcome for patients treated with the recMAGE-A3 + AS15 ASCI [GSK, unpublished].

In this study, tumor samples were tested for gene expression using Affymetrix HU-U133.Plus 2.0 gene chips covering about 47,000 transcripts. Biopsies from 69 patients were tested. In a first step, a supervised comparison was performed in order to find a group of genes able to cluster 11 patients considered as presenting clinical benefit (complete response, partial response, mixed response or stable disease) in one group, and 11 patients with progressive disease in the other group. From this analysis, 41 differentially expressed probe sets (34 genes) that could segregate the patients with progressive disease and the patients with clinical activity were selected. In a second step, these 41 probe sets were used with the gene expression data from 69 patients to predict their clinical status in a hierarchical clustering approach. As a result, 2 clusters were clearly identified: one associated with patients who have progressive disease, and another one associated with clinical benefit. Interestingly, mixed-responders and patients with stable disease clustered with the group of objective responses, suggesting an association between the gene signature and a favorable clinical outcome following the MAGE-A3 ASCI treatment.

Estimated Kaplan-Meier (KM) curves of the Time to Treatment Failure for the recMAGE-A3 + AS15 group of patients from the GSK 249553/008 melanoma trial also suggest that the presence of the gene signature correlates with a favorable clinical benefit in response to the recMAGE-A3 + AS15 therapy. In the GSK 249553/004 Phase II study of stage IB/II MAGE-A3 positive NSCLC patients, the same gene signature was found to be predictive of clinical activity. In both settings (metastatic melanoma and primary NSCLC tumor), approximately 50% of patients present with this predictive gene signature.

This set of genes differentially expressed in patients with clinical benefit in response to the MAGE-A3 ASCI treatment will in this protocol be referred to as the predictive gene signature. Overall, it is considered that selection of NSCLC or melanoma patients with MAGE-A3 positive tumors presenting with the predictive gene signature may increase the efficacy of treatment with recMAGE-A3 ASCIs by a factor of 2. Based on the gene profile data, GSK Biologicals has initiated a Phase II trial to prospectively validate the identified gene signature as a predictive marker of the clinical outcome for patients with unresectable stage III or stage IV M1a disease treated with the recMAGE-A3 + AS15 ASCI.

1.2.4 Rationale for the use of Poly IC:LC in combination with recMAGE-A3 + AS15 ASCI

Polyinosinic-Polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose (Poly-ICLC) is a synthetic double-stranded ribonucleic acid (dsRNA) with broad immune-enhancing effects. These effects include induction of interferons (IFNs) and other cytokines, activation of cellular immunity (T4 cells, natural killer [NK] cells, and macrophages), an immune adjuvant effect, and activation of several nuclear enzyme systems (oligoadenylate synthetase [OAS] and the dsRNA dependent p68 protein kinase [PKR]) involved in antiviral and antitumor host defenses. More recently it has been shown to have broad gene regulatory actions as well.

Poly-IC:LC is a Toll-like receptor 3 agonist (TLT3) has been under clinical investigation since the 1970s, including human trials for a wide variety of neoplastic, viral, and neurologic conditions [Levy 1975, Levy 1984, Levy 1992; Houston 1976, Carter 1987]. The original US IND, held by Dr. Hilton Levy, investigated dose levels of greater than 100 µg/kg of Poly-ICLC.

A separate IND, No. 43,984, was opened in 1995 under which 6 clinical studies have thus far been conducted in approximately 350 glioma or glioblastoma patients. Dose regimens used in these trials generally consisted of 20-µg/kg Poly-ICLC 3 times each week. The degree of adverse effects seen with of Poly-ICLC depends on 3 factors: (1) dose, (2) route of injection, and (3) health status of the patient. Early phase 1 studies were done to determine the maximum tolerated dose, under the assumption that this was also the most effective dose. In these studies of cancer patients, it was found that the maximum tolerated dose was about 12 mg/m^2 when given intravenously in patients who were not terminally ill. Patients typically developed fevers of 40°C, myalgias, arthralgias, malaise, and some nausea and vomiting. Fever was the primary dose-limiting factor. At this dose, the mean serum interferon level was 2000 IU/mL. While the dose of exogenous interferon rarely attains this level, levels of 100 IU/mL after exogenous interferon are associated with the same adverse effects as those in high-dose Poly-ICLC. In most of the early cancer trials, doses around 6 mg/m^2 of Poly-ICLC IV were generally used. Mild (grade 1), transient (less than 7 days) hepatic enzyme elevations were described in a trial of 100 µg/kg Poly-ICLC given intravenously in multiple sclerosis patients. In 3 patients, the elevated enzyme levels were prolonged for greater than 7 days, but in all patients, the enzyme levels returned to normal after temporary discontinuation of the Poly-ICLC. One paralyzed multiple sclerosis patient in this group suffered a fatal pulmonary embolus that was not judged to be due to the drug. Poly-ICLC has been associated with a coagulopathy in dogs, but not in other species (including primates); and there has been no change in the expected incidence of deep venous thrombosis, pulmonary embolus, or coagulopathy in multiple sclerosis, AIDS, or malignant glioma patients on low-dose intramuscular Poly-ICLC. It was subsequently shown that a low dose of Poly-ICLC was better than a high dose for enhancing immune effects, and that the higher dose actually inhibited a number of cell-associated immune functions. It was also found that intramuscular injection brought about much milder side effects. Representative safety data in humans at a dose of 20-µg/kg Poly-ICLC 3 times each week have been reported in 2 clinical trials: Protocol NABTC 01-05 entitled: "An open multicenter trial of Poly-ICLC treatment of newly diagnosed glioblastoma with Poly-ICLC as an adjuvant to external beam radiation" and Protocol NABTC 01-06 entitled: "An open multicenter trial of Poly-ICLC in subjects with recurrent anaplastic glioma." Treatment with Poly-ICLC in these 2 clinical trials appeared to be well tolerated; adverse reactions were usually mild or moderate in nature (grade 1 or 2 by the National Cancer Institute Common Terminology Criteria for Adverse Events scale).

Toll like receptor agonists have been shown to be effective adjuvants and in pre-clinical models poly IC:LC has been shown to be an effective booster of immunity when added to a peptide vaccine. Celis and colleagues have shown that in melanoma mouse models that polyIC:LC is a potent adjuvant for a peptide vaccine with thre addition of an anti-CD40 antibody, or with the addition of other type TLR agonists (Cho and Celis, 2009, Wells et al, 2008)). Studies in infectious disease vaccine models have confirmed the synergy of multiple TLR agonists within a vaccine strategy (Raman al 2010), Different TLR agonists signal via different pathways, again suggesting that combinations of TLR agonists may induce optimal immune responses (Agrawal et a, 2003). Based on the compiled data in which different TLR agonists have been shown to have immunostimulatory activity, it was felt that the combination of the TLR 3 agonist poly IC:LC with ASCI, which contains a CpG ODN TLR9 agonist, was rational.

Based on the doses used in the above trials, and the side effect profile of the drug, a single 1000 µg dose of Hiltonol will be used subcutaneously in the same limb as the recMAGE-3 + AS15 ASCI injections are given. As a function of surface area, the Human Equivalent Dose of 1000µg

of Poly-ICLC corresponds to 5-10µg in the mouse, which is a dose that has marked immunomodulatory effects in multiple animal models. For further details of preclinical safety and toxicology tests of Poly IC:LC, see the Investigator's Brochures.

1.3. Rationale for the study: relapse of patients with resectable stage IV melanoma after surgery

Surgery of stage IV melanoma is not generally curative and approximately 90% of the patients will ultimately die of metastatic disease [Markovic, 2007]. There is thus a need for adjuvant therapy to prevent disease relapse after surgical resection of the primary tumor. The role of chemotherapy as adjuvant treatment remains unclear with no tangible benefit in terms of prolonged overall survival [Nathan, 1995]. Non-specific immunotherapy with high-dose interferon has shown activity on disease-free survival, but its impact on overall survival in stage III resected melanoma is less clear, and there is simply no track record for interferon in resected stage IV melanoma [Garbe, 2001]. Low dose Interferon has been investigated in several studies with patients with stage III disease and did not show any significant improvement in Relapse-Free Survival or Overall Survival. The recent Phase III trial with pegylated interferon showed a significant long-term impact of this treatment on relapse-free survival, but not on overall survival in resected stage III disease [Eggermont, 2007]. Subgroup analyses in this study further showed that patients with macroscopic lymph node involvement did not derive a significant clinical benefit from this treatment, warranting the development of new treatment options for these patients. Active immunization against tumor antigens is certainly one such possible approach.

The recMAGE-A3 ASCI has shown promising results in Phase II studies: In the recent Phase II proof-of-concept trial of two different formulations of the recMAGEA3 ASCI in melanoma patients with early metastatic disease (GSK study 249553/008), a strong and robust immunological response was seen, and the safety of the treatments was considered acceptable, raising no specific safety concerns. Objective clinical response was observed for 5 of the 75 patients treated and another 7 patients showed disease stabilization (over periods varying between 5 and 12 months, some still ongoing). These preliminary findings support the development of the recMAGE-A3 ASCI in the adjuvant melanoma setting, particularly in the stage IV NED setting in which microscopic residual disease makes relapse of disease likely within a year of surgical resection.

Additional support for developing the recMAGE-A3 ASCI in the adjuvant melanoma setting may be found in the Phase II proof-of-concept trial of the recMAGE-A3 ASCI as adjuvant therapy for patients with resectable stage IB and II NSCLC. This study (GSK 249553/004, see Section 1.2.3.2) showed a relative reduction of the risk of disease recurrence of 27% in the group receiving the ASCI compared to the placebo group. The immunological responses observed in melanoma patients and NSCLC patients in the adjuvant and metastatic settings, respectively, are very similar, so it is reasonable to expect that an equivalent tumor response will be seen in the adjuvant resected stage IV melanoma setting.

The justification for adding Poly IC:LC as an adjuvant to recMAGE-A3 + AS15 ASCI are data suggesting in pre-clinical murine models that the use of two different TLR Agonists added to a

vaccine or other immunotherapy approach can augment its anti-tumor activity and immunogenicity, as cited in section 1.2 above. Since the AS15, containing CpG709 and MPL that are a TLR 9 and TLR3 agonists respectively, is well tolerated when added to a recMAGE-3 ASCI, and the Poly IC:LC is a TLR3 agonist that is quite well tolerated as well, the addition of the different agonists seems sensible and is likely to be safe and well tolerated.

Taking into account the tumor-specificity of MAGE-A3, the MAGE-A3 expression levels in stage IV melanomas, the acceptable tolerability of the recMAGE-A3 + AS15 ASCI and promising results from Phase II proof-of-concept trials (GSK 249553/008 and 249553/004), it is proposed to initiate a randomized Phase II trial to evaluate the immunogenicity, safety and tolerability of the recMAGE-A3 + AS15 ASCI with or without TLR 3 agonist Poly IC:LC in patients with stage IV resected melanoma at very high risk of relapse.

2. OBJECTIVES

2.1. Primary objectives

The primary objectives of this clinical trial are:

- To evaluate the safety and tolerability of recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC in patients with resected stage IV melanoma.

- To evaluate the immunogenicity of recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC as measured by antibodies serum titers (such as anti-MAGE-A3) in patients with resected stage IV melanoma.

  Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

- To evaluate the clinical activity of the recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC in terms of relapse-free survival (RFS) and overall survival (OS) in the overall study population.

- To evaluate the immunogenicity of the recMAGE-A3 + AS15 ASCI compared to recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC measured by T cell responses against MAGE-A3.

- To assess the gene profile of tumor tissue in the two study arms and evaluate the activity of the recMAGE-A3 + AS15 ASCI +/- Poly IC:LC in terms of RFS in the sub-population of patients presenting a potentially favorable gene signature (see Section 6.4.4), and in the sub-population of patients without this gene signature.
  Refer to section 10.2 for definitions of secondary endpoints.

2.3. Translational research objectives

- Translational research will include assessment of MAGE-A3 expression of tumor tissue from recurrent lesions and gene profiling of recurrent or new lesions.

3. STUDY DESIGN OVERVIEW

3.1. Study design

This is an open, randomized, two-arm, Phase II study in MAGE-A3 positive patients with completely resected stage IV melanoma to assess the safety, tolerability, immunogenicity and clinical activity (RFS and OS) of recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC as adjuvant therapy compared to recMAGE-A3 + AS15 ASCI alone.

Patients will be randomized (1:1 ratio) to receive either recMAGE-A3 + AS15 ASCI or recMAGE-A3 + AS15 ASCI in combination with Poly IC:LC.

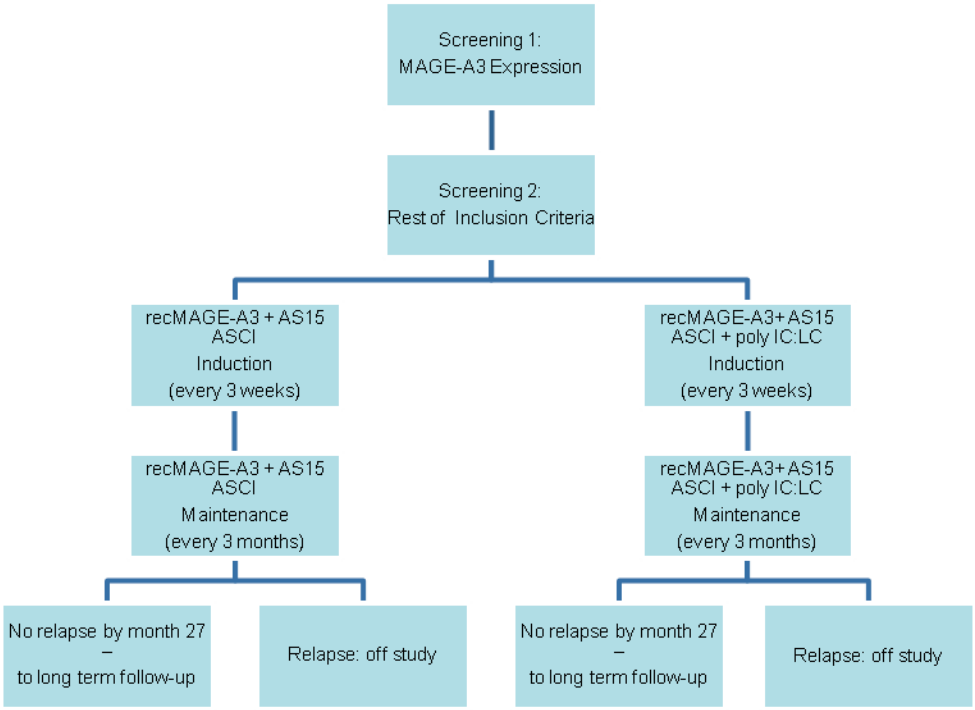


Figure 1. Overview of Study Design.

3.2. Duration of study participation

The total duration of the study treatment phase (from first study visit to concluding visit) is 30 months per patient.

The duration of active follow-up for survival, recurrence and serious adverse events (SAEs) related to the study participation will be 5 years from the first administration of study treatment (refer to Section 8.6).

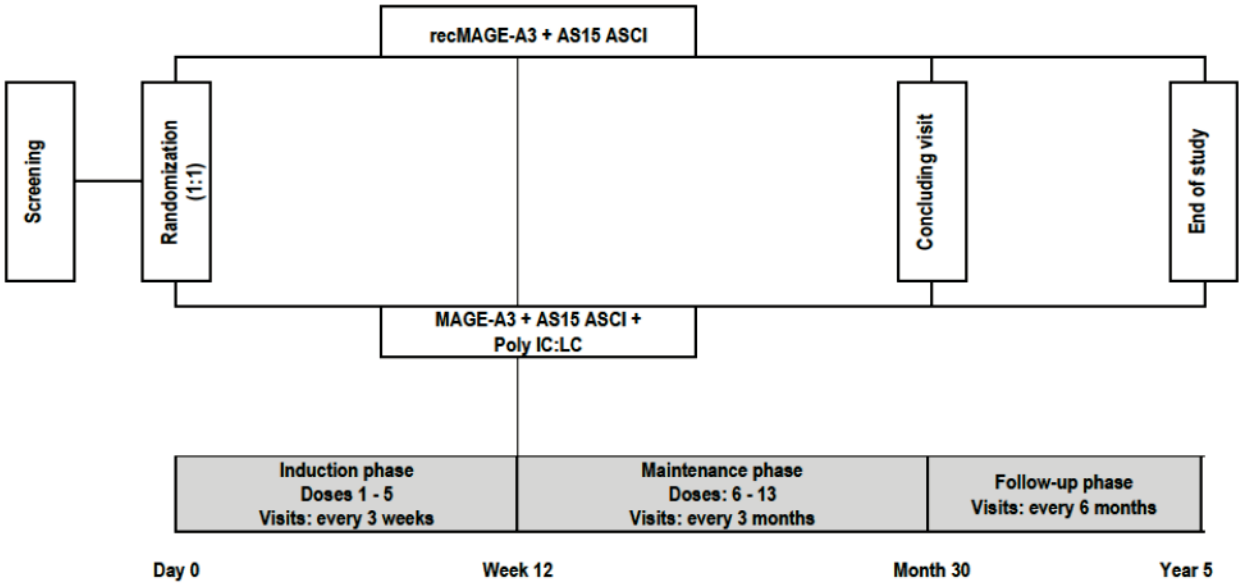


Figure 2. Overview of Design and Duration of Study.

3.3. Treatment allocation

For patients meeting all of the eligibility criteria, the randomization will take place a maximum of 12 weeks after tumor resection and the first dose of study treatment will be administered within 1 week of the date of randomization.

Refer to Section 5.3 for a complete description of the randomization method.

4. STUDY POPULATION

4.1. Number of patients

According to our current assumptions, up to 44 patients will be enrolled in this trial to end up with 40 evaluable patients (considering a possible 10% withdrawal rate from the study) in two cohorts of 20 patients each.

Refer to Section 10.3 of the protocol for a detailed description of the assumptions applied for the calculation of the sample size.

4.2. Inclusion criteria

The following criteria are to be checked at the time of randomization. **A patient may only be included in the study if ALL of the following criteria are FULFILLED:**

1. Written informed consent for the study will be obtained prior to the performance of MAGE-A3 expression screening on resected tumor tissue or any other protocol-specific procedure.

2. Male or female patient with histologically proven and completely resected stage IV cutaneous or mucosal melanoma. In terms of the AJCC classification [AJCC, 2009, see Appendix D], this means that patients with resected M1a-b-c (stage IV) disease may be enrolled.

3. The patient must have been surgically rendered free of disease no more than 12 weeks before the randomization.

4. Patient is equal to or greater than 18 years old at the time of signing the informed consent form.

5. The patient's tumor shows expression of the MAGE-A3 gene, as determined by RT-PCR analysis on formalin-fixed paraffin-embedded (FFPE) tumor tissue. In all patients in whom it can be obtained, a fresh tumor portion of the resected tumor will be stored in RNA later and analyzed for gene profiling (section 6.3.2; section 6.4).

6. The patient has fully recovered from surgery.

7. ECOG performance status of 0 or 1 at the time of randomization.

8. The patient must have adequate bone-marrow reserve, adequate renal function and adequate hepatic function as assessed below by standard laboratory criteria.

Absolute neutrophil count	**$\geq 1.5 \times 10^9$/L**
Platelet count	**$\geq 75 \times 10^9$/L**
Serum creatinine	**≤ 1.5 times the Upper Limit of Normal (ULN)**
Total bilirubin	**≤ 1.5 times the ULN**

Transaminase (ALT - AST) **≤ 2.5 times the ULN**

9. If the patient is female, she must be of non-childbearing potential, i.e. have a current tubal ligation, hysterectomy, ovariectomy or be post menopausal, or if she is of childbearing potential, she must practice adequate contraception for 30 days prior to randomization, have a negative pregnancy test and continue such precautions during the entire study treatment period and for 2 months after completion of the injection series. For further details, refer to Section 6.3.1.2.

10. Men must also agree to use an adequate method of contraception.

11. In the opinion of the investigator, the patient can and will comply with all the requirements of the protocol.

4.3. Exclusion criteria

The following criteria should be checked at the time of randomization. **If any apply, the patient must not be included in the study:**

1. The patient has an ocular melanoma.

2. The patient has in-transit metastases.

3. The patient has been treated or is scheduled to be treated with an adjuvant anticancer therapy after the metastasectomy that qualifies the patient for inclusion in the present trial.

• One prior systemic treatment with an immunomodulator (i.e., interferon, vaccine and/or anti-CTLA-4) after a previous surgery is permitted, provided that the last dose has been administered at least 45 days before randomization in the present trial.

• Previous radiotherapy is permitted, provided that the treatment has been completed before the surgery that qualifies the patient for participation in the present trial .

4. The patient requires concomitant chronic treatment (more than 7 consecutive days) with systemic corticosteroids or any other immunosuppressive agents. The use of prednisone, or equivalent, at a dose of < 0.125 mg/kg/day (absolute maximum 10 mg/day) or topical steroids is permitted.

5. Use of any investigational or non-registered product (drug or vaccine) other than the study treatment within 30 days preceding the randomization or planned use during the study period.

6. The patient has a history of autoimmune disease such as, but not limited to, multiple sclerosis, lupus, and inflammatory bowel disease. Patients with vitiligo are not excluded.

7. The patient has a family history of congenital or hereditary immunodeficiency.

8. The patient is known to be positive for Human Immunodeficiency Virus (HIV) or has another confirmed or suspected immunosuppressive or immunodeficient condition.

9. History of allergic disease or reactions likely to be exacerbated by any component of the treatments.

10. The patient has psychiatric or addictive disorders that may compromise his/her ability to give informed consent or to comply with the trial procedures.

11. The patient has concurrent severe medical problems, unrelated to the malignancy, that would significantly limit full compliance with the study or expose the patient to unacceptable risk.
12. The patient has previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers or carcinoma in situ of the cervix or effectively treated malignancy that has been in remission for over 5 years and is highly likely to have been cured.

13. The patient has an uncontrolled bleeding disorder.

14. For female patients: the patient is pregnant or lactating.

5. INVESTIGATIONAL PRODUCTS AND ADMINISTRATION

5.1. Study treatment: recMAGE-A3 + AS15 ASCI and Poly IC:LC

The recMAGE-A3 + AS15 ASCI to be used in this study have been developed and manufactured by GSK Biologicals; Oncovir manufactures the Poly IC:LC (Hiltonol).

The Quality Control Standards and Requirements for these products are described in separate release protocols, and the required approvals have been obtained by manufacturers.

5.1.1. recMAGE-A3 + AS15 ASCI

In the study, the recMAGE-A3 + AS15 ASCI will be administered by using a sterile two-vial set comprising:

• One vial with the lyophilized preparation containing 300 µg recMAGE-A3 antigen plus 420 µg of CpG7909 (a part of the Adjuvant System AS15),

• One vial with liquid adjuvant diluent AS01B (liposomes containing 50 µg of MPL®, 1mg of DOPC, 250 µg of cholesterol and 50 µg of QS21 in phosphate-buffered saline), making up the remainder of the Adjuvant System AS15. The final recMAGE-A3 + AS15 ASCI for administration is obtained by reconstitution of the lyophilized preparation with the adjuvant diluent. One recMAGE-A3 + AS15 ASCI dose consists of 0.5 ml.

5.1.2. Poly IC:LC (Hiltonol)

Poly IC-LC (Hiltonol) is a synthetic, nuclease resistant, hydrophilic complex of polyinosinic and polycytidylic acid, stabilized with poly-L-lysine and carboxymethylcellulose. Poly-ICLC is an opalescent solution in 2-mL vials. Each 1 mL of Poly-ICLC for injection contains 2-mg poly-IC, 1.5-mg poly-L-lysine, and 5-mg sodium carboxymethylcellulose in 0.9% sodium chloride solution and adjusted to pH 7.6 to 7.8 with sodium hydroxide**.**

How supplied
Poly-ICLC is supplied in single-use vials containing 1 mL of a 2 mg/mL opalescent solution. A total of 0.5 ml = 1 mg is withdrawn from the vial using sterile technique and is administered deep subcutaneously as supplied.

Each vial poly-ICLC will be labeled with the following information:

Drug Name
Concentration
Storage Conditions
Lot Number
Date of Manufacture, Manufacturer
Investigational Use Statement

Storage and stability
Poly-ICLC is stable at room temperature for brief periods (days). Treatment sites are asked to store the drug at approximately 40° F. Patients should be advised to store their doses in a standard refrigerator; when necessary, vials may be kept at room temperature up to 24 hours. The vials should not be frozen.

Supplier
The drug to be used in this study is prepared and packaged under GMP, under contract to Oncovir, Inc. It is then tested for quality, activity and pyrogenicity by Oncovir, Inc.

Drug accountability
The intent of drug accountability is to assure that supplied agents are only used for patients enrolled on an approved trial. According to FDA guidelines the investigator is ultimately responsible for all agents shipped in his/her name. FDA regulations require investigators to establish a record of the receipt, use, and disposition of all investigational agents. The sponsor of investigational trials has the responsibility to assure the FDA that systems for drug accountability are being maintained by investigators in their clinical trial program. Investigators may delegate responsibility for drug ordering, storage, accountability and preparation to his/her designee.

Drug ordering information: [redacted]

[redacted]

[redacted] [redacted]

5.2 Dosage and administration

The investigator or designate will subsequently withdraw the reconstituted ASCI mixture, change the needle, and 0.5 ml will be injected slowly (over approximately 30 seconds) intramuscularly into the deltoid or the lateral region of the thigh, alternately on the right and left side. The injections may not be administered in anatomical regions where lymph nodes have been excised. The Poly IC:LC will then be administered in the same thigh deep subcutaneously, 10 minutes later, just proximal by 5 cm.

Criteria for postponement or permanent discontinuation of administration of the study treatment are described in Sections 5.2.1.1 and 5.2.1.2.

The patients will be observed closely for at least 30 minutes following the administration of the study medication, with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

<table>
<tr><th rowspan="2">Treatment</th><th rowspan="2">Dose</th><th colspan="2">Administration</th></tr>
<tr><th>Timing</th><th>Route and site</th></tr>
<tr><td colspan="2">ASCI Arm</td><td rowspan="5">Induction: q3w x 5
Maintenance: q3m x 8</td><td rowspan="3">IM
Deltoid or lateral region of the thigh
Alternate on right and left side</td></tr>
<tr><td>recMAGE-A3 + AS15 ASCI</td><td>0.5 ml corresponding to 300 µg of recMAGE-A3 antigen and 420 µg CpG reconstituted in AS01B</td></tr>
<tr><td colspan="2">ASCI + Poly IC:LC Arm</td></tr>
<tr><td rowspan="2">recMAGE-A3 + AS15 ASCI + Poly IC:LC</td><td>0.5 ml corresponding to 300 µg of recMAGE-A3 antigen and 420 µg CpG reconstituted in AS01B</td></tr>
<tr><td>+plus additional IM injection of 0.5 ml or 1 mg Poly IC:LC</td><td>Deep subcutaneously, 10 minutes later and proximal by 5 cm to ASCI</td></tr>
</table>

Table 2. Dosage and administration.

5.2.1. Contraindications to subsequent treatment administration

The criteria in the following subsections should be checked at each visit subsequent to the first. If any of these events occurs during the study, this will require appropriate action, i.e., interruption of the treatment with postponement of the next study treatment administration (Section 5.2.1.1) or permanent stopping of study treatment (see Section 5.2.1.2).

5.2.1.1. Criteria for postponement of study treatment

If any one of the following events occurs at the time scheduled for administration of the study treatment, the patient may be treated at a later date (i.e., the entire program of study visits and immunizations is interrupted), within the time window specified below, or withdrawn at the discretion of the investigator. The patient must be followed until resolution of the event, as with any AE.

- Acute disease at the time of treatment administration. (Acute disease is defined as the presence of a moderate or severe illness with or without fever). Study treatment can be administered to persons with a minor illness such as diarrhea or mild upper respiratory infection.

- Any Grade 2 or more adverse event possibly related to the study treatment and that is present at the time of treatment administration. In case of postponement of study treatment administration for any of the above reasons, the following rules have to be followed:

- During the induction phase (study treatment administration number 1 to 5), the maximum delay for postponement of study treatment administration is 3 weeks.

- During the maintenance phase (study treatment administration number 6 to 13), the maximum delay for postponement of study treatment administration is 3 months. When a study treatment administration has to be postponed, a visit to administer the missed treatment should be planned as soon as possible to catch up with the originally planned schedule.

If the administration occurs within the specified delay, the treatment dose to administer corresponds to the next one in the initial order of administration. Example: if a patient has already received doses 1 and 2 of study treatment but the administration of dose 3 of study treatment has to be postponed, the patient will receive dose 3 if (s)he comes for her/his next administration a maximum of 3 weeks after the originally planned date of Visit 3 (refer to Table 3).

If the administration does not occur within the delay stated above, the missed dose will not be administered. At the time the patient reintegrates the study, (s)he will receive the dose as planned in the initial schedule of administration. Example: if a patient has already received doses 1 and 2 of study treatment but the administration of dose 3 of study treatment has to be postponed for more than 3 weeks, the patient will receive dose 4 if (s)he comes for his/her next administration (refer to Table 4).

The next doses will be planned at a time allowing:

- A minimum of 14 days between 2 treatment administrations,

• To keep up with the schedule as based on the date of first study treatment administration.

	Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Initial schedule	Visit	1			2			3			4			5
	Dose	1			2			3			4			5
Actual schedule due to postponement	Visit	1			2			~~3~~		3		4		5
	Dose	1			2					3		4		5

Administration postponed for 2 weeks

2 weeks delay for next doses

a. Also applies for postponement up to 3 months during maintenance phase.

Table 3. Example of postponement of study treatment dose for a maximum of 3 weeks during Induction Phase[a].

	Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Initial schedule	Visit	1			2			3			4			5
	Dose	1			2			3			4			5
Actual schedule due to postponement	Visit	1			2			3				4		5
	Dose	1			2			X				4		5

Administration postponed for 4 weeks

2 week delay for next dose

a. Also applies for postponement up to 3 months during maintenance phase.

Table 4. Example of postponement of study treatment dose for more than 3 weeks during Induction Phase[a].

5.2.1.2. Criteria for permanent stopping of study treatment and Dose Limiting Toxicity

If any of the following criteria becomes applicable during the study, the patient will be required to discontinue the study treatment:

a. Evidence of disease relapse (see Section 6.3.12 for the definition of relapse).

b. Treatment for melanoma with one of the following:

• Investigational product or non-registered product other than the study recMAGE-A3 + AS15 ASCI +/- Poly IC:LC.

• Other anticancer treatments, including but not limited to chemotherapeutic or immunomodulating agents and radiotherapy.

c. Any Grade 2 or more allergic reaction following the administration of study treatment.

d. Any intolerable adverse event defined as any grade 3 or 4 toxicities felt to be treatment related; or, any persistent moderate adverse event defined as a grade 2 toxicity that could be worsened by subsequent administration of the study treatment, at the investigator's discretion.

e. Clinical signs or symptoms indicative of vasculitis, glomerulonephritis or any autoimmune disorder of grade 3 or more, excluding vitiligo or thyroiditis that can be treated with replacement therapy; in such cases, appropriate clinical and laboratory testing will be performed to identify and characterize that disorder.

f. Appearance of any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection, or any medical condition requiring the administration of immunosuppressive agents or systemic corticosteroids.

g. Inability of the patient to complete the study evaluations/visits because of unforeseen circumstances.

h. The patient develops other conditions for which, in the investigator's opinion, it is in the patient's best interest to be withdrawn from the study treatment.

i. The patient requests to be withdrawn from the study.

j. For female patients, pregnancy or decision to become pregnant (see Section 8.12).

Procedures to be followed in any of these situations are described in Section 6.3.10.2.

5.3. Treatment assignment and randomization

5.3.1. Patient identification

Patient numbers will be assigned sequentially to patients as soon as they sign the informed consent form consenting to participate in the study.

After the patient has signed the informed consent form, the investigator will enter the patient into the screening section of the CRF. General demographic details and tumor characteristics will be entered in the screening section for each patient for whom a tumor sample is sent for analysis of MAGE-A3 expression (GSK Biologicals or contracted lab). When a patient is eligible (i.e., meets all the inclusion criteria and does not meet any of the exclusion criteria), the investigator or an authorized designee will continue with the actual CRF for this patient.

5.3.2. Randomization

Randomization will take place when it has been ascertained that the patient is fully eligible and at most 1 week before administration of the first injection of the study product, which will take place a maximum of 12 weeks after surgery.

Randomization of patients and treatment allocation at the investigator site will be performed utilizing the Moffitt Cancer Center's Subject Registration and Randomization Server, a web-based interactive randomization system (available 24H/day, 7D/week). It will be open-label and stratified on the following variables:

1. M Stage of the disease (M1a vs. M1b vs. M1c)

2. Prior treatment with IFN or anti-CTLA-4 (Yes or No)

The list of randomization numbers will be generated by the study statistician and passed on to Moffitt Research IT at MCC to be programmed in the automated web-based randomization system for this specific trial.

Randomization will be performed a maximum of 1 week before the first study treatment administration, which is assigned as Visit 1. Figure 3 presents the timeline for obtainment of patients' informed consent and the procedures to be performed before the beginning of the study.

After having verified that the patient is fully eligible and having obtained the patient's informed consent to participate in the study, the person in charge of the treatment administration will access the randomization system on Internet. Upon providing a patient number and the stage, and prior treatment with IFN or anti-CTLA-4, the randomization system will use the stratified randomization method to determine the treatment number to be used for the patient.

The actual treatment number used for each treatment administration of the patient must be recorded in the CRF. As soon as the targeted number of randomized patients has been reached, the enrollment of patients will be frozen. However, to allow patients at the screening phase or those who have signed the informed consent form at the time of enrollment hold to be enrolled, an over-enrollment of 5% (4 patients) will be allowed.

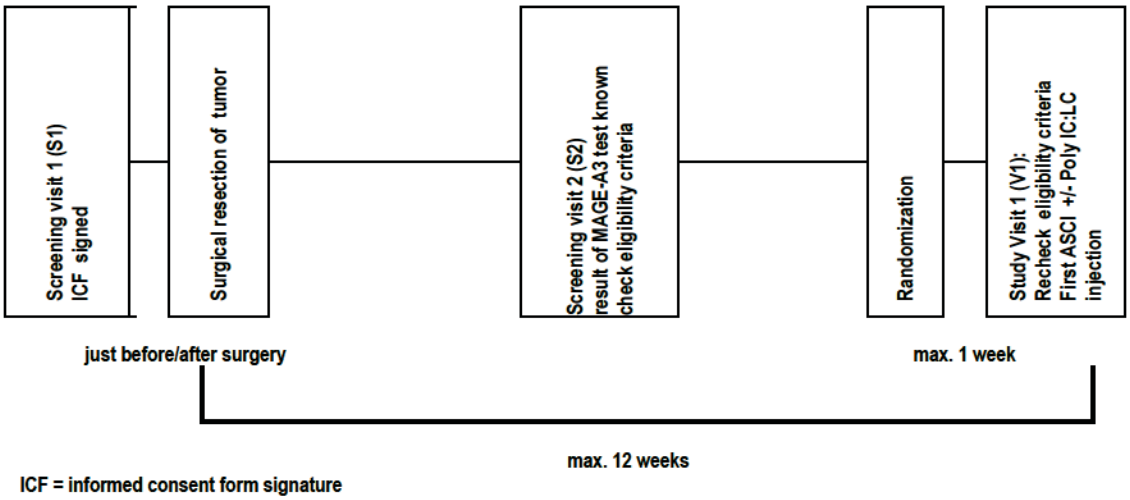


Figure 3. Timelines for pre-study procedures and obtaining informed consent.

5.4. Storage

All investigational products must be stored in a safe and locked place with no access by unauthorized personnel.

The ASCI treatments will be stored at the defined temperature range (i.e., +2 to +8°C/ 36°F to 46°F).

The storage temperature of treatments will be monitored daily by means of validated temperature monitoring devices and the temperature measurements will be recorded during working days, preferably at the same time of the day (e.g., at the beginning of the day). Freezing indication will be continuously controlled by an appropriate device placed close to the treatment(s) and recorded daily during working days, preferably at the same time of the day (e.g., at the beginning of the day).

Please refer to the Pharmacy Manual for further details.

5.5. Packaging

Please refer to the Pharmacy Manual for further details.

5.6. Treatment accountability

The Sponsor, MCC, is responsible of the Study Drug accountability.

5.7. Concomitant medication/treatment

At first study visit (Visit 1), the investigator should record the chronic medication, i.e., any medications taken by the patient from a minimum of 6 months before the surgical resection of the tumor.

At each study visit, the investigator should question the patient about any medications taken.

All concomitant medications (including changes in chronic medication but not chronic medication itself - see next paragraph), with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with administration of each dose of study treatment and ending 30 days after each dose of study treatment are to be recorded with generic name of the medications (trade names are allowed for combination drugs, i.e., multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment.

5.7.1. Permitted medications

Patients should receive medication appropriate to their health condition during the whole study.

During the period starting with administration of each dose of study treatment and ending 30 days after the administration of each dose, concomitant medications administered for the treatment of an AE must be recorded in the CRF with generic name of the medications (trade names are allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment. Similarly, concomitant medications administered for the treatment of a SAE, at any time, must be recorded on the SAE screens in the CRF, as applicable (Refer to Section 8.2 for the definition of a SAE).

5.7.2. Prohibited medications or non-drug therapies

Patients may not receive concomitant treatment during the study with any of the following:

a. Investigational or non-registered product for melanoma other than the recMAGE-A3 + AS15 ASCI ± Poly IC:LC.

b. Other anticancer treatments, including but not exclusively, chemotherapeutic, immunomodulating agents and radiotherapy.

c. Chronic use (more than 7 consecutive days) of systemic corticosteroids or any other immunosuppressive agents.

The use of prednisone, or equivalent, < 0.125 mg/kg/day (absolute maximum 10 mg/day), inhaled corticosteroids or topical steroids is permitted.

d. Administration of a vaccine not foreseen by the study protocol during the period within the prohibited time as specified in Section 5.8.3.

e. Repetitive administration of immunoglobulins and/or any blood products during the study period.

Any of these specifically contraindicated treatments and/or medications administered at any time during the study period are to be recorded in the CRF with generic name of the medications (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment.

If any of these is taken, it will require either permanent discontinuation of study treatment (see Section 5.2.1.2) or may determine a patient's evaluability in the according to protocol (ATP) analysis (see Section 10.3.1 for definition of study populations to be evaluated).

5.7.3. Time-window for prophylactic vaccination against infectious diseases

Immunization with any commercial anti-infectious vaccine may be performed during the study. However, this may not take place during the period from 7 days before any study treatment administration to 7 days after it. Thus, if the study treatment is to be given on a notional Day 0, then immunization with any commercial vaccine may be performed on or before Day -8, and on or after Day 8.

Any commercial vaccine administered in the period beginning 30 days preceding each dose of study treatment and ending one month (minimum 30 days) after each dose of study treatment is to be recorded with trade name, route of administration and date(s) of administration.

Any investigational medication or treatment administered throughout the study period (i.e., from Day 0 through Visit 13) must be recorded in the CRF.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. General study aspects

6.1.1. Attendance for study visits

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed.

The timing for study visits can be found in Section 6.2. Permitted deviations from the stipulated date of visit (due e.g., to week-ends or public holidays) will be as follows:

Induction phase ± 4 calendar days.

Maintenance and follow-up phases ± 14 calendar days.

In case of deviations exceeding these limits, the sponsor, MCC will decide whether the violation is to be regarded as:

- A minor violation (i.e., without consequence),
- A major violation (resulting in exclusion of the patient from the population of patients evaluable according to protocol).

When a study treatment has to be postponed (refer to Section 5.2.1.1 for details on postponement of study treatment), the next study visit should be planned at a time allowing:

- A minimum of 14 days between 2 treatment administrations,
- To keep up with the schedule as based on the date of first study treatment administration (Visit 1).

6.2. Outline of study procedures

6.2.1. Induction phase

The first administration of study treatment (Visit 1) will take place a maximum of 12 weeks after surgical resection of the tumor.

Study phase:	**INDUCTION (V1-V5)**						
Time with respect to resection			max. 12 w after resection	-	-	-	-
Study visit no.	**S1** [a]	**S2**	**1**	**2**	**3**	**4**	**5**
Study treatment administration no.			1	2	3	4	5
Time after first study treatment administration			0	3 w	6 w	9 w	12 w
Informed consent	● [a]						
MAGE-A3 expression analysis [b]	●						
Inclusion and exclusion criteria	●	●					
Medical history	●	●					
Patient randomized		●					
Efficacy assessments							
Neck, chest , abdomen and pelvic CT scans		●					●
Brain MRI scan		● [c]	[c]	[c]	[c]	[c]	[c]
Physical examination	●	●	●	●	●	●	●
Safety assessments							
Adverse events recorded			●	●	●	●	●
pIMD recorded			●	●	●	●	●
Serious adverse events recorded		● [e]	●	●	●	●	●
Laboratory assays							
Blood samples taken for:							
Haematology	●	●					●
Blood chemistry	●	●					●
Blood samples taken for							
Humoral immunity [d]			●		●		●
Leukapheresis for cellular immune assays			●				●
Cellular immune assays [h]			●				●
Pregnancy test (for female patients) [f,g]		●	●	[g]	[g]	[g]	●
Investigational product							
Criteria for permanent stopping or postponement of study treatment				●	●	●	●
Recording of concomitant medications			●	●	●	●	●
recMAGE-A3 + AS15 +/- Poly IC:LC administration			●	●	●	●	●

w = weeks. Pts = patients.

a. Since fresh tissue is to be used, the informed consent must be signed before surgery.
b. MAGE-A3 screening must be performed on tissue removed during surgical resection. For the rapidity of testing and quality of the slides, tissue should be analyzed as soon as possible after operation. Part of the tissue will be used for the predictive gene list associated to treatment. Only tumor tissue from patients likely to meet all inclusion criteria should be sent for testing.
c. Brain MRI scan performed up to 4 weeks before treatment. As an alternative, brain CT is allowed if an MRI is contraindicated.
d. 10 mL of blood sample taken for examination of humoral immunity.
e. SAEs related to study participation and concomitant medications should be recorded.
f. A pregnancy test must be performed every 3 months for female patients of childbearing potential.
g. A pregnancy test should be performed at any time during the study if the investigator/patient suspects that pregnancy has occurred.
h. Eight green tops totalling 70 mL of blood for PBMC will be taken in patients who agree on days 1, 3, 7, 14 and 21 after the first and 5th treatments for assays of cellular immunity

Note: ● is used to indicate a study procedure that requires documentation in the individual CRF. ○ is used to indicate a study procedure that does not require documentation in the individual CRF.

Table 5. Timing of study visits and the assessments to be performed (Induction Phase)

6.2.2. Maintenance phase

Study phase:	MAINTENANCE (V6-V13)								Concluding visit
Study visit no.	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14** [a]
Study treatment administration no.	6	7	8	9	10	11	12	13	-
Weeks after 1. study treatment administration	24	36	48	60	72	84	96	108	120
Months after 1. study treatment administration	6	9	12	15	18	21	24	27	30
Efficacy assessments									
Neck, chest, abdomen and pelvic CT scans	●	[b]	●	[b]	●	[b]	●	[b]	●
Physical examination	●	●	●	●	●	●	●	●	●
Safety assessments									
Adverse events recorded	●	●	●	●	●	●	●	●	●
pIMD recorded	●	●	●	●	●	●	●	●	●
Serious adverse events recorded	●	●	●	●	●	●	●	●	●
Laboratory assays									
Blood samples taken for:									
Haematology			●				●		●
Blood chemistry			●				●		●
Humoral immunity		●	●		●				●
PBMC for cellular immune assays		●			●		●		●
Pregnancy test (for female patients) [c, d]	●	●	●	●	●	●	●	●	●
Investigational product									
Criteria for permanent stopping or postponement of study treatment	●	●	●	●	●	●	●	●	
Recording of concomitant medications	●	●	●	●	●	●	●	●	●
recMAGE-A3 + AS15 +/- Poly IC:LC administration	●	●	●	●	●	●	●	●	
Treatment conclusion									● [e]

As a convention, 1 month is defined as 4 weeks, i.e., 28 days, during the treatment phase.

a. The procedures of this visit are also to be carried out in case of relapse or early withdrawal.
b. To be repeated/performed at any time if clinically indicated.
c. A pregnancy test must be performed every 3 months for female patients of childbearing potential.
d. A pregnancy test should be performed at any time during the study if the investigator/patient suspects that pregnancy has occurred.
e. After concluding visit, patients will be followed-up every 6 months until relapse or for up to 5 years from the first administration of study treatment. Refer to Table 7 for details on the follow-up phase.
f. 10 mL of blood sample taken for examination of humoral immunity. It may also be used for translational research.
g. Pictures should be taken document cuatneous recurrences

Table 6. Timing of study visits and the assessments to be performed (Maintenance Phase and Concluding Visit)

6.2.3. Follow-up period

The duration of active follow-up for survival, recurrence and serious adverse events (SAEs) related to study participation and concurrent medications will be up to 5 years from the first

study treatment. The procedures described in the table below will be performed for patients having completed study treatment or for patients withdrawing from treatment prior to completion for reasons other than recurrence.

After relapse, annual post-study contacts, e.g., by telephone, will be instituted to follow the patients for survival.

Study phase:	**FOLLOW-UP (F1 - F n+1)**					
Study visit no.	**F1**	**F2**	**F3**	**F4**	**F5 to Fn** [a]	**Fn+1**
Date of concluding visit (CV) + no. of months	CV+6m	CV+12m	CV+18m	CV+24m	CV+…[a]	60 m
Safety assessments						
pIMD recorded	•	•	•	•	•	•
Serious adverse events related to study participation and GSK concomitant medications recorded	•	•	•	•	•	•
Laboratory assays						
Blood samples taken for: Humoral immunity[c]		•				
Efficacy assessments						
Neck, chest, abdomen and pelvic CT	•	[b]	•	[b]	•	•
Physical examination	•	•	•	•	•	•

Months are here defined as calendar months.

a. These visits will be started 6 months after the concluding visit (whether the patient completed the scheduled 13 injections or was withdrawn from the study treatment before completion) and will be repeated every 6 months until 5 years after first study treatment administration are reached.

b. To be repeated at any time if clinically indicated..

c. 10 ml of blood sample taken for examination of humoral immunity. It may also be used for optional translational research.

Table 7. Timing of study visits and the assessments to be performed (Follow-up Phase)

6.3. Detailed description of study visits

The patients will be observed closely for at least 30 minutes after the administration of study treatment with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the injection.

The patients will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

6.3.1. Screening phase: Procedures from surgical resection until Visit 1 of the study

6.3.1.1. Visit S1

In addition to whatever other medical procedures are performed, the following (study specific procedures) will be carried out:

Before or after the tumor resection, the patient will be informed about specific aspects of the study (Section 11.1.2) and will sign the informed consent which includes retention and testing of

tumor tissue for MAGE-A3 expression and expression of a predictive gene list associated to treatment. Testing for MAGE-A3 expression will not be completed until informed consent has been obtained regardless of when the tumor resection was performed.

6.3.1.2 Visit S2

This visit will take place after V1, once the results of MAGE-A3 expression testing are known.

The inclusion and exclusion criteria will be evaluated. Only patients who, in the opinion of the investigator, meet all inclusion criteria and none of the exclusion criteria may be included in this study. The following will also be performed at visit S2:

Pregnancy test (for women of child-bearing potential)

When considering the enrollment of females of childbearing potential, please take note of the following definitions:

• Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly (when applicable, as mentioned in the product label) for example abstinence, combined or progestogen oral contraceptives, injectable progestogen, implants of levonorgestrel, oestrogenic vaginal ring, percutaneous contraceptive patches or intrauterine device (IUD) or intrauterine system (IUS), vasectomy with documented azoospermia of the sole male partner or double barrier method (condom or occlusive cap plus spermicidal agent).

For azoospermia, “documented” refers to the outcome of the investigator's or his/her designee’s medical examination of the patient or review of the patient's medical history for study eligibility, as obtained via a verbal interview with the patient or from the patient’s medical records.

• Post-menopause: Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 12 consecutive months without menses with an appropriate clinical profile (for example, at the appropriate age e.g., > 45 years).

• The patient’s medical history (inclusive cancer history) will be recorded.

• SAEs related to study participation or concomitant medications are recorded (see Section 8.2).

• Blood sampling for safety haematological and chemical assays (15 ml, as described in Section 6.4.2).

• Neck and chest CT scan, complete abdomen CT scan and pelvic CT scan within 4 weeks preceding treatment.

• Brain MRI scan. If such a scan has been performed up to 4 weeks before treatment, this need not be repeated. Brain CT may be used instead of brain MRI scan if patients are unable to have an MRI, i.e. due to placement of a pacemaker or defibrillator, etc.

• Physical examination

• When the patient is eligible (meets all of the inclusion criteria and none of the exclusion criteria), randomization via the internet will take place (for procedure see Section 5.3.2). A maximum period of 2 weeks is allowed between randomization and the first administration of the study drugs.

6.3.2. Resection procedure

After resection, formalin-fixed paraffin-embedded (FFPE) tumor tissue will be tested for MAGE-A3 expression. A paraffin-embedded tissue block sample of at least 10 mm^3 or alternatively 20 unstained slides (19 slides of 10 µm and 1 slide of 5 µm for a total of at least 100 mm^2 tumor tissue) will be provided to GSK Biologicals or a contracted lab. The laboratory will then extract the RNA from these samples and assess the MAGE-A3 expression by quantitative PCR. If there are several melanoma blocks, it is preferred that 2 of these are sent for determination of MAGE-A3 expression (As described above, a FFPE block of at least 10 mm^3 is preferred). The second block will only be tested, in case the first tested is MAGE-A3-negative. The patient will be considered eligible on this criterion, if at least one tested block is MAGE-A3-positive. The gene profile analysis performed by GSK Biologicals or a contracted laboratory will be performed on RNA extracted from fresh tumor tissue obtained from the biopsy and stored in RNA later. Gene expression profiling including the presence or absence of the predictive gene signature will be assessed by an appropriate technology such as qRT-PCR, microarray or IHC on these samples and correlated with the patient's clinical data. Additional gene profiling might be performed in the screening FFPE tumor samples sent for MAGE-A3 screening.

Confirmation of the pathological diagnosis (melanoma stage IV) will be made by the pathologist at MCC using a FFPE section. The extent of sampling is to be entered into the patient's CRF.

6.3.3. Visit 1: First study treatment administration

This visit will take place a maximum of 12 weeks after resection.

The following pre-administration procedures will be performed:

- Physical examination including ECOG performance status and disease assessment.
- Blood sampling for baseline humoral immunity assays will be taken (10 ml, as described in Section 6.4.2).
- Leukapheresis
- Female patients will undergo a urine or serum ßHCG pregnancy test (if applicable; see Section 6.3.1.2 for definition of female of childbearing potential). For female patients of

childbearing potential, pregnancy test results must be negative before the first administration of study treatment. For these patients, a pregnancy test will be repeated every 3 months and should be performed at any time during the study if the investigator or patient suspects that pregnancy has occurred while the patient was being treated on protocol therapy.
- Recording of concomitant medications (as described in Section 5.8)
- Recording of potential immune-mediated disease (pIMD).
- SAEs related to study participation or concomitant medications are recorded (see Section 8.2)

The leukapheresis will be performed within 1 week of starting treatment .

Study treatment administration and other procedures will be as follows:

- The patient will receive the randomized study treatment (recMAGE-A3+AS15 ASCI +/- Poly IC:LC given intramuscularly in the deltoid or preferably in the lateral region of the thigh; see Section 5.2) and will thereafter be kept under close observation for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the injection.

- Any (serious) adverse events that occurred during the study treatment will be recorded.

- For patients who agree, eight green tops of blood totaling 70 mL will be taken on days 1, 3, 7, 14 and 21 after the first and fifth doses of study drugs for assessment of T cell reactivity. Day 21 after the first dose of study drug would be the day of the second injection of study drug. These assays will be performed by [redacted]

6.3.4. Visit 2: Second study treatment administration

This visit will take place 3 weeks ± 4 calendar days after the day of the first administration (Visit 1).

The pre-administration procedures for this visit will be:

- Physical examination (as at Visit 1, including ECOG performance status and disease assessment).
- Recording of (serious) adverse events and autoimmune diseases.
- Recording of pIMD.
- A pregnancy test should be performed at any time during the study for all women of child-bearing potential if the investigator or patient suspects that pregnancy has occurred while the patient was being treated on protocol therapy.

In addition:
- Before administration, the criteria for permanent stopping (Section 5.2.1.2) or postponement of study treatment (Section 5.2.1.1) will be checked; if any of these is met, the patient will

either be withdrawn from study treatment or the present administration of study treatment will be postponed. Study treatment will then be administered, provided that this is not contra-indicated by the findings of the previous 2 steps.

6.3.5. Visit 3: Third study treatment administration

This visit will take place 6 weeks ± 4 calendar days after the day of the first treatment administration (Visit 1). Study procedures will include all those of Visit 2.

In addition:

- Blood sampling for humoral immunity assays will be done (10 ml, as described in Section 6.4.2). If the second study treatment administration had to be postponed (refer to Section 5.2.1.1 for criteria for postponement of study treatment), Visit 3 should be planned as close as possible to the 6 weeks ± 4 calendar days after Visit 1 schedule, but a minimum of 14 days after the second treatment administration.

6.3.6. Visit 4: Fourth study treatment administration

This visit will take place 9 weeks ± 4 calendar days after the day of the first administration (Visit 1). Study procedures will be identical to those of Visit 2.

If the third study treatment administration had to be postponed (refer to Section 5.2.1.1 for criteria for postponement of study treatment), Visit 4 should be planned as close as possible to the 9 weeks ± 4 days after Visit 1 following the original schedule, but a minimum of 14 days after the third treatment administration.

6.3.7. Visit 5: Fifth study treatment administration

This visit will take place 12 weeks ± 4 calendar days after the day of the first administration (Visit 1). Study procedures will be identical to those of Visit 3.

- For patients who agree, eight green tops of blood totaling 70 mL will be taken on days 1, 3, 7, 14 and 21 after the first and fifth doses of study drugs for assessment of T cell reactivity. Day 21 after the first dose of study drug would be the day of the second injection of study drug. Those assays will be performed by [redacted]

In addition:

- A CT scan of the neck, chest and upper abdomen and pelvic CT scans will be performed.
- Blood sampling for safety haematological and chemical assays (15 ml, as described in Section 6.4.2).
- A pregnancy test will be performed for females of childbearing potential. 6.3.8.
- Leukapheresis will be repeated.

Blood sampling for humoral immunity assays will be done (10 ml, as described in Section 6.4.2).

6.3.8. Visits 6-13: Three-monthly maintenance treatment administrations

These visits will take place at 3-month intervals, i.e., at time-points 6, 9, ..., 27 months after Visit 1, with a permitted deviation from the scheduled time-point of up to 14 calendar days.

The following procedures will be performed at each of these visits:

- Physical examination (as at Visit 1, including ECOG performance status and disease assessment).
- A CT scan of the neck, chest and upper abdomen and pelvic CT scan.
- Before administration of study treatment the criteria for permanent stopping or postponement of study treatment (Sections 5.2.1.1 and 5.2.1.2) will be checked; if any of these is met, the patient will either be withdrawn from study treatment or the administration of study treatment will be postponed.
- Recording of (serious) adverse events and pIMD.
- A pregnancy test for females of childbearing potential.
- Recording of concomitant medications.
- Administration of the study treatment.

The following procedures will be performed before the administration of study treatment at Visits 7, 8 and 10:

- Blood samples (10 ml, as described in Section 6.4.2) for humoral immunity assays will be taken.

The following procedures will be performed once every year after Visit 1 (i.e. at Visits 8 and 12):

- Blood sampling (15 ml as described in Section 6.4.2) for haematological and chemical safety assays.

If any of the sixth to twelfth study treatment administrations had to be postponed (refer to Section 5.2.1.1 for criteria for postponement of study treatment), the subsequent Visit should be planned as close as possible to the 3-monthly interval of the original schedule, but with a minimum of 14 days between any two treatment administrations.

6.3.9. Visit 14: Concluding or end of study examination

This visit will take place 3 months after Visit 13, i.e., approximately 30 months after the first administration of study treatment (Visit 1), with a permitted deviation of up to 14 calendar days.

If a patient on trial relapses, or if the patient withdraws for any reason, including toxicity, they will also be asked to return to Moffitt for this end of study visit.

If the thirteenth study treatment administration had to be postponed (refer to Section 5.2.1.1 for criteria for postponement of study treatment), the concluding Visit should be scheduled 3 months after the actual date of the last administration.

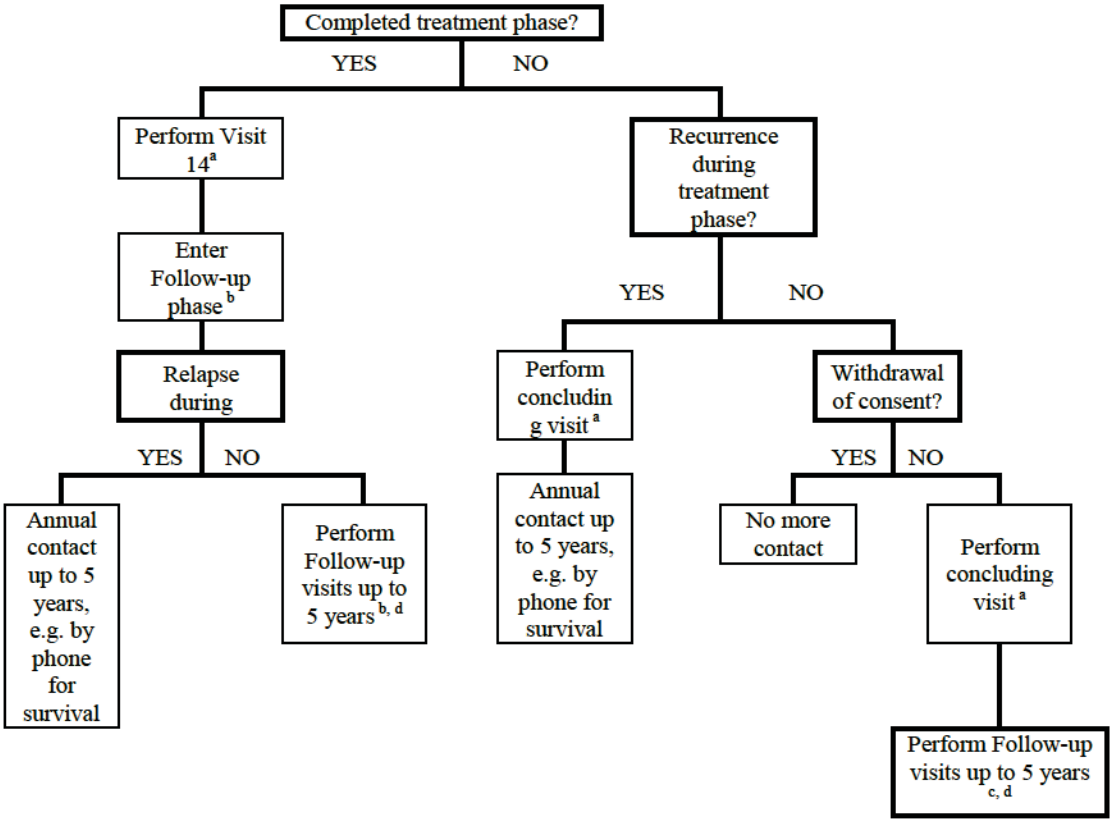
The following procedures will be performed:

- A CT scan of the neck, chest and upper abdomen and pelvic CT scans.
- Physical examination (as at Visit 1).
- Recording of (serious) adverse events and pIMD.
- Blood sampling (15 ml as described in Section 6.4.2) for laboratory safety assays.
- Blood sampling (10 ml as described in Section 6.4.2) for humoral immunity assays.
- Blood sampling of 80 ml for cellular immune assays

In addition, these samples could be used for translational research for patients having given their specific informed consent to this.

- Pregnancy test for females of childbearing potential.
- Recording of concomitant medications.
- Treatment conclusion.

6.3.10 Post-treatment follow-up



a. For procedures of Visit 14 - concluding visit, refer to Section 6.3.9 .
b. For 5-year follow-up of patients who have completed the treatment phase, refer to Section 6.3.10.2.
c. For 5-year follow-up of patients who have not completed the treatment phase, refer to Section 6.3.10 2.
d. Five-year follow-up is performed until five years after first administration or until recurrence of disease.

6.3.10.1. Follow-up of patients who have completed the study treatment

For patients who have completed the study treatment (up to and including Visit 14), follow-up visits will take place every 6 months after the concluding visit (Visit 14) for a maximum of 5 years after first study treatment administration.

The following procedures will be performed:

- A routine physical examination including assessment of ECOG performance status. Determination of disease status, on the basis of the patient's medical records and all other available information. If the patient has relapsed, the investigator will obtain information about the recurrence (date, type), as far as this is possible.
- CT scan of the neck, chest and upper abdomen as well as the pelvis (at Months 36, 48 and 60, or at any other time if clinically indicated).
- Recording of pIMD.
- Recording of SAEs related to study participation and concurrent medications.
- In addition, one year after the concluding visit, a blood sample (10 ml as described in Section 6.4) will be taken for humoral immunity testing.

Follow-up visits will be numbered consecutively from Visit F1 onwards. Findings at these visits will be recorded using Moffitt CRFs.

If relapse of disease is established at one of the follow-up visits, no further follow-up visits will take place. As for patients who have withdrawn from the study treatment (Section 6.3.10.2) because of disease relapse, annual post study contacts, e.g., by telephone, will be instituted and continued up to 5 years after the first study treatment administration.

6.3.10.2. Follow-up of patients who were withdrawn from the study treatment

Patients will be free to withdraw from the study at any time and for any reason and without prejudice to their further treatment. However, all patients who have withdrawn from study treatment will be examined at least 30 days after the last administration of study treatment and before starting any other anti-cancer treatment. The procedures to be performed at this examination are those defined for Visit 14 (see Section 6.3.9). Note that if a CT-scan has been performed at the last administration of study treatment this will not be repeated.

In addition, all patients who have withdrawn from study treatment will be followed every 6 months after the last contact for up to 5 years from the date of first study treatment administration to document disease recurrence, survival and safety parameters (until another cancer treatment is initiated). The procedures at these examinations are the same as for patients who have completed study treatment (See Section 6.3.10.1).

For female patients withdrawing because of pregnancy or decision to become pregnant, in addition to the follow-up of the melanoma, there will be a follow-up of the pregnancy as described in Section 8.12.

There are two exceptions to this follow-up:

a. Patients who have withdrawn from the study because of withdrawal of consent will not be contacted again.

b. Patients who were withdrawn from study treatment because of disease relapse or who relapsed during the post-treatment study period will not be asked to return for study follow-up visits. These patients will be contacted yearly, e.g., by telephone, to follow them for survival.

6.3.11. Annual contact

The survival of patients withdrawn from the study treatment because of relapse during the treatment phase or who relapsed during the follow-up period will be monitored by contacting them once a year up to 5 years after the first administration. These contacts will be made by the investigator (or a delegate) and may be done for example by telephone.

6.3.12. Relapse

Relapse of melanoma will include distant metastases. Any new primary cancer, including second primary melanoma, will not be considered as a recurrence and should be reported as a SAE.

All relapses must be documented by photographic or radiological evidence or by biopsy, as determined by the investigator. Suspicion of relapse based on physical examination findings only or laboratory signs must be confirmed by radiological examination and/or biopsy. Equivocal findings on standard radiological imaging should be confirmed by repeated examinations or cytology/histology or other imaging techniques.

In the event of unequivocal, objective recurrence (at scheduled or unscheduled visit), the investigator will determine and record the recurrence, withdraw the patient from the study treatment and perform all procedures as defined for Visit 14 (see Section 6.3.9) before any new anti-cancer treatment or procedure to treat the recurrence is initiated.

In case a biopsy of the relapse is performed, it will be useful to test MAGE-A3 expression in FFPE recurrent tumor tissue and gene profiling research on the fresh tissue tumor samples stored in RNA later and taken during biopsy. The informed consent form will have an optional section for patients to consent to allow these assays to be performed by GSK Bio. Instruction for sample handling and dispatch are given in the GSK Bio recommendations.

As soon as a planned examination shows objective relapse, the patient will be considered to have had a relapse on the day of this planned imaging.

If a planned imaging is equivocal, a confirmatory examination (imaging or biopsy) will be planned within 8 weeks after the first equivocal imaging. If this confirmatory examination shows an objective relapse, the patient will be considered to have had a recurrence on the day of the

first equivocal imaging. On the other hand, if the patient's condition does not allow for this confirmatory examination and another anti-cancer treatment is started, the patient will be considered to have had relapse on the day of the first equivocal examination.

If a planned imaging does not show any objective relapse but the patient is symptomatic, additional examinations will be conducted as clinically indicated (Chest X-Ray, CT scan, bone scan, brain CT scan, brain MRI, biopsy, etc.). If objective relapse is demonstrated, the date of this additional imaging or biopsy will be considered as the date of relapse. However, if these additional examinations are equivocal or if symptoms persist without any explanation, a confirmatory examination will be performed within 8 weeks. If relapse is confirmed or if the patient requires immediate treatment with another anticancer therapy, the patient will be considered to have had relapse.

If a patient comes to an unplanned visit due to symptoms, additional examinations will be conducted as clinically indicated (Chest X-Ray, CT scan, bone scan, brain CT scan, brain MRI, biopsy, etc.). If objective relapse is demonstrated, the date of this additional imaging or biopsy will be considered as the date of relapse. If these additional examinations are equivocal, a confirmatory examination will be performed within 8 weeks as. If relapse is confirmed or if the patient requires immediate treatment with another anti-cancer therapy, the patient will be considered to have had relapse. However, if these additional examinations are negative but symptoms persist without any explanation, and the patient requires immediate treatment with another anti-cancer therapy, the patient will be considered to have had relapse on the date of the unplanned visit.

6.4. Biological sample handling and analysis

6.4.1. Treatment and storage of biological samples

See Appendix B and GSK Bio recommendations.

6.4.2. Laboratory assays and immunological read-outs

Please refer to the GSK recommendations for details of biospecimen management (handling, storage and shipment) for specimens shipped to GSK Bio or contracted lab.

Samples will not be labeled with information that directly identifies the patients but will be coded with the identification number for the patient (patient number or requisition number).

Collected samples may be used for purposes related to the quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these current tests, the maintenance or improvement of these current tests, the development of new test methods for the markers described in this protocol, as well as making sure that new tests are comparable to previous methods and work reliably.

Table 8 specifies the laboratory assays and immunological read-outs that must be performed.

Assay type	Test	Sample type	Laboratory	Timing
MAGE-A3 screening (mandatory)				
	MAGE-A3 expression testing on the tissue removed during resection	FFPE tumor tissue	GSK Bio or contracted lab	During screening
MAGE-A3 (optional)				
	If tissue from multiple lesions (e.g. primary tumor, lymph node, etc) are also available, this may be tested to examine whether they all expresses MAGE-A3	FFPE tumor tissue	GSK Bio or contracted lab	During study
Laboratory assays (mandatory)				
	Haematology	Blood (15 ml)	Moffitt CC laboratory	See Section 6.3
	White blood cell count			
	Neutrophils			
	Platelets			
	Lymphocytes			
	Haemoglobin			
	Biochemical values			
	LDH			
	Renal function			
	Creatinine			
	Hepatic function			
	Serum bilirubin			
	Aspartate transaminase (ASAT)			
	Alanine transaminase (ALAT)			
	Alkaline phosphatase			
Humoral Immunological read-outs (mandatory)				
	Humoral response (serum antibodies titers)	Blood (2 x 5 ml)	GSK or contracted lab	V1- wk 0 V3- wk 6 V5- wk 12 V7- wk 36 V8-wk 48 V10- wk 72 V14 (CV)-wk 120 F2- CV + 12m
Translational research (optional)				
	MAGE-A3 expression testing on relapse or new lesions	FFPE tumor tissue	GSK or contracted lab	In case of confirmed recurrence. Section 7.1
	Gene profiling			
	Gene profiling of resected lesions	Fresh tumor tissue stored in RNA later [a]	GSK or contracted lab	Screening Samples. Section 7.3
	Gene profiling of new lesions	Fresh tumor tissue stored in RNA later [a]	GSK or contracted lab	In case of confirmed recurrence. Section 7.4
	Serum analysis			
	Cellular Immunity	Blood	Moffitt CC or designated	See section 7.2

a. FFPE could be accepted if no fresh tissue can be provided.

Table 8. Laboratory assays and immunological read-outs.

The decision to accept or reject additional testing of either kind, as described above, will not affect the ability of the patient to enter the study. Any sample testing will be done strictly in line with the consent of the individual patient and will be subject to the laws and regulations concerning such testing in the respective countries. In addition, this additional research will only

be performed once the relevant Ethics Committees have been informed and have reviewed the tests to be performed, and has had the possibility of deciding to obtain the specific informed consent of the patient for this/these test(s).

Any human pharmacogenetic testing will require specific consent from the individual patients and the ethics committee approval. Any anti-HIV testing will also require specific consent and ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

Collected samples will be stored for up to 5 years (counting from when the last patient performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the patient consent. Patient will be asked for consent in ICF to store and possible use in a secondary research by MCC or GSK Bio of the remaining samples analyzed in this study prior the approval by an IRB of any possible secondary research.

Collection of Immunology samples will discontinue October 1, 2015 although analysis will continue on existing samples. [redacted]

6.4.3. MAGE-A3 expression screening of tumor tissue

In order to be eligible for this study, the patients must have a resected MAGE-A3-positive tumor (as described in Section 4.2, Inclusion Criteria). Therefore, the MAGE-A3 expression of the resected tumor tissue will be tested before the final enrollment of the patients, i.e., during the screening period of the study.

Because of their experience in the field of assays on formalin-fixed paraffin-embedded (FFPE) tissues, Response Genetics has been chosen to collaborate with GSK Biologicals for the MAGE-A3 expression screening. If required, this testing could be performed by another laboratory contracted by GSK Biologicals and meeting the same quality level.

After surgery, a paraffin-embedded tissue block sample of at least 10 mm^3 or alternatively 20 unstained slides (19 slides of 10 µm and 1 slide of 5 µm for a total of at least 100 mm^2 tumor tissue) of the resected tumor - or alternatively 15 unstained slides (14 slides of 10 µm and 1 slide of 5 µm) will be provided by the study centre to GSK Biologicals or contracted lab designated by GSK Bio. The laboratory will then extract the RNA from these samples and assess the MAGE-A3 expression by quantitative PCR. If there are several tumor blocks, it is preferred that 2 of these are sent for determination of MAGE-A3 expression (As described above, a FFPE block of at least 10 mm^3 is preferred). The second block will only be tested, in case the first tested is MAGE-A3-negative. The patient will be considered eligible on this criterion, if at least one

tested block is MAGE-A3- positive. Upon reception of the tumor tissue sample, the MAGEA3 screening will be done within 5 working days. The cut-off value for the MAGE-A3 expression assay is defined as 1% of the positive MAGE-A3 control included in the assay.

If tissue from the primary tumor is also provided to the laboratory, this may be tested to examine whether it expresses MAGE-A3 (See Section 7.1).

The gene profile analysis performed by GSK Biologicals or a contracted laboratory will be performed on RNA extracted from fresh tumor tissue obtained from the biopsy and stored in RNA later. Gene expression profiling including the presence or absence of the predictive gene signature will be assessed by an appropriate technology such as qRT-PCR, microarray or IHC on these samples and correlated with the patient's clinical data. Additional gene profiling might be performed in the screening FFPE tumor samples sent for MAGE-A3 screening.

For details on the handling and shipment of tumor tissue samples, refer to GSK recommendations.

6.4.4. Gene expression signature associated with treatment benefit of resected lesions

6.4.4.1. Background

Gene expression profiling of the tumor by microarray has been shown in the literature to be useful in defining the patient's prognosis and also response to therapy [Dave, 2004; Weigelt, 2005; Hu, 2006].

Because it is therefore more beneficial to target a patient population that will specifically benefit from treatment, GSK Biologicals has already started evaluating in another clinical trial (GSK 249553/008) whether patients with MAGE-A3-positive cancer could present a specific gene expression signature predictive of their response to recMAGE-A3 + AS15 ASCI treatment. Using biopsies of the tumor taken prior to any recMAGE-A3 + AS15 ASCI administration, they were able to identify a gene expression signature that identify patients who might benefit from treatment with recMAGE-A3 ASCI. The identified, potentially predictive signature defines an immune microenvironment in the tumor that is present prior to any therapeutic intervention and correlates strongly with the clinical benefit following the MAGE-A3 ASCI administration. Such molecular signature could select patients with a higher likelihood of clinical response to MAGE-A3.

A secondary goal of this study is to evaluate the gene signature as a potential marker of clinical benefit according to treatment, recMAGE-A3 + AS15 ± Poly IC:LC

6.4.4.2. Practical aspects

Testing will be performed by GSK Biologicals or contracted lab on RNA extracted from fresh tumor tissue obtained during the surgical resection.

The presence or absence of the gene signature will be assessed by quantitative PCR (qPCR) on these samples and correlated with the patient's clinical data.

For handling and shipment of tumor tissue samples, refer to the GSK recommendations.

For gene profile and other biomarkers analysis, refer to Section 10.8.

6.4.5. Laboratory assays

Safety laboratory assays assessing the hematological parameters as well as renal and hepatic functions will be performed by the laboratory at the investigational site.

These assays (detailed in Table 8) will be performed before the first administration of the study treatment and then each year after Visit 1 until the end of the maintenance phase and at Visit 14 (Refer to Table 5 and Table 6). These parameters will not be recorded anymore during the follow-up phase (Table 7).

If a clinically significant abnormality in any laboratory parameter is detected at one of these assessments, it should be followed up as adequate until it has returned to normal or a satisfactory explanation has been provided. Refer to Section 8.5 for AE and SAE reporting.

6.4.6. Immunological read-outs

Specific antibodies (humoral response) induced by the recMAGE-A3 + AS15 ASCI will be measured by ELISA or upgraded technologies, and the results will be provided in EU/ml or other appropriate units (Table 8). A patient will be considered as seropositive if the value of the antibody titre is superior or equal to the assay cut-off value.

These assays will be performed at GSK Biologicals or by a contracted lab chosen and contracted for this task by GSK Biologicals. For handling and shipment of tumor tissue samples, refer to the GSK recommendations.

7. -TRANSLATIONAL RESEARCH

This section provides details on the research that may be done on samples collected during this study. The specified tests will be performed on samples from all patients. Based on the data generated during the study and in other studies, not all samples will be processed if there is a problem with performing leukaphereses.

7.1. MAGE-A3 expression on multiple resected lesions

When multiple lesions are obtained from a patient at the time of screening (primary tumor(s), lymph node(s)), it is of interest to investigate how MAGE-A3 is expressed in these different lesions. For example, one would like to establish whether recurrent lesions are MAGE-A3 positive, when the primary lesion is positive. In order to establish this information, the MAGE-A3 test, as it is applied for patient accrual, would be applied to all material that is collected from the patient.

7.2. Cellular Immune assays

The aim of a cancer immunotherapeutic is to stimulate the patient's cellular and humoral immune response in order to eliminate the cancer cells. Although such immune responses can be detected upon administration of a cancer immunotherapeutic, the direct impact of this response, especially the T-cell response, on the clinical activity has not yet been demonstrated; some patients who show evidence of tumor regression upon administration of a cancer immunotherapeutic have very low T-cells directed against the target antigen of the immunotherapeutic [Lurquin, 2005].

7.3. Gene profiling on fresh tissue

If fresh tumor tissue stored in RNA later is available at the time of tumor resection, it would be interesting to test such samples to exploratory define a gene signature predictive of response to therapy.

An adequate amount of RNA will be used to hybridize a human expression chip containing a locked gene set (for example, Affymetrix; this commercial expression chip contains a locked set of over 47,000 defined gene transcripts annotated from the human genome sequencing project). Genes expressed in the resected tumor tissue of the cutaneous melanoma patients will be analyzed and correlated with the patients' clinical data.

For handling and shipment of tumor tissue samples, refer to the GSK recommendations.

For gene profile and other biomarkers analysis, refer to Section 10.8.

7.4. Gene profiling research of a relapse or a new tumor

In the event of tumor relapse or the occurrence of a tumor of new histology in patients that have been included in the study and if a biopsy is scheduled by the investigator, the patient will be proposed to allow gene profiling on the recurrent or new tumor (including MAGE-A3 expression screening of the recurrent tumor).

Details of this research are the same as for gene profiling research of the resected metastasis (see Section 6.4.4)

This test will not require tissue sampling additional to the tissue removed during biopsy.

(N.B. a cytological sample obtained by fine-needle aspiration is not sufficient). The patient's decision to participate in this optional research must be documented by his/her initials of a check-off section in the informed consent form.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigators are responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

Each patient or patient's guardians will be instructed to contact the investigator immediately should the patient manifest any signs or symptoms they perceive as serious.

8.1. Definition of an adverse event

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medications (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with treatment administration.
- Blood counts or chemistries that were abnormal at baseline and worsen outside the patient's usual range of fluctuations after the start of protocol therapy Examples of an AE DO NOT include: Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Blood counts or chemistries that were abnormal at baseline and did not worsen outside the patient's usual range of fluctuations after the start of protocol therapy AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of patient's previous therapeutic regimen).

Example of events to be recorded in the medical history section of the CRF:

- Pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., prior to the first study treatment administration).

8.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. Results in death,
b. Is life-threatening,

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization,

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

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

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study patient.
f. Is a Grade 4 adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (cf. Appendix F)

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

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

In this study, Grade 3 autoimmune disorders according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (cf. Appendix F), will be considered as medically significant and will therefore be notified as SAE.

8.3. Adverse events of specific interest

8.3.1 Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the table below. However, the investigator will exercise his/her medical and scientific judgement in deciding whether other immune-mediated diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis) • Multiple sclerosis (including variants) • Transverse myelitis • Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants) • Other demyelinating diseases (including acute disseminated encephalomyelitis) • Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) • Non-infectious encephalitis/ encephalomyelitis • Neuritis (including peripheral neuropathies)	• Systemic lupus erythematosus • Scleroderma (including, CREST syndrome and morphoea) • Systemic sclerosis • Dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, • Juvenile chronic arthritis, (including Still's disease) • Polymyalgia rheumatica • Reactive arthritis • Psoriatic arthropathy • Ankylosing spondylitis (including undifferentiated spondylarthritides) • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Raynaud's phenomenon • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Cutaneous lupus erythematosus • Alopecia areata • Lichen planus • Sweet's syndrome
Liver disorders	**Gastrointestinal disorders**	**Metabolic diseases**
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis.	• Crohn's disease • Ulcerative colitis • Ulcerative proctitis • Celiac disease	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease

Vasculitides	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitis, allergic granulomatous angiitis, Henoch-Schonlein purpura, anti-neutrophil cytoplasmic antibody positive vasculitis, Behcet's syndrome, leukocytoclastic vasculitis. • Vasculitides secondary to other immune mediated diseases such as lupus vasculitis and rheumatoid vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenias • Antiphospholipid syndrome • Pernicious anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Uveitis • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome

Table 9. List of potential immune-mediated diseases.

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the CRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available.

8.4. Relapse of disease

An event which is part of the natural course of the disease under study (i.e., disease relapse) is captured in the study as an efficacy measure; therefore it does not need to be reported as an SAE.

Relapse of the tumor will be recorded in the clinical assessments in the CRF. Death due to progressive disease is to be recorded on a specific form in the CRF but not as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with the recMAGE-A3 + AS15 ASCI +/- Poly IC:LC or protocol design/procedures and the disease progression/recurrence, then this must be reported as an SAE.

Any new primary cancer (not related to the cancer under study) must be reported as an SAE.

8.5. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events and serious adverse events

All laboratory results (normal and abnormal) will be recorded in the patient's CRF as described in the study procedures (Table 5 and Table 6).

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinanalysis) or other abnormal assessments will be recorded as AEs or SAEs:

- If they occur after the start of protocol therapy and meet the definition of an AE, as defined in Section 8.1 or SAE, as defined in Section 8.2.
- If they are present at baseline and worsen outside the patient's usual range of fluctuations after the start of protocol therapy.

- If they are associated with the disease being studied but are more severe than expected for the patient's condition.

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinanalysis) or other abnormal assessments will NOT be recorded as AEs or SAEs:

If they are present at baseline and DO NOT worsen outside the patient's usual range of fluctuations after the start of protocol therapy.If they are associated with the disease being studied and are in line with what is expected for patient's condition.

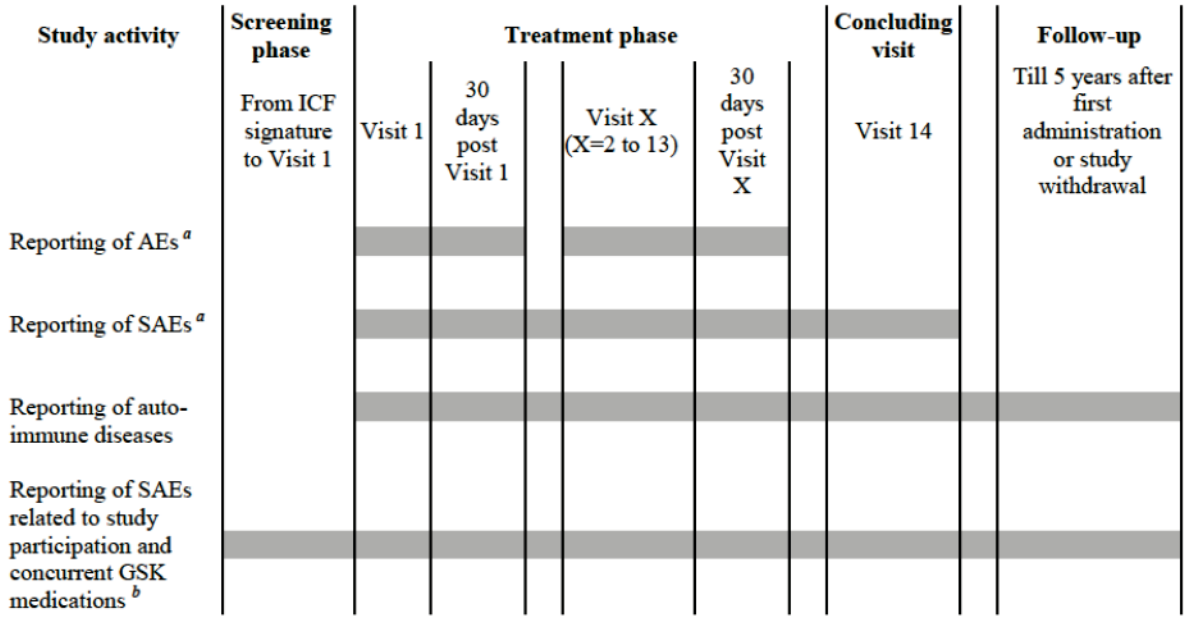
8.6. Time period, frequency, and method of detecting adverse and serious adverse events

All AEs occurring within 30 days following dministration of each dose of the study treatment must be recorded on the Adverse Event form in the patient's CRF, irrespective of intensity or whether or not they are considered to be related to the treatment administration.

The standard time period for collecting and recording SAEs (except autoimmune SAEs see below) will begin at randomization or the first receipt of study treatment and will end at the concluding visit (Visit 14, Month 30) or until 30 days after the administration of the last dose of study treatment in the event of early discontinuation of study treatment administration. See Section 8.9 for instructions on reporting and recording SAEs.

Onsets of potential immune mediated diseases (pIMD) or autoimmune disease occurring throughout the study (from Visit 1 until the end of the follow-up period) must be recorded as AE or SAE, as appropriate, in the patient CRF (see Section 8.3). Appropriate documentation of the diagnosis of autoimmune diseases must be provided in each instance.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 9.



i. Except autoimmune AEs and SAEs which are reported till end of follow-up.
j. Surgical resection of the tumor and adjuvant chemotherapy administration are not considered as study procedures; SAEs related to these treatments should not be recorded.

Table 10. Reporting periods for adverse events and serious adverse events

The investigator will inquire about the occurrence of AEs/SAEs and pIMD at every visit/contact during the study and throughout the follow-up period.

All AEs, either observed by the investigator or one of her/his clinical collaborators or reported by the patient spontaneously or in response to a direct question will be evaluated by the investigator. AEs not previously documented in the study will be recorded in the Adverse Event form within the patient's CRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and possible relationship to treatment administration should be established. Details of any corrective treatment should be recorded on the appropriate page of the CRF. Refer to Section 5.8.

As a consistent method of soliciting AEs, the patient should be asked a non-leading question such as:

"Have you felt different in any way since receiving the treatment or since the previous visit?"

N.B. The investigator should record only those AEs having occurred within the time frame defined above. AEs already documented in the CRF, i.e. at a previous assessment, and designated as “not recovered/not resolved” or “recovering/resolving” should be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the CRF should be completed.

When an AE or a SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator or designate will then record all relevant information regarding the AE/SAE on the CRF or SAE Report Form as applicable.

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

All SAEs will also be reported to the FDA directly by the sponsor, MCC. See section 8.9.1 for reporting of SAEs to GSK Bio and Oncovir.

8.7. Evaluating adverse events and serious adverse events

8.7.1. Assessment of intensity

Severity of AEs will be assessed according to the International Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).

The investigator will make an assessment of intensity for all AEs, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE recorded in the CRF will be graded according to the table given in the CTCAE (version 4.0; cf. Appendix F).

An AE assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets the definition in Section 8.2.

8.7.2. Assessment of causality

The investigator is obliged to assess the relationship between the investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochures and/or Product Information, for marketed products, in considering his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to the FDA. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to the FDA. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple treatments, it may not be possible to determine the causal relationship of general AEs to the individual treatments given. The investigator should therefore assess whether the AE could be causally related to treatment administration rather than to the individual treatments.

Causality of all AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO: The AE is not causally related to administration of the study treatment(s). There are other, more likely causes and administration of the study treatment(s) is not suspected to have contributed to the AE.

YES: There is a reasonable possibility that the treatment(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets the criteria to be determined "serious" (see Section 8.2 for definition of serious adverse event), it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors include:

- Medical history
- Other medications
- Protocol required procedure
- Other procedure not required by the protocol
- Erroneous administration
- Other cause (specify)

8.8. Follow-up of adverse events and serious adverse events and assessment of outcome

After the initial AE/SAE report, the investigator is required to proactively follow each patient and provide further information to the FDA on the patient's condition.

All AEs and SAEs documented at a previous visit and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts.

Investigators will follow-up patients:

- with SAEs or patients withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilized, disappeared, the event is otherwise explained, or the patient is lost to follow-up;
- or, in the case of other non-serious AEs, until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to baseline, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such an abnormality noted for any patient must be made available to the Study Monitor.

The outcome of any non-serious AE occurring within 30 days post-treatment administration (i.e., unsolicited AE) or any SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.9. Prompt reporting of serious adverse events

The paper SAE Report Forms and the facsimile (Fax) system will be the primary method for reporting SAEs during the study period.

8.9.1. Time frames for submitting serious adverse event reports to GSK Bio and Oncovir

SAEs (including any grade of pIMD) will be reported promptly to GSK Bio and Oncovir once the investigator determines that the event meets the protocol definition of an SAE. The investigator or designate will complete and submit relevant information on the SAEs in the paper SAE form **WITHIN 24 HOURS OF HIS/HER BECOMING AWARE OF THESE EVENTS**. Additional or follow-up information relating to the initial SAE report is also to be completed and submitted in the paper SAE form within 24 hours of receipt of such information.

GSK Biologicals and Oncovir may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE.

[redacted]

[redacted]

[redacted]

[redacted]

24/24 hour and 7/7 day availability

8.9.2. Completion and transmission of serious adverse event reports to FDA

Once an investigator becomes aware that a SAE has occurred in a study patient (including a screened patient), the investigator or designate will complete and submit the information in the paper SAE form within 24 hours as outlined in Section 8.9.1. Submission of safety information to FDA will follow 21 CFR 312.32. The SAE form will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator or designate. If the investigator or designate does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying FDA of the event and completing the SAE forms. The SAE form should be updated when additional information is received and forwarded to FDA WITHIN 24 HOURS as outlined in Section 8.9.1.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 8.7.2.

For paper SAE Report Form the investigator or designate will report relevant information on SAEs to FDA within the 24 hours as outlined in Section 8.9.1. The SAE Report Form will

always be completed as thoroughly as possible with all available details of the event, signed by the investigator or designate, and forwarded to FDA within the designated time frames. If the investigator or designate does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying FDA of the event and completing the form.
When additional information is received on a SAE after freezing of the patient's CRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be resent to FDA WITHIN 24 HOURS of receipt of the follow-up information as outlined in Section 8.9.1.

8.10. Regulatory reporting requirements for serious adverse events

The investigator, as the sponsor's representative will promptly report all SAEs to FDA in accordance with the procedures detailed in Section 8.9 and to GSK on a quarterly basis. The sponsor, MCC has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB/IEC and, if required, to the applicable government authority.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK Biologicals or Oncovir will file it with the respective Investigator Brochure or other appropriate study documentation and will notify the IRB or IEC, if appropriate according to local requirements.

8.11. Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 8.6. Investigators are not obligated to actively seek AEs or SAEs in former study participants.

However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and (s)he considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.12. Pregnancy

Patients who become pregnant during the study treatment phase must not receive additional doses of study treatment but may continue other study procedures at the discretion of the investigator.

The investigator or designate will collect pregnancy information on any patient who becomes pregnant while participating in this study, i.e., from signature of the first informed consent till the end of the 5-year follow-up period, or till recurrence/death if occurring before the end of the 5-year follow-up period. The investigator or designate will record pregnancy information on the Pregnancy Report Form and submit it to FDA, GSK Biologicals and Oncovir within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether that be full-term or prematurely, information on the status of the mother and child will be forwarded to GSK Biologicals and Oncovir. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date.
While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Sections 8.1 and 8.2, and will be followed as described in Section 8.6.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.9. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to FDA as described in Section 8.9. While the investigator is not obliged to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

Information on pregnancies identified during the screening phase prior to treatment administration does not need to be collected; this information need not be communicated to safety.

8.13. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medications administered for the treatment of an AE should be recorded in the patient's CRF. Refer to Section 8.8.

9. PATIENT COMPLETION AND WITHDRAWAL

9.1. Patient completion of study treatment

A patient will be considered to have completed the study treatment when he/she has been under treatment until Month 27 and turns up for the concluding examination 30 months after the first administration of the study treatment.

Administration of the investigational treatment (recMAGE-A3 + AS15 ASCI +/- Poly IC:LC) should continue until completion, documented disease recurrence, withdrawal due to an unacceptable toxicity, or withdrawal for other reasons (see Section 9.2).

Once the patient has been withdrawn from the investigational treatment, the reason must be documented in the patient's medical records and CRF.

9.2. Patient withdrawal

Patients who are withdrawn because of AEs must be clearly distinguished from patients who are withdrawn for other reasons. Investigators will follow patients who are withdrawn as a result of a SAE/AE until resolution of the event (see Section 8.8).

Once a patient has been withdrawn, the reason must be documented in the patient's medical records and CRF.

Withdrawn patients will not be replaced.

9.2.1. Patient withdrawal from investigational product

A patient will be considered as being withdrawn from the investigational product when he/she does not receive any further planned dose after the date of withdrawal.

The investigator will document in the CRF whether the decision to discontinue further treatment was made by the patient or the investigator and which of the following possible reasons was responsible for withdrawal:

- (Serious) adverse event (including intercurrent illness, unacceptable toxicity)
- Disease recurrence
- Protocol violation
- Other (specify)

In case of withdrawal from the investigational product, the concluding visit will be performed as described in Section 6.3.9 and the patient will enter the follow-up phase with follow-up visits up to five years after first study dose. If the withdrawal from the study treatment is due to disease recurrence, the patient should be asked to come for the concluding visit but will not be asked to return for the six-monthly follow-up visits. The investigator will contact these patient once a year, e.g., by telephone, until 5 years after the first administration of the study treatment.

If the patient refuses or cannot undergo these study procedures, (s)he will be considered as withdrawn from the study (Section 9.2.2).

9.2.2. Patient withdrawal from the study

A patient will be considered as being withdrawn from the study when (s)he does not undergo any further planned study activity after the date of withdrawal.

A patient may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the patient from participating in this study at any time. In addition, if the sponsor decides to discontinue the study, no further study procedures (including administration of the study treatment) will occur.

Information relative to the withdrawal will be documented on the Study Conclusion page of the CRF. The investigator will document whether the decision to withdraw from the study was made by the patient or the investigator and which of the following possible reasons was responsible for withdrawal:

- Death (any cause),
- (Serious) adverse event (including intercurrent illness, unacceptable toxicity),
- Disease recurrence,
- Consent withdrawal, not due to an adverse event,
- Lost to follow-up,
- Other (specify).

The investigator will contact these patients once a year, e.g., by telephone, until 5 years after the first administration of the study treatment.

9.3. Screen and baseline failures

A patient is considered to be a screen/baseline failure if the patient signs the first ICF but withdraws before receiving study treatment.

All patients having given consent to undergo MAGE-A3 expression screening and gene expression signature analysis upon resection of their tumor will be referenced into a screening section of the CRF.

10. STATISTICAL CONSIDERATIONS

10.1. Primary endpoints

Safety and Toxicity of the two regimens: adverse events and serious adverse events.

10.1.1. Safety and tolerability endpoints

Occurrence of adverse events up to 30 days after each study dose, including abnormal haematological and biochemical parameters.

Occurrence of serious adverse events and autoimmunity during the whole study duration (up to 30 days after the last administration of study treatment). For methods of analysis, see Section 10.7.5.

10.1.2. Immunogenicity endpoints

The primary laboratory endpoint is an assessment of the immunogenicity of the two regimens. Serum antibodies (such as Anti-MAGE-A3) seropositivity status (a seropositive patient is a patient whose titre is greater than or equal to the cut-off value) will be the primary immune endpoints assessed. Seropositivity will be assessed at baseline, after 2, 4, 6, 7 and 9 administrations, post-treatment (i.e., at concluding visit) and one year after concluding visit (i.e., at follow-up visit 2). Cellular immune assays will also be determined as a secondary endpoint. For methods of analysis, see Section 10.7.4.

Refer to Section 10.3 for details on the statistical analyses.

10.2. Secondary endpoints

10.2.1. Secondary clinical activity endpoints

Relapse-Free Survival (RFS), defined as the time from randomization to either the date of first recurrence of the disease or the date of death (whatever the cause), whichever occurs first.

Therefore, any death occurring without prior documentation of tumor relapse will be considered as an event (and will not be censored in the statistical analysis) as this approach is less prone to introduce bias. If no event has occurred by the time of the analysis, then the time to event will be censored at the date of the last assessment of the patient in question.

Any new primary cancer at another site, including second primary melanoma, will not be considered as a relapse and should be reported as a SAE.

Overall Survival (OS) defined as the interval from randomization to the date of death, irrespective of the cause of death; patients still alive will be censored at the date of the last assessment.

10.3. Study design/sample size and power/data analyses

Study Design

This is a 1:1 randomized, two-arm, open-label, Phase II, single-center study to evaluate the safety, tolerability and immunogenicity of recMAGE-A3 + AS15 ASCI with Poly IC:LC as adjuvant therapy compared to recMAGE-A3 + AS15 ASCI alone in MAGE-A3 positive patients with completely resected stage IV melanoma. Secondary objectives include: to describe the efficacy in terms of Relapse-Free Survival (RFS) and Overall Survival (OS) of the two arms; to collect preliminary data on the T cell immune response to the ASCI in the overall study population as well as subsets of patients of interest (e.g., arms and gene signature groups), and to evaluate the gene signature in all patients when possible. The study treatment will consist of an induction phase and a maintenance phase. During the induction phase, immunization with or

without Poly IC:LC will be administered 5 times at 3-week intervals. During the maintenance phase, immunization with recMAGE-A3 + AS15 with or without Poly IC:LC will be administered 8 times at 3-month intervals. The 13 immunizations with or without Poly IC:LC will be administered over a period of 27 months. The total duration of the study treatment phase (including concluding visit) is 30 months per patient. The duration of active follow-up for survival, recurrence and serious adverse events (SAEs) related to the study participation and concurrent GSK medications will be 5 years from the first administration of study treatment.

Sample Size/Power Calculations and Accrual

The sample size for this trial is calculated based on the primary immune endpoint of a serologic response to treatment. In a GSK trial using recMAGE-A3 + AS15 ASCI in a similar patient population, the total anti-MAGE-A3 IgG antibody measured at approximately 6 months at the first vaccine of the maintenance phase for the ASCI arm without Poly IC:LC had a geometric mean of about 7,000 and a standard deviation of no more than 0.28 on the log scale. It is anticipated that the ASCI arm with Poly IC:LC will further increase such anti-MAGE-A3 IgG antibody measurement at 6 months to about 10,500 for a 50% enhancement of the effect. Therefore, 20 patients per arm will yield 62% power for such detection of the anti-MAGE-A3 IgG antibody difference between the two arms at a one-sided significance level of 0.05. Power calculations for this trial will be only for the immune primary endpoint, since little toxicity is expected from either of the treatment arms on which to base a power calculation. Table 1 lists the change in power if the standard deviation deviates from the assumed value of 0.28 when everything else is the same. We plan to enroll 20 patients per arm for a total of 40 patients. To account for an approximate 10% loss-to-follow-up rate in this study, up to 44 patients may be enrolled.

The change in power if the standard deviation deviates from the assumed value of 0.28:

Standard Deviation	0.28	0.26	0.24	0.22	0.20
Power	0.62	0.68	0.74	0.80	0.86

A median RFS of about 8 months was observed for similar patients treated without adjuvant therapy. A median RFS of 12 months is expected of patients treated with recMAGE-A3 + AS15 ASCI alone in resected stage IV melanoma. Adding Poly IC:LC to this ASCI regimen might double the median RFS to 24 months. The power calculation shows that 20 patients per arm would have a power of about 61% for detecting such difference in RFS between the two arms with a one-sided type error rate of 0.05, assuming an accrual rate of 2.5 patients per month and a 3-year follow-up after the completion of accrual.

Assuming an accrual rate of 2.5 patients per month, it would take up to18 months to enroll 44 patients to this trial.

Data Analyses Plan

Demographic and disease characteristics as well as other baseline variables for all patients randomized will be tabulated and analyzed using the standard descriptive statistics such as frequency and percentage tables for discrete variables and mean, median, SD, range, and interquartiles for continuous variables. These data will be reported by arm and may be further stratified by subgroups, e.g., those patients with favorable/unfavorable gene signature, of interest.

The total anti-MAGE-A3 IgG antibody measured at various time points over the course of treatment will be descriptively reported by arm with the usual summary statistics as well as with plots and confidence intervals (CIs) to discern any time change pattern of interest. Comparisons between the two arms will be on the log scale using the two sample t test. If the normal distribution assumption is violated for log (total anti-MAGE-A3 IgG antibody), then non-parametric Wilcoxon test and/or other transformations such as ln and square root will be considered as well.

In order to determine whether recMAGE-A3 + AS15 ASCI +/- poly IC:LC is able to induce a specific T-cell response to the MAGE-A3 protein and to evaluate the T-cell response in both treatment groups, the percentage of T-cells simultaneously producing IFNγ and IFNα will be assessed after 5, and after 9 recMAGE-A3 + AS15 ASCI +/- poly IC:LC injections.

The cutoff value for a positive response is defined as 2 standard deviations over the mean percentage of double positive events in control wells. Anti-MAGE-A3 T-cell response is considered as positive when there are at least 3 more positive wells at any point after immunization than at baseline. This variable will be reported using both point estimates and 95% CIs for various subgroups of patients, e.g., arms or patients with favorable/unfavorable gene signature. Antibodies (such as Anti-MAGE-A3) seropositivity status, defined for a patient whose anti-body titer is greater or equal to the cutoff value, will be analyzed similarly.

RFS and OS will be analyzed using the Kaplan-Meier product-limit method as well as the Cox proportional hazards regression models. The Log-rank test for comparing RFS between the two arms will be performed and reported. Confidence interval for the median and survival rates at different time points will be constructed if needed.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE v.4) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE. Toxicity data will be summarized using the usual toxicity table by category and worst grade for the two ASCI regimens.

10.4. Study populations to be evaluated

10.4.1. Total Treated Population (TTP)

The Total Treated Population will include all the enrolled patients that have received at least one dose of the study product (recMAGE-A3 + AS15 ASCI +/- poly IC:LC).

The total treated population will be used for the analysis of clinical activity.

10.4.2. Total Treated Population (TTP) for analysis of efficacy

The intent-to-treat approach will define the Total Treated Population to be used for data analysis of this trial. That means all evaluable patients (i.e. those meeting the eligibility criteria) enrolled in this trial who have received at least one dose of the study treatment, i.e., recMAGE-A3 + AS15 ASCI with or without Poly IC:LC, will be included in the final data analyses. Patients who are lost to follow-up or drop out of study prior to their scheduled evaluation time due to any reason will be treated as non-responders for response determination and censored for time-to-event type of endpoints at the time of their last assessment/follow-up if no relevant event has occurred by then. By-arm analysis will be presented as the main analysis.

10.4.3. According to Protocol (ATP) population for analysis of clinical activity and immunogenicity

A secondary analysis that includes only all eligible patients may be conducted in addition to the primary analysis described above at the discretion of the trial PI and study biostatistician. Other subanalyses may also be considered on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. Missing data will not be imputed. A p-value of <0.05 will be considered significant. No multiplicity adjustment will be made in this study.

10.5. Elimination criteria for analysis

As defined in Section 5.8.2, certain medications are prohibited during this study. Among those medications, the following will not require withdrawal of the patient from the study but may determine the patient's evaluability in the according-to-protocol (ATP) analysis.

- Chronic administration of immunosuppressants or other immune-modifying drugs during the study period. The use of prednisone, or equivalent, < 0.125 mg/kg/day (absolute maximum 10 mg/day), inhaled corticosteroids or topical steroids is permitted.
- Administration of a vaccine not foreseen by the study protocol during the prohibited time period as specified in Section 5.8.3.
- Repetitive administration of immunoglobulins and/or any blood products during the study period.

Patients to be excluded from the ATP populations will be identified during a review of data.

10.6. Derived and transformed data

10.6.1. Group definition

The patients will be analyzed according to the treatment group assigned by randomization.

10.6.2. Immunogenicity

The cut-off value of the ELISA assay is defined by the laboratory before the analysis and is described in Section 6.4.6.

- A seropositive patient is a patient whose titre is greater than or equal to the cut-off value. The seropositivity rate is defined as the proportion of seropositive patients.
- Antibody response is defined as antibody concentrations ≥ the cut-off value among patients with concentrations < the cut-off value before treatment initiation and as antibody concentration at least twice the patient's own baseline value among patients with concentrations ≥ the cut-off value before treatment initiation.
- The Geometric Mean Titre (GMT) is calculated by taking the anti-logarithm of the mean of the log concentration transformations. Antibody titres below the cut-off value of the assay will be given an arbitrary value of half the cut-off value for the purpose of this calculation.
- For a given patient and a given immunogenicity measurement, results of missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude patients with missing or non-evaluable measurements.

10.6.3. Safety

For the analysis of adverse events, such as serious adverse events or adverse events by primary MedDRA term, all patients treated will be considered. Patients who did not report an event will be considered as patients without the event.

10.7. Final analyses

All statistical analyses will be performed using SAS, R and/or StatXact statistical software.

10.7.1. Analysis of demographics and other baseline characteristics

Demographic characteristics (age, gender, etc.) and other baseline characteristics such as MAGE-A3 expression of the tumor specimen, tumor classification, previous surgery etc. for all patients randomized will be tabulated and analyzed by appropriate descriptive statistics:

- Frequency tables will be generated for categorical variables such as gender;
- Mean, median, SD, range, and interquartiles will be provided for continuous data such as age. These data will be tabulated by treatment group, and the tables will be repeated for the different analysis populations: Total Treated Population, ATP cohort for \clinical activity and ATP cohort for immunogenicity.

10.7.2. Analysis of treatment compliance and treatment modifications

The total number of doses administered and the length of follow-up will be summarized.

For the Total Treated population cohort, overall compliance will be calculated for each dose as the percentage of patients who received the dose as per protocol (see Section 10.4) among all patients still on treatment at the target day of dose administration. Compliance will be considered unknown if it cannot be calculated because of missing data. Dose delays recorded on the CRF will not be taken into account in the measure of compliance.

The number of patients discontinuing treatment with the investigational product, as well as the reason for discontinuation, will be summarized and listed.

These data will be tabulated by treatment group for the total treated population.

10.7.3. Analysis of clinical activity

10.7.3.1. Relapse-free survival (RFS)

10.7.3.1.1. Relapse-free survival in the overall study population (secondary objective)

The analysis of RFS will be performed on the overall study Total Treated population. The primary analysis will be based on the adjusted Cox regression model.

Estimates of HR and their 95% CI will be obtained and the Wald test will be used to compare the groups.

Events of relapse of disease will be assigned to the visit at which they are detected (see Relapse Algorithm in Section 6.3.12), ignoring previously missed evaluation visits.

Or rather, interval-censored time-to-event data analysis methods such as Turbull's (1976) and Finkinstein's (1985) could be used.)

This primary analysis will be complemented by the following sensitivity analyses:

- an analysis of RFS based on the adjusted Cox regression model (see above) performed on the Total treated population, taking the date of first missed evaluation visit before detection of recurrence as date of event for patients not compliant with the scheduled evaluations;

- an unadjusted analysis of RFS based on the Logrank test, performed on the Total treated population. For the purpose of this sensitivity analysis, estimates of HR and their 95% CIs will be obtained by an unadjusted Cox model. More details will be given in the Report Analysis Plan (RAP).

10.7.3.2. Overall survival (Secondary objective)

The analysis of Overall survival will include the analysis of Overall survival in the overall study population, the analysis of Overall survival in the population of patients presenting the potentially favorable gene signature and the analysis of Overall survival in the population not presenting this gene signature. These analyses will be performed using the same methods as those described for the primary analysis of RFS (see Section 10.7.3.1.1).

10.7.4. Analysis of immunogenicity

The analysis of immunogenicity will be performed on the ATP population, cf. Section 10.4.3.

The immunogenicity induced by the recMAGE-A3 + AS15 +/- poly IC:LC ASCI will be assessed through calculation of the geometric mean titres (with 95% CI), the proportion of seropositive patients and antibody response in the two treatment groups. This will be done for antibodies at baseline, after 2, 4, 6, 7, and 9 dose administrations and post-treatment (i.e., at the concluding examination at Visit 14, 3 months after the injection of dose 13, cf. Section 6.3).

Antibody titres may also be investigated using reverse cumulative curves.

A possible correlation between the immunological response (such as antibody response to MAGE-A3) and RFS may be explored using a time-dependent Cox model.

The immunogenicity will also be evaluated in the gene signature-positive and gene signature negative populations, separately.

10.7.5. Analysis of safety

The safety analyses will be based on the Total Treated population.

The duration of treatment and total number of doses of investigational product administered will be summarized by treatment group.

10.7.5.1. Adverse events

Adverse events (AEs), including abnormal laboratory values, will be graded according to the CTCAE, Version 4.0 and coded to the preferred term (PT) level using the MedDRA dictionary.

The percentage of patients with adverse event(s) within 30 days of each recMAGE-A3 + AS15 ASCI dose +/- Poly IC:LC will be reported by treatment group with exact 95% confidence intervals, as per MedDRA terminology, by Preferred Term (PT) and System Organ Class (SOC), if appropriate. The same tabulation will be presented for grade 3, grade 4, related, grade 3 related and grade 4 related events, if appropriate.

10.7.5.2. Serious adverse events

Serious adverse events occurring at any time after study initiation will be summarized by treatment group and described in detail by patient narratives.

10.7.5.3. Deaths

Time to death will be analyzed as described in Section 10.7.3. Causes of death (e.g., hematological toxicity, non-hematological toxicity, disease under study, or other) will be summarized by treatment group.

10.7.5.4. Concomitant medications

For the analysis of the use of concomitant medications, the Total Treated population will be considered. Patients, for whom no use of concomitant medications has been reported, will be considered as patients without any use of concomitant medications.

10.8. Gene profile analyses and translational research

10.8.1. Gene profile

The gene profile will be evaluated by an interaction test between the treatment status (recMAGEA3+AS15 versus recMAGEA3+AS15 in combination with Poly IC:LC) and the gene signature status (positive versus negative) in a Cox regression analysis using the secondary clinical endpoint (RFS) as dependent variable in an exploratory hypothesis driven analysis.

11. CONDUCT OF THE STUDY

11.1. Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice (GCP), the Declaration of Helsinki (US 21 CFR Part 50—Protection of Human Patients, and Part 56— Institutional Review Boards) and local rules and regulations of the country.

Submission of the protocol and any protocol amendments to regulatory agencies will occur in accordance with local regulatory requirements at the Moffitt Cancer Center.

11.1.1. Institutional Review Board/Independent (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. The ICH Harmonized Tripartite Guideline for Good Clinical Practice recommends that the IRB/IEC should include:

a. At least five members.
b. At least one member whose primary area of interest is in a non-scientific area.
c. At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote or provide opinion on a study-related matter.

A list of IRB/IEC members, their professions and other qualifications should be obtained by the Study Monitor.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including patient recruitment procedures and information about payments and compensation available to patients, will be submitted to the IRB/IEC by the Study Monitor. Written and dated unconditional approval from the IRB/IEC of the protocol and amendment (if any and applicable), written informed consent form, consent form updates (if any), patient recruitment procedure(s) (e.g. advertisements), and any other written information to be provided to patients must be in the possession of the investigator and sponsor, MCC, before commencement of the study. This approval must refer to the study by study title and number with exact protocol version and date, and should identify the documents reviewed and state the date of review. Relevant GSK Biologicals and Oncovir's data such as the Investigator Brochures will be supplied by the Study Monitor to the appropriate IRB/IEC for review and approval of the protocol. Verification of the unconditional approval of the IRB/IEC will be transmitted by the Study Monitor prior to shipment of treatment supplies and CRFs to the site.

No deviations from, or changes to, the protocol should be initiated without prior written sponsor and IRB/IEC approval of an appropriate amendment, except when necessary to eliminate immediate hazards to the patients or where permitted by all applicable regulatory requirements or when the change(s) involves only logistic or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). Administrative changes and amendments not submitted for approval are submitted to the IRB/IEC for information only. However, written verification that such documents were submitted should be obtained.

The IRB/IEC must be informed by the Sponsor of:

- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review,
- serious and/or unexpected adverse events occurring during the study, where required,

- all subsequent protocol administrative changes (for information, except for US studies),
- new information that may affect adversely the safety of the patients or the conduct of the study,
- an annual update and/or request for re-approval, where required,
- when the study has been completed, where required.

If a trial is prematurely terminated or suspended for reasons including, but not limited to, safety or ethical issues or severe non-compliance, the sponsor will promptly inform the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

11.1.2. Informed consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval of the written informed consent form and any other written information to be provided to the patients.

Informed consent will be obtained in accordance with 21 CFR 50.25.

Freely given informed consent should be obtained from every patient prior to clinical trial participation.

Information should be given in both oral and written form whenever possible and as deemed appropriate by the IRB/IEC.

An investigator or designate will describe the protocol to potential patients face to face. The Informed Consent Form may be read to the patients, but, in any event, the investigator or designate shall give the patients ample opportunity to inquire about details of the study and ask any questions before dating and signing the Informed Consent Form.

While informed consent information can be presented to groups at an initial information session, each patient must be given the opportunity to individually pose questions to the investigator or designate prior to the patient dating and signing the Informed Consent Form.

The Informed Consent Form must be in a language fully comprehensible to the prospective patients. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patients and by the person who conducted the informed consent discussion. The signature confirms that the consent is based on information that has been understood. All illiterate individuals will have the study and the Informed Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness will personally sign and date the consent form. Orally witnessed consent will replace written consent only in countries where the local custom is contrary or if the patient's incapacity precludes this and provided that the local legal obligations are fulfilled.

Each patient's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities. The patients should receive a copy of the signed and dated written informed consent form and any other written information provided to the patients and should receive copies of any signed and dated consent form updates. Any amendments to the written information will be provided to the patients.

Both the informed consent discussion and the written informed consent form and any other written information to be provided to the patients should include explanations of the following:

a. That the trial involves research.
b. The purpose of the trial.
c. The trial treatments and the probability for random assignment to each treatment.
d. The trial procedures to be followed, including all invasive procedures.
e. The patient's responsibilities.
f. Those aspects of the trial that are experimental.
g. The reasonably foreseeable risks or inconvenience to the patients and, when applicable, to an embryo, fetus or nursing infant.
h. The reasonable expected benefits. When there is no intended clinical benefit to patients, the patients should be made aware of this.
i. The alternative procedures or courses of treatment that may be available to patients and their important potential benefits and risks.
j. The compensation and/or treatment available to patients in the event of trial-related injury.
k. The anticipated prorated payment, if any, to patients or patients' guardians for participating in the trial.
l. The anticipated expenses, if any, to patients for participating in the trial.
m. That the patients' participation in the trial is voluntary and patients may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which patients are otherwise entitled.
n. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the patient's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of patients, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent, the patient authorize such access.
o. That records identifying patients will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, patients' identity will remain confidential.
p. That the patients will be informed in a timely manner if information becomes available that may be relevant to the patients' willingness to continue participating in the trial.
q. The person(s) to contact for further information regarding the trial and the rights of trial patients, and who to contact in the event of trial-related injury.
r. The foreseeable circumstances and/or reasons under which a patient's participation in the trial may be terminated.
s. The expected duration of a patient's participation in the trial.
t. The approximate number of patients involved in the trial.

The Sponsor has the final responsibility for the final presentation of the Informed Consent Form, respecting the mandatory requirements of local regulations. The consent form generated by the sponsor, MCC, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

11.2. Administrative Matters

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

12. REFERENCES

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Appendix A. Overview of the Recruitment Plan

The recruitment of patients will include the following essential aspects:

- There will be one study centre at the Moffitt Cancer Center, which is the sponsor
- Enrollment will cease when the target of 40 evaluable patients (up to 44 patients recruited) is reached.
- An anticipated average of 2-3 patients per month will be recruited.
- Recruitment is anticipated to commence in March 2011and is expected to be complete by February 2013.
- Recruitment tracking will be provided by the centralized randomization procedure.

Appendix B. Laboratory assays

1. Laboratory assays part of the study protocol: Laboratory assays part of the study protocol are summarized in Table 8. Refer to Section 6.4 for details of the mandatory assays and to Section 7 for the optional translational research assays.

2. Handling and shipment of biological samples collected by the Investigator: For the samples to be analyzed by GSK Bio materials to be used will be agreed between the Sponsor and GSK Bio. GSK Bio will provide to the Sponsor some recommendations for the collection, storage and shipments of samples to be analyzed by GSK Bio or contracted lab (refer to Table 8). However, when GSK Biologicals does not recommend material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used.

Appendix C. Treatment supplies, packaging and accountability

1. Treatment and/or other supplies

GSK Biologicals will supply the following study treatments, sufficient number of doses to administer to all patients as described in the present protocol.

recMAGE-A3 + AS15 ASCI in two vials

Oncovir will ship the Poly IC:LC, in a sufficient number of doses to administer to all patients as described in the present protocol.

2. Treatment packaging
The treatments will be packed in labelled boxes. The box label will contain, as a minimum, the following information: study number, treatment number, lot number, instructions for treatment administration and any other relevant regulatory requirements.

3. Treatment shipment from GSK Biologicals Rixensart to the investigational site: on reception of the shipment, its content, quality and maintenance of the cold-chain must be checked.

The supplies receipt documents must then be returned to:

[redacted]

4. Treatment accountability
Treatment accountability is responsibility of the Sponsor, MCC. At all times, the figures on the treatment supplied by GSK Bio and Oncovir, used and remaining treatment doses should match. Used and unused treatment vials should be destroyed at the study site using locally approved biosafety procedures and documentation and a copy of the certificate of destruction must be sent to GSK Bio and Oncovir. If no adequate biosafety procedures are available at the study site, the used and unused treatment vials are to be returned to an appropriate site for destruction.

5. Transfers of clinical treatments or products from GSK Bio to the study sites: Storage temperatures must be maintained during transport and deviations must be reported to GSK Bio for guidance.

Appendix D. TNM classification of malignant melanoma

The TNM staging system characterizes melanoma with respect to several factors. The current version of the staging system used has been published in the Seventh Edition of the AJCC Cancer Staging Manual (AJCC 2010, *Balch CM et al, Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009*)

http://www.mmmp.org/MMMP/import.mmmp?page=tnm_staging mmmp

Melanoma TNM Classification

T Classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and mitotic rate <1/mm2
		b: with ulceration or mitotic rate 1 or greater
T2	1.01 – 2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01 – 4.0 mm	a: without ulceration
		b: with ulceration
T4	> 4.0 mm	a: without ulceration
		b: with ulceration

N Classification	# of Metastatic Nodes	Nodal Metastatic Mass
N1	1 node	a: micrometastasis*
		b: macrometastasis†
N2	2 – 3 nodes	a: micrometastasis*
		b: macrometastasis†
		c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellites(s) with metastatic node(s)	

M Classification	Site	Serum Lactate Dehydrogenase
M1a	Distant skin, subcutaneous	Normal

	or nodal mets	
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastatsis	Elevated

* Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

† Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Stage Groupings for Cutaneous Melanoma

	Clinical Staging			**Pathologic Staging**		
	T	**N**	**M**	**T**	**N**	**M**
0	Tis	N0	M0	Tis	N0	M0
IA	T1a	N0	M0	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0	T4b	N0	M0
III‡	Any T	N1 N2 N3	M0			
III A				T1-4a T1-4a	N1a N2a	M0 M0
III B				T1-4b T1-4b T1-4a T1-4a T1-4a/b	N1a N2a N1b N2b N2c	M0 M0 M0 M0 M0
III C				T1-4b T1-4b Any T	N1b N2b N3	M0 M0 M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

† Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathology stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes.

‡ There are no stage III or IV subgroups for clinical staging.

Appendix E. Eastern Co-operative Oncology Group (ECOG) Performance Status

Grade	Performance
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix F. U.S. National cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The severity of adverse events will be assessed by reference to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 published May 28, 2009 (v4.03: June 14, 2010). A copy can be downloaded from the internet website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf