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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

Targovax ASA Study No: CT TG02-01

[redacted]

Statistical Analysis Plan

Version: Final

Date: 16th April 2019

[redacted]

For Targovax ASA

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Contents

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
CEA	Carcinoembryonic Antigen
CPI	Checkpoint Inhibitor
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumour DNA
DLT	Dose Limiting Toxicity
DTH	Delayed Type Hypersensitivity
DNA	Deoxyribonucleic acid
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDG	Fluorodeoxyglucose
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
IMP	Investigational Medicinal Product
KRAS	Kirsten Rat Sarcoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PBMC	Peripheral Blood Mononuclear Cells
PET-CT	Positron Emission Tomography – Computed Tomography
PPAS	Per Protocol Analysis Set
PT	Preferred Term
RAS	Rat Sarcoma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SD	Standard Deviation
SI	Stimulation Index
SOC	System Organ Class
SSC	Safety Steering Committee
SUV	Standard Uptake Value
TEAE	Treatment-emergent Adverse Event
TNM	Tumour, Nodes, Metastasis
WHO Drug	World Health Organization Drug dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on protocol version 6.0 dated 9 October 2018.

The SAP will be reviewed prior to database lock to ensure that any relevant changes in study conduct, data issues etc. are captured. Any additional details or amendments required as a result of this review will be discussed with the sponsor and included in a revised version of the SAP if applicable. The SAP will be finalised prior to any analysis of data and prior to database lock.

The table, listing and figure shells will be supplied in a separate document.

2 GENERAL PRINCIPLES

The analysis and statistical reporting will be conducted at Syne qua non using SAS® version 9.4 or higher.

Data will be presented separately for patients in Part I and Part II. The same set of tables, listings and figures will be used for the two parts.

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum, unless specified otherwise. The precision of these variables is defined in the table, figure and listing shells document.

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. Screen failures will not be entered into the database.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

The primary objectives of the study are:

- To determine the safety of TG02-treatment (Part I) in combination with pembrolizumab (Part II)
- To evaluate the systemic TG02-specific immune responses and to investigate tumour T cell infiltration in tumour specimens

The secondary objectives of the study are:

- To investigate changes in immunological and pathological markers in tumour tissue
- To investigate changes in fluorodeoxyglucose (FDG) positron emission tomography – computed tomography (PET-CT) images
- To investigate changes in carcinoembryonic antigen (CEA)

The exploratory objectives of the study are:

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

3.2 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 granulocyte macrophage colony stimulating factor (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 patients to ensure an acceptable safety profile.

The safety data collected during the first 4 weeks for the first 3 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 National Cancer Institute Criteria for Adverse Events (NCI CTCAE) v4.03: June 14, 2010) for reactions considered to be related to TG02 and/or GM-CSF:

- Injection site reaction of $\geq$ 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 $\geq$ 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 adverse event (AE) should be assessed as a dose limiting toxicity (DLT).

- ≥ Grade 3 'allergic reaction/anaphylactic reaction' in spite of prophylaxis with antihistamine and steroids

All AEs and serious adverse events (SAEs) will also be compared to those of the precursor vaccine TG01.

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 tests (DTHs)) and tumour material (analysed for intra-tumoural T cells infiltration) are available for all patients in Part I of the study, SSC will evaluate the data to assess safety, 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 six 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 patients to ensure an acceptable safety profile.

The safety data collected during the first 6 weeks for the first 3 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.

3.3 Visit Structure

The visit structure and scheduled assessments are detailed in Table 6-1: Schedule of visits, of the protocol.

3.4 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 samples size calculation has been performed. However, it is estimated that a sample size of 6 patients 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.

3.5 Changes from the Protocol Planned Analysis

The efficacy analysis set is defined in Section 11.3 of the protocol and includes all patients who undergo surgery after the treatment period. This analysis set has been modified to include patients from whom a biopsy is obtained at the time of surgery, for patients who do not proceed to surgery.

4 STUDY PATIENTS

The tables will present the two treatment groups for both parts of the study side-by-side as 'Part I (TG02)' and 'Part II (TG02 + Checkpoint Inhibitor (CPI))'.

4.1 Disposition of Patients

The number and percentage of all patients enrolled and included in the efficacy analysis set, per protocol analysis set and safety analysis set, who completed the study and prematurely withdrew (including a breakdown of the primary reason for withdrawal) will be presented.

4.2 Analysis Sets

The **Safety Analysis Set** (SAF) comprises all patients who receive any amount of TG02/GM-CSF and/or pembrolizumab. This analysis set will be applied for demographic, baseline and safety data.

The **Efficacy Analysis Set** (EAS) comprises all patients who undergo surgery after the treatment period or patients from whom a biopsy was obtained at the time of planned surgery (for patients who do not proceed to surgery). This analysis set will be applied for demography, baseline and efficacy data.

The **Per Protocol Analysis Set** (PPAS) is a subset of the EAS but patients with major protocol deviations are excluded. The analysis set will be applied for efficacy data.

The list of patients to be included in each of the analysis sets is to be agreed between the study statistician and the sponsor prior to database lock, once all study data are available.

All enrolled patients will be listed indicating their membership to each analysis set together with the reason for exclusion.

All listings will be based on all enrolled patients separately for Part I and Part II unless specified otherwise.

The outputs will be reported using the following analysis sets:

Output	SAF	EAS	PPAS
Demography	×	×	
Medical History	×	×	
Details of Previous Cancer Treatment (Before/After + up to First IMP)	×	×	
Concomitant Medications	×	×	
Administrations (Patient + Visit Level)	×	×	
Standard Uptake Value (kBq/mL) Values and Change from Baseline over Time		×	×
Carcinoembryonic Antigen (ug/L) Values and Change from Baseline over Time		×	×

Immune Response		×	×
DTH Skin Test Reactions		×	×
T-cell Responders / Biopsy / Cytokines / ctDNA		×	×
AE / Labs / Vitals / ECOG	×		
Listings + Figures	×		

If any of the analysis sets overlap (e.g. SAF = EAS) the outputs will not be repeated.

4.3 Eligibility

All eligibility data will be listed in full.

4.4 Protocol Deviations

Prior to database lock, Targovax ASA will review the individual deviations and classify them as major or minor during a data review meeting. Details of all protocol deviations including start and end dates, deviation category (treatment deviation, subject not withdrawn as per protocol requirements, eligibility criteria not met, assessment outside time window), classification as major/minor and deviation details will be listed separately for patients in Part I and Part II.

4.5 Background and Demographic Characteristics

For sections 4.5.1 to 4.5.5, including disposition, the data will be summarized for each treatment group (Part I and Part II) and Overall.

4.5.1 Demography

Demographic characteristics (age, sex and race) and body measurements (height and weight) will be summarised.

Age will be calculated in years from date of birth to the date of informed consent.

Individual patient demographic and baseline data, including pregnancy test results and details, will be listed.

4.5.2 Medical History of Colorectal Cancer

Details of colorectal cancer history will include:

- Diagnosis at time of screening
- Time from diagnosis primary advanced disease or recurrent disease, whichever is latest, to first investigational medicinal product (IMP) administration (weeks), calculated as (date of first IMP administration – date of diagnosis primary advanced disease or recurrent disease, whichever is latest + 1)/7
- Time from diagnosis primary advanced disease or recurrent disease, whichever is latest, to surgery (weeks), calculated as (date of surgery – date of diagnosis primary advanced disease or recurrent disease, whichever is latest,+ 1)/7

- Tumour, nodes, metastasis (TNM) stage at diagnosis primary advanced disease and at diagnosis of recurrent disease
- Number and percentage of patients with Kirsten rat sarcoma (KRAS) mutation detected (yes/no)
- Mutation type (12/13) and specific KRAS mutation, where percentages are based on the number of patients with oncogenic KRAS confirmation
- Extent of disease

All colorectal cancer medical history details will be listed.

4.5.3 Medical History (Excluding Colorectal Cancer)

Medical history events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

Previous medical history is defined as anything that started and ended prior to the first IMP administration. Medical history that is ongoing at the first IMP administration or started after first IMP administration will be deemed to be current. If medical history dates are incomplete and it is not clear whether the medical history was ongoing, it will be assumed to be current.

The number and percentage of patients who had any previous or current medical history will be presented by system organ class (SOC) and preferred term (PT) SOCs will be ordered in decreasing frequency of the total number of patients with the medical histories reported in each SOC and PTs will be ordered within a SOC in decreasing frequency of the total number of patients with each medical history.

All medical history events (excluding colorectal cancer) will be listed by SOC and PT.

4.5.4 Previous Cancer Treatment

Previous cancer treatment will be divided into treatment before and after recurrence of the disease.

The number and percentage of patients with any previous cancer treatment and with each type of cancer therapy will be presented separately for previous cancer treatment administered before and after recurrence of disease but before entering the study.

All previous cancer treatment data will be listed in full and previous cancer treatment after recurrence of disease will be flagged.

4.5.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the latest World Health Organization Drug dictionary (WHO Drug) version.

Prior medications are defined as those that started and ended prior to the first IMP administration. Medications that are ongoing at the first IMP administration or started after first IMP administration will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of patients who had any concomitant medications will be presented separately by medication class and standardised medication name sorted alphabetically.

All prior and concomitant medication data will be listed. All medications which start up to four weeks prior to the first dose of IMP will also be flagged in the listings.

4.5.6 Diagnostic Imaging

Details of diagnostic imaging collected at screening will be listed.

4.6 Administration of Investigational Product

All details of GM-CSF, TG02 and pembrolizumab administration are described in Section 5.1

4.7 Surgery

All surgery data will be listed in full.

5 SAFETY EVALUATION

All safety evaluations will be performed on the safety analysis set unless specified otherwise.

The safety endpoints of interest are the incidence and severity of AEs by NCI Criteria for Adverse Events (CTCAE v4.03) and changes from baseline in laboratory variables, physical examination, vital signs and European Cooperative Oncology Group (ECOG) performance status.

5.1 Study Drug Exposure

The duration of exposure to TG02-treatment in days, as well as the total dose of GM-CSF and the total dose of TG02 separately for vaccination, DTH testing and vaccination and DTH testing combined will be summarised.

Duration of exposure to study drug will be calculated as: date of administration of the last dose – date of administration of the first dose of study drug + 1.

The dose of study drug administered for DTH testing, vaccination and DTH testing and vaccination combined will be calculated in the following way:

- the total dose of GM-CSF will be calculated as the sum of the dose administered at each visit
- the total dose of TG02 for DTH testing will be calculated as the sum of the dose administered for DTH testing at each visit
- the total dose of TG02 for vaccination will be calculated as the sum of the dose administered for vaccination at each visit
- the total dose of TG02 for vaccination and DTH testing combined will be calculated as the sum of the dose administered for vaccination at each visit + sum of dose administered for DTH testing at each visit,

where the dose administered is calculated as dose strength*volume.

The number of injections of GM-CSF and TG02, the number of injections of TG02 for DTH testing and the total number of injections (GM-CSF and TG02, including DTH testing) will be summarised. The number and percentage of patients with dose delays and discontinuation with GM-CSF/TG02, together with the frequency and reasons for such dose modifications will be summarised by visit and overall. A summary of whether TG02-treatment was received (yes/no) will also be presented by visit.

For all patients in Part II of the study, the duration of exposure to pembrolizumab, the number of injections of pembrolizumab, as well as the total dose and reason for reduction, delay or discontinuation with pembrolizumab will be summarised. The total dose of pembrolizumab administered is the sum of the doses administered at each injection.

All IMP administration data will be listed.

5.2 Adverse Events

Any events that are unequivocally due to progression of disease will not be reported as AEs or SAEs.

Adverse events will be coded according to the latest MedDRA dictionary version.

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

There will be no imputation of unknown dates for the calculation of duration or study day. However, for sorting and assignation, if the start date is unknown then it will be assumed to be treatment emergent unless the partial start date or other data (i.e. stop date) indicates differently.

Assessment of AE severity will be based on the NCI CTCAE which includes five grades, with grade 5 being death. If the severity of an event changes during the course of that event, only the maximum severity/grade will be summarised in the tables.

The relationship to each IMP (TG02, GM-CSF, pembrolizumab) is assessed as not related or related.

An overview summary table will summarise the number of events and the number and percentage of patients with at least one of the following TEAEs:

- total TEAEs
- total serious TEAEs
- total IMP related serious TEAEs
- TEAEs leading to TG02 and GM-CSF withdrawal
- TEAEs leading to pembrolizumab withdrawal
- TEAEs leading to study withdrawal
- TEAEs leading to death
- TEAEs by severity

- TEAEs by relationship to each IMP (related, not related) separately
- SAEs by relationship to each IMP separately

The number of events and the number and percentage of patients experiencing TEAEs will be presented by SOC and PT for the following TEAEs:

- Total TEAEs: If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT. This summary will be repeated for serious TEAEs only.
- Total TEAEs by severity: If a patient experienced more than one TEAE, the patient will be counted once for each severity experienced during the study.
- TEAEs by relationship to each IMP: If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT at the closest relationship to study drug. This summary will be repeated for serious TEAEs only.
- TEAEs related to TG02 by severity. For this table, grade 1 and 2 events will be pooled. If a patient experienced more than one TEAE, the patient will be counted once for each severity experienced during the study. TEAEs related to GM-CSF, TEAEs related to TG02 and/or GM-CSF, TEAEs related to TG02 and/or GM-CSF only (i.e. events not related to pembrolizumab) and TEAEs related to pembrolizumab only will be summarised in an identical fashion.
- TEAEs leading to death.

In all of the tables described above, SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs.

All TEAEs will be listed with a separate listing for pre-treatment AEs. Separate listings of serious TEAEs and pre-treatment SAEs will also be presented.

5.3 Clinical Laboratory Evaluation

The clinical laboratory tests to be performed are presented in Table 9-1: Clinical laboratory parameters of the protocol. For each laboratory parameter, the baseline value will be defined as the last scheduled or unscheduled value collected prior to the first dose of IMP. If the times of assessments have not been recorded, assessments carried out on the day of first IMP administration are considered to have taken place before IMP administration. For post baseline, only data from scheduled visits will be included in the summary tables. Percent change from baseline will be calculated as 100 * (observed value – baseline value)/baseline value.

5.3.1 Haematology

Summary statistics of haematology observed values, change from baseline and percent change from baseline will be presented for all patients by parameter and visit.

In addition, a shift table showing the movement of patients with respect to CTC grade (according to NCI CTCAE v4.03) from baseline to each study visit will be presented by parameter. Patients will only be included in the missing category if they attended the respective post baseline visit but have no data available for that

parameter. Patients withdrawing prior to baseline will not be included in the missing category.

Individual patient haematology values will be plotted, with separate pages for each treatment group and parameter. Additionally, box plots will be produced to summarize values over time, with separate pages for each treatment group and parameter.

All haematology values will be listed showing reference ranges and flagging all abnormal findings and their clinical significance. Out of reference ranges will be flagged as high (H) or low (L).

5.3.2 Clinical Chemistry

Clinical chemistry data will be summarised and plotted in the same way as the haematology data.

All clinical chemistry values will be listed showing reference ranges and flagging all abnormal findings and their clinical significance. Out of reference ranges will be flagged as high (H) or low (L).

5.4 Vital Signs

Summary statistics of vital sign observed values and change from baseline from baseline will be presented by parameter and visit for all patients. For each parameter, the baseline value will be defined as the last scheduled or unscheduled value collected prior to the first dose of IMP. If the times of assessments have not been recorded, assessments carried out on the day of first IMP administration are considered to have taken place before IMP administration.

All vital sign data will be listed in full, flagging any unscheduled assessments.

5.5 Electrocardiogram (ECG)

All ECG data will be listed.

5.6 Physical Examination and ECOG Performance Status

The number and percentage of patients will be presented by ECOG performance status and study visit. In addition, a shift table presenting the shift from baseline in ECOG performance status by visit will be produced. The baseline value will be defined as the last scheduled or unscheduled value collected prior to first dose of IMP. Assessments carried out on the day of first IMP administration are considered to have taken place before the IMP administration, if the corresponding times have not been recorded. For post baseline, only data from scheduled visits will be included in the tables. Patients who attended a visit but have no ECOG data available will be included in the missing and total categories. Patients who withdrew prior to the visit will not be included in the summary for that visit and will be excluded from the denominator for calculation of percentages at that visit.

A listing will present ECOG assessment date and ECOG performance status together with whether a physical examination was performed and the date and time of examination.

6 EFFICACY EVALUATION

All efficacy evaluations will be performed on the efficacy and per protocol analysis sets unless specified otherwise.

6.1 Primary Immune Endpoints

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 study. Change in intra-tumoural T-cells in resected tumour tissue at surgery compared to pre-TG02-treatment core biopsy will be investigated.

The systemic immune responses are assessed by:

- TG02-specific DTH response. The DTH test is considered positive if erythema and/or induration are recorded as positive on the DTH response electronic case report form (eCRF) page.
- Presence of TG02 specific T-cells in peripheral blood. A patient is considered to have a positive T-cell response if the stimulation index (SI) is ≥ 2.

The SI will be derived as follows:

$$\frac{\text{Mean (T cells + PBMC + TG02)}}{\text{Mean (T cells + PBMC (negative control))}}$$

For SI, mean is derived as the sum of the non-missing measurements divided by the number of non-missing measurements, rounded to the nearest whole number.

- Change in intra-tumoural lymphocytes in resected tumour tissue at surgery compared to pre-TG02-treatment core biopsy will be investigated.

6.1.1 TG02-specific DTH response

A TG02-specific DTH immune response is defined as any positive DTH test during the course of the study. A DTH-test will be considered positive if erythema and/or induration are recorded as positive on the DTH response assessment eCRF.

The number of positive DTH skin reactions (categorical variable) as well as the number and percentage of patients who have at least one positive DTH skin reactions will be presented by time point and overall.

All DTH assessment data will be listed in full.

6.1.2 Presence of TG02-specific T-cells

Immunology-processed blood samples for peripheral blood mononuclear cells (PBMC) will be drawn at baseline and week 8 (Day 50). If surgery is after week 10, a third sample will be drawn as close as possible to the date of surgery. PBMCs will be analysed for the presence of TG02-specific T-cells. Summary statistics of patients with TG02-specific T-cells will be presented by time point and overall.

All PBMC and TG02-specific T-cell data will be listed.

6.1.3 Change in intra-tumoural lymphocytes

Tumour samples will be taken pre TG02-treatment in the form of a study specific biopsy and at the time of surgery in the form of resected tumour tissue (the post treatment sample). If for any reason a patient does not proceed to surgery, a biopsy will be obtained at the time of planned surgery if possible. Summary statistics of intra-tumoural lymphocytes observed values and change from baseline will be presented.

All intra-tumoural lymphocyte data will be listed.

6.2 Secondary Efficacy Variables

6.2.1 Immune suppression factors in tumour specimens

Immune suppression factors (such as PD-L1, Treg and MDSC) will be summarised in the same way as the intra-tumoural lymphocyte data.

All PD-L1, Treg and MDSC data will be listed.

6.2.2 Pathological responses and markers of apoptosis in tumour specimens

Pathological response and markers for apoptosis (such as Granzyme B, Cleaved caspase-3) data will be summarised in the same way as the intra-tumoural lymphocyte data.

All pathological response data will be listed.

6.2.3 Change in standard uptake values assessed by FDG PET-CT

FDG uptake reflects the tumour activity independent of the morphologic characteristics. FDG PET-CT images will be obtained at screening and as close as possible up to the date of surgery. Standard uptake value (SUV) at baseline and post treatment will be assessed.

Summary statistics of SUV observed values and change from baseline will be presented by time point and overall for all patients.

All FDG PET-CT examination and assessment data will be listed.

6.2.4 Non-Target Lesions

Non-target lesion data will be listed in full.

6.2.5 Change in CEA

Tumour marker assessment will take place at screening and week 8 and if surgery is after week 10, a sample will be taken as close to possible to surgery. Summary statistics of observed values of CEA, change from baseline and percent change from baseline will be presented by time point for all patients.

All CEA data will be presented in the listings.

6.3 Exploratory Efficacy Variables

6.3.1 Change in ctDNA

Change in ctDNA will be measured to follow the levels of ctDNA during the treatmentperiod. Summary statistics of observed individual values of ctDNA, mean of the observed results together with fold change from baseline will be reported by time point for all patients.

If only one result is available, no mean will be calculated, and this value will be usedto produce the fold change from baseline.

All ctDNA data will be listed.

The above will be repeated for cytokines.

6.3.2 Functionality of RAS mutation specific T cells in tumour tissue andperipheral blood

The reporting of the functionality of RAS mutation specific T cells in tumour tissueand peripheral blood will be reported separately per patient and included as an appendix to the study report.

6.4 Statistical Analysis

6.4.1 Hypotheses to be Tested

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

6.4.2 Handling of Dropouts or Missing Data

In general, the denominator for percentage calculations will be the number of patients in the analysis set. However, unless specified otherwise, for tables by time points the percentages and summary statistics will be calculated using the number ofpatients with available data at that time point.

6.4.3 Interim Analyses and Data Monitoring

No interim analysis is planned for this study.