CLINICAL STUDY PROTOCOL

Protocol Name:	CT TG 02-01
Protocol Title:	A Non-Randomised Open-Label Phase Ib Exploratory Study of TG02-treatment as Monotherapy or in Combination with Pembrolizumab to Assess Safety and Immune Activation in Patients with Locally Advanced Primary and Recurrent Oncogenic RAS Exon 2 Mutant Colorectal Cancer
Clinical Phase:	Ib
Version:	Final version 6.0
Date:	09 OCT 2018
Sponsor:	Targovax ASA

Statement about proper study conduct

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

Confidentiality Statement

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

CLINICAL STUDY PROTOCOL APPROVAL

PROTOCOL TITLE: A Non-Randomised Open-Label Phase Ib Exploratory Study of TG02-treatment as Monotherapy or in Combination with Pembrolizumab to Assess Safety Immune Activation in Patients with Locally Advanced Primary and Recurrent Oncogenic RAS Exon 2 Mutant Colorectal Cancer

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This protocol/protocol amendment has been approved by:

_____ _____

Magnus Jäderberg **Date**
Chief Medical Officer
Targovax ASA

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This protocol/protocol amendment has been approved by:

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Dr. Michael Michael **Date**
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Melbourne, Australia
Coordinating Principal Investigator

CLINICAL STUDY PROTOCOL APPROVAL

PROTOCOL TITLE: A Non-Randomised Open-Label Phase Ib Exploratory Study of TG02-treatment as Monotherapy or in Combination with Pembrolizumab to Assess Safety Immune Activation in Patients with Locally Advancer Primary and Recurrent Oncogenic RAS Exon 2 Mutant Colorectal Cancer

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This protocol/protocol amendment has been approved by:

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[redacted] **Date**

Senior Statistician

[redacted]

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2. ABBREVIATIONS

List of Abbreviations and definitions of terms:

ADR	Adverse Drug Reaction
AE	Adverse Event
CEA	Carcinoembryonic Antigen
CRC	Colorectal Cancer
CRT	Conventional chemoradiotherapy
CRF	Case Report Form
CRO	Contract Research Organisation
CTC	Circulating Tumour Cells
DCF	Data Clarification Form
DE	Data Enterer
DMP	Data Management Plan
DTH	Delayed Type Hypersensitivity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDG	Fluorodeoxyglucose
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
ICH	International Conference on Harmonization
IB	Investigator`s Brochure
ICH GCP	International Conference of Harmonization Good Clinical Practice
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
KRAS	Kirsten rat sarcoma
LPLV	Last Patient Last Visit
MDT	Multi-Disciplinary Team
MSDC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute, common terminology criteria for adverse events
NSTEMI	non-ST segment elevation myocardial infarction
PBMC	Peripheral Blood Mononuclear Cells
PET-CT	Positron Emission Tomography - Computed Tomography
PIS/ICF	Patient Information Sheet and Informed Consent Form
RAS	Rat sarcoma
SCCRT	Short course chemoradiotherapy
SAE	Serious Adverse Event
SDHP	Study Drug Handling Plan
SmPC	Summary of Product Characteristics
SSC	Safety Steering Committee

SSCC	Safety Steering Committee Charter
SUV	Standard Uptake Value
QA	Quality Assurance
QC	Quality Control
WHO DD	World Health Organization Drug Dictionary

3. PROTOCOL SYNOPSIS

Name of sponsor: Targovax ASA (Oslo, Norway)**,** although [redacted] will act as the local sponsor and legal representative in Australia
Study identification code: CT TG02-01
Title of the study: A Non-Randomised Open-Label Phase Ib Exploratory Study of TG02-treatment as Monotherapy or in Combination with Pembrolizumab to Assess Safety and Immune Activation in Patients with Locally Advanced Primary and Recurrent Oncogenic RAS Exon 2 Mutant Colorectal Cancer
Investigational medicinal products (IMP): TG02 administered with granulocyte macrophage stimulating factor (GM-CSF) in the form of recombinant human GM-CSF expressed in E-coli, the PD-1 inhibitor pembrolizumab (only in Part II) The TG02-treatment consists of an intradermal injection of GM-CSF followed by an injection of TG02. The GM-CSF is to be given 15-30 minutes before TG02. The doses to be administered are 0.10 mL of reconstituted, lyophilized GM-CSF (0.30 mg/mL) and 0.1 mL reconstituted, lyophilized TG02 (8.0 mg/mL).
Study period: The start date of the study (first patient first visit) is anticipated to be mid-2016. The total duration of the study is expected to be 2.5 years, approximately 15 months for Part I and 15 months for Part II. The total duration of the study will be dependent on whether the study proceeds to Part II or not. Patients will be on study for approximately 14-20 weeks. **<u>Part I (Monotherapy activation - Only TG02-treatment):</u>** 12 months enrolment (Assumption: 0.3 patients/site/month at 2-5 sites) After screening, a minimum of 8 and a maximum of 14 weeks between initiation of TG02 treatment and surgical resection is anticipated with a follow up period of up to 6 weeks after surgery. Total study duration for Part I: approximately 15 months First patient first visit (FPFV): 3Q 2016 Excepted last patient last visit (LPLV): 4Q2018 **<u>Part II (Combination activation - TG02-treatment + pembrolizumab):</u>** 12 months enrolment (Assumption: 0.3 patients/site/month at 2-5 sites) After screening a minimum of 8 and a maximum of 14 weeks between initiation of TG02-treatment+pembrolizumab and surgical resection is anticipated with a follow up period of up to 6 weeks after surgery. Total study duration for Part II: approximately 15 months Excepted FPFV: 1Q2019

Excepted LPLV: 4Q 2019

Phase of development: Ib

Participating countries and number of sites: 2-5 sites (Australia and New Zealand). Other sites may be added as required.

Number of subjects: In Part I approximately 4-6 patients will be enrolled, in Part II up to 10 patients will be enrolled.

Study objectives:

Primary Objectives:

- To determine the safety of TG02-treatment
- To evaluate the systemic TG02 specific immune responses and to investigate tumour T cell infiltration in tumour specimens

Secondary Objectives:

- To investigate changes in immunological and pathological markers in tumour tissue
- To investigate changes in FDG PET-CT images
- To investigate changes in CEA

Exploratory Objectives:

- To investigate changes in circulating tumour cells and/or circulating tumour DNA
- To investigate the functionality of RAS mutation specific T cells in tumour tissue and peripheral blood

Study design:

This is a non-randomised, open label Phase Ib exploratory study to investigate the safety of and immune responses to TG02-treatment, first as monotherapy (Part I) and thereafter as combination therapy with pembrolizumab (Part II) in patients with locally advanced primary and recurrent RAS mutant colorectal cancer eligible for radical pelvic surgery at time of enrolment.

Part I

Approximately 4-6 patients diagnosed with locally advanced and recurrent RAS mutant colorectal cancer will be given TG02-treatment for up to 10 weeks (up to six TG02-treatments; week 1, 2, 3, 4, 6 and 10 if surgery occurs beyond week 10) prior to surgery.

TG02 is an eight peptide vaccine. Significant clinical data exist for its precursor vaccine, TG01, which contains 7 of the 8 mutant RAS peptides present in TG02. TG01 in combination with GM-CSF has been shown to be immunogenic and well tolerated up to 11 weeks of treatment.

Since one of the eight peptides in TG02 has not previously been administered to humans, the first 3 patients will be enrolled in a sequential manner with a minimum lag time of 4 weeks between dosing of the first 3 subjects to ensure an acceptable safety profile.

The safety data collected during the first 4 weeks for the 3 first patients will be reviewed by a Safety Steering Committee (SSC) consisting of Sponsor representatives, the Principal Investigator, relevant Sub-Investigators and one Independent Physician.
As a general rule the following will be reviewed to provide a guide to safety decisions:

Unacceptable toxicities will be defined as follows (based on NCI Criteria for Adverse Events (CTCAE) (v4.03: June 14, 2010) for reactions considered related to TG02 and/or GM-CSF:

- Injection site reaction of ≥ grade 3 (grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated, grade 4: Life-threatening consequences; urgent intervention indicated, grade 5: death).
- Other relevant clinically significant toxicity ≥ grade 3 (excluding treatable nausea and vomiting). However for certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion in the SSC may take place to evaluate if this AE should be assessed as DLT.
- ≥ Grade 3 'allergic reaction/anaphylactic reaction' in spite of prophylaxis with antihistamine and steroids.

All AEs and SAEs will be reviewed and will also be compared to those of the precursor vaccine TG01 (see Investigator's Brochure).

If more than 1 out of the 3 patients has DLT the SSC will review the nature of the events and make a final decision if the rest of the patients may be enrolled.

When all safety data, systemic immune responses (Delayed-Type Hypersensitivity (DTHs)) and tumour material (analysed for intra-tumoural T cells infiltration) are available for all patients in Part I of the study, the Safety Steering Committee will evaluate the data to assess safety and preliminary immune activity and efficacy to make a recommendation whether the study will proceed or not to Part II of this protocol. In Part II 10 new patients, not previously treated with TG02, will be recruited. No patients treated in Part I will be treated in Part II. The SSC's recommendation will form the basis for sponsor to make a final decision.

Part II

At the discretion of the sponsor, a decision will be made to initiate Part II of the study where up to 10 patients will be treated with TG02-treatment plus pembrolizumab for up to 10 weeks (up to 6 TG02-treatments) prior to surgery. The first 3 patients will be enrolled in a sequential manner with a minimum lag time of 6 weeks between dosing of the first 3 subjects to ensure an acceptable safety profile.
The safety data collected during the first 6 weeks for the 3 first patients will be reviewed by the SSC in a similar manner as in Part I, as TG02-treatment in combination with pembrolizumab is a novel treatment.

Schedule of events:

Patients will be evaluated for safety at scheduled visits until surgery and at the end of study visit approximately 4 weeks after surgery. In addition, after any TG02-treatment the patients will be monitored for heart rate and blood pressure at 5, 10 and 30 minutes and then every 30 minutes thereafter for up to 2 hours post administration.

A FDG PET-CT will be performed before TG02-treatment is initiated (baseline scan should be within the last 4 weeks prior to first TG02-treatment) and a second scan as close as possible before surgery.

Tumour samples for assessment of immune response will be taken pre TG02-treatment in the form of a study specific biopsy and at time of surgery by analysis of the resected tumour tissue. If a pre TG02-treatment biopsy has been taken for diagnostic workup at the hospital, this biopsy, if adequate for the study specific immune analysis and no intervening treatment has been given, can be used as the study specific biopsy if taken within the last 4 week prior to first TG02-treatment. If for any reason the patient does not proceed to surgery, a biopsy will be obtained at the time of planned surgery if possible. In addition, archival biopsy samples from both initial staging (primary diagnosis) and re staging will be utilised, as needed. In the patient information sheet and informed consent form (PIS/ICF), patients will be asked to give consent to the use of archived biopsy material. These archival samples will be used to assess RAS-mutation status and other baseline immune assessments.

Delayed-Type Hypersensitivity (DTH) tests will be performed at week 1, week 4, week 6 and week 8 (if surgery is scheduled for week 8, the DTH test should be performed two days before surgery). If surgery is scheduled for after week 10, and the patient has had only negative DTH tests up to and including week 8, an additional DTH test should be performed at week 10.

Blood samples will be collected for in vitro assessment of TG02-specific immune responses (Immunology sample, PBMC) will be collected at baseline (Day 1, Week 1) and week 8 (Day 64). If surgery is scheduled to occur after week 10, a third sample will be taken as close as possible to the date of surgery.

In total, the study will enrol up to 16 patients for Part I and II.

Subject population: The target population is patients with locally advanced primary and recurrent oncogenic KRAS exon 2 mutant colorectal cancer eligible for radical pelvic surgery at time of enrolment.

Inclusion Criteria:

1. Patients with locally advanced primary and recurrent colorectal cancer (CRC) (histologically or cytologically confirmed adenocarcinoma), with a confirmed oncogenic KRAS exon 2, codon 12 or 13 mutations, eligible for radical pelvic surgery at time of enrolment.
2. Patient is ≥18 years of age and able to consent
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
4. Patient has adequate organ and bone marrow function within 28 days of study
   a. Neutrophil count >1.5 x10^9/L

b. Platelets >100 x10^9/L
c. Hb >90g/L
d. Total bilirubin <1.5 upper limit of normal, ULN
e. ALT and AST <3.0 x ULN
f. Serum creatinine < 3 x ULN or Creatinine Clearance ≥ 30ml/min (Cockroft-Gault or Nuclear GFR method)
g. PT and APTT <1.3 x ULN

5. The patient is willing to provide study specific pre TG02-treatment biopsy of tumour mass and allow use of archival tumour biopsies. For patients where there are technical reasons a baseline biopsy cannot be performed but who fulfil all the other inclusion criteria, the investigator shall contact the medical monitor to discuss the possibility of including such patient.
6. The patient is willing and able to comply with the protocol, and agrees to return to the hospital for study visits and examinations.
7. Men and women of childbearing potential must use adequate contraception to prevent pregnancy during the study. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care. An adequate contraception includes hormonal contraception with implants or combined oral, transdermal or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation, hysterectomy, or vasectomy of partner. A combination of male condom with either cap, diaphragm or sponge with spermicide are also considered acceptable. For women of childbearing potential a negative pregnancy test needs to be confirmed before inclusion.
8. The patient has been fully informed about the study and is willing to participate in the study, and has provided written informed consent form prior to any trial specific screening procedures.

Exclusion Criteria:

1. The patient has previously received an anticancer vaccine or immune checkpoint inhibitor, or participated in a trial involving the use of an anticancer vaccine or immune checkpoint inhibitor
2. Patients where pre-surgery radiotherapy, chemotherapy or other anti-cancer therapy has not been completed ≥ 2 weeks prior to TG02-treatment.
3. The patient is receiving anti-cancer therapy for concurrent illness
4. The patient has had a prior different malignancy within the last 3 years (excluding adequately treated basal cell or squamous cell carcinoma of the skin cancer, or localised low grade tumours considered cured and not requiring systemic therapy)
5. The patient has uncontrolled or significant intercurrent or recent illness including:
a. auto-immune disorder or history of autoimmune disease requiring immunosuppressive treatment.

b. cardiac disorder such as uncontrolled cardiac failure, unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) or myocardial infarction, uncontrolled arrhythmia less than 3 months before screening
c. stroke or thromboembolic event within 3 months of study commencement
d. active or uncontrolled severe infection
e. history of solid organ transplantation or any condition requiring chronic treatment with corticosteroids or other immunosuppressive agents
f. active coagulopathy/bleeding diathesis
g. cirrhosis, chronic active or untreated persistent hepatitis
h. history of adverse reactions to peptide vaccines

6. The patient is pregnant or lactating.
7. Has received an investigational drug within 4 weeks prior to study drug administration, or unless other has been agreed with the medical monitor
8. Is currently receiving any agent with a known effect on the immune system, unless at dose levels that are not immunosuppressive (e.g. prednisone at 10 mg/day or less or as inhaled steroid at doses used for the treatment of asthma)
9. Known history of positive tests for HIV/AIDS

10. Are planned to receive yellow fever or other live (attenuated) vaccines during the course of study
11. For Part II – any contraindication to receiving pembrolizumab:
    If using the 50 mg lyophilized powder; hypersensitivity to the active substance (pembrolizumab) or to any of the excipients; L-histidine, L-histidine hydrochloride monohydrate, Sucrose, Polysorbate 80.
    If using the 100 mg concentrate; hypersensitivity to the active substance (pembrolizumab) or to any of the excipients; L-histidine, Sucrose, Polysorbate 80.

Investigational medicinal product, dose and form of administration:
The TG02-treatment consists of an intradermal injection of GM-CSF followed by an injection of TG02. The GM-CSF is to be given 15-30 minutes before TG02.

TG02: provided as a lyophilised solid powder for reconstitution in sterile water for injection to be given via intradermal injection. TG02 is supplied as a single dose in 2 mL clear glass vials. Each vial of TG02 contains 2.4 mg of the drug substance peptides. Patients will receive TG02 at a dose of 0.80 mg/injection (individual peptides comprising 0.10 mg each).

GM-CSF: provided as a lyophilised solid powder for reconstitution in sterile water for injection to be given via intradermal injection. Patients will receive GM-CSF at a dose of 0.03 mg/injection.

GM-CSF and TG02 are administered as 2 separate intradermal injections, 15 to 30 minutes apart, at the same site in the upper arm. In addition, TG02 will, at certain time points, be administered intradermally (without prior administration of GM-CSF) in the lower area of the contralateral arm to test for a DTH response. The administration of GM-CSF (0.10 mL reconstituted GM-CSF) and TG02 (0.10 mL reconstituted TG02) has to be strictly intradermal. Study staff will be trained appropriately.

Pembrolizumab: a fixed dose of 200 mg pembrolizumab will be administered as an intravenous infusion. The product will be provided as a 50 mg lyophilized powder in a single-use vial for reconstitution in sterile water for injection, or as a vial of 4 mL of concentrate containing 100 mg. When Part II is initiated, pembrolizumab should be administered according to the latest version of the Summary of Product Characteristics (SmPC). Dependent on time of surgery, a patient will receive pembrolizumab 2 to 4 times throughout the treatment period.
All handling of the Investigation Medicinal Products (IMPs) should be in compliance with normal handling of sterile products for injections.

Reference therapy, dose and mode of administration:
Not applicable

Duration of treatment:
Part I:
TG02-treatment will be given at the same site in the upper arm up to 6 times to the patient during the course of the study. In addition to the above mentioned administration of TG02-treatment, TG02 will be administered intradermally (without prior administration of GM-CSF) at given time points (week 1, week 4, week 6, week 8 and possibly week 10), in the lower area of the contra lateral arm as a DTH test to evaluate the patient's immunological response to the TG02-treatment.
Part II:
TG02-treatment and DTH testing will occur in an identical manner to that described for the Part I of the study. Pembrolizumab should be administered as described previously. During the course of the study, the patient can expect to receive 2-4 intravenous infusions; week 4, week 6, and week 8 if surgery takes place Day51-63/Week8-10, and week 10 if surgery is delayed after day 64/Week 10. The dosing regimen should be the same for all patients at all sites.

Baseline and screening assessments:
Demographic details, medical and medication history, physical examination, vital signs (blood pressure, heart rate, tympanic temperature, weight, height), 12-lead ECG, ECOG performance status, routine laboratory testing (haematology and clinical chemistry), PET-CT, tumour biopsy, collection of blood for immune activity (PBMCs, serum and whole blood) and CEA.

Efficacy assessments:
- TG02-specific DTH response
- Presence of TG02 specific T-cells
- Change in intra-tumoural lymphocytes

- Change in immunological and pathological markers in tumour tissue
- Changes in FDG PET-CT images e.g. change in standard uptake value (SUV)
- Changes in CEA from baseline throughout treatment
- Changes in circulating tumour cells and/or circulating tumour DNA
- Functionality of RAS mutation specific T cells in tumour tissue and peripheral blood

Safety assessments:
Safety will be assessed by incidence and severity of adverse events as per NCI Criteria for Adverse Events (CTCAE) (v4.03: June 14, 2010), and by changes from baseline in laboratory variables, physical examination, vital signs and ECOG performance status.

Statistics:
The results from this study will be presented using descriptive statistical methods.
Data will be presented by time of measurement, e.g. at baseline, week 1, week 4, week 8 etc. In general, continuous variables will be described using standard summary statistics such as number of observations, mean value, standard deviation, minimum and maximum value, median, and first and third quartiles. Categorical variables will be summarised in frequency tables as counts and percentages. All individual data collected will be presented in data listings. Patients screened but not included in the study will not be presented in any tables or listings.

Safety summaries will be provided for treatment exposure, patient disposition, adverse events leading to discontinuation, serious adverse events and all events resulting in death during the study period. The frequency of adverse events will be tabulated and reviewed for potential significance and clinical importance.

4. BACKGROUND AND STUDY RATIONALE

4.1. Antigen specific anticancer immunotherapy

Significant advances in the rapidly evolving area of anticancer immunotherapy over recent years have led to the availability of several immunotherapeutic agents for patients with various advanced solid tumours. These include checkpoint inhibitors for metastatic melanoma and advanced lung cancer, and vaccine therapy for metastatic prostate cancer. Sipuleucel T, an autologous cellular vaccine, was shown to increase overall survival in patients with metastatic prostate cancer (Kantoff 2010), resulting in FDA approval of the vaccine. Previously, clinical trials evaluating various antigen specific immunotherapeutic agents in patients with colorectal cancer have shown promising results, however, none of these agents have since translated to clinical use and the effect of generating RAS-specific immunity is not known.

KRAS mutations occur in about 50% of colorectal cancers, and mostly (40%) within exon 2 codons 12 and 13 of the RAS oncogene (Markman 2014). In patients with KRAS mutant colorectal tumours, mutant RAS peptides are considered to be attractive targets for vaccine therapy with the aim of improving overall survival and/or reducing recurrence rate. Previous immunotherapeutic strategies using KRAS mutant peptides as vaccines have been shown to be feasible for colorectal cancer, lung cancer, and pancreatic cancer, with evidence for their induction of specific immune responses and early phase studies supporting their safety and tolerability. In a Phase I/II study by Gjertsen et al., a KRAS mutant peptide vaccine in combination with GM-CSF administered to patients with advanced pancreatic cancer resulted in RAS mutation specific T cell immune responses (DTH and/or T cell proliferation) in 58% of the evaluable patients, with increased overall survival in this patient subgroup (Gjertsen 2001).

The presence of RAS mutations has also been shown to be a negative factor for the additional treatment of patients with EGFR inhibitors and data generated has demonstrated that patients receiving cetuximab in combination with chemotherapy do not derive any benefit versus chemotherapy alone (Sorich 2014; Van Cutsem 2015). Even in patients eligible for cetuximab therapy, resistance may occur due to RAS mutation (Misale 2012). This demonstrates a need for therapy targeted at RAS mutated colorectal cancer.

To further enhance patient immune response to a mutant RAS peptide vaccine, the addition of a checkpoint inhibitor, e.g. pembrolizumab, may be of benefit. Preclinical data suggests that colorectal cancer, considered in general poorly immunogenic even in the presence of RAS mutations, may potentially become more responsive to checkpoint inhibition through priming of the immune system e.g. following radiation, cytotoxics, vaccination, or a combination of such therapies (Dovedi 2014; Cross 2015). Very recently FDA has granted breakthrough therapy designation to pembrolizumab, an anti-PD-1 therapy for treating patients with microsatellite instability high (MSIhigh) metastatic colorectal cancer (FDA News Nov. 9, 2015) (Le 2015). Since patients with both RAS mutation and MSIhigh colorectal cancer are very uncommon (Breivik 1997) this represent a further step forward for check point inhibitors for the treatment of colorectal cancer.

4.2. TG02

RAS exon 2 mutations are only found in cancer cells and mutant RAS peptide vaccines can, if given in combination with GM-CSF, induce specific anti-cancer immune response

and underlie the rationale for RAS peptide vaccination in colorectal cancer patients. The presence of peptides reflecting the common single amino acid substitutions found in RAS exon 2 mutations leads to host T cell recognition of the specific tumoural targets containing these single amino acid substitutions in mutant RAS proteins. A number of clinical studies have been performed confirming the feasibility of vaccination of patients with colorectal cancer using vaccines containing mutated RAS peptides (of codons 12 and 13) in colorectal and pancreatic cancer patients. Pilot studies have been performed demonstrating safety with 17-mer mutant RAS peptide vaccination in pancreatic and colorectal cancer patients, with no systemic side effects or delayed toxicities. The addition of immune adjuvants e.g. IL-2, GM-CSF or both, to mutant RAS peptide vaccines has also been evaluated (Rahma 2013).

TG02 is a peptide vaccine that contains a mixture of 8 synthetic peptides (all 17-mer) representing fragments of the 8 most common RAS exon 2 oncogenic mutant p21RAS proteins. The induction of host immune response against these RAS mutant epitopes would potentially result in tumour cell killing. Subsequent in-situ exposure of the RAS mutant antigens to specific T cells previously induced and activated by TG02 may lead to further epitope spreading i.e. cross presentation and T cell recognition of a range of tumour associated antigens.

The pre-clinical development of TG02 to date has comprised of a series of in-vitro studies using human lymphocytes and murine splenocytes as well as repeated dosing in the mouse using the intended clinical route. As expected, the resultant toxicology study findings were unremarkable. In a local tolerance study in mice, TG02 was shown to induce slight erythema and to bear minimal inflammatory potential (GM-CSF was considered the major trigger of inflammation, which supports the use as adjuvant). In-vitro studies confirmed the generation of immune responses with increased cellular proliferation and cytokine release following repeated administration of TG02. As the effects of TG02 are thought to be mediated via local immunological processing at the intradermal administration site, its effects are not considered to be directly associated with serum concentrations of drug and thus would be immeasurable; consequently, formal pharmacodynamics studies have not been conducted (TG02 Investigator Brochure).

TG02 has been administered to 4 humans. The RAS oncogene peptides have no intrinsic activity per se, but in combination with GM-CFS immune activity can be elicited. The Safety Steering Committee evaluated the safety data after 3 patients had each completed 4 weeks of treatment. There were no safety issues in these patients. Furthermore, no SAE related to trial medication has been reported for any patients including the 4th patient who has completed the trial. In addition, significant clinical data exists for its precursor vaccine, TG01, which contains 7 of the 8 mutant RAS peptides present in TG02. TG01 in combination with GM-CSF has been shown to be immunogenic, with acceptable tolerability. TG01 has been investigated in an early Phase II clinical trial, with evaluation of its efficacy in the adjuvant setting for pancreatic cancer patients in combination with gemcitabine. In the modified cohort of this trial, where the induction course of TG01 is similar to that used in the TG02 study, only expected adverse events have been related to the treatment and all of these have been mild in severity (see Investigators Brochure) with the exception of one Grade 3 event of fatigue. No SAEs related to TG01 or GM-CSF were reported. The trial has completed recruitment. Final report is expected Q4 2018.

As TG01 has been shown to be immunogenic with acceptable tolerability with the exception of hypersensitivity reactions which appear to be associated with the use of

gemcitabine as events occurred only after several cycles of chemotherapy or in the period immediately after the end of gemcitabine treatment (Palmer 2015). It is anticipated that TG02 will have a similar good safety profile in the absence of chemotherapy.

TG02 has no intrinsic activity per se and is administered in combination with the immunomodulator GM-CSF. This GM-CSF/TG02 combination is referred to as TG02-treatment in this study protocol.

4.3. PD-1 (Programmed Cell Death 1) receptor and its inhibition

PD-1 is a key immune inhibitory receptor present on the surface of T lymphocytes that on binding to programmed cell death ligands (PD-L1 or PD-L2) on tumour cells or antigen presenting cells, results in a negative T cell effector immune response. Phase I studies assessing efficacy of anti-PD-1 antibodies, including nivolumab, have shown anti-tumour efficacy in melanoma, renal cell carcinoma, and lung carcinoma; these tumours were found to have upregulation of PD-L1 on cell surfaces. This suggested that disruption of the PD-1/PD-L1 signalling pathway mediated the objective response of the anti-PD-1 antibody. Several recent clinical studies of nivolumab and pembrolizumab showed impressive response rates and significantly increased overall survival in melanoma and non-small cell lung cancer patients, leading to FDA and TGA approval for these agents.

4.4. Pembrolizumab

Pembrolizumab (MK3475, formerly known as lambrolizumab), is a fully humanized humanised monoclonal IgG4-kappa isotype antibody against PD-1. A Phase I study of pembrolizumab confirmed safety and tolerability at doses of 1 mg/kg, 3 mg/kg and 10 mg/kg administered intravenously every two weeks, with maximal tolerated dosing not reached, and efficacy demonstrated in all dose levels. Subsequently, data from a Phase I study expansion cohort of melanoma patients receiving 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks or 2 mg/kg every 3 weeks showed equivalent response rates across all three cohorts, with significantly reduced toxicities in the latter two groups of 4% and 9% respectively. More recently, a Phase I study of pembrolizumab in non-small cell lung cancer patients, previously treated or untreated, revealed objective response rates of 19.4% in unselected patients, versus 45% in those with greater than 50% of PD-L1 expression; in this enriched population, the median progression free survival was 6.3 months, with overall survival not reached (Garon 2015).

In a long term follow up study of patients who had received the anti-PD1 antibody BMS-936558, one patient with metastatic colorectal cancer patient, of MSI high subtype, undergoing intermittent dosing of BMS-936558 achieved a complete and prolonged response, remaining disease free at 3 years (Lipson 2013). Subsequently, a Phase II study showed that pembrolizumab (at 10 mg/kg administered intravenously 2 weekly) increased progression free survival in microsatellite unstable metastatic colorectal cancer patients with a disease control rate of 90% and overall response rate of 40%. Unfortunately, results from this study, in addition to previous first in human Phase I anti-PD-1 antibody trials revealed minimal response rates in patients with microsatellite stable disease, which comprises the majority of colorectal cancers (Le 2015).
Data from preclinical models suggest that colorectal cancers could potentially be converted to a more “immunogenic” cancer type through priming of the immune system e.g. following radiation or vaccine therapy, leading to increased responses to check point inhibitors and immunomodulation (Dovedi 2014; Cross 2015; Gerber 2014). Thus, the

combination of anti-PD1 therapy and mutant RAS peptide vaccine therapy may be a promising strategy.

4.5. Locally Advanced Primary and Recurrent Colorectal Cancer

Neo-adjuvant chemoradiation prior to total mesorectal excision is considered the standard of care in patients with locally advanced rectal cancer where R0 resection can be expected, with significant improvements in long term overall survival rates over the past two decades. Chemoradiotherapy, either conventional or short course (CRT or SCCRT)), is usually given as neoadjuvant treatment. Standard total mesorectal excision should achieve a curative resection. The use of CRT or SCCRT aims to reduce local recurrence (Glynne-Jones 2017). Despite this, 5-20% of these patients will experience local recurrence, at which time, their disease is more often than not incurable, with five year survival rates reported between 13% and 47% (Rahbari 2011).

Patients presenting with pelvic disease recurrence are often considered for resection, including aggressive radical debulking surgery or pelvic exenteration, which is associated with significant operative risks. Pre-operative re-irradiation may be offered prior to resection in selected patients, however, late toxicities are of concern with some patients not being suitable candidates. A recent publication evaluating five year survival rates of patients who achieved an R0 resection was 39% compared to only 22% in patients who were treated without surgery or underwent subtotal tumour removal.

Routinely there is a period of more than 8 to 12 weeks between diagnosis and resection and treatment of locally advanced disease or recurrence to resection according to the usual practise of the hospital, which allows a window of opportunity for patients to undergo systemic therapy (e.g. with vaccination and/or check point inhibition) whilst awaiting surgery. As per Figure 1, patients will be consented for the trial at the time of the diagnosis of the disease recurrence, once they have completed other anti-cancer therapy as applicable (such as radiotherapy/chemoradiotherapy).

The presence of locally advanced disease or recurrence will be confirmed by appropriate diagnostic imaging (the actual types of scans and other tests can vary in different institutions and this protocol does not define the nature of these tests) as per standard clinical practice at each hospital.

This provides justification for evaluation of TG02, with or without PD-1 inhibition, in patients with newly diagnosed locally advanced primary and recurrent colorectal cancer prior to radical surgery.

This is a window of opportunity study and, because surgery will not be delayed as a result of the TG02-treatment, it is not expected that the immunotherapy will have any direct benefits on the outcomes of surgery or the rate of cure. In the time that the patient is normally expected to wait from the time of the diagnosis and treatment of their disease and the time of surgery there is an opportunity to see what effect immunotherapy with this specific RAS vaccine has in eliciting a specific intra-tumoural T cell response.

While it would not be anticipated that any clinically relevant changes to tumour size would occur as a result of vaccination alone the ability to generate RAS specific T cells is important for two principal reasons: 1. The finding of cytotoxic T cells in the tumour will provide a rationale for vaccination overall and 2. It would add weight to the argument that

even if R0 resection is possible, adjuvant immunotherapy might be an important addition to other therapy post-surgery, which may enhance disease-free and overall survival.

4.6. Rationale for the study

Patients with locally advanced primary and recurrent colorectal cancer are often considered for radical pelvic surgery. This "window" allows an opportunity to use RAS peptides to induce an immune response and study whether this promotes a cytotoxic T-cell infiltration into the tumour and induce histologically at least tumour cell death. TG02-treatment alone or in combination with a PD-1 inhibitor, given prior to resection in patients with locally advanced primary and recurrent colorectal cancer may stimulate this immune response and provide evidence that vaccination with TG02 peptides induces enhanced specific T-cell tumour killing and this provides an important therapeutic intervention in the treatment of colorectal cancer. The hypothesis that there may be a requirement for a PD-1 inhibitor to facilitate the immune response induced by the TG02 vaccination is supported by the preliminary data from Part 1 of the study. The data suggest that PD-1 expression is seen on the cytotoxic T-cells as well as the T-helper cells in the peripheral blood as well as PDL-1 and PD-1 expression is seen on T cells in the surgical specimens. These results may indicate that the tumours would possibly respond to the addition of a PD-1 inhibitor.

4.7. Rationale for dose

The traditional approach to dose selection for cytotoxic anticancer agents is to escalate the dose until dse limiting toxicity. This concept of maximum tolerated dose is not applicable for peptides that generally lack any inherent toxicity and that are for local administration in the skin. TG02 is for induction of cellular immune responses, and consequently the immune response rate is the most important parameter to consider for determining an appropriate dose.

The rationale for the dose is based on studies performed with its precursor vaccine, TG01, which contains 7 of the 8 mutant RAS peptides present in TG02. The rationale for selecting the dose of 0.1 mg of each peptide per administration stems from the observations from a dose exploring study in colorectal cancer patients (CTN RAS 97005). In this trial the patients were first given four weekly administrations of a single RAS peptide at the dose of 0.1 mg per administration and subsequently, after three weeks rest, four weekly administrations of 0.3 mg peptide. An additional dose of 0.1 mg peptide was administered without GM-CSF at a separate site to elicit DTH. Indeed, more immune responders were seen after the second cycle, 13 versus 7 after the first cycle. Other studies with constant dose (0.1 mg per peptide) have demonstrated a similar increase in number of recorded immune responders after administration of boosters after the initial 4 week cycle. In a study with a cocktail containing four RAS peptides (dose 0.10 mg per peptide) in patients with advanced pancreatic cancer (CTN RAS 97004) the number of DTH responders was increased from 11 after the initial 4 week cycle, to 16 responders after only two additional administrations (week 6 and 10). This suggested that the 0.10 mg and 0.30 mg per peptide were immunologically equivalent in the CTN RAS 98005 study and that increasing the TG01 dose beyond the current 0.7 mg dose (0.1 mg per peptide) is unlikely to heighten further the levels of specific immune responses. Alternatively, reducing the TG01 dose to levels lower than 0.1 mg per peptide may result in sub-optimal T cell responses.

Given the acceptable safety profile and levels of T cell responses observed to date with the current dose of 0.7 mg (0.1mg each peptide) of TG01 , the clinical development of TG02 will commence using the same dose for each peptides (0.1 mg) with a total TG02 dose of 0.8 mg. TG02 will be given together with GM-CSF as immunomodulator. Please see the TG02 Investigators Brochure (IB) for more information.

4.8. Rationale for dose regimen

TG02

TG02 given in the TG02-treatment will be administered to the patient at week 1, 2, 3, 4, and 6. If surgery is scheduled after week 10 one more TG02-treatment will be given in week 10. In addition to this TG02 will at certain time points (week 1, week 4, week 6, week 8 and possible week 10), be administered intradermally (without prior administration of GM-CSF) as a DTH test to evaluate the immunological response. The rationale for this regimen is based on the results from the previous and ongoing studies with TG01/GM-CSF that demonstrate that prevailing RAS mutation specific T cells responses are induced in cancer patients after 4-6 weeks of vaccination.

Pembrolizumab

Although the licensed dosing regimen for pembrolizumab is 3-weekly, in this window of opportunity study there is limited time between the start of TG02 vaccinations and surgery. Also, in order that the scheduling of study visits can be minimised to avoid extra patient visits, it is proposed to administer the pembrolizumab 2-weekly. Based on the data reported from the KEYNOTE 006 study for melanoma (Schachter 2017), the efficacy was similar between the 2-weekly and 3-weekly schedule with very similar safety profiles. Additionally, time needs to be allowed for a TG02 specific immune response to be induced; therefore, pembrolizumab will be started at week 4 and continued two-weekly until surgery

5. STUDY OBJECTIVES

Primary Objectives:

- To determine the safety of TG02-treatment
- To evaluate the systemic TG02 specific immune responses and to investigate tumour T cell infiltration in tumour specimens

Secondary Objectives:

- To investigate changes in immunological and pathological markers in tumour tissue
- To investigate changes in FDG PET-CT images
- To investigate changes in CEA

Exploratory Objectives:

- To investigate changes in circulating tumour cells and/or circulating tumour DNA
- To investigate the functionality of RAS mutation specific T cells in tumour tissue and peripheral blood

6. STUDY DESIGN AND DESCRIPTION OF THE STUDY

This is a non-randomised open labelled Phase Ib exploratory study to investigate the safety and immune responses of TG02-treatment.

The study is divided into two parts, where after Part I the sponsor will make a decision as to the initiation of Part II. Part II will start after Part I has been completed. Patients will only be allowed to participate in either Part I or Part II of the study.

Part I is designed to investigate the objectives of the study with TG02-treatment as monotherapy, and the Part II is to investigate TG02-treatment in combination with pembrolizumab. Part I and Part II will enrol approximately 4-6 and up to 10 patients respectively.

6.1. Endpoints

Primary endpoints:

- Safety:
  - Adverse events
  - Laboratory assessments
  - Vital signs
- Systemic immune responses assessed by:
  - TG02-specific DTH response
  - Presence of TG02 specific T-cells in peripheral blood
  - Change in intra-tumoural lymphocytes

Secondary endpoints:

- Immune suppression factors in tumour specimens
- Pathological responses and markers of apoptosis in tumour specimens
- Change in standard uptake values (SUV) assessed by FDG PET-CT
- Change in CEA

Exploratory Endpoints:

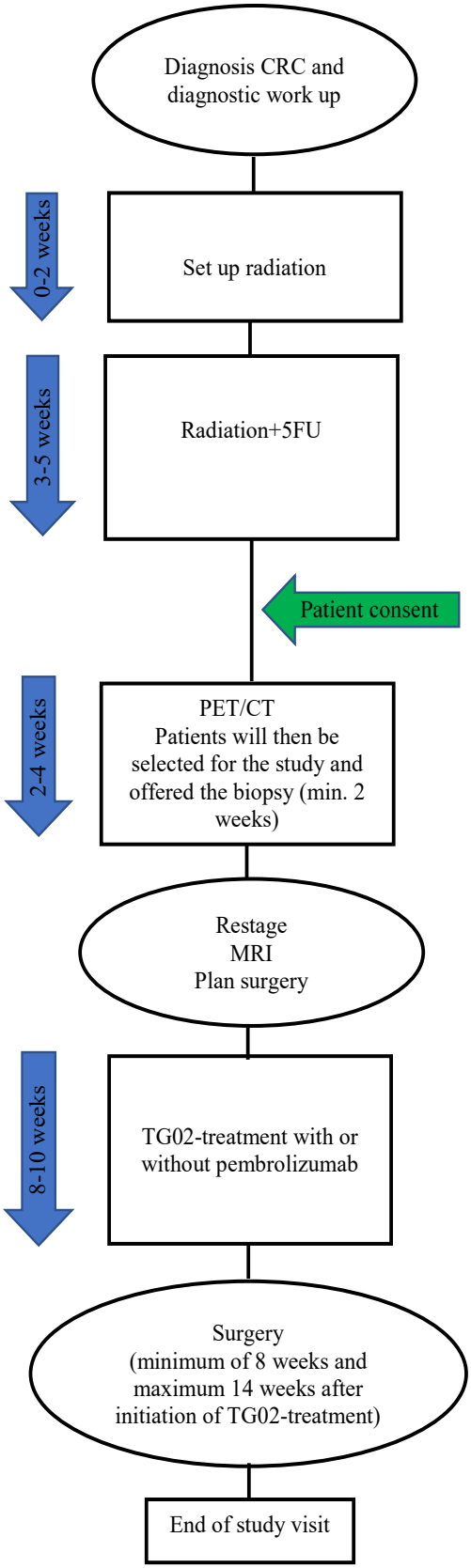
- Change in circulating tumour cells and/or circulating tumour DNA
- Functionality of RAS mutation specific T cells in tumour tissue and peripheral blood

6.2. Study Design

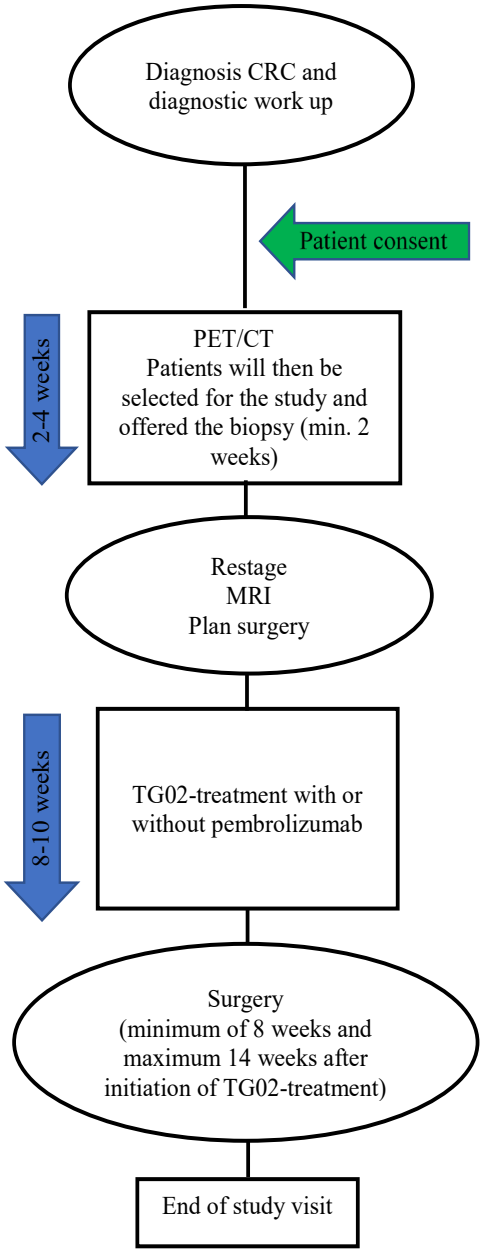
The patients with locally advanced primary and recurrent colorectal cancer will be considered for the study. A multi-disciplinary team (MDT) at the sites will coordinate the staging and work up of the patients and select appropriate patients for curative surgery. Selected patients for surgery will either receive chemo-radiation treatment (3-5 weeks) or have no further treatment before they are being consented for the study, see patient flow and timelines in Figure 1.

Figure 1: Patient flow and timelines

Patient flowchart with pre-surgery chemo/radiation



Patient flowchart without pre-surgery chemo/radiation



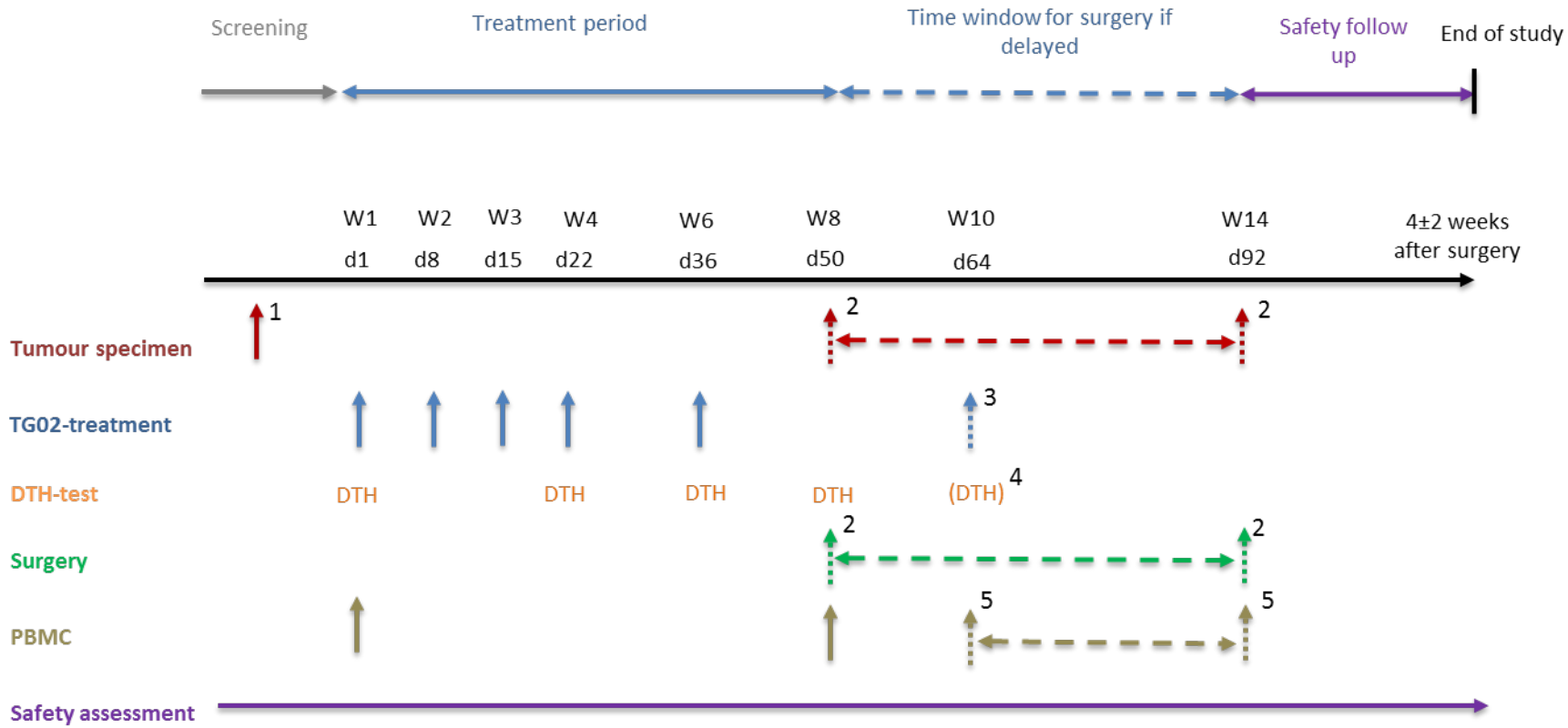
The patient will be defined as on study from the date of signed informed consent until the end of study (EOS) visit which should be scheduled after surgery.

The study is divided into two parts, Part I followed by Part II if decision of such will be made by the sponsor. Part II may start when all safety data, systemic immune responses (Delayed-Type Hypersensitivity (DTHs)) and tumour material (analysed for intra-tumoural T cell infiltration) are available for 4-6 patients in Part I of the study. The sponsor, after input from the Steering Committee, will evaluate the data to assess safety and preliminary immune activity and efficacy of TG02-treatment, and make a recommendation to proceed or not to Part II of this protocol.

Patients from Part I will not participate in Part II.

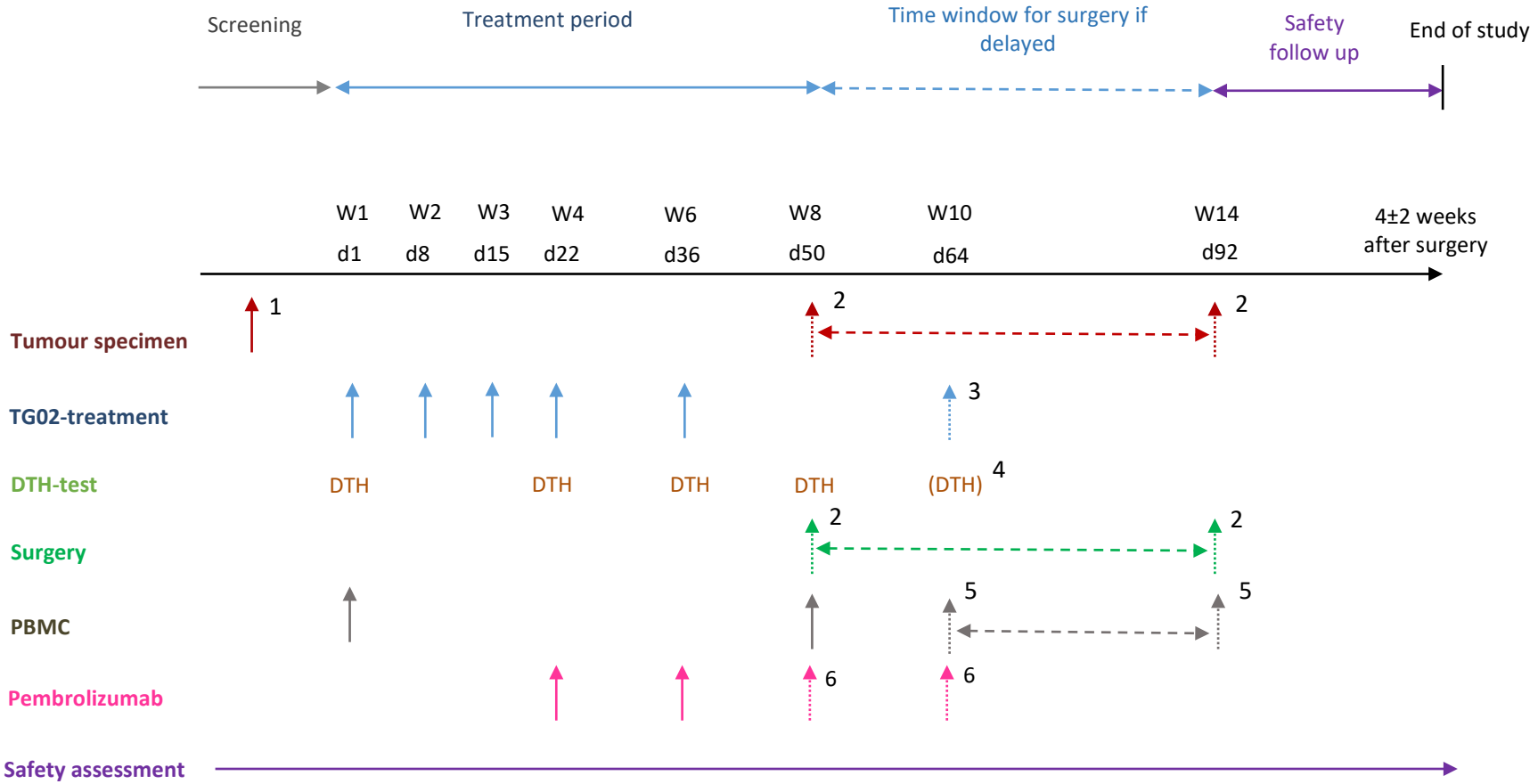
The study design for Part I is shown in Figure 2 and the study design for Part II in Figure 3.

Figure 2: Study design graphics Part I



1: Core needle biopsy pre TG02-treatment.
2: Tumour tissue at resection, at time of surgery.
3: If no surgery before week 10, a TG02-treatment will be given.
4: Only to be taken for patients who have surgery at week 10 or later and had a negative DTH outcome at week 8.
5: If surgery is after week 10, a sample will be taken as close as possible to surgery.

Figure 3: Study design graphics Part II



1: Core needle biopsy pre TG02-treatment.
2: Tumour tissue at resection, at time of surgery.
3: If no surgery before week 10, a TG02-treatment will be given.
4: Only to be taken for patients who have surgery at week 10 or later and had a negative DTH outcome at week 8.
5: If surgery is after week 10, a sample will be taken as close as possible to surgery.
6: If surgery is scheduled after Day50/Week 8, pembrolizumab will be given at Day 50/Week 8. If surgery scheduled after Day 64/Week 10, a further pembrolizumab infusion will be given at Day 64/Week 10.

Part I
Approximately 4-6 patients diagnosed with locally advanced primary and recurrent colorectal cancer will be given TG02-treatment for up to 10 weeks (up to 6 TG02-treatments) prior to surgery.

TG02 is an eight peptide vaccine. Significant clinical data exists for its precursor vaccine, TG01, which contains 7 of the 8 mutant RAS peptides present in TG02. TG01 in combination with GM-CSF has been shown to be immunogenic and well tolerated up to 11 weeks of treatment.

Since one of the eight peptides in TG02 has not previously been administered to humans, the first 3 patients will be enrolled in a sequential manner with a minimum lag time of 4 weeks between dosing of the first 3 subjects to ensure an acceptable safety profile.

The safety data collected during the first 4 weeks for the three first patients will be reviewed by a SSC consisting of Sponsor representatives, the Principal Investigator, relevant Sub-Investigators and one Independent Physician.

As a general rule the following will be reviewed to provide a guide to safety decisions:

Unacceptable toxicities will be defined as follows (based on NCI Criteria for Adverse Events (CTCAE) (v4.03: June 14, 2010) for reactions considered related to TG02 and/or GM-CSF:
- Injection site reaction of ≥ grade 3 (grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated, grade 4: Life-threatening consequences; urgent intervention indicated, grade 5: death).
- Other relevant clinically significant toxicity ≥ grade 3 (excluding treatable nausea and vomiting). However, for certain toxicities such as laboratory assessments without a clear clinical correlate, a discussion in the SSC may take place to evaluate if this AE should be assessed as DLT.
- ≥Grade 3 'allergic reaction/anaphylactic reaction' in spite of prophylaxis with antihistamine and steroids.

All AEs and SAEs will be reviewed and will also be compared to those of the precursor vaccine TG01 (see Investigator's Brochure).

If more than 1 out of the 3 patients has DLT the SSC will review the nature of the events and make a final decision if the rest of the patients may be enrolled.

When all safety data, systemic immune responses (DTHs) and tumour material (analysed for intra-tumoural T cells infiltration) are available for all patients in Part I of the study, the sponsor, with input from the Steering Committee, will evaluate the data to assess safety and preliminary immune activity and efficacy to make the decision to proceed or not to Part II of this protocol. In Part II up to10 new patients, not previously treated with TG02, will be recruited. No patients treated in Part I will be treated in Part II.

The SSC will review the tolerability of TG02-treatment in accordance with the SSC charter and this review will be based on an assessment of adverse events, laboratory

findings and, in particular the occurrence of hypersensitivity reactions. Toxicity grading will use NCI CTCAE version 4.03.

Part II
Up to 10 patients will be treated with TG02-treatment plus pembrolizumab for up to 10 weeks (up to six TG02-treatments and up to 4 pembrolizumab infusions) prior to surgery.
Again, since one of the eight peptides in TG02 is first in human, and that the use of pembrolizumab will be in a novel setting, as a precaution, the combination of TG02-treatment and pembrolizumab will be initiated first in 3 patients and evaluated for safety prior to subsequent recruitment of patients according to the same procedure as described above for Part I. The first 3 patients will be enrolled in a sequential manner with a minimum lag time of 6 weeks between dosing of the first 3 subjects to ensure an acceptable safety profile. The safety data collected during the first 6 weeks for the 3 first patients will be reviewed by the SSC.

6.3. Study Duration
The total duration of the study is expected to be 2.5 years, approximately 15 months for Part I and 15 months for Part II. The total duration of the study will be dependent on whether the study proceeds to Part II or not.
The patient will be in the study for a maximum of 20 weeks. The treatment period will be up to 10 weeks, dependent on the timing of scheduled surgery. The patient will be followed up to 6 weeks after surgery.

6.4. Study Visit Schedule
The schedule of visits (Table 6-1, Schedule of visits) reflects the assessments that will occur during the study, i.e. screening period, treatment period, and end of study. Patients will be screened for the study over a period of 14 days. The TG02-treatment period will be up to maximum 10 weeks and the end of study visit will be approximately 6 weeks after surgery.

- Weekly visits should occur within a window of ± 2 days.
- Two weekly visits should occur within a window of ± 4 days.
- End of study visit (EOS) should occur within 6 weeks after surgery.

Surgery should occur between week 8 and 14, if not postponed due to some unforeseen reasons, which will be documented. If for any reason, the patient will not have surgery, a biopsy will be obtained at the time of planned surgery if possible.
All trial treatment-related toxicities and SAEs must be followed until resolution unless, in the investigator's opinion, the condition is unlikely to resolve because of the patient's underlying disease.

6.4.1. Screening Period
Before initiating any screening activities, the scope of the study should be explained to each patient. Patients should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy. After this explanation, patients should be asked to sign an EC approved statement of informed consent.
The screening visit will determine patient eligibility according to the inclusion/ exclusion criteria (section 7.3 and 7.4). The following assessments will be performed during this period:

- Demographics and medical history (including detailed information about medical history of colorectal cancer and previous treatments)
- Medication and treatment history and concomitant medication (including medication taken in the 4 weeks before screening period, relevant information should be captured in the CRF)
- Urine or serum pregnancy test (for women of childbearing potential)
- Physical exam (review of the major body systems, vital signs (height, weight, heart rate, blood pressure, tympanic body temperature)
- 12-lead ECG evaluation
- ECOG Performance status
- Blood samples for routine haematology, serum biochemistry and CEA biomarker (Table 6-1)
- FDG PET-CT scan for tumour assessment of standard uptake value (SUV-max) as close as possible to first visit (should be within the last 4 weeks prior to first TG02-treatment)
- For patients receiving chemo-radiation before enrolment into study, core biopsy of target colorectal tumour should be taken after chemo-radiation and during the screening window (2 week) and as close as possible to the first TG02-treatment (day 1, week 1). For patients not having chemo-radiation before enrolment into the study, a core biopsy of target colorectal tumour can be taken within the last 4 weeks but as close as possible to the first TG02-treatment (day 1, week 1). If a pre TG02-treatment biopsy has been taken for diagnostic workup as hospital procedure, this biopsy, if adequate for the study specific immune analysis and no intervening treatment has been given, can also be used.
- Diagnostic CT/MRI scan according to hospital practice

6.4.2. Treatment period (before surgery):

The treatment period will be from Day 1 (Week 1) and up to surgery, which is planned for week 8 but can occur in a window up to week 14. The following assessments will be performed on Day 1, Day 8, Day 15, Day 22, Day 36, Day 50 and if surgery is after week 10 (Day 64):

- Vital signs (heart rate, blood pressure and tympanic body temperature) and ECOG performance status
- Concomitant medications and adverse events will be monitored continuously
- Physical examination, haematology and serum biochemistry (Table 9-1) before treatment (Day 1) and during treatment on Day 15, Day 36, Day 50 and if surgery after week 10 (Day 64).
- TG02 treatment will be administered on Days 1, 8, 15, 22 and 36. If surgery after week 10 TG02 treatment will also be given at week 10 (Day 64).
- Pembrolizumab will be given on Days 22 and 36. If surgery is scheduled after Day50/Week 8, pembrolizumab will be given at Day 50/Week 8. If surgery scheduled after Day 64/Week 10, a further pembrolizumab infusion will be given at Day 64/Week 10.
- DTH tests will be performed at baseline (Day 1), week 4 (Day 22), week 6 (Day 36) and week 8 (Day 50) (if surgery is scheduled for week 8 the DTH test should be performed two days before surgery). If surgery is after week 10, and the patient has had negative DTH tests up to and including week 8, an additional DTH test should be performed at week 10 (Day 64).

- Blood samples for in vitro assessment of TG02-specific immune responses (Immunology sample, PBMC) will be taken at baseline (Day 1) and Day 50. If surgery is after week 10, an additional sample should be taken as close as possible up to the date of surgery (see separate Immune monitoring plan).
- The CEA biomarker will be evaluated at Day 50. If surgery is after week 10 a third sample will be taken at Day 64 or just prior to surgery, whichever is the more appropriate.
- Tumour samples for assessment of immune response will be taken at time of surgery. If for any reason the patient will not have surgery a biopsy will be obtained if possible at the latest by week 14 (see separate Immune monitoring plan).
- FDG PET-CT scan for tumour assessment of standard uptake value (SUV-max) as close as possible up to date of surgery.
- Circulating Tumour Cells (CTC) will be evaluated at Day 1 and Day 50. If surgery is after week 10, an additional sample can be taken as close as possible up to the date of surgery.

Additional monitoring during the first 2 hours after any TG02-treatment:
Following any TG02-treatment patients will be monitored for signs and symptoms of hypersensitivity as well as heart rate and blood pressure. A finger pulsometer or similar should be used to monitor heart rate for the first 30 minutes and blood pressure should be measured at 5 and 10 and 30 minutes and then every 30 minutes for up to 2 hours post administration. Additional blood pressure measures should be taken if the patient experiences any of the following: dizziness, feeling cold or clammy, sweating, tingling in the mouth/tongue, itchy palms, feeling lightheaded, abdominal pain or breathlessness.

Measures in case of anaphylaxis should follow the hospital policy and include the availability of intravenous access, oxygen, adrenaline and hydrocortisone.

The administration of TG02 and post-treatment monitoring will occur in the Chemotherapy Treatment Unit or equivalent unit for each the institution with the patient sitting in an appropriate treatment chair or similar.

6.4.3. End of Study visit (Up to 6 weeks after surgery)

End of study visits to be scheduled during the hospitalized post-operative recovering period, up to 6 weeks after surgery.

- Physical exam (review of the major body systems, vital signs (weight, heart rate, blood pressure and tympanic body temperature)
- ECOG Performance status
- Blood samples for routine haematology and serum biochemistry (Table 9-1) or will be recorded if already available in the patient medical record.
- Adverse events and concomitant medications deemed to be related to TG02-treatment

6.4.4. Study Flow Chart

The schedule of visits is presented in Table 6-1. After screening a minimum of eight and maximum 14 weeks between initiation of TG02-treatment and resection surgery is anticipated with a follow up period of 4 weeks after surgery.

Table 6-1: Schedule of visits

	Screening within 2 weeks	Treatment period (Pre-surgery) (weeks 1-6)					Wk 8±4 days Surgery	If Surgery Wk 8-10	If surgery is Wk 10	If Surgery Wk 10-14	End of study visit[o] Up to 6 wk after surgery
Week		1	2	3	4	6	8	8-10	10	10-14	See footnote[o]
Day		1	8	15	22	36	50	51-63	64	65-92	See footnote[o]
Informed Consent	X										
Patient eligibility	X										
Pregnancy Test	X										
Medical History	X										
Physical Examination[h]	X	X		X		X	X		X		X
Vital Signs[h]	X	X	X	X	X	X	X		X		X
12-lead ECG	X										
ECOG[h]	X	X	X	X	X	X	X		X		X
DTH (TG02) test[jq]		X			X	X	X[b]		(X[i])		
Immunology Sample[h] (PBMC)		X					X[e]			X[g]	
TG02-treatment [p] (TG02/GM-CSF)		X	X	X	X	X			(X[f])		
Pembrolizumab[k]					X	X	X[s]		X[t]		
Haematology[h]	X	X		X		X	X		X		X[n]
Biochemistry[h]	X	X		X		X	X		X		X[n]
CEA (biomarker)	X						X[l]		X[g]	X[g]	
CTC (Circulating Tumour Cells)		X					X[l]			X[g]	
CT chest/abdomen/ Pelvic	X										
MRI (if standard Hospital procedure (re-staging)	X	As indicated									
FDG PET/CT	X[r]						X[g]	X[g]	X[g]	X[g]	
Tumour Biopsy	X[c]										
Surgery and resection of tumour tissue[m]							X[d]	X[d]	X[d]	X[d]	
Adverse Events		Continuously									X[a]
Concomitant medications	X	Continuously									X[a]

a: Deemed to be related to TG02-treatment
b: If surgery is scheduled to be done in week 8, DTH (TG02) injection to be done approximately 48 hours prior to surgery.
c: For patients receiving chemo-radiation before enrolment into study, core biopsy of target colorectal tumour should be taken after chemo-radiation and during the screening window (2 week) and as close as possible to the first TG02-treatment (day 1, week 1). For patients not having chemo-radiation before enrolment into the study, a core biopsy of target colorectal tumour can be taken within the last 4 weeks but as close as possible to the first TG02-treatment (day 1, week 1). If a pre TG02-treatment biopsy has been taken for diagnostic workup as hospital procedure, this biopsy, if adequate for the study specific immune analysis and no intervening treatment has been given, can also be used.
d: Tumour tissue taken during resection. If for any reason, the patient will not have surgery a biopsy will be obtained if possible.
e: To be done 2-0 days before surgery
f: If surgery is scheduled for week 10, there will be no TG02-treatment given at week 10. If no surgery at week 10, the last TG02-treatment to be given at week 10.
g: As close as possible up to the date of surgery.
h: At the visits when TG02 and/or TG02-treatment (and pembrolizumab in Part II) is scheduled, the assessments should be performed prior to the treatments.
i: Only to be taken for patients who have surgery after week 10 and had a negative DTH outcome at week 8. DTH (TG02) injection to be done 48 hours prior to surgery.
j: Assessment of DTH (TG02) injection site to be done 48 hours (+/- 4 hours) after each DTH (TG02) injections by the patient in a study specific diary.
k: Only applicable in Part II of the protocol
l: To be done prior to surgery
m: Allowed time for surgery (resection specimen) scheduled for week 8 is + 2 week and allowed time for surgery (resection specimen) scheduled for week 10 is + 4 week
n: Blood samples for routine haematology and serum biochemistry to be recorded if already available in the patient medical record (standard of care)
o: End of study visits to be scheduled during the hospitalized post-operative recovering period, up to 6 weeks after surgery.
p: TG02-treatment is a combination of the two IMPs: GM-CSF and TG02. When TG02-treatment is administered, GM-CSF is to be given as an intradermal injection 15-30 minutes before the TG02 intradermal injection. GM-CSF and TG02 are administered as 2 separate intradermal injections, 15 to 30 minutes apart, at the same site in the upper arm. After any TG02-treatment the patients will be monitored for heart rate and blood pressure at 5, 10 and 30 minutes and then every 30 minutes thereafter for up to 2 hours post administration
q: In addition, TG02 will, at certain time points, be administered intradermally (without prior administration of GM-CSF) in the lower area of the contra lateral arm as DTH test. The administration of GM-CSF (0.10 mL reconstituted GM-CSF) and TG02 (0.10 mL reconstituted TG02) has to be strictly intradermal.
r: Should be within the last 4 weeks prior to first TG02-treatment.
s: If surgery is scheduled after Day 50/Week 8, pembrolizumab will be given at Day 50/Week 8.
t: If surgery is scheduled after Day 64/Week 10, a further pembrolizumab infusion will be given at Day 64/Week 10.

7. SUBJECT SELECTION

7.1. Description of Study Population

The target population is patients with locally advanced primary and recurrent colorectal cancer, with confirmed positive RAS mutation eligible for radical pelvic surgery at time of enrolment.

7.2. Number and Source of Subjects

In this study approximately 4-6 (Part I) and up to 10 patients (Part II) will be enrolled, divided into the two sequential parts of the study. Patients will only be allowed to participate in either Part I or Part II of the study. Part II will only start after Part I has been completed. As stated above the start of Part II of the study will depend upon the level of immune activation and the safety profile in Part I. Patients will be recruited at 3-5 sites. Potential patients will be identified when patients are diagnosed with locally advanced primary and recurrent colorectal cancer by referrals.

7.3. Inclusion Criteria

1. Patients with locally advanced primary and recurrent colorectal cancer (CRC) (histologically or cytologically confirmed adenocarcinoma), with a confirmed oncogenic KRAS exon 2, codon 12 or 13 mutations, eligible for radical pelvic surgery at time of enrolment.
2. Patient is ≥18 years of age and able to consent
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
4. Patient has adequate organ and bone marrow function within 28 days of study
   a. Neutrophil count >1.5 $x10^9$/L
   b. Platelets >100 $x10^9$/L
   c. Hb >90g/L
   d. Total bilirubin <1.5 upper limit of normal, ULN
   e. ALT and AST <3.0 x ULN
   f. Serum creatinine < 3 x ULN or Creatinine Clearance ≥ 30ml/min (Cockroft-Gault or Nuclear GFR method)
   g. PT and APTT <1.3 x ULN
5. The patient is willing to provide study specific pre TG02-treatment biopsy of tumour mass and allow use of archival tumour biopsies. For patients where there are technical reasons a baseline biopsy cannot be performed but who fulfil all the other inclusion criteria, the investigator shall contact the medical monitor to discuss the possibility of including such patient.
6. The patient is willing and able to comply with the protocol, and agrees to return to the hospital for study visits and examinations
7. Men and women of childbearing potential must use adequate contraception to prevent pregnancy during the study. Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care. An adequate contraception includes hormonal contraception with implants or combined oral, transdermal or injectable contraceptives, certain intrauterine devices, bilateral tubal ligation, hysterectomy, or vasectomy of partner. A combination of male condom with either cap, diaphragm or sponge with spermicide are also considered acceptable.

For women of childbearing potential, a negative pregnancy test needs to be confirmed before inclusion.

8. The patient has been fully informed about the study and is willing to participate in the study, and has provided written informed consent form prior to any trial specific screening procedures.

7.4. Exclusion Criteria

1. The patient has previously received an anticancer vaccine or immune checkpoint inhibitor, or participated in a trial involving the use of an anticancer vaccine or immune checkpoint inhibitor
2. Patients where pre-surgery radiotherapy, chemotherapy or other anti-cancer therapy has not been completed ≥ 2 weeks prior to TG02-treatment.
3. The patient is receiving anti-cancer therapy for concurrent illness
4. The patient has had a prior different malignancy within the last 3 years (excluding adequately treated basal cell or squamous cell carcinoma of the skin cancer, or localised low grade tumours considered cured and not requiring systemic therapy)
5. The patient has uncontrolled or significant intercurrent or recent illness including:
   a. auto-immune disorder or history of autoimmune disease requiring immunosuppressive treatment
   b. cardiac disorder such as uncontrolled cardiac failure, unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) or myocardial infarction, uncontrolled arrhythmia less than 3 months before screening
   c. stroke or thromboembolic event within 3 months of study commencement
   d. active or uncontrolled severe infection
   e. history of solid organ transplantation or any condition requiring chronic treatment with corticosteroids or other immunosuppressive agents
   f. active coagulopathy/bleeding diathesis
   g. cirrhosis, chronic active or untreated persistent hepatitis
   h. history of adverse reactions to peptide vaccines
6. The patient is pregnant or lactating.
7. Has received an investigational drug within 4 weeks prior to study drug administration, or unless other has been agreed with the medical monitor
8. Is currently receiving any agent with a known effect on the immune system, unless at dose levels that are not immunosuppressive (e.g. prednisone at 10 mg/day or less or as inhaled steroid at doses used for the treatment of asthma)
9. Known history of positive tests for HIV/AID.S
11. Are planned to receive yellow fever or other live (attenuated) vaccines during the course of study
12. For Part II – any contraindication to receiving pembrolizumab:
    For the 50 mg lyophilized powder: Hypersensitivity to the active substance (pembrolizumab) or to any of the excipients; L-histidine, L-histidine hydrochloride monohydrate, Sucrose, Polysorbate 80
    For the 100 mg concentrate: Hypersensitivity to the active substance (pembrolizumab) or to any of the excipients; L-histidine, Sucrose, Polysorbate 80.

7.5. Discontinuation Criteria

Patient Withdrawal

Single patient termination is by definition when the patient is withdrawn or when the patient has died or completed the study. The study termination page in the eCRF must be completed.

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time without giving their reason(s).
The investigator also has the right to withdraw patients from the study in the event of:

- withdrawal of the patient's consent
- surgery does not proceed and the patient is unable or unwilling to provide a biopsy at the time of cancelled surgery
- occurrence of an exclusion criterion which is clinically relevant and affects the patient's safety, and discontinuation is considered necessary by the Investigators and/or Targovax.
- therapeutic failure requiring urgent additional medication (if applicable)
- occurrence of AEs, if discontinuation of trial medication is desired or considered necessary by the Investigator and/or patient (if applicable)
- intake of non-permitted concomitant medication where the predefined consequence is withdrawal from the trial
- patient non-compliance with study procedures/requirements
- major protocol violation which potentially impacts the study endpoints

Study Termination
The whole study may be discontinued at the discretion of the Investigator or Sponsor in the event of any of the following:

- Occurrence of AEs not seen previously which by virtue of their nature, severity and duration are considered to necessitate study termination; OR the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of the drug development as such or for the given indication

7.6. Replacement Policy

If a patient during the treatment period before surgery is withdrawn, the patient will be considered to be replaced. All safety data collected will remain part of the safety analysis.

8. TRIAL TREATMENT(S) AND REGIMEN OF INVESTIGATIONAL MEDICINAL PRODUCTS

8.1. Identity of Investigational Medicinal Product(s) (IMPs)

The TG02-treatment (GM-CSF/TG02) is manufactured according to Good Manufacturing Practice (GMP) standard.

In Part I the IMPs consists of two different products in two separate vials, 1 vial containing TG02 and 1 vial containing GM-CSF. In Part II, in addition to TG02 and GM-CSF, a third IMP, pembrolizumab will be used.

TG02
TG02 is a sterile dry white solid powder consisting of the eight drug substance peptides in equal amounts (weight net peptide) (Baccinex SA, Courroux, Switzerland/Bachem Distribution Services, GmbH).

TG02 is produced by lyophilisation of a sterile aqueous solution of the drug substance peptides. No additional ingredients are present in the TG02 drug product. Each vial of TG02 contains 2.4 mg of the drug substance peptides.

TG02 is supplied as a single dose in 2 mL clear glass vials. All the primary packaging materials used are in conformance with the European Pharmacopoeia (EP) and US Pharmacopoeia (USP).

TG02 drug product is to be reconstituted in water for injection (WFI) before administration to the patient. Patient will receive TG02 at a dose of 0.80 mg/injection.

An accountability log will be kept to track the use of TG02.

GM-CSF (Immunomodulator)
GM-CSF in the form of lyophilised recombinant human GM-CSF expressed in E-coli (Amoytop Biotech Co, Ltd, Xiamen, China) is used as immunomodulatory.

GM-CSF is a sterile dry white solid powder consisting of human recombinant GM-CSF and the excipients mannitol, macrogol 4000, human albumin, dibasic sodium phosphate and monobasic potassium phosphate. Each vial of GM-CSF contains 100 µg (1.0x106 IU) Molgramostim. GM-CSF is supplied in a 2 mL clear glass vial.

GM-CSF is to be reconstituted in water for injection (WFI) before administration to the patient.

An accountability log will be kept to track the use of GM-CSF.

Pembrolizumab (Only Part II):
A fixed dose of 200 mg pembrolizumab will be administered as an intravenous infusion. The product will be provided as a 50 mg lyophilized powder in a single-use vial for reconstitution in sterile water for injection, or as a vial of 4 mL of concentrate containing 100 mg. Pembrolizumab should be administered according to the latest version of the

Summary of Product Characteristics (SmPC), and dosed according to available guidelines for the use of this drug.

An accountability log will be kept to track the use of Pembrolizumab.

8.2. Dosing, Mode of Administration, Duration of Treatment

TG02 and GM-CSF will be given as intradermal injections by trained study staff authorized to do such procedures. Training of study staff will be performed by Sponsor before any patients are treated**.** In addition, the administration of TG02 and GM-CSF is described in the Study Drug Handling Plan (SDHP).

GM-CSF and TG02 are administered as 2 separate intradermal injections, 15 to 30 minutes apart, at the same site in the upper arm. In addition, TG02 will at certain time points be administered intradermally (without prior administration of GM-CSF) in the lower area of the contra lateral arm as DTH test.

The administration of GM-CSF (0.10 mL reconstituted GM-CSF) and TG02 (0.10 mL reconstituted TG02) has to be strictly intradermal. Utmost care has to be taken that no material is administered subcutaneously. When done correctly, a small bleb should appear following the injection. An injection that is too superficial will result in loss of volume from the injection site during injection or after withdrawal of the needle. The administration should be performed at the same site every time, if possible.

TG02: provided as a lyophilised solid powder for reconstitution in sterile water for injection to be given via intradermal injection.

TG02 given in the TG02-treatment will be administered in the upper arm at weeks 1, 2, 3, 4, and 6. If surgery is scheduled after week 10 one more TG02-treatment will be given in week 10. **TG02 is to be given 15-30 minutes after GM-CSF.**

TG02 will at certain time points (week 1, week 4, week 6, week 8 and possible week 10), be administered intradermally (without prior administration of GM-CSF) in the lower area of the contra lateral arm as a DTH test to evaluate the immunological response (see Table 6-1).

Where a DTH (TG02) injection is being performed the TG02 DTH dose should be administered **30 minutes** before the TG02-treatment and patients should be observed for at least 30 minutes after ALL TG02 treatments.

GM-CSF: provided as a lyophilised solid powder for reconstitution in sterile water for injection to be given via intradermal injection.

GM-CSF given in the TG02-treatment will be administered in the upper arm at weeks 1, 2, 3, 4, and 6. If surgery is scheduled after week 10 one more TG02-treatment will be given in week 10 (see Table 6-1).

In the TG02-treatment GM-CSF is to be given 15-30 minutes before TG02.

The drug handling of TG02-treatment will be described in a separate Study Drug Handling Plan.

Table 8-1: Treatment schedule

Time point	DTH test (TG02)	TG02-treatment (GM-CSF followed by TG02)	Pembrolizumab (Part II of the study)
Week 1	X	X	
Week 2		X	
Week 3		X	
Week 4	X	X	X
Week 6	X	X	X
Week 8	X*		X***
Week 10 (only if surgery is after week 10)	X**	X	X

*If surgery is scheduled to be done in week 8, DTH (TG02) injection to be done approximately 48 hours prior to surgery.
** Only to be taken for patients who have surgery at week 10 or later and had a negative outcome at week 8.
*** If surgery is taking place Day 51-63, pembrolizumab will be given at Day 50/Week 8.

Pembrolizumab: A fixed dose of 200 mg pembrolizumab will be administered as an intravenous infusion. Pembrolizumab should be administered according to the latest version of the Summary of Product Characteristics (SmPC), and dosed according to available guidelines for the use of this drug. Dependent on time of surgery, a patient will receive pembrolizumab 2 to 4 times throughout the treatment period.

All handling of the IMPs/drug products should be in compliance with normal handling of sterile products for injections.

8.3. Packaging and Labelling

From the documentation of the trial medication, it must be possible to retrace the handling, composition and pharmaceutical quality of the investigational products according to the current Good Manufacturing Practice (GMP) guidelines.

TG02 will be packed and labelled by [redacted], a specialised pharmaceutical clinical supply company located in [redacted], in accordance with GMP and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements. The vials and boxes will be labelled according to local regulatory requirements.
The trial medication will be supplied to the investigational site(s) in boxes containing a defined number of vials. TG02 will be shipped to the investigational sites under controlled, frozen (-20±5 ºC) conditions.

GM-CSF will be packed and labelled by [redacted], a specialised pharmaceutical clinical supply company located in [redacted] in accordance with GMP and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements. The vials and boxes will be labelled according to local regulatory requirements.
The trial medication will be supplied to the investigational sites in boxes containing "a defined number of vials". GM-CSF will be shipped to the investigational site(s) under controlled, refrigerated conditions (2 -8 ºC).

Pembrolizumab, in the Part II of the study, will be supplied from commercial stock at the clinical site(s) or sourced, packed and labelled and supplied by [redacted], a specialised pharmaceutical clinical supply company located in [redacted] in accordance with GMP and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements. The vials and boxes will be labelled according to local regulatory requirements.

The trial medication will be supplied to the investigational sites in boxes containing "a defined number of vials". Pembrolizumab will be shipped to the investigational site(s) under controlled, refrigerated conditions (2 -8 ºC).

8.4. Storage, Handling and Dispensing of Investigational Product(s)

Upon receipt of the medication, the Investigators, or the responsible pharmacist, will inspect the medication and send back the acknowledgment of receipt form that is enclosed with the parcel, duly completed and signed and further follow up on the instructions given in the shipment documents. A copy of the signed receipt will be kept in the trial files.
TG02 must be kept frozen at -20±5 °C and GM-CSF must be kept at 2-8 °C during storage prior to reconstitution. Pembrolizumab must be stored at 2-8 °C in original carton to protect from light. Do not freeze. Do not shake.
All study drugs are to be stored safely and separately from other drugs. The trial medication cannot be used for any purpose other than the present study. After the trial is completed, all unused trial medication must be destroyed by the pharmacy after sponsor's approval.
The Investigators will be responsible for the storage, dispensing, inventory, and accountability of all clinical supplies at the clinical sites. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor (Targovax) on request, and must include the information below:

- the identification of the patient to whom the drug was dispensed
- the date(s) and quantity of the drug dispensed to the patient
- the product lot number

The preparation of the Study Drugs must be documented on a 'Drug Preparation and Dispensing Log Form'.

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be submitted by the Investigators to the Sponsor (Targovax). This form must include the information below:

- the number of administered units
- the number of unused units
- the number of units destroyed at the end of the trial
- the date and method of destruction and the location

8.5. Blinding Procedures

The study will be an open labelled study.

8.6. Randomization and Subject Allocation

This is a non-randomized study.

8.7. Treatment Compliance

The Investigator(s) will record the time and dose of all administrations in the medical source documents. Any reasons for non-compliance will also be documented, including:

- missed visits
- interruptions in the schedule of administration
- non-permitted medications

Management of Toxicity

If a patient experiences GM-CSF or TG02 related toxicity on the days of the scheduled TG02 treatment, TG02 treatment should be delayed until toxicity resolved to CTC grade 1. The patient should then restart at the next planned visit.

Management of TG02 or GM-CSF related reactions:

- At any time during the vaccination schedule – if a patient exhibits signs of an allergic reaction (not just a local reaction) then they should be treated symptomatically and for all subsequent TG02-treatment administrations they should be pre-medicated with intravenous antihistamine treatment (e.g. chlorpheniramine or dexchlorpheniramine) 30 minutes before any TG02-treatment administration.
- Patients who have local reactions only – It is permissible to use topical therapies such as anti-histamine or steroid creams or EMLA cream for pain
- Where a DTH injection is being performed the TG02 DTH dose should be administered **30 minutes** before the TG02-treatment and patients should be observed for at least 30 minutes after ALL TG02-treatments.
- In patients who have not had prophylaxis
  - If after the TG02 DTH dose the patient exhibits a Grade 1 or 2 allergic reaction then the TG02-treatment should be delayed and the patient is to be given intravenous antihistamine treatment as above
  - If a Grade 3 or 4 reaction occurs then no more vaccinations should be given.
- In patients who have had prophylaxis
  - If after the DTH dose the patient exhibits a Grade 1 reaction then the TG02-treatment should only be given if the investigator believes it is reasonable to do so based on the nature of the reaction
  - if a Grade $\geq$2 reaction occurs then no more vaccinations should be given.
- Precautions should be in place in case of anaphylaxis

Management of pembrolizumab related reactions:

- Toxicities should be managed according to SmPC for pembrolizumab. The patient should be discontinued if immunosuppressive agents are used at immunosuppressive doses. Please see *Section 8.8 Prior and Concomitant Medication* for further details.

8.8. Prior and Concomitant Medications

No systemic anti-cancer therapy is to be used during the study treatment period before surgery.

Other vaccinations must not be administered during the treatment period.
Vaccination with yellow fever or live (attenuated) vaccines is prohibited until after surgery.

Any agent with a known effect on the immune system should be excluded during the treatment period before surgery, unless it is being given at dose levels that are not

immunosuppressive, e.g. prednisone at 10 mg/day or less or as inhaled steroid at doses used for the treatment of asthma.

No specific studies of interactions between TG02 and other agents have been conducted.

9. STUDY ASSESSMENTS

9.1. Assessment of Efficacy

9.1.1. Primary Efficacy Variables

A systemic immune response is defined as having a positive in vivo DTH and/or a positive in vitro T-cell response at least once during the treatment period. Change intra-tumoural T-cells in resected tumour tissue at surgery compared to pre TG02-treatment core biopsy will be investigated.

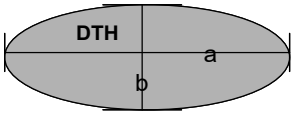
Delayed Type Hypersensitivity (DTH)

DTH tests are performed in order to demonstrate whether a TG02 RAS mutation specific immune response has been elicited.
Administration of TG02 only (without GM-CSF or proceeded by TG02-treatment) must be injected intradermally in the lower area of the contralateral arm to TG02-treatment as a Delayed Type Hypersensitivity (DTH) test.
The DTH test is administered at baseline (Day 1 before treatment) week 4, week 6 and week 10 if surgery is scheduled after week 10 and the patient has not shown positive DTH reaction.

The DTH skin reaction assessment is to be performed 48 hours (+/- 4 hours) after each administration by the patient in a study specific diary. The patient will be instructed by the study nurse how to record the DTH response and how to enter the results into the diary. The DTH-test will be considered positive if the area of the skin reaction has an average diameter* of $\geq$ 5 mm at the 48 hours (+/- 4 hours) assessment (Figure 4).

Figure 4: DTH Skin Reaction Registration (induration and erythema)

* Average diameter: $\frac{a\ mm + b\ mm}{2}$



T-cell Analyses

Immunology-processed blood samples (PBMC) will be taken at baseline (Day 1, Week 1) and week 8 (Day 50). If surgery is after week 10, a third sample will be taken as close as possible up to the date of surgery. All samples will be processed and stored under appropriate conditions until being analysed in batches to minimize day to day assay variability. PBMCs will be analysed for the presence of TG02 specific T-cells which will be described in a study specific Immune Monitoring Plan.

Tumour biopsy assessment

Tumour samples for assessment of immune response will be taken pre TG02-treatment (baseline) in the form of a study specific biopsy as per site specific standard protocol (optimally 2 cores will be needed) and at time of surgery in the form of resected tumour tissue (post treatment sample). If for any reason the patient does not proceed to surgery, a biopsy will be obtained at the time of planned surgery if possible. In addition, archival biopsy samples from both initial staging (primary diagnosis) and re staging will be utilised, as needed.

The tissue samples should be fixed in 10% neutral buffered formalin as soon as practical after collection of the specimen. Processing of tumour tissue into blocks will occur according to the respective sites standard histology sampling procedure. These tumour tissue samples will be used for pathological review and subsequent immunohistochemically evaluation of potential biomarkers.

In addition, from some patients, fresh tumour tissue will be sent directly to the laboratory at Peter MacCallum Cancer Centre following the respective sites standard procedures. These fresh tissue samples will be processed to isolate tumour infiltrating cells (TILs) and to generate tumour-derived organoid/spheroid cultures as part of other outcome measures.

As for the primary efficacy variables, tumour infiltrating lymphocytes in resected tumour tissue at surgery and baseline biopsies will be analysed by immunohistochemistry.

The collection, storage, shipment, parameters and analyses to be used will be described in the study specific Immune Monitoring Plan.

9.1.2. Secondary Efficacy Variables

Tumour biopsy assessment

The same processing procedure as described for primary efficacy variables will be followed.

Immunohistochemical staining will be performed to investigate; pathological responses and markers of apoptosis (such as activated Caspase 3, granzyme B), immune cell subsets (such as T effector cells, B cells, NK cells, T-regs, MDSC), and PD-L1 expression on epithelial cells in baseline biopsies and resected tumour tissue at surgery.

The collection, storage, parameters and analyses to be used will be described in a study specific Immune Monitoring Plan.

FDG PET/CT assessment

FDG uptake reflects the tumour activity independent of the morphologic characteristics. Sequential FDG-PET/CT can provide vital information in monitoring treatment response in tumour.

FDG PET/CT images will be performed at screening (should be within the last 4 weeks prior to first TG02-treatment), and as close as possible up to the date of surgery. The scans will be captured according to the site's standard imaging procedure.
Standard uptake value (SUV) will be measured at baseline and post treatment will be assessed.

The images will be anonymized and provided with a unique study identification number, one for the Investigators file and one for the Sponsor file

Changes in Tumour Marker CEA

Tumour marker assessment will be done to follow the evolution of the disease under treatment. The marker of choice will be CEA. This marker will be evaluated at screening, week 8 and if surgery is after week 10, a sample will be taken as close as possible to surgery.

The analysis of this marker will be performed locally at each site according to local procedures.

9.1.3. Exploratory Efficacy Variables

Changes in circulating tumour cells and/or circulating tumour DNA

Change in circulating tumour cells (CTC) will be measured to follow the evolution of levels of CTC during the treatment period. The Investigators will arrange to have the plasma sample transported directly to the central laboratory for analyses according to the procedures detailed in a laboratory manual.

Functionality of RAS mutation specific T cells in tumour tissue and peripheral blood

Cytotoxic functionality of RAS mutation specific T cells grown from fresh tumour tissue or PBMC will be studied as described in the study specific Immune Monitoring Plan.

9.2. Assessment of Safety

9.2.1. Adverse Events

It is important that all the staff involved in the trial is familiar with the content of this section of the protocol.

9.2.1.1. Definitions

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition in a patient under clinical investigation who has been administered an investigational pharmaceutical product (in this case GM-CSF/TG02 but which does not necessarily have a causal relationship with this treatment. An undesirable medical condition can be symptoms (e.g., nausea, chest pain) signs (e.g., tachycardia, enlarged liver) or abnormal results of an investigation (e.g., laboratory findings, ECG). An AE can include any undesirable condition occurring at any time after inclusion in the study, even if no trial treatment has been administered or recently administered. A grading severity scale is provided for each AE term. NCI Criteria for Adverse Events (CTCAE) (v4.03: June 14, 2010) includes five grades (1-5), with grade 5 being death.

Any events that are unequivocally due to disease recurrence must not be reported as AEs.

A serious AE (SAE) is an event that is known with certainty, or suspected with good reason, to constitute a threat to life or to cause severe or permanent damage. A SAE can occur during any phase of the trial and at any dose of the investigational product. This is particularly true for an AE that:

- results in death
- is immediately life-threatening
- requires patient hospitalisation or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
- is an important medical event that may have jeopardised the patient or may have required medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Drug misuse and drug overdose and should be regarded as serious, even if they may not result in the above mentioned outcomes.
Hospitalisation for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalisation (see Appendix I and Appendix II for additional safety information).

The causality of AE/SAEs (i.e., their relationship to trial treatment) will be assessed by the individual investigators at each trial centre who must while completing the CRF answer yes/ no to the question 'do you consider that there is a reasonable possibility that the AE/SAE may have been caused by the investigational drug?

Any events that are unequivocally due to disease recurrence must not be reported as AEs.

The specialist group handling the pharmacovigilance for the study is:

[redacted]

The [redacted] is specialised and has the appropriate expertise in handling and reporting SAEs.

9.2.1.2. Adverse Event Reporting

For the purpose of this trial, any detrimental change in a patient's condition, subsequent to their entry into the trial and during the 28-day follow-up period after the final treatment, should be considered an AE.
The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for the administration of the trial treatment and have been identified after the patient's inclusion into this clinical trial.

Any events that are unequivocally due to disease recurrence must not be reported as AEs.

If the same AE occurs at several investigation times in one patient, then the AE in question must be documented and assessed as new each time.
All AEs are to be recorded on the CRFs provided and Serious Adverse Events also on the Serious Adverse Event Form. A description of the event, including its severity, duration, any action taken (e.g. treatment and follow-up tests) and the outcome is to be provided, along with the investigator's assessment of the relationship to the trial treatment. AEs and laboratory values will be graded according to the NCI Criteria for Adverse Events (CTCAE) (v4.03: June 14, 2010) and recorded on the appropriate CRF page.
The reporting of laboratory/vital signs abnormalities as both laboratory findings and adverse events should be avoided. They should not be reported as AEs unless any criterion of clinical significance and/or a SAE is fulfilled, the laboratory/vital signs abnormalities cause study drug dose adjustment, lead to patient discontinuation of their trial treatment, or the investigator insists that the abnormality is reported as an AE. If an abnormal laboratory

value/vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.
All patients who have new or worsening NCI-CTC grade 3 or 4 laboratory values at the time of withdrawal must have further tests performed and the results recorded on the appropriate CRF, until the laboratory values have returned to NCI-CTC grade 1 or 2, unless these values are not likely to improve because of the underlying disease. In these cases, the investigators must record their opinions on the CRFs and in the patients' medical records.
For an AE to be a suspected drug-related event there should be at least a reasonable possibility of a causal relationship between the trial medicinal product and the AE (see Appendix II for guidelines on interpretation of causality).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in section 9.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

Lack of efficacy
When there is deterioration in the condition for which the medicine is being used there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless Targovax or the reporting physician considers that the medicine contributed to the deterioration or local regulations state to the contrary, **the deterioration should be considered to be a lack of efficacy and not an AE.**

Handling unresolved SAEs/AEs at completion/withdrawal
All trial treatment-related toxicities and SAEs must be followed until resolution unless, in the investigator's opinion, the condition is unlikely to resolve because of the patient's underlying disease.

Procedure for reporting serious adverse events
Investigators and other site personnel must inform the study monitor of any SAE that occurs in the course of the study as soon as possible but definitely within 24 hours of when he or she becomes aware of it.

The following minimal information must be faxed immediately to +44 870 710 7157
- Patient identifier – patient number, investigator
- Details of the event or outcome (see section 9.2)

To discuss the medical aspects of the SAE investigators should call:

[redacted]

This number should also be called to report a life-threatening or fatal adverse event within 2 hours of knowledge of the event if this occurs before recognised recurrence of disease.

The dedicated email address for SAE information is:
[redacted]

The SAE must be documented in the patient's medical source documents and the outcome described.

The monitor will work with the investigator to compile all the necessary information and ensure that the appropriate Drug Safety Department receives a report within 24 hours for all fatal and life-threatening cases and by day 5 for all other SAEs.
Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to safety group within 24 hours as described above.
All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the CRF. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Additional information will be requested, if necessary, by the Trial Physician within 5 days of the receipt of the SAE report. This is to ensure that the initial reporting of SAEs is made to the regulatory authorities within the required time-frame. All withdrawals from trial treatment must be notified to the trial physician. Withdrawals from treatment due to a new, previously unreported SAE must be notified to the Trial Physician, along with the SAE. Withdrawal from trial treatment for a previously reported SAE can be made within the 7 days after the decision has been made to withdraw the patient and for a non-serious AE within 21 days of the decision to withdraw. After withdrawal from treatment patients must be followed up for AEs for 28 days after the last dose of trial medication. All SAEs recorded during that period must be reported to the safety group, and followed up until resolved unless in the Investigator's opinion the condition is unlikely to resolve due to the patient's underlying progressive disease.

9.2.2. Safety Laboratory Variables

Safety serum chemistry and haematology parameters will be analysed at hospitals local laboratory.

Blood samples for the determination of serum chemistry and haematology will be drawn at pre-specified time-points, see Schedule of visits (Table 6-1) Additional haematology and chemistry are under the investigator's judgement.
The following laboratory tests will be performed:

Table 9-1: Clinical laboratory parameters

Chemistry	**Haematology**
Total Alkaline Phosphatase (total ALP)	RBC count
ALT (SGPT)	Hb
AST (SGOT)	Haematocrit
Lactate Dehydrogenase (LDH)	PLT count
Gamma-GT	WBC count
Total Protein	WBC diff.
Albumin	Neutrophils
Bilirubin	Lymphocytes
Creatinine	Monocytes
Sodium	Eosinophils

Chemistry	Haematology
Potassium	Basophils
Magnesium	
Calcium	
Phosphate	
Chloride	
Urea	
Oestradiol (females at screening only)	

Reference ranges from each laboratory will be provided to the Sponsor. If during the study, ranges should be changed, investigators are requested to provide updated laboratory normal values.

Laboratory values with CTCAE grade 3 or higher and/or considered clinically significant by the treating physician have to be reported as an AE during the treatment period. At the follow-up visit only changes in laboratory values judged to be related to the study drug will be reported.

Volume to be drawn from each patient
The total volume of blood that will be drawn from each patient in this trial will vary depending on how long the patient stays on study. Table 9-2 indicates the range for patients completing the whole study period.

Table 9-2: Volume of blood to be drawn from each subject

Assessment		Sample volume (ml)	No. of samples	Total volume (ml)
PBMC		50 ml	2-3	100-150 ml
Biomarkers (CEA)/ other immune subsets		7 ml	2-3	14-21 ml
Safety	Clinical chemistry	7 ml	5-6	35-42 ml
	Haematology	7 ml	5-6	35-42 ml
CTCs		6 ml	2-3	12-18 ml
Total		67 ml		196-273 ml

9.2.3. Other Safety Variables

Medical and surgical history of colorectal cancer
A summary of the patient's relevant medical and surgical history of colorectal cancer (i.e. time period from diagnosis of underlying malignancy to enrolment in the study) should be recorded on the appropriate CRF page.

Vital Signs
Vital signs variables include measurements of body temperature, heart rate, systolic and diastolic blood pressures. Vital signs will be assessed pre- and post-treatment as detailed in Schedule of visits (see Table 6-1). Additional vital signs assessments will be done under investigator's judgment. Normal ranges for vital signs are provided below (Table 9-3).

Table 9-3: Normal Ranges for Vital Signs for healthy adults

Vital signs parameter	Normal range	
	Low	High
Systolic BP (mm Hg)	85	139
Diastolic BP (mm Hg)	60	89
Heart rate (bpm)	60	100
Body temperature	36.4 °C 97.5 °F	37.7 °C 99.5 °F

In addition, after any TG02-treatment the patients will be monitored for heart rate and blood pressure at 5, 10 and 30 minutes and then every 30 minutes thereafter for up to 2 hours post administration.

Notable vital signs results should be interpreted in conjunction with the clinical situation of the patient. Once AE notification is decided upon, investigators are required to follow the procedure described for AE notification and document the clinically notable abnormality on the AE eCRF page. Any notable abnormal vital signs finding or related AE must be followed until the outcome is known.

Before vital signs are recorded, the patient should be resting for at least 5 minutes. The same position will be used each time vital signs are recorded for a given patient and blood pressure will be measured preferably from the same arm.

Physical examination
An abbreviated physical examination consisting of general appearance, lungs, cardiovascular system and abdomen and other physical findings will be done at each hospital visit where the patient meets with the treating physician.

Any physical examination finding that is classified by the Investigator as a clinically significant change (worsening compared to previous examination) will be considered as an AE, documented on the patient's eCRF, and followed until the outcome is known.
ECOG performance status

Performance status will be evaluated using the ECOG scale:

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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

12-lead ECG
A standard 12–lead ECG will be performed at screening. Results will be recorded as normal or abnormal; abnormal findings will be described in the CRF and when clinically

relevant, findings should be recorded as an AE and should be followed up during study as needed per investigator's judgement. The 12-lead ECG will be evaluated by the local Investigator. A copy of the 12-lead ECG page, signed, dated and diagnosed should be stored in the patient's medical record.

12-lead ECG does not need to be repeated during the study unless clinically indicated.

10. DATA MANAGEMENT

10.1. Case Report Forms

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

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

10.2. Data Management Plan and Database Design

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

10.3. Data Entry and Validation

All computerized data processing will be performed by Sponsor's representative. All eCRFs will be entered electronically by staff into a validated database. Data entry will be source data verified by a sponsor representative. Comprehensive edit checks will be used to clean data. Patient data will be entered continuously. All changes to the data and the database structure will be recorded in an automatic audit trail.

Data queries will be generated at data entry or if questions arise during the data validation or detected during a manual review (safety data). The queries are entered into the eCRF and resolved according to the electronic data capture user manual.

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

10.4. Medical Coding

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

10.5. Database Lock

A final database will be declared when all data has been entered, the data verified, the data validated and the database defined clean by the Responsible Data Manager. After declaration of a final database the data will be exported from the database to SAS datasets and both the database and the SAS datasets will locked and protected from changes. All

statistical analyses for the final analysis will be performed on the locked datasets. Data management will be carried out as described in the sponsor's representative's SOPs for clinical studies.

11. STATISTICAL ANALYSES

11.1. Power Considerations and Determination of Sample Size

The study will include up to 16 patients; approximately 4-6 patients in Part I and up to 10 patients in Part II if sponsor decision to initiate such. As this is an exploratory study, no formal sample size calculation has been performed. However, it is estimated that a sample size of approximately 6 subjects in each group (monotherapy and combined treatment) is sufficient to explore the potential effect of TG02 to induce immune responses and to assess safety in the induction phase.

11.2. Statistical Hypothesis

No statistical hypothesis is defined, only descriptive statistics will be produced.

11.3. Datasets to be Analysed

Efficacy analysis set
The efficacy analysis set comprises all patients who go to the surgery after treatment period. This analysis set will be applied for demography, baseline and efficacy data.

Per protocol analysis set
The per protocol analysis set is a subset of efficacy, but patients with major protocol deviations are excluded. This analysis set will be applied for efficacy data.

Safety analysis set
The safety analysis set comprises all patients who receives any amount of TG02/GM-CSF and/or pembrolizumab. This analysis set will be applied for demography and baseline and safety data.

11.4. General Statistical Considerations

Data will be presented by time of measurement. In general, continuous variables will be described using standard summary statistics such as number of observations, mean value, standard deviation, minimum and maximum value, median, and first and third quartiles. Categorical variables will be summarised in frequency tables as counts and percentages. All individual data collected will be presented in data listings. Patients screened but not included in the study will not be presented in any tables or listings.

A detailed plan for data presentation will be prepared for the Statistical Analysis Plan, which will be finalized before completion of Part I of the study.

11.5. Demographic and Baseline Characteristics

Demographic data, medical and cancer history, all other relevant background data will be summarised in terms of descriptive statistics as described in section 11.4.

11.6. Analysis of Endpoints

11.6.1. Primary Endpoints

11.6.1.1. Safety Endpoints

Adverse events
All adverse events will be classified by MedDRA, version 19 or higher.

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

The following summary tables will be created, reporting number of events and number of patients with events by MedDRA System Organ Class and Preferred Term for the TEAEs:
- total TEAEs
- total serious TEAEs
- total IMP related serious TEAEs
- TEAEs leading to GM-CSF/TG02 withdrawal
- TEAEs leading to study withdrawal
- TEAEs leading to death
- TEAEs by severity
- Related TEAEs by severity
- TEAEs by relationship to each IMP (related, not related) separately

Safety laboratory data
Numerical laboratory data, separately for each parameter, will be summarized in terms of descriptive statistics, as described in section 11.4, by time point of measurement, for absolute value, absolute and relative change from baseline. Further, number of patients with abnormal and/or clinical significant values will be presented by time point.

Vital signs
Blood pressure, heart rate and body temperature will be summarized in terms of descriptive statistics, as described in section 11.4, by time point of measurement, for absolute value, absolute and relative change from baseline.

ECG
Number of patients with abnormal findings in ECG evaluation will be reported by time point of measurement.

11.6.1.2. Immune Endpoints

Immune response
TG02-specific DTH immune response is defined as any positive DTH test during the course of the study. Number of patients with TG02-specific DTH response will be reported. Furthermore, the number of patients with TG02-specific DTH response by time point measurement will be reported.

Presence of TG02 specific T-cells:
Number of patients with TG02 specific T-cells at Day 1, Day 50 and, if applicable, at Day 64 (pre-surgery) will be reported.

Change in intra-tumoural lymphocytes (TILs):

The absolute count and relative change in TILs measured from tumour tissue collected prior TG02 treatment and from resected tumour will be presented in terms of descriptive statistics, as described in section 11.4.

11.6.2. Secondary Endpoints

Immune suppression factors in tumour specimens
Immune suppression factors (PD-L1, Treg, MSDC) and pathological responses (cleaved-casp3) are measured with IHC from tumour tissue, similarly to TILs. The data presentation will follow the same principles.

Details of any further analysis from tissue or blood will be described in the Statistical Analysis Plan, which will be finalized before end of Part 1 of the trial.

PET Imaging and biomarkers
Change in SUV by FDG PET-CT
The change in SUV from pre TG02 treatment to pre surgery in primary tumour, measured by PET-CT will be summarized in terms of descriptive statistics, as described in section 11.4.

Change in CEA
The absolute value, absolute and relative change as compared to pre-treatment value of CEA will be summarized by time point of measurement in terms of descriptive statistics, as described in section 11.4.

11.6.3. Exploratory Endpoints

- Change in circulating tumour cells and/or circulating tumour DNA: including the absolute value, absolute and relative change as compared to pre-treatment value. These will be summarized by time point of measurement in terms of descriptive statistics, as described in section 11.4
- Functionality of RAS mutation specific T cells in tumour tissue and peripheral blood

11.7. Hardware and Software

All statistical analyses will be produced using SAS software.

12. QUALITY CONTROL AND ASSURANCE

12.1. Monitoring

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

12.2. Audits and Inspections

Authorised representatives of Targovax, a regulatory authority, an IEC or an IRB may visit the centre to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted, and whether data were recorded, analysed and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact Targovax immediately if they are contacted by a regulatory agency about an inspection at their centre.

12.3. Record Keeping and Archiving

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

13. ETHICS

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

The final trial protocol, including the final version of the Written Informed Consent Form, must be approved or given a favourable opinion in writing by an IEC or IRB as appropriate. The investigator must submit written approval to the sponsor before he or she can enrol any patient into the trial.

The principal investigator(s) is responsible for informing the IEC or IRB of any amendment to the protocol in accordance with local requirements. In addition, the IEC or IRB must approve all advertising used to recruit patients for the trial. The protocol must be reapproved by the IEC or IRB annually, as local regulations require.

Either the investigator(s) or Targovax must submit progress reports to the IEC or IRB according to local regulations and guidelines. The principal investigator(s) must also provide the IEC or IRB with any reports of SAEs from the trial site.

13.2. Guidelines and Regulations

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

13.3. Subject Information and Consent

Written (which has been approved by the IRB/IEC) and oral information about the study in a language understandable by the patient will be given to all patients. The Investigator will explain the nature of the study, its purpose and associated procedures, the expected duration, and potential benefits, constraints and risks associated with the study. Written informed consent will be obtained from each patient before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. The same form will be signed and dated by the Investigator. The Investigator will keep the original consent forms and copies will be given to the patients.

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

13.4. Subject Confidentiality

The Investigator(s) must assure that the privacy of the patients, including their personal identity and all other personal medical information, will be maintained at all times. In the eCRFs and other documents or image material (including materials from all bone scans, CT, MRI examinations) submitted to the Sponsor, patients will not be identified by their names, but by an identification code (*e.g.,* allocation number). Personal medical information may be scrutinised for the purpose of verifying data recorded in the CRF.

This may be done by the monitor(s), properly authorised persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.
The Investigators must agree to maintain the confidentiality of the trial at all times and must not reveal information relating to the Investigator's Brochure, protocol, CRFs or associated documents to unauthorised third parties.

13.5. Safety Steering Committee (SSC)

A SSC will be appointed to oversee the safety findings as the study progresses. The SSC will consist of the sponsor, the principal investigator, relevant sub-investigators and one independent physician. The work of the SSC will be described in a Safety Steering Committee Charter (SSCC). In particular, the safety of TG02-treatment will be evaluated by the SSC. All available data will be taken into account in the evaluation.

The SSC will review every patient until three patients have been recruited into the study. The first three patients will be enrolled in a sequential manner with a minimum lag time of 4 weeks between dosing of the first 3 subjects to ensure an acceptable safety profile. The safety data collected during the first 4 weeks for the 3 first patients will be reviewed by a SSC consisting of Sponsor representatives, the Principal Investigator, relevant Sub-Investigators and one Independent Physician. If no safety concerns arise, then subsequent patients will be recruited when they are ready to enrol. In addition, when all safety data, systemic immune responses (Delayed-Type Hypersensitivity (DTHs)) and tumour material (analysed for intra-tumoural T cells infiltration) are available for all patients in Part I of the study, the SSC will evaluate the data to assess safety and preliminary immune activity and efficacy to make a recommendation to proceed or not to Part II of this protocol. The SSC recommendation will form the basis for sponsor’s final decision.

The same staggered recruitment approach as for Part I will be performed in Part II as TG02-treatment and pembrolizumab in combination is a novel treatment.

The SSC will meet by teleconference on a regular basis and email correspondence as required in between.

14. FINANCING AND INSURANCE

14.1. Financial Issues

According to the Food and Drug Administration (FDA) 21 CFR, part 54, the Sponsor is required to completely and accurately disclose or certify information to the FDA concerning the financial interests of a clinical Investigator(s) who is not a full-time or part-time employee. Therefore, the Investigator must provide the Sponsor with sufficient, accurate financial certification that no financial arrangements (further defined in 21CFR 54.2) exist with the Sponsor, or fully disclose the nature of the arrangement.

A separate financial agreement (Clinical Trial Agreement) will be signed between the Sponsor and the Investigators and/or the institution involved. Before the study begins, the Investigator will provide the Sponsor with a proposed budget, itemised on a per patient basis and the payee name(s) and tax identification number(s). Additionally, the Investigator should not begin the study until the Sponsor has confirmed the agreed final budget in writing. The investigator must comply with all the terms, conditions and obligations of the trial agreement for this trial. In the event of any inconsistency between this protocol and the trial agreement, the trial agreement shall prevail

14.2. Insurance and Indemnity

This study is covered under the sponsor's liability insurance policy. A certificate of insurance can be provided upon request.

15. STUDY REPORT AND PUBLICATIONS

All information concerning TG02 and Targovax research and product development including patent applications and manufacturing processes not previously published are considered confidential and shall remain the sole property of Targovax.

Targovax is responsible for preparing a Clinical Study Report, in cooperation with the co-ordinating Investigator. The report will be added to the Targovax data file and may be used for regulatory purposes and/or in company publications. The Clinical Study Report will be made after sufficient events have been observed according to the statistical hypothesis.

If the trial is terminated prematurely for any reason an abbreviated report will be prepared. By signing the protocol, the Investigators agree that the results of this study may be used for submission to national and/or international registration and supervising authorities. The authorities will be notified of the Investigators name, address, qualifications and extent of involvement.

The publication of study results will be agreed between the sponsor and the investigator(s). The sponsor is interested in publishing the results of the study but to prevent publication of any confidential information, the sponsor retains right to review all publications and presentations before they are made public.

16. REFERENCES

Breivik J , Lothe R. A., Meling G. I., Rognum T. O., Børresen-Dale A-L. and Gaudernack G. (1997) Different genetic pathways to proximal and distal colorectal cancer influenced by sex-related factors. Int. J. Cancer (Pred. Oncol.) 74, 664-669 (1997).

Cross, R.S., et al., Therapeutic DNA vaccination against colorectal cancer by targeting the MYB oncoprotein. Clin Transl Immunology, 2015. 4(1): p. e30.

Dovedi, S.J., et al., Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res, 2014. 74(19): p. 5458-68.

Garon, E.B., et al., Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. N Engl J Med, 2015

Gerber, S.A., et al., Radio-responsive tumors exhibit greater intratumoral immune activity than nonresponsive tumors. Int J Cancer, 2014. 134(10): p. 2383-92

Gjertsen, M.K., et al., Intradermal ras peptide vaccination with granulocyte-macrophage colony-stimulating factor as adjuvant: Clinical and immunological responses in patients with pancreatic adenocarcinoma. Int J Cancer, 2001. 92(3): p. 441-50.

Glynne-Jones R, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (Supplement 4): iv22–iv40.

Kantoff, P.W., et al., Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med, 2010. 363(5): p. 411-22.

Le DT, Uram JN,Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–2520

Le, D.T., et al., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med, 2015. 372(26): p. 2509-20.

Lipson, E.J., Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res, 2013.

Lipson, E.J., Re-orienting the immune system: Durable tumor regression and successful re-induction therapy using anti-PD1 antibodies. Oncoimmunology, 2013. 2(4): p. e23661.

Markman M. Colorectal Cancer and KRAS/BRAF. Mescale 2014 (http://emedicine.medscape.com/article/1690010-overview#showall)

Misale S, Yaeger R, Hobor S, Scala E, et al. Emergence of KRAS mutations and acquired resistance to anti EGFR therapy in colorectal cancer. Nature 2012; 486: 532–536.

Palmer, D. H., Dueland, S., Valle, J. W., Otterhaug, T., Eriksen, J. A., Muller, H., Iversen, B., Miller, R. M.. A prospective, single-arm, phase I/II trial of RAS peptide vaccine

TG01/GM-CSF and gemcitabine as adjuvant therapy for patients with resected pancreatic adenocarcinoma. ASCO 2015

Rahbari, N.N., et al., Surgery for locally recurrent rectal cancer in the era of total mesorectal excision: is there still a chance for cure? Ann Surg, 2011. 253(3): p. 522-33.

Rahma, O.E., et al., The immunological and clinical effects of mutated ras peptide vaccine in combination with IL-2, GM-CSF, or both in patients with solid tumors. J Transl Med, 2014. 12: p. 55

TG02 An Antigen-Specific Cancer Immunotherapy (ASCI) Targeting RAS Mutations, INVESTIGATOR'S BROCHURE, Edition Number: 1.0, Date: **4** Dec 2015

Schachter J, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017; 390: 1853–1862.

Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, et al. Extended RAS mutations and anti-EGFR monoclonal
antibody survival benefit in metastatic colorectal
cancer: a meta-analysis of randomized, controlled trials. Ann Oncol 2015; 26: 13-21.

Van Cutsem E, Lenz H-J, Köhne C-H, Heinemann V, et al, Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Treatment and RAS Mutations in Colorectal Cancer. J Clin Oncol 2015; 33: 692-700.

Appendix I: Further guidance on the definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an adverse event occurred in a more severe form it might have caused death (i.e. hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered adverse events if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in a situation where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity, but may jeopardise the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious. Examples of such events are:

- Angio-oedema not severe enough to require intubation but requiring iv. hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g. neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Appendix II: Further guidance on the assessment of causality

The following factors should be considered when deciding if there is a "reasonable possibility" that an adverse event (AE) may have been caused by the investigational product.

- **Time course of events and exposure to suspect drug**. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of suspect drug?
- **Consistency with known drug profile**. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- **Dechallenge experience**. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- **No alternative cause**. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- **Rechallenge experience**. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? Targovax would not normally recommend or support a rechallenge.
- **Laboratory tests**. Has a specific laboratory investigation confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this.

Any events that are unequivocally because of progression of disease must not be reported as an adverse event.

Appendix III: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse

consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

3. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

4. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

5. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

6. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

7. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

8. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

9. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

10. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

11. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

12. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

13. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

14. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

15. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

16. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

17. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

18. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

19. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

20. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

2. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

3. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

4. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

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