

Document type:	Study Protocol
Official Title:	A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas
NCT Number:	NCT02261714
Document date:	27/06/18

CLINICAL TRIAL PROTOCOL	
Trial Protocol No.	CT TG01-01
Title	A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas
EUDRACT/IND #	2012-002400-40
Trial Phase	Phase I/II trial
Trial Physician	
Date	27 June 2018
Version	Final version 10.0

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MEDICAL EMERGENCY CONTACT DETAILS:

Principal Investigator(s):	<i>[Name(s) and 24 hour contact number(s)]</i>
Trial Physician	
Notification of serious adverse events	SAE Tel/Fax line:
Contact at your study centre: 1.	<i>[Name(s) and 24 hour contact number(s)]</i>
Contact at your study centre: 2	<i>[Name(s) and 24 hour contact number(s)]</i>

Sponsor Signature Page

Trial number: CT TG01-01

Trial Title: A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant
Therapy for Treating Patients with Resected
Adenocarcinoma of the Pancreas

Clinical Trial Sponsor :

Signature:

Date:

Responsible Trial Physician:

Signature:

Date:

Investigator Signature Page

Trial number: CT TG01-01

Trial Title: A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas

Trial centre:

I agree to conduct this trial in accordance with the protocol including any trial protocol amendments and in compliance with Good Clinical Practice and applicable regulatory requirements.

Signature:

Date:

Printed Name:.....

Address:

.....

.....

Tel:

Fax:

Mobile:

Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ASCI	antigen- specific cancer immunotherapy
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CK	Creatinine kinase
CRF	Case report form
CRA	Clinical Research Associate
CR	Complete response
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
DC	Dendritic cell
DFS	Disease free survival
DTH	Delayed-type hypersensitivity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good clinical practice
GM-CSF	Granulocyte macrophage colony stimulating factor
GMP	Good manufacturing practice
hENT1	Human equilibrative nucleoside transporter 1
HLA	Human leucocyte antigene
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalised ratio
IRB	Institutional review board
ITT	Intention-to-treat
iv	Intravenous
kg	Kilogram(s)

Abbreviation	Term
KRAS	Kirsten rat sarcoma viral oncogene homolog
L	Litre
LDH	Lactate dehydrogenase
LPLV	Last patient Last visit
mg	Milligram(s)
mL	Millilitre
mm	Millimetre(s)
μM	Micromolar
NCI	National Cancer Institute
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PI	Principal investigator
PR	Partial response
PS	Performance status
PTT	Prothrombin time
PV	Pharmacovigilance
QoL	Quality of life
RAS	Rat sarcoma
RBC	Red blood cells
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
TAA	Tumour associated antigen
UNL	Upper normal limit
WBC	White blood cells
5-FU	5-Fluorouracil

1. SYNOPSIS

Title of Trial:	A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas
Trial Number:	CT TG01-01
Sponsor:	Targovax ASA
Trial Physician:	
Trial Centres:	4-5 centres located in Norway, UK and Spain
Estimated Trial Duration:	<p>Phase I and Phase II part (main and concomitant group): 104 weeks enrolment 104 weeks treatment Duration: 5 years and 4 months Survival follow-up until end of life.</p> <p>Phase II (modified vaccination group): 48 weeks enrolment 104 weeks treatment Duration: 2 years and 11 months Survival follow-up until end of life.</p> <p>Total study duration: 5 years and 4 months</p>
Trial Phase:	Phase I/II Trial
Objectives:	<ol style="list-style-type: none"> 1. To assess the safety of GM-CSF/TG01 vaccination and adjuvant chemotherapy 2. To assess the immune response to GM-CSF/TG01 and the effect of adjuvant chemotherapy in patients receiving GM-CSF/TG01 after primary resection of pancreatic adenocarcinoma 3. To assess at 2 years the clinical efficacy of GM-CSF/TG01 in patients with resected pancreatic cancer 4. To assess the relationship of KRAS status to recurrence 5. To monitor CA19-9 levels
Trial Design:	<p>Phase I Part Up to 12 patients will be assessed for safety and the effect of Gemcitabine on immune response.</p> <p>Initially, 6 patients will be treated with GM-CSF/TG01 within 1-8 weeks after surgery and when these 6 patients have reached week 11:</p> <ul style="list-style-type: none"> • If 0/6 patients have an immune response and/or >3/6 patients have a DLT the study will be terminated • If 1-3/6 patients have an immune response and/or 3/6 patients have a DLT a further 6 patients will be enrolled

<ul style="list-style-type: none"> • If $\geq 4/6$ patients have an immune response and $\leq 2/6$ patients have a DLT then phase II study will be initiated <p>If the phase I enrolment is expanded to 12 patients then at week 11:</p> <ul style="list-style-type: none"> • If $< 4/12$ patients have an immune response and/or $> 4/12$ patients have a DLT the study will be terminated • If $\geq 4/12$ patients have an immune response and $\leq 4/12$ patients have a DLT, phase II will be initiated <p>The Phase II part of the study will therefore be initiated if:</p> <ul style="list-style-type: none"> ○ $\geq 4/6$ patients have an immune response and $\leq 2/6$ patients have a DLT or ○ $\geq 4/12$ patients have an immune response and $\leq 4/12$ patients have a DLT <p>Patients who are withdrawn for reasons other than toxicity may be replaced if they received less than 4 weeks of vaccination and have not started Gemcitabine</p> <p><u>Phase II Part</u></p> <p>A further 18-25 patients treated with GM-CSF/TG01 + gemcitabine will be added in the Phase II part of the study to provide a total of up to 30 patients in the study as a whole.</p> <p>These patients will follow the same schedule of assessment as in the Phase I part (Table 1) and will constitute the main group. Vaccination should be initiated as soon as possible after surgery. Should for medical or other reasons, a patient be unable to start Gemcitabine either within the 12 week window or at all, vaccinations will be continued. In exceptional circumstance, due to medical reasons, where vaccination cannot be started soon after surgery, a maximum of 6 patients can start vaccination at the same time as chemotherapy (Table 2). These patients will constitute the concomitant group.</p> <p>Patients who are withdrawn for reasons other than toxicity may be replaced if they received less than 4 weeks of vaccination and have not started gemcitabine.</p> <p>The above Phase II part has established a vaccination protocol that provides a positive immune response. A new cohort with up to 13 patients is to be enrolled to test if a modified schedule of administration of GM-CSF/TG01 can induce and maintain the same immune response and reduce the severity of or avoid side effects related to allergic reactions (Table 3). These patients will constitute the modified vaccination group.</p> <p><u>Phase I and Phase II Parts</u></p> <p>Patients will receive GM-CSF followed by TG01, 10-15 minutes later. Between 3-7 weeks after GM-CSF/TG01 injections have started, patients will also receive Gemcitabine on the same day and after TG01 administration. The patients will all be assessed for safety and immune responses by week 11 after receiving at least 1 cycle of gemcitabine treatment. In the Phase II part, vaccination will start</p>
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as soon as the vaccination schedule can be adhered to and gemcitabine (or 5FU/Leucovorin as per protocol in case of impaired liver function) will be started at least 3 weeks later and where possible within 12 weeks from surgery (main group). Patients for whom chemotherapy timing cannot be assured will start vaccination as soon as the vaccination schedule can be adhered to and will receive chemotherapy or not according to their needs. Patients, who for medical reasons, cannot start vaccination early may start this at the same time as chemotherapy to the limit of 6 patients (concomitant group).

Treatment will be interrupted in any individual patient in case of unacceptable toxicity. If the toxicity is considered to be due to gemcitabine alone then immunisation with GM-CSF/TG01 will be continued. With the exception of patients who have received less than 4 weeks of immunisation with GM-CSF/TG01 and no gemcitabine, all patients will complete the study follow up (even if withdrawn from therapy) unless they withdraw consent.

After completion of the gemcitabine treatment, patients who are recurrence-free (with or without a detected immune response) will continue to receive GM-CSF/TG01 every 4 weeks until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Patients who recur during the study and had a positive immune response during the study treatment period should continue to receive GM-CSF/TG01 every 4 weeks until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Patients who recur and haven't had a positive immune response during the study treatment period will be withdrawn. The same applies to patients who never start chemotherapy.

For all patients, where possible, a survival follow-up will continue to be performed every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.

Modified vaccination group

Patients will start vaccination as soon as possible after surgery. Patients will receive GM-CSF followed by TG01 15-20 minutes later. Gemcitabine will commence preferably at least 3 weeks later and vaccination will be put on hold until chemotherapy completion. In the event that chemotherapy cannot be started patients should continue to be vaccinated 4-weekly. After completion of the gemcitabine treatment, patients who are recurrence-free (with or without a detected immune response) will continue to receive 4-weekly GM-CSF/TG01 (plus one vaccination at week 5 post-chemotherapy) until week 52 then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Patients who recur during the study and had a positive immune response during the study treatment period should continue to receive 4-weekly GM-CSF/TG01 (plus one vaccination at week 5 post-chemotherapy) until week 52 then every 12 weeks until 2 years, until withdrawal of consent or toxicity

	<p>whichever is the earliest. Patients who recur and haven't had a positive immune response during the study treatment period will be withdrawn. Where possible, a survival follow-up will continue to be performed every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.</p> <p>The efficiency of this modified vaccination group will be assessed after 6 patients have data for DTH assessments after 8 weeks. The cohort will continue if the tolerability is acceptable and there are at least 4/6 patients with a positive immune response by week 8. If <4/6 patients have an acceptable immune response, the next patients will revert to the previous induction schedule of 3 vaccinations in the first week.</p>
Inclusion Criteria:	<ol style="list-style-type: none"> 1. Histologically or cytologically confirmed diagnosis of adenocarcinoma of the pancreas 2. Stage I or II disease (clinical stage T1-3, N0-1, M0 by AJCC staging criteria). 3. Successful surgical resection <ul style="list-style-type: none"> • Complete resection (R0) or with microscopic residual disease (R1) • Expected to receive gemcitabine monotherapy as adjuvant chemotherapy 4. Laboratory Values: <ul style="list-style-type: none"> • Absolute neutrophil count $\geq 1.5 \times 10^9/l$ • Platelets $\geq 100 \times 10^9/l$ • Haemoglobin ≥ 9 g/dl • Total bilirubin $\leq 1.5 \times$ UNL • Serum creatinine $\leq 1.5 \times$ UNL • Albumin ≥ 2.5 g/dl • AST or ALT $\leq 5 \times$ UNL 5. 18 years of age or older. 6. ECOG performance status (PS) of 0-1. 7. Life expectancy of at least 6 months 8. Men and women of childbearing potential must be willing to use effective methods of contraception to prevent pregnancy 9. Provide written (signed) informed consent to participate in the trial prior to any trial specific screening procedures
Exclusion Criteria:	<ol style="list-style-type: none"> 1. Has received an investigational drug within 4 weeks prior to Trial drug administration 2. Has received previous therapy for pancreatic cancer including radiation or chemotherapy (except for the primary resection or primary neoadjuvant chemotherapy) 3. 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) 4. Has any other serious illnesses or medical conditions such as, but not limited to:

	<ul style="list-style-type: none"> Any uncontrolled infection Uncontrolled cardiac failure classification III or IV (NY Heart Association) Uncontrolled systemic and gastro-intestinal inflammatory conditions Bone marrow dysplasia History of auto-immune disease History of adverse reactions to vaccines <ol style="list-style-type: none"> Known history of positive tests for HIV/AIDS, hepatitis B or C Pregnant or lactating females or have no pregnancy test at baseline (postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential) Contraindication to gemcitabine treatment Have had any other malignancies within last 3 years (except for adequately treated carcinoma of the cervix or basal or squamous cell skin cancer) Known malignant brain lesion(s) Are unlikely to start chemotherapy within 12 weeks of surgery (e.g. delayed wound healing, or infection, etc.) Are not expected to complete 6 cycles of chemotherapy Are planned to receive yellow fever or other live (attenuated) vaccines during the course of study (see concomitant medication section)
Investigational Products and Mode of Administration:	<p>TG01: provided as a lyophilised powder for reconstitution in sterile water for injection to be given via intradermal injection.</p> <p>GM-CSF: provided as a lyophilised powder for reconstitution in sterile water for injection to be given via intradermal injection</p> <p>GM-CSF to be given 10-15 minutes before TG01 in the main group and concomitant group. In the modified vaccination group GM-CSF is to be given 15-20 minutes before TG01.</p> <p>Gemcitabine: provided as a lyophilised powder (vials of 200 mg and 1 g) for reconstitution in saline to be given via intravenous injection. To be reconstituted according to Prescribing Information for gemcitabine</p> <p>Or</p> <p>Optional 5-FU and Leucovorin (in patients with ALT/AST >2.5 x ULN at time of chemotherapy start):</p> <p>5-FU and Leucovorin: To be administered according to the Prescribing Information for 5-FU and in accordance with the standard procedure of the institution.</p>
Treatment Description:	<p>GM-CSF/TG01</p> <p>Patients will receive the first dose of GM-CSF/TG01 as soon as feasible after surgery. Patients will receive TG01 at a dose of 0.70 mg/injection (individual peptides comprising 0.10 mg each) 10-15 minutes (or 15-20 minutes in the modified vaccination group) after 30 µg GM-CSF at each time point as an intradermal injection into the back of the upper arm.</p> <p>Patients will be observed for at least 30 minutes after each injection of TG01.</p>

	<p>Hospitalisation of patients for administrative reasons only will be at the investigator's discretion and would not qualify as a serious adverse event.</p> <p><u>TG01 for DTH testing</u> As a DTH skin reactivity test control patients will be given TG01 at a dose of 0.70 mg /injection (individual peptides comprising 0.10 mg each) without GM-CSF as an intradermal injection into the lower area of the contralateral arm. When a DTH test is being performed the DTH TG01 injection will be given at least 30 min before the GM-CSF administration and the TG01 administration 10-15 minutes after GM-CSF (15-20 minutes in the modified vaccination group).</p> <p><u>Chemotherapy</u> At start of chemotherapy:</p> <ul style="list-style-type: none"> • Patients who have AST or ALT $\leq 2.5 \times$ UNL will receive gemcitabine according to protocol • Patients who have AST or ALT $> 2.5 \times$ UNL may receive 5-FU and continue vaccination with TG01 as per protocol (at the investigator's discretion) <p>Gemcitabine will be given as 1000 mg/m² iv over 30 minutes on days 1, 8 and 15 of a four-week cycle for 6 cycles in total.</p> <p>Should 5-FU be given instead of gemcitabine, the recommended regimen is 500 mg/m², bolus i.v on day 1 and 2 and leucovorin 60mg/m² (or 100mg) on day 1 and 2 every 2 weeks of a four-week cycle for 6 cycles.</p> <p>When applicable, chemotherapy is to be given on the same day and after TG01 injection. In this respect, in the main group and concomitant group, patients will receive GM-CSF/TG01 in combination with chemotherapy for 6 cycles of 4 weeks.</p> <p><u>Treatment schedule</u> The first day of GM-CSF/TG01 treatment will be considered Day 1 for the Visits.</p> <p>Main group: Chemotherapy should start not less than 3 weeks after the start of GM-CSF/TG01 and if possible within 12 weeks from surgery. In the event that chemotherapy cannot be started patients should continue to be vaccinated. All these patients will follow the schedule of assessments defined in Table 1. GM-CSF/TG01 will be given on days 1, 3, 5, 8, 15, 22 and then every 2 weeks until the end of chemotherapy treatment.</p> <p>Concomitant group: Where vaccination cannot be started soon after surgery, it is permissible to start GM-CSF/TG01 at the same time as chemotherapy and patients will follow Table 2 schedule of assessments. GM-CSF/TG01 will be given on days 1, 3, 5, 8, 15, 22 and then every 2 weeks until the end of chemotherapy treatment.</p> <p>Modified vaccination group: Chemotherapy should start not less than 3 weeks after the start of GM-CSF/TG01. Patients will be given GM-CSF/TG01 on days 1, 8, 15, 22 and 36 then if chemotherapy hasn't started, 4-weekly until the start</p>
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	<p>of chemotherapy at which point vaccination will be put on hold until the end of chemotherapy treatment. Vaccination will resume after end of chemotherapy treatment (Table 3).</p> <p>All groups: In the case of early termination of chemotherapy treatment (prior to completion of 6 cycles), GM-CSF/TG01 will be continued as per the treatment schedule.</p> <p>Main group and concomitant group: After the end of chemotherapy treatment for all patients who are recurrence-free (with or without a positive immune response), further booster injections will be given every 4 weeks until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Patients who recur and have a positive immune response during the study treatment period should continue to receive GM-CSF/TG01 every 4 weeks until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. From 26 January 2015 onward, for all these subsequent GM-CSF/ TG01 administrations the patients should be given prophylactic treatment (30 minutes before treatment) to prevent possible occurrence of allergic reactions. Patients who recur and do not have a positive immune response during the study treatment period will be withdrawn from the study. The same applies to patients who follow the vaccination schedule but never start chemotherapy.</p> <p>Modified vaccination group: Patients will receive under the same rules as above, further booster injections 4 and 5 weeks after last chemotherapy injection and every 4 weeks from week 8 post-chemotherapy up to week 52, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Prophylactic treatment will not be required.</p> <p>From 26 January 2015 onward,</p> <ul style="list-style-type: none"> • All groups: 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 TG01 administrations they should be pre-medicated with intravenous antihistamine treatment (e.g. chlorpheniramine or dexchlorpheniramine) 30 minutes before either the DTH injection (TG01 alone) when done before vaccination or before vaccination (i.e. before the GM-CSF injection which is followed by TG01 10-15 minutes later or 15-20 minutes in the modified vaccination group) • Main group and concomitant group: For patients who have completed/finished chemotherapy – All TG01 administrations should be preceded by intravenous antihistamine treatment as above • All groups: Patients who have local reactions only – It is permissible to use <u>topical</u> therapies such as anti-histamine or steroid creams or EMLA cream for pain • All groups: Where a DTH injection is being performed the TG01 DTH dose should be administered 30 minutes before the GM-CSF/TG01 administration and patients should be observed for at least 30 minutes after
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	<p>ALL GM-CSF/TG01 administrations</p> <p><u>Modified vaccination group:</u> Prophylaxis will not be required at any stage of the study except if the patient continues vaccination after experiencing an event of hypersensitivity reaction.</p>
Endpoints	<p>Primary</p> <ul style="list-style-type: none"> • Safety <ul style="list-style-type: none"> • Adverse events • Laboratory assessments • Immune response <ul style="list-style-type: none"> • DTH responses • Proliferative T-cell responses <p>Secondary</p> <ul style="list-style-type: none"> • Efficacy at 2 years • Disease free survival • Overall survival <p>Exploratory</p> <ul style="list-style-type: none"> • Relationship between KRAS status in resected primary tumour and recurrence survival outcomes (including disease recurrence and overall survival) • Monitor CA19-9 levels
Schedule of Key Assessments:	<p><u>Screening / Baseline:</u></p> <p>The aim of this protocol is to include patients that have undergone pancreatic resection with curative intent and to subsequently treat the patients with the TG01 vaccine as soon as possible after the surgery. Patients must have signed the informed consent before starting baseline assessments/treatment.</p> <p>Screening assessments to be done prior to GM-CSF/TG01 treatment</p> <ul style="list-style-type: none"> • Surgical Resection (once resection is undertaken, TG01 treatment to start as soon as possible) • Tumour sample from surgery stored for KRAS analysis • Informed consent <p>Baseline assessments to be done within 7 days prior to anticipated TG01 treatment</p> <ul style="list-style-type: none"> • Demographic data and medical history • ECG • Pregnancy test (if appropriate) • Physical examination and performance status • Vital signs • Haematology / Biochemistry assessment • Urinalysis • Assessment of concurrent illness/therapy • CT-scan <p><u>Treatment Period for patients starting TG01 vaccination first – main group</u></p>

	<p><u>(timings based on start of GM-CSF/TG01 treatment)- Table 1: GM-CSF/TG01 +/- chemotherapy</u></p> <p>Initial Treatment Period (possibly up to week 11) +/- chemotherapy cycles</p> <ul style="list-style-type: none"> • GM-CSF/TG01 to start as soon as possible after surgical resection. Day 1 will be the first day of TG01 treatment. GM-CSF/TG01 will be administered on Days 1, 3, 5, 8, 15 and 22 and then 2-weekly until the end of chemotherapy treatment. Patients who do not start chemotherapy at all can move to a 4-weekly vaccination from vaccination week 10 to week 52 and will follow the “post-chemotherapy-52 weeks” schedule of Table 1. • Chemotherapy will commence at least 3 weeks after start of GM-CSF/TG01 and preferable within 12 weeks from surgery (e.g. at day 22, day 36 or day 50). Patients can, however, start chemotherapy later or not start at all if needed. For patients receiving chemotherapy, 6 cycles of chemotherapy will be given and GM-CSF/TG01 will be administered on Days 1 and 15 of the 4-week cycles. • DTH skin test injections on days 1, 8, 15, 22, 36, 50 and day 64. DTH reaction is assessed 48 h \pm 4 h after each injection • Haematology and blood chemistry at days 1, 8, 22, 36, 50, and 64 taken prior to injection of GM-CSF/TG01 and Days 1, 8 and 15 of each gemcitabine cycle. Key laboratory values in accordance with the Prescribing Information for chemotherapy should be available prior to chemotherapy dosing. For patients who do not start chemotherapy at all, haematology and blood chemistry should be taken at days 1, 8, 22, 36, 50 and 64 and then every 12 weeks • Urinalysis as clinically indicated • Vital signs, concomitant medications and adverse events at each visit. • Physical examination and Performance Status before the start of each gemcitabine cycle. For patients who do not start chemotherapy, these assessments should be done every 12 weeks. • Blood sampling for immunology – samples taken prior to GM-CSF/TG01 injection on day 1 and day 71 (or 78) • Blood sampling for CA19.9 on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy, these assessments should be done on Day 1 and prior every 4-weekly vaccination cycle • A further 10 ml sample (5 ml serum; 5 ml plasma) will be taken and stored for potential analysis of additional biomarkers on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy, these assessments should be done on Day 1 and prior every 4-weekly vaccination cycle • CT scan every 6 months from the start of vaccination and at any other time point if indicated <p><u>Treatment Period for patients starting vaccination and chemotherapy at the same time – concomitant group (timings based on start of GM-CSF/TG01</u></p>
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	<p><u>treatment) – Table 2: GM-CSF/TG01 +/- chemotherapy</u></p> <p>Initial Treatment Period (possibly up to week 13) +/- chemotherapy cycles</p> <ul style="list-style-type: none"> • Day 1 will be the first day of TG01 treatment. GM-CSF/TG01 will be administered on Days 1, 3, 5, 8 and 15 and then 2-weekly until the end of chemotherapy treatment. • Chemotherapy will commence at the same time as GM-CSF/TG01 and 6 cycles of chemotherapy will be given. • DTH skin test injections on days 1, 8, 15, 29, 43, 57 and day 71. The DTH reaction is assessed 48 h \pm 4 h after each injection • Haematology and blood chemistry at days 1, 8 and 15 of each gemcitabine cycle. Key laboratory values in accordance with the Prescribing Information for chemotherapy should be available prior to chemotherapy dosing • Urinalysis as clinically indicated • Vital signs, concomitant medications and adverse events at each visit. • Physical examination and Performance Status before the start of each gemcitabine cycle • Blood sampling for immunology – samples taken prior to GM-CSF/TG01 injection on day 1 and week 13 • Blood sampling for CA19.9 on day 1 of each chemotherapy cycle, prior to GM-CSF/TG01 administration • A further 10 ml sample (5 ml serum; 5 ml plasma) will be taken and stored for potential analysis of additional biomarkers on day 1 of each chemotherapy cycle, prior to GM-CSF/TG01 administration • CT scan every 6 months from the start of vaccination and at any other time point if indicated <p><u>Treatment Period for patients in the modified vaccination group (timings based on start of GM-CSF/TG01 treatment)- Table 3: GM-CSF/TG01 +/- chemotherapy</u></p> <p>Initial Treatment Period (up to week 8) +/- chemotherapy cycles</p> <ul style="list-style-type: none"> • GM-CSF/TG01 to start as soon as possible after surgical resection. Day 1 will be the first day of TG01 treatment. All patients will receive at least 5 vaccinations independent of the start of chemotherapy (Days 1, 8, 15, 22 and 36) then if chemotherapy hasn't started, vaccination will be given 4-weekly until the start of chemotherapy at which point vaccination will be put on hold until the end of chemotherapy treatment. Patients who do not start chemotherapy at all will continue to receive 4-weekly vaccinations until week 52 (Table 3). • Chemotherapy will preferably commence at least 3 weeks after start of GM-CSF/TG01. Patients can however start chemotherapy later or not start at all if more appropriate. For patients receiving chemotherapy, 6 cycles of chemotherapy will be given. Note that chemotherapy will not be delayed if it is considered important to start within 3 weeks of the start of vaccinations. • DTH skin test injections on days 36 and 50. DTH reaction is assessed 48 h \pm 4 h after each injection
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	<ul style="list-style-type: none"> • Haematology and blood chemistry at days 1, 8, 22, 36, 50, and 64 taken prior to injection of GM-CSF/TG01 and Days 1, 8 and 15 of each gemcitabine cycle. Key laboratory values in accordance with the Prescribing Information for chemotherapy should be available prior to chemotherapy dosing. For patients who do not start chemotherapy at all, haematology and blood chemistry should be taken at days 1, 8, 22, 36, 50 and 64 and then every 12 weeks • Urinalysis as clinically indicated • Vital signs, concomitant medications and adverse events at each visit. • Physical examination and Performance Status before the start of each gemcitabine cycle. For patients who do not start chemotherapy, these assessments should be done every 12 weeks. • Blood sampling for immunology – samples taken prior to GM-CSF/TG01 injection on day 1 and at week 8 • Blood sampling for CA19.9 on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy, these assessments should be done on Day 1 and prior every 4-weekly vaccination cycle • A further 10 ml sample (5 ml serum; 5 ml plasma) will be taken and stored for potential analysis of additional biomarkers on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy, these assessments should be done on Day 1 and prior every 4-weekly vaccination cycle • CT scan every 6 months from the start of vaccination and at any other time point if indicated <p><u>Post-Chemotherapy period or period from week 10 for patients who do not get chemotherapy</u></p> <p>Main group and concomitant group</p> <ul style="list-style-type: none"> • GM-CSF/TG01 every 4 weeks until 52 weeks and then every 12 weeks for up to 2 years. For all these subsequent GM-CSF/TG01 administrations the patients should be given prophylactic treatment (30 minutes before treatment) to prevent possible occurrence of allergic reactions. • DTH skin test injections at the 2nd GM-CSF/TG01 injection after end of chemotherapy (8 weeks after last chemotherapy injection) and at week 52. The DTH reaction is to be assessed 48 h ± 4 h after TG01 injection. For patients not starting chemotherapy at all, DTH assessment is to be done at week 52 only. • Blood sampling for immunology– samples taken prior to GM-CSF/TG01 injection at 52 weeks • Blood sampling for CA19.9 and additional biomarkers – samples taken prior to GM-CSF/TG01 injection at 52 weeks. For patients not starting chemotherapy, samples should be taken prior every 4-weekly vaccination cycle and at week 52 • Physical examination and performance status at 52 weeks. For patients
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	<p>who do not start chemotherapy, these assessments should be done every 12 weeks and at week 52</p> <ul style="list-style-type: none"> • Vital signs, haematology and biochemistry at 12 weekly intervals • Concomitant medications and adverse events at each visit • CT scan every 6 months from the start of vaccination and at any other time point if indicated <p><u>Modified vaccination group:</u></p> <ul style="list-style-type: none"> • GM-CSF/TG01 will be given 4 weeks and 5 weeks after end of chemotherapy and then every 4 weeks from week 8 post-chemotherapy until week 52. • DTH skin test at 3rd vaccination post-chemotherapy (8 weeks post-chemotherapy). The DTH reaction is to be assessed 48 h \pm 4 h after TG01 injection. For patients not starting chemotherapy at all, the DTH test and assessment are to be done at week 52 • Blood sampling for immunology– sample to be collected 4 weeks after the last chemotherapy injection (1st vaccination injection) and at week 52 • Blood sampling for CA19.9 and additional biomarkers – samples to be taken prior to GM-CSF/TG01 injection at week 52. For patients not starting chemotherapy, samples should be taken prior every 4-weekly vaccination cycle and at week 52 • Physical examination and performance status to be taken at week 52. For patients who do not start chemotherapy, these assessments should be done every 12 weeks and at week 52 • Vital signs, haematology and biochemistry at 12 weekly intervals • Concomitant medications and adverse events at each visit • CT scan every 6 months from the start of vaccination and at any other time point if indicated <p><u>End of Study Visit (104 weeks or 4 weeks after last GM-CSF/TG01 injection if patients is to be withdrawn)</u></p> <ul style="list-style-type: none"> • Haematology and blood chemistry • Physical exam and Performance Status • Vital signs, concomitant medications and adverse events • CT scan • Blood sampling for immunology, CA19.9 and additional biomarkers <p>If patient is recurrence-free with or without an immune response, GM-CSF/TG01 will be given as per schedule until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. If patient has a positive immune response and recurs during the study treatment period, the patient should continue as per schedule until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. The same applies to patients who do not start chemotherapy.</p> <p>For all patients where possible, a survival follow-up will continue to be performed every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or</p>
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	withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.
Sample size	<p>Up to 32 patients will be enrolled in this study: 7 patients have been enrolled in the Phase I part 18-25 will be enrolled in the Phase II part with up to 13 patients enrolled in the modified vaccination group</p> <p>The modified vaccination group will consist of up to 13 patients. A review of data of the first 6 patients for DTH assessments after 8 weeks will determine whether the cohort should continue. At least 4/6 patients with a positive immune response are required to continue</p>
Statistical Methods and Planned Analyses:	<p>No formal statistics will be performed.</p> <p>All patients (treated with chemotherapy or not) will contribute to the interpretation of the whole trial.</p> <p>The proportion of patients with immune responses will be assessed.</p> <p>The safety and efficacy of the combination of GM-CSF/TG01 and chemotherapy will be descriptive. The incidence of pancreatic cancer recurrence and KRAS status during the Trial will be listed.</p>

2. INTRODUCTION

Investigators should be familiar with the Investigator's Brochure (IB).

2.1 Background

2.1.1 Pancreatic cancer

Pancreatic cancer is one of the major causes of cancer death globally, with a 5-year survival rate of less than 5%. The outlook for those patients who can undergo surgical resection is better, and in specialised centres, resection rates greater than 15% can be achieved. Although surgery cannot guarantee a cure, the 5-year survival does improve to around 10% following resection. There is a clear need to improve long-term survival in these patients. While the added survival benefit of adjuvant chemoradiotherapy with or without maintenance chemotherapy remains unclear, a more certain survival benefit has been demonstrated from adjuvant chemotherapy.

2.1.2 Rationale for the trial

TG01 is an antigen-specific cancer immunotherapy (ASCI) containing a mixture of 7 different synthetic peptides designed to encompass all common RAS mutations at positions 12 and 13. The peptide sequences are identical to the amino acid sequence of wild-type RAS, except for one substitution of the amino acid at either position 12 or 13, which corresponds to amino acid substitutions found in the mutated p21 RAS protein expressed by pancreatic, colon and lung cancer cells.

The occurrence of oncogenic mutations in p21 RAS in pancreatic cancer is very frequent (Capella et al., 1991) and may be one of the reasons why every standard chemotherapy drug and new “targeted” drug tested in pancreatic adenocarcinomas have uniformly failed to significantly increase the survival of patients with pancreatic cancer.

In Europe, chemotherapy alone is now recommended as adjuvant therapy based on the results of the ESPAC-1 and CONKO-001 trials (Neoptolemos et al., 2010; Oettle et al., 2007; Neuhaus et al., 2008). In particular, the CONKO-001 trial indicates that the use of gemcitabine in patients undergoing R0 or R1 resection for pancreatic cancer provides a regimen with minimal toxicity and a chance for a prolonged disease-free-survival compared to observation alone (13.4 months compared to 6.9 months although there was no difference in overall survival). Gemcitabine is therefore the most frequently used adjuvant in this setting.

Combining gemcitabine with an immunotherapy approach would, in theory, offer a regimen with minimal toxicity with the aim to improve the recurrence rate and potentially offer an improved overall survival.

TG01 is administered to the patients by intradermal injection in combination with an adjuvant (GM-CSF/Molgramostim). After administration, the peptides are taken up by antigen presenting cells like dendritic cells (DCs) which thereafter travel to the draining

lymph nodes and present the vaccine peptides, eventually after being trimmed by intracellular enzymatic antigen processing, in HLA molecules. This will enable the induction of T-cells with specificity for the various RAS mutations of TG01. Finally the induced T-cells will enter circulation and get activated upon recognition of cancer cells presenting relevant mutated RAS peptide epitopes in their HLA molecules. In addition to efficient killing of cancer cells by T-cells induced by TG01, also a broader immune response may be induced locally by enhanced stimulation of cross presentation and epitope spreading (local cytokine production by TG01 induced T-helper cells stimulate DCs to take up debris from killed cancer cells and present all sorts of tumour associated peptide epitopes).

2.1.3 Pre-clinical experience

TG01 is an antigen specific cancer immunotherapy (ASCI) consisting of seven synthetic 17-mer ras-oncogene peptides aimed to stimulate CD4⁺ Th-cells against tumour cell targets expressing mutated RAS peptides and, intended to be administered at a low dose 0.7 mg (0.1 mg each peptide) by intradermal injection. Due to the nature of TG01 a number of non-clinical studies that would normally be undertaken as part of a formal development programme were not conducted in the case of TG01 and the rationale for this is given below.

The seven synthetic, naturally occurring, 17-mer ras-oncogene peptides that comprise TG01 have no intrinsic activity *per se*. Moreover, the effects of TG01 are not related to blood or plasma concentrations but are mediated through local peptide uptake into dendritic cells (DC's) in the skin and immunological processing at the injection site. Subsequently DC's in the skin migrate to the draining lymph node where they activate T-cells. The breakdown of proteins from dead cells takes place locally, in the tissue, where peptide fragments are rapidly degraded by tissue proteases/peptidases and do not reach the bloodstream. Indeed, even in an improbable 'worst case' scenario, in which the peptides were to reach the systemic circulation, evidence indicates that they would be rapidly degraded in the blood, being undetectable 1 min after injection (Yamada et al., 2006).

Thus, taking into account the lack of intrinsic activity of the peptides, the lack of systemic exposure following intradermal injection and data from clinical studies, in which TG01 has been administered repeatedly to over 80 pancreatic cancer patients with only minor, transient adverse effects, a formal development programme, based on systemic exposure following administration, was not considered relevant.

The non-clinical pharmacodynamics and rationale for developing TG01 was assessed in a number of published *in vitro* studies using T-cells from patients to demonstrate the ability of the peptides to elicit effector T-helper cells and cytotoxic T-lymphocytes (CTL) in humans. Initial studies, investigating whether specific immune responses could be generated against RAS, reported that immunization of a number of strains of mice with RAS peptides, bearing various point mutations at positions 12 or 61, elicited T-cells that specifically proliferated in response to RAS peptide stimulation (Peace et al., 1991). Moreover, several studies using synthetic RAS-oncogene peptide-loaded peripheral

blood mononuclear cells (PBMC's) from both healthy individuals and cancer patients have reported the induction of RAS-specific T-cell responses *in vitro*. Furthermore, both CD4⁺ and CD8⁺ T-cells have been identified and their ability to kill RAS-expressing target cells or inhibit the growth of cancer cell lines harbouring the corresponding RAS mutations has been demonstrated (Gedde-Dahl et al., 1992 & 1994; Fossum et al., 1993 & 1994). Taken together, these reports, in addition to other published observations, indicated that targeting RAS by immunotherapy offered a feasible approach to potentially controlling pancreatic cancer cell growth *in vivo*.

Single dose intravenous toxicology studies using either single, two or five KRAS peptide mixtures were undertaken in pigs, rabbits, rats and mice. Collectively, the 2 and 5 KRAS peptide single dose toxicity studies used all 7 of the KRAS peptides which comprise TG01. Overall, these studies revealed no significant toxicological findings, presumably as a consequence of rapid degradation of the peptides in the blood following intravenous bolus injection and subsequent lack of systemic exposure.

However, an exception to these observations was noted in a single dose, iv study following administration of the val 12 peptide in mice (study 927/002). In this study, administration of the highest dose of the val 12 peptide (50 mg/kg) led to subdued behaviour or convulsions in all 5 males and 5 females and two males and one female died within 2 min of injection. All surviving animals recovered after 2 h. In contrast, no mortalities or clinical effects were noted following administration of the low (0.5 mg/kg) or intermediate (5 mg/kg) dose-levels. Moreover, no mortalities, clinical signs or macroscopic abnormalities were reported when the same doses of the val 12 peptide were administered to rats. Taken together, the most plausible mechanism to account for these observations, recorded specifically in the mouse, is related to the exceptionally small diameter of blood vessels in the murine brain, which may readily become clogged following injection of excessive amounts of peptides or macromolecules resulting in rapid death or clinical symptoms such as lethargy, convulsions or subdued behaviour. Indeed, the val 12 peptide is considerably less soluble and more hydrophobic than the other 6 peptides in TG01, lending support to the idea that blocked microvessels in the murine brain resulted in the rapid deaths or clinical symptoms reported. Moreover, the dose of val 12 administered in this study was circa 5000 times the dose (of total peptides using the 7-peptide formulation) that has been routinely administered to humans in clinical studies. Hence, it is considered that a sufficient safety margin exists between the currently utilised clinical dose and the dose at which toxicity was specifically observed following administration of this single peptide in the mouse.

The complete seven mutated RAS peptide mixture that comprises TG01 has not been tested in animal toxicity studies to date. This was primarily due to the initial development plan for TG01 which explored the safety of RAS immunotherapy based on the use of single peptides in pancreatic cancer patients. However, due to the high probability of a mismatch between the point mutation in the immunising peptide and the mutation expressed by the patients' tumour, there was a requirement for each patient to be genotyped for RAS mutations in order to optimise therapy. Due to the tedious and costly nature of this approach, particularly with respect to the rapid deterioration of

pancreatic cancer patients and the time required for RAS gene sequencing, it became obvious that such a strategy was impractical. Consequently, it was decided to develop a product containing a mixture of seven peptides that encompassed all significant RAS mutations, thus negating the requirement for prior tumour typing.

Although current regulatory guidelines indicate that the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals such as synthetic peptides, prior to the issue of these guidelines, an Ames test was undertaken using a single KRAS peptide 12-V- p21 RAS(5-21). Concentrations of 31.2, 62.5, 125, 250, and 500µg/plate did not result in any mutagenic findings either in the presence or absence of liver S-9 mix. These naturally occurring peptides would not be expected to interact directly with DNA or other chromosomal material, and in view of the current guideline, no further studies are planned.

Additionally, these natural peptides have no potential to support or induce proliferation of transformed cells or clonal expansion leading to neoplasia and taken together with the rapid degradation, consequent lack of systemic exposure and the target patient population, no carcinogenicity have been undertaken.

Moreover, whilst many biotechnology-derived products are immunogenic and have the potential to stimulate antibody production, the seven synthetic, 17-mer ras-oncogene peptides in TG01 are comprised entirely of naturally occurring amino acids and have no capacity to stimulate the formation of antibodies. Indeed, after processing by DC's, the peptides elicit a highly specific immune response, stimulating CD4⁺ T-cells against specific tumour cell targets expressing mutated RAS peptides. This was evidenced in clinical data from Phase I/II studies indicating that a specific delayed-type hypersensitivity (DTH) reaction could be generated at skin sites in almost 50% of cancer patients.

This body of clinical data also provides significant experience concerning local tolerance. In the case of TG01, repeated intradermal injections of the seven peptide mixture, co-administered with GM-CSF, have been given to more than 80 patients with pancreatic cancer using a 1, 2, 3, 4, 6 and 10 week dosing schedule. These clinical studies reported that injections were well tolerated, with only one patient reporting itching and one patient showing erythema at injection sites. Moreover, these injection-related local effects were transient and resolved without sequelae. Consequently, no additional non-clinical studies investigating local effects are planned.

2.1.4 Clinical experience

During the earlier phases of development, a significant body of clinical data from over 230 cancer patients has been established and indicates that the RAS peptides comprising TG01 are safe, well tolerated and have the capacity to elicit immune responses in man. To date, 120 patients with pancreatic cancer have received treatment with TG01 in combination with GM-CSF (studies CTN RAS 98010 and EMR 62200-001) and 55 patients with pancreatic cancer have received either several injections of RAS peptide-pulsed autologous PBMC (7 patients), or active immunization with 1 or 4 mutated RAS peptides combined with GM-CSF (48 patients; Studies CTN RAS 93001,

CTN RAS 95002, CTN RAS 97004). Sixty three patients with colorectal cancer have received treatment RAS peptide-pulsed autologous PBMC (8 patients), or active immunization with 1 or 5 mutated RAS peptides combined with GM-CSF (55 patients; Studies CTN RAS 95003, CTN RAS 97005 and CTN RAS 98008).

Immunization with a single RAS peptide pulsed PBMC in study CTN RAS 93001 resulted in specific T cell responses in only 2 out of 5 patients which led to the selection of active immunization as the optimal approach for induction of measurable immune responses. Using this approach, both DTH and proliferative responses could be demonstrated in approximately half of the pancreatic cancer patients who received active immunisation with either one or 4 RAS peptide ASCI (Studies CTN RAS 95002 and 97004). In the clinical study with the 7 RAS peptide ASCI (CTN RAS 98010), the results showed that all (100%) of the evaluable patients in the resected group and 14 (56%) in the non-resected group reported a DTH immune response.

From all the clinical studies so far in patients with resected and advanced pancreatic cancer it seems that the ability to induce an effective immune response may be reduced as the disease burden increases. It is therefore of outmost importance to start to vaccinate as soon as possible after diagnosis and to use an aggressive initial immunotherapy regimen in order to induce an immune response as quickly as possible. Long term follow up of resected pancreatic cancer patients immunised with a single peptide – specific RAS peptide vaccine (Study CTN RAS 95002) and the 7 RAS peptide vaccine (Study CTN RAS 98010) suggest that the induction of a RAS-specific cellular response may confer a survival advantage since patients who develop a DTH response seem to live longer than those who do not. Five year survival rates were 3 out of 10 patients in Study CTN RAS 95002 and 2 out of 11 patients in Study CTN RAS 98010. Collectively these data suggest that vaccination with TG01 could induce potent anti-tumour activities capable of improving the patient's survival and pivotal studies are being planned to test this hypothesis.

Whilst the safety of co-administration of GM-CSF/TG01 with gemcitabine has not been established, their mode of action and toxicity profiles should not be additive and it is not expected that toxicity will be a factor in progressing to the formal Phase II/III study. The production of immune responses with this combination is also not known and it is considered prudent to explore this initially before embarking on the main Phase II/III study.

2.2 Trial objectives

2.2.1 Primary objective

The primary objective of the study is defined as:

- To assess the safety of GM-CSF/TG01 vaccination and adjuvant chemotherapy
- To assess the immune response to GM-CSF/TG01 and the effect of adjuvant chemotherapy in patients receiving GM-CSF/TG01 after primary resection of pancreatic adenocarcinoma.

2.2.2 Secondary objective

The secondary objective of the study is:

- To assess at 2 years the clinical efficacy of GM-CSF/TG01 in patients with resected pancreatic cancer

2.2.3 Exploratory objectives

The exploratory objectives are:

- Assess the relationship of KRAS status to recurrence
- Monitor CA19-9 levels

3. INVESTIGATIONAL PLAN

3.1 Overall trial design and plan

This is a Phase I/II trial of TG01 and gemcitabine as adjuvant therapy for treating patients with resected adenocarcinoma of the pancreas.

Patients will be enrolled in 4-5 study centre(s) and the study duration will be approximately 5 years.

The phase I part of the study (Figure 1) will be initiated with 6-12 patients enrolled within 1-8 weeks after surgery to receive GM-CSF given 10-15 minutes before TG01. Gemcitabine will be started at least 3 weeks after the initiation of immunotherapy but not later than 12 weeks after surgery. Note that, in some centres where transaminases are $> 2.5 \times \text{ULN}$ at the time of chemotherapy, 5-FU/Leucovorin may be substituted. However, the number of patients in the study refers to those receiving gemcitabine and therefore, for every patient who receives 5-FU rather than gemcitabine, a further patient will be added. The patients' safety will be reviewed on an on-going basis and the immunological response will be monitored (DTH) and assessed by week 11 (DTH and T cell proliferation).

Initially, 6 patients will be treated with GM-CSF/TG01 within 1-8 weeks after surgery and when these 6 patients have reached week 11:

- If 0/6 patients have an immune response and/or there are $> 3/6$ patients with GM-CSF/TG01 related dose-limiting toxicities observed, the study will be terminated.
- If 1-3/6 patients have an immune response and/or if there are 3/6 patients with GM-CSF/TG01 related dose-limiting toxicities observed, 6 new patients will be enrolled and will be treated in the same way as the previous patients.
- If $\geq 4/6$ patients have an immune response and $\leq 2/6$ patients have a GM-CSF/TG01 related dose-limiting toxicity, the phase II study will be initiated

If the enrolment of the phase I part is expanded to 12 patients, then at week 11:

- If $< 4/12$ patients have an immune response and/or there are $> 4/12$ patients with GM-CSF/TG01 related dose-limiting toxicities, the study will be terminated
- If $\geq 4/12$ patients have an immune response and $\leq 4/12$ patients have a GM-CSF/TG01 related dose-limiting toxicity, the phase II study will be initiated

The Phase II part of the study (an additional 18-24 patients - Figure 2) will be initiated if:

- $\geq 4/6$ patients have an immune response and $\leq 2/6$ patients have a GM-CSF/TG01 related dose-limiting toxicity
- $\geq 4/12$ patients have an immune response and $\leq 4/12$ patients have a GM-CSF/TG01 related dose-limiting toxicity

The above Phase II part has established a vaccination protocol that provides a positive immune response. A new cohort with up to 13 patients is to be enrolled to test if a modified schedule of administration of GM-CSF/TG01 can induce and maintain the same immune response and reduce the severity of or avoid side effects related to allergic reactions (Table 3). These patients will constitute the modified vaccination group. The efficiency of this modified vaccination group will be assessed after 6 patients have data for DTH assessments after 8 weeks. The cohort will continue if the tolerability is acceptable and there are at least $4/6$ patients with a positive immune response by week 8. If $< 4/6$ patients have an acceptable immune response, the next patients will revert to the previous induction schedule of 3 vaccinations in the first week.

There will therefore be a total number of up to 32 patients for the whole study.

In both parts of the study, patients who are withdrawing for reasons other than toxicity may be replaced if they received less than 4 weeks of vaccination and have not started gemcitabine treatment.

Dose Limiting Toxicities will be defined as follows (based on CTCAE V4):

- Injection site reaction of grade 3
- $ANC < 0.5 \times 10^9/L$ associated with fever (temperature $> 38.5^\circ C$)
- $ANC < 0.5 \times 10^9/L$ lasting ≥ 5 days without fever
- Grade 4 thrombocytopenia for ≥ 5 days
- Grade 3 or 4 renal or hepatic toxicity
- Grade 3 or 4 diarrhoea despite aggressive anti-diarrhoeal therapy
- Other non-haematological toxicity \geq grade 3 (excluding treatable alopecia or treatable nausea and vomiting)
- \geq Grade 3 'allergic reaction/anaphylactic reaction' in spite of prophylaxis with antihistamine and steroids
- Treatment delay > 2 weeks prior to start of next cycle of treatment due to unresolved toxicity

- In the case of grade 4 ANC or thrombocytopenia, haematology should be assessed daily until recovery to < grade 2

GM-CSF and TG01

The first day of GM-CSF/TG01 treatment will be considered Day 1 for the Visits.

Phase I and phase II part - **main group**: the GM-CSF/TG01 will be given on days 1, 3, 5, 8, 15 and 22 and then every 2 weeks until the end of chemotherapy treatment. If patients do not start chemotherapy at all, they will receive GM-CSF/TG01 on days 1, 3, 5, 8, 15, 22, 36, 50, 64 and then every 4 weeks until week 52. In the case of early termination of chemotherapy treatment (prior to completion of 6 cycles) GM-CSF/TG01 will be continued as per the treatment schedule.

Phase II part - **concomitant group**: GM-CSF/TG01 will be given on days 1, 3, 5, 8, 15 and then every 2 weeks until the end of chemotherapy treatment. In the case of early termination of chemotherapy treatment (prior to completion of 6 cycles) GM-CSF/TG01 will be continued as per the treatment schedule.

Phase II part – **modified vaccination group**: GM-CSF/TG01 will be given on days 1, 8, 15, 22 and 36 and then after the end of chemotherapy treatment. If patients start chemotherapy after week 10 or do not start chemotherapy at all, they will receive GM-CSF/TG01 every 4 weeks from week 10 until chemotherapy starts or until week 52. In the case of early termination of chemotherapy treatment (prior to completion of 6 cycles) GM-CSF and TG01 will be continued as per the treatment schedule.

Main group and concomitant group: Patients who are recurrence-free (with or without a detected immune response), will continue to receive GM-CSF/TG01 treatment every 4 weeks until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Patients who recur and have an immune response during the treatment period should continue every 4 weeks until 52 weeks, then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. The same applies to patients who do not start chemotherapy.

Modified vaccination group: patients who are recurrence-free (with or without a detected immune response) will continue to receive 4-weekly GM-CSF/TG01 (plus one vaccination at week 5 post-chemotherapy) until week 52 then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest. Patients who recur during the study and had a positive immune response during the study treatment period should continue to receive 4-weekly GM-CSF/TG01 (plus one vaccination at week 5 post-chemotherapy) until week 52 then every 12 weeks until 2 years or until withdrawal of consent or toxicity whichever is the earliest.

All groups: Patients who recur and do not have an immune response during the treatment period will be withdrawn.

For all patients where possible, a survival follow-up will continue to be performed every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.

Chemotherapy

Phase I and phase II part - **main group**: Patients will receive chemotherapy starting a minimum 3 weeks after the start of GM-CSF/TG01 treatment and not later than 12 weeks from surgery. Chemotherapy will start on a day when TG01 is administered (GM-CSF/TG01 treatment Day 22, 36 or 50). For patients who do not receive chemotherapy, vaccinations will be continued according to the same schedule except that from week 10 the vaccinations will be 4-weekly until week 52.

Phase II part - **concomitant group**: Patients will receive GM-CSF/TG01 and chemotherapy starting between 9 and 12 weeks after the surgery and not later than 12 weeks from surgery.

Phase II part – **modified vaccination group**: Chemotherapy will preferably commence at least 3 weeks after start of GM-CSF/TG01 on a day when GM-CSF and TG01 is administered (TG01 treatment Day 22, 36 or 50). Patients can however start chemotherapy later or not start at all if more appropriate. Chemotherapy should however not be delayed if it is considered important to start within 3 weeks of the start of vaccinations. For patients who do not receive chemotherapy, vaccinations will be 4-weekly from week 10 until week 52.

Gemcitabine will be given as 1000 mg/m² iv over 30 minutes on days 1, 8 and 15 of a four-week cycle for 6 cycles in total.

However if at start of chemotherapy or prior to next gemcitabine administration, AST and ALT are >2.5 x UNL, patients may receive 5-FU/Leucovorin instead of gemcitabine and continue vaccination with TG01 as per protocol. The use of 5-FU/leucovorin under these circumstances is not mandatory but depending on the usual practice at the study site

When applicable, chemotherapy is to be given on the same day and after TG01 injection. In this respect, in the main group and concomitant group, patients will receive GM-CSF/TG01 in combination with chemotherapy for 6 cycles of 4 weeks.

Figure 1: Study Design – Immune response assessment

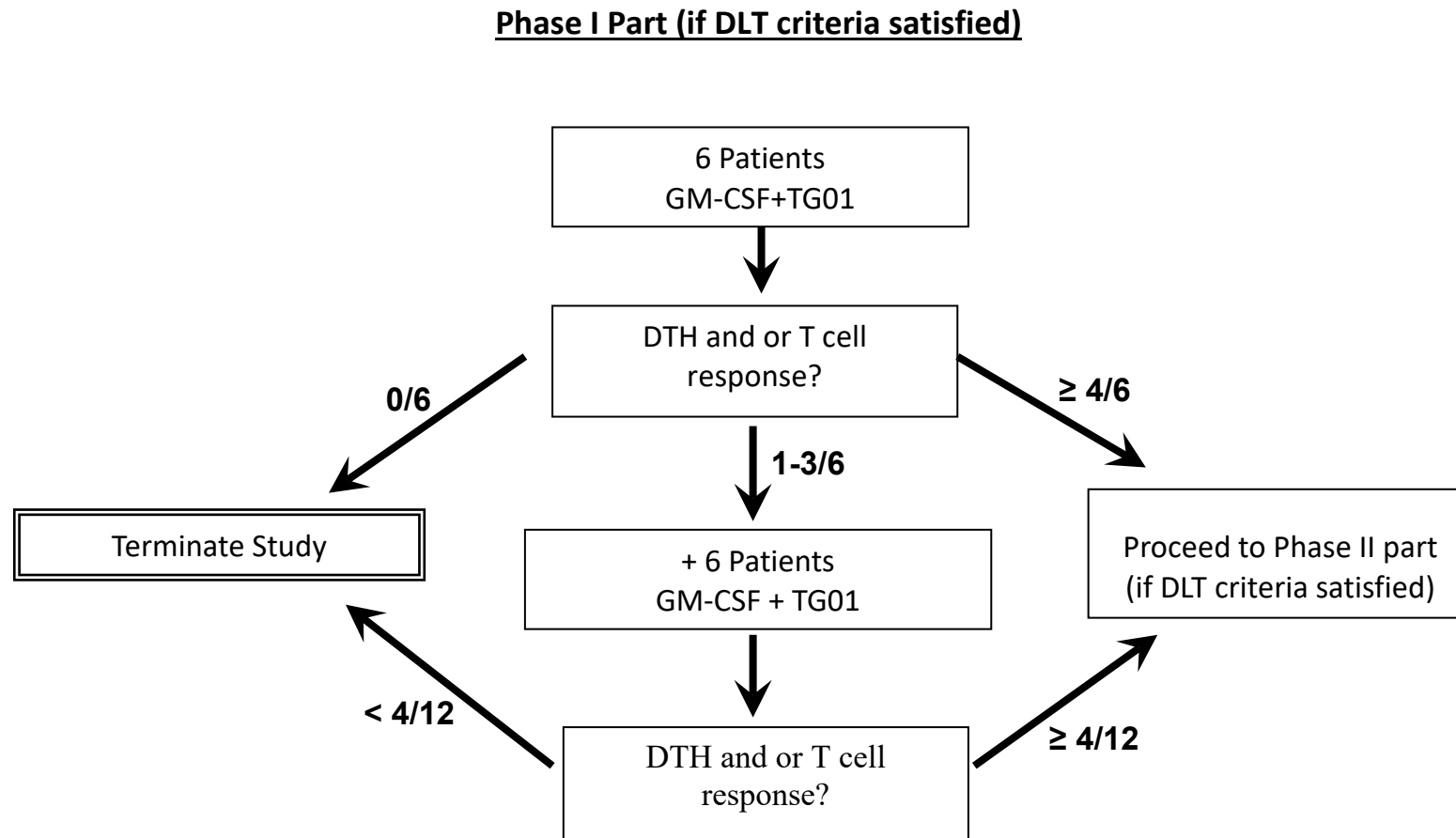


Figure 2: Study Design – Dose Limiting Toxicity Assessment

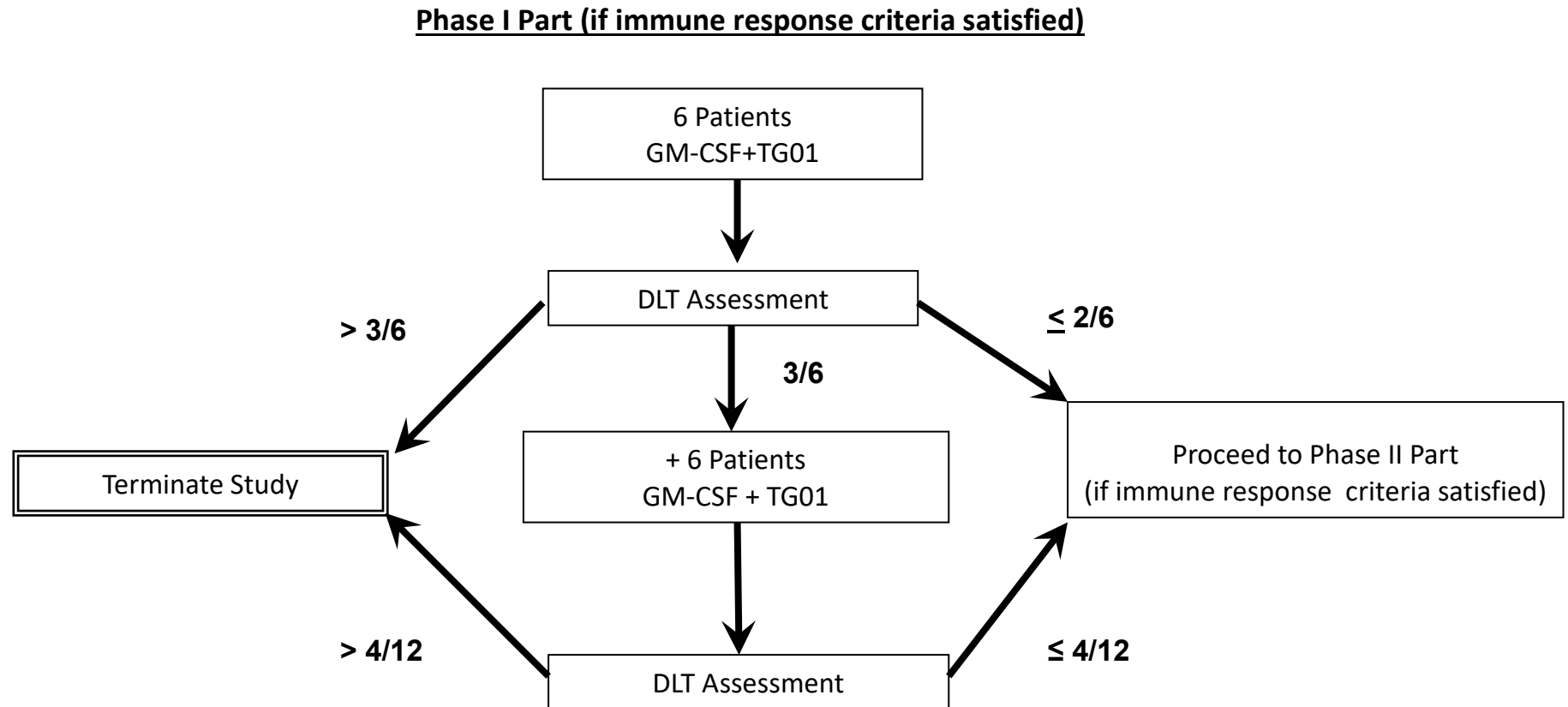


Figure 3: Treatment schedule for patients starting vaccination and receiving chemotherapy later – Main group

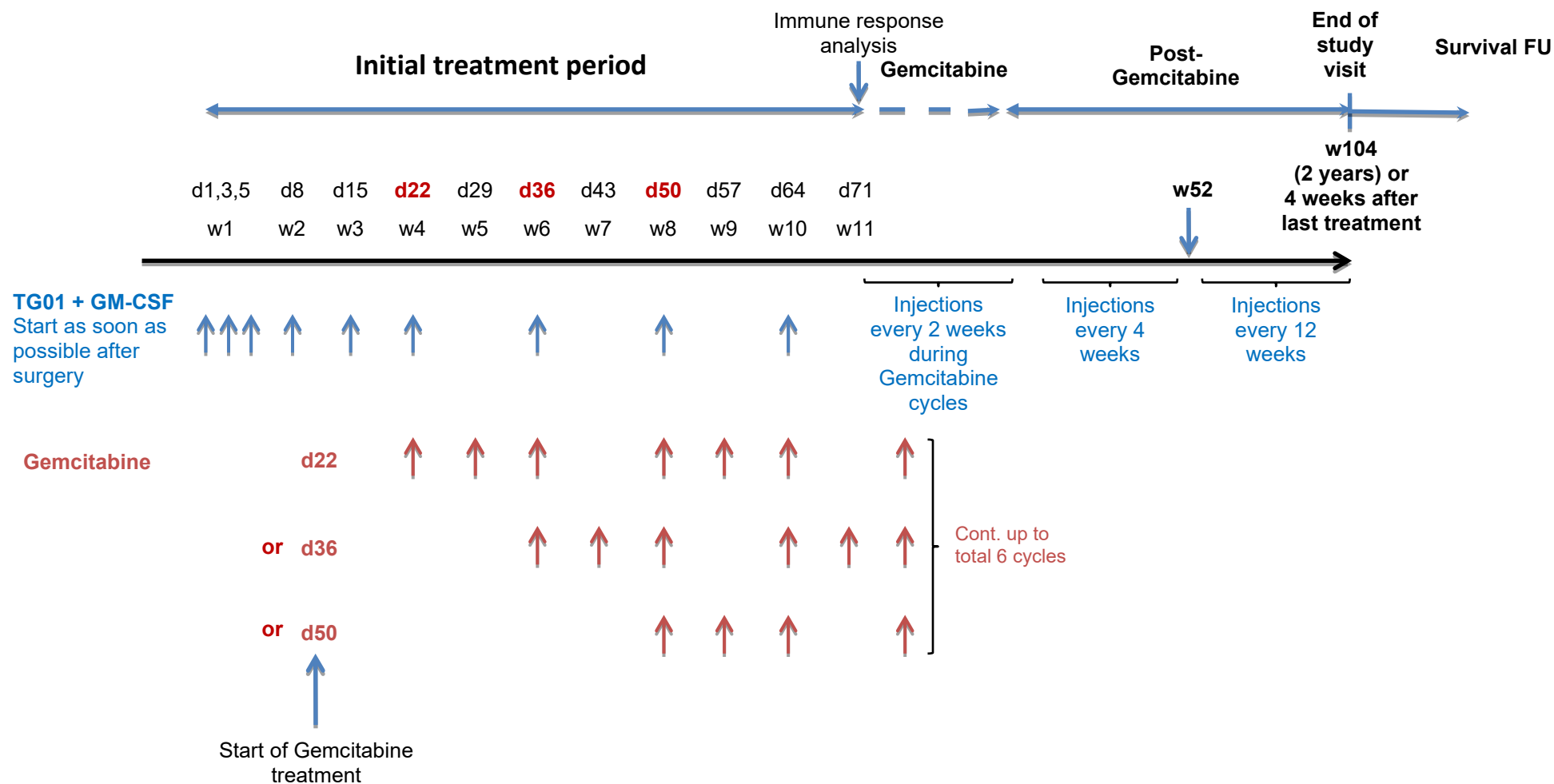


Figure 4: Treatment schedule for patients starting vaccination and chemotherapy at the same time – concomitant group

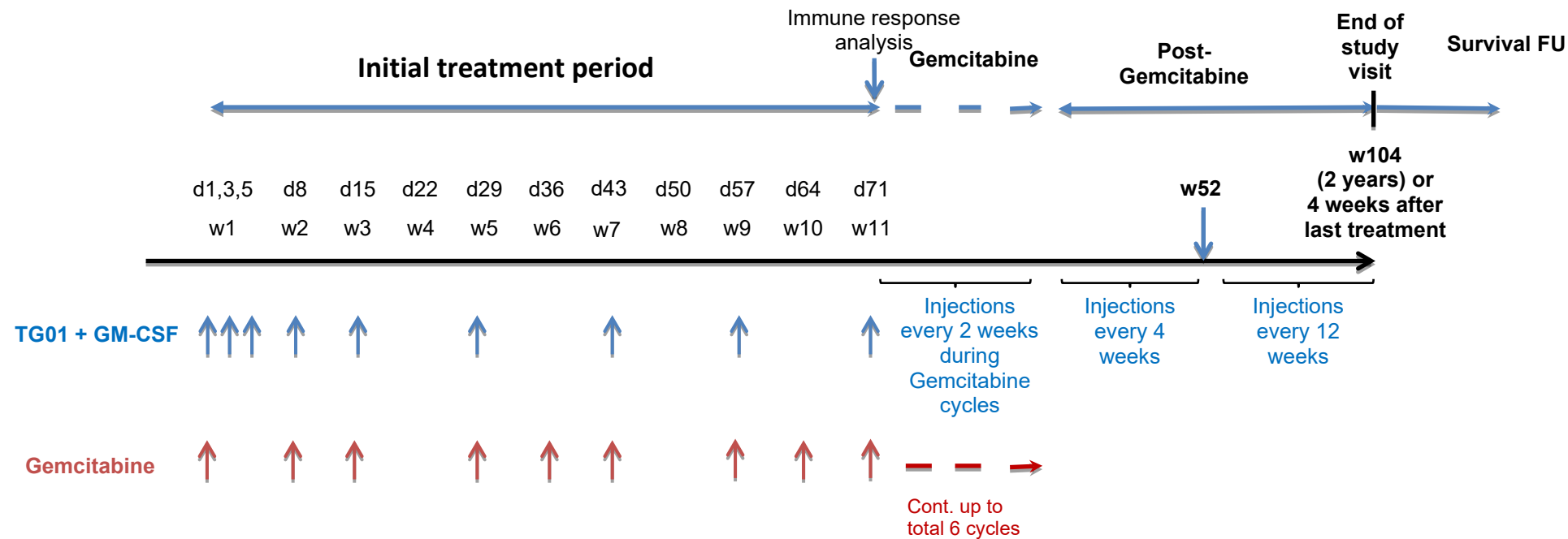


Figure 5: Treatment schedule for patients starting vaccination and receiving chemotherapy later – Modified vaccination group

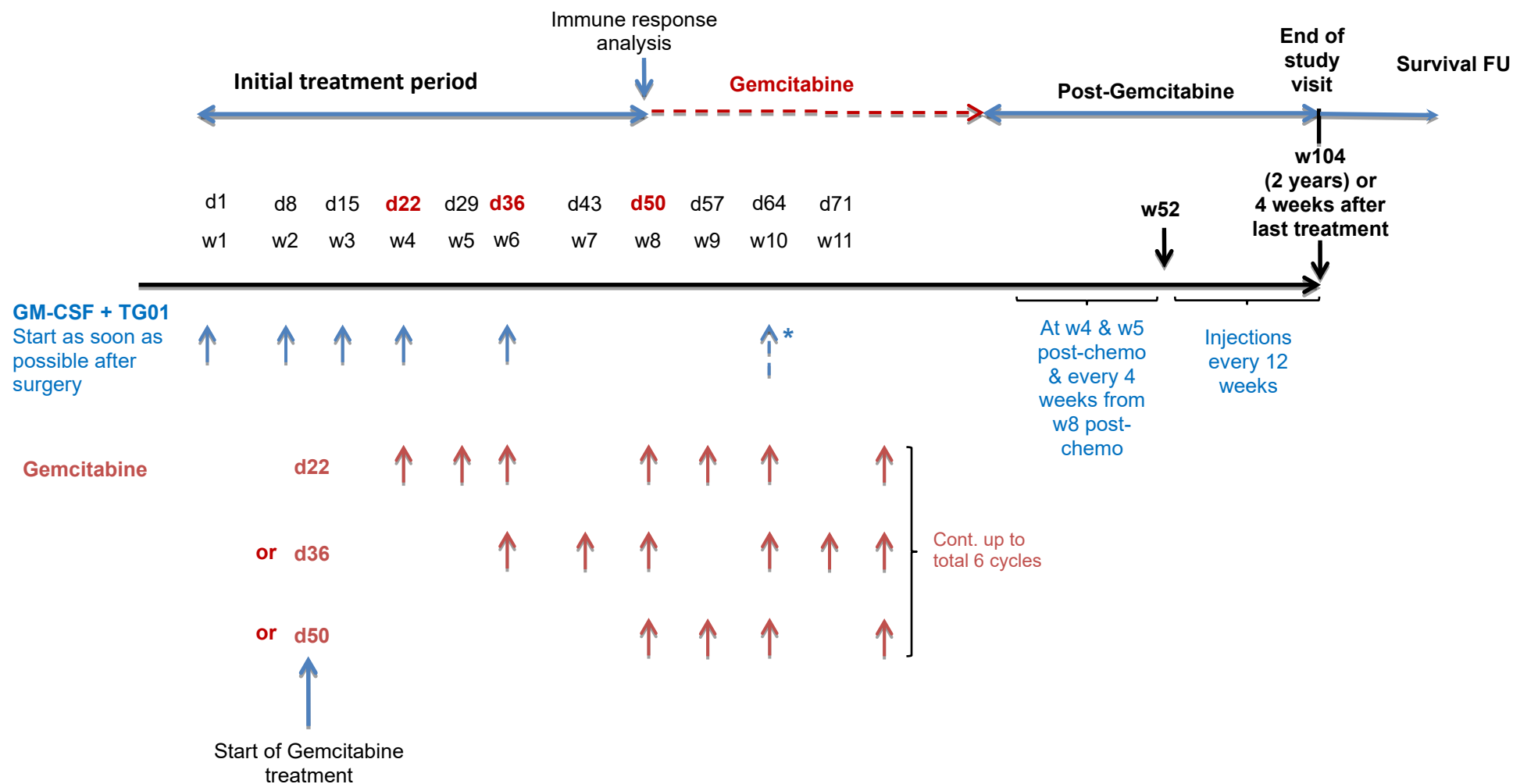


Table 1: Schedule of visits

	Page in protocol	Screening		Initial Treatment Period*												Repeat Cycles with chemotherapy*				After chemo to W52 ***	W52-104	Patient end of Study visit**	Survival FU		
Study Week (W)				1		1	1	2	3	4	5	6	7	8	9	10	11 ^j	1 5 9 13 17 21	2 6 10 14 18 22	3 7 11 15 19 23	4 8 12 16 20 24	Every 4 weeks**	Every 12 weeks **	W104 or 4 weeks after last TG01 / GM-CSF ^k	Every 6 months and at study end** Thereafter ~every 12 months
Study Day		-56 to -7	-7	1		3	5	8	15	22	29	36	43	50	57	64	71 ^j	Cycle D1	Cycle D8	Cycle D15	Cycle D22				
TG01 / GM-CSF ^a	51 to 59			x		x	x	x	x	x		x		x		x		x		x		x ⁿ	x ⁿ		
DTH injection ^b	51 to 59			x				x	x	x		x		x		x						x ^l	x ^e		
Gemcitabine ^c	51 to 59																	x	x	x					
5-FU and Leucovorin ^g	51 to 59																	x		x					
Informed Consent	60	x																							
Patient eligibility	60	x																							
Demography/Medical history	60		x																						
Resect pancreas	60	x																							
Tumour sample	60	x																							
ECG	61, 68		x	----- As clinically indicated ----->																					
Physical Exam/ PS	61, 68		x															x				x ^m	x ^e	x	
Vital Signs	61		x	x		x	x	x	x	x		x		x		x	x	x	x	x		x ^f	x	x	
Haematology / Chemistry ^d	61, 68		x	x			x			x		x		x		x		x	x	x		x ^f	x	x	
Pregnancy test	61		x																						
Concurrent illness	61		x																						
DTH assessment ^b	55, 66			x			x	x	x	x		x		x		x						x ⁱ	x ^e		
Immunology sample ^d	65, 66			x													x						x ^e	x	
CA19.9 / other biomarkers ^d	67			x														x				x ^l	x ^e	x	
Urinalysis	61, 68		x	----- As clinically indicated ----->																					
CT/MRI / assess disease ^h	61, 66		x	----- Every 6 months ----->																			x		
Adverse events	67, 71			----- As clinically indicated ----->																					
Concomitant medications	60, 61		x	----- As clinically indicated ----->																					
Survival follow-up																									x

- a: Start as soon as possible after surgery. GM-CSF given 10-15 min before TG01.
During chemotherapy treatment: every 2 weeks
After end of chemotherapy treatment may be given for up to 2 years or until withdrawal of consent, toxicity or the need for additional treatment for pancreatic cancer whichever is the earliest
Patients should be observed for at least 30 minutes after all vaccinations
- b: DTH injection should be performed 30 minutes before the GM-CSF/TG01 injection. Assessment of DTH injection site to be done 48 hours (+/- 4 hours) after each GM-CSF/TG01 injections.
- c: Start at Study Day 22, 36 or 50 (once patients are able to receive chemotherapy see repeated cycles)
- d: Blood samples to be taken prior to all treatments.
- e: At 52 weeks
- f: Every 12 weeks
- g: Given on Day 1 and 2 every 2 weeks. 5-FU/Leucovorin should be used as an alternative if required due to raised ALT.
- h: CT-scan to be done at baseline (if possible), then every 6 months from the start of vaccination (+/- 4 weeks' time window) and at end of the study visit.
- i: Only for patients who received chemotherapy. To be done at 2nd GM-CSF/TG01 injection after end of chemotherapy (8 weeks after last chemotherapy injection).
- j: can be done at day 78 if more appropriate
- k: For patients who discontinue before the 2 years, a survival follow-up will be performed where possible at week 104.
- l: Only for patients not starting chemotherapy at all and to be done prior each vaccination (every 4 weeks)
- m: for patients not starting chemo; to be done every 12 weeks
- n: For all GM-CSF/TG01 administrations after chemotherapy the patients should be give prophylactic treatment (30 minutes before treatment) to prevent possible occurrence of allergic reactions. At visits where the patients will receive a DTH injection(TG01) before the GM-CSF/TG01 administration then the prophylactic treatment should be given 30 minutes prior the DTH injection.

*: +/- 1 day window for visits in the initial treatment period and for other weekly visits (Initial treatment period or chemotherapy treatment period)

**: window of +/- 1 week for 4 weekly injections and 12 weekly injections

***: Applies also to patients not starting chemotherapy at all and the period will be from week 10 to week 52

Table 2: Schedule of visits – Concomitant group

	Page in protocol	Screening		Initial Treatment Period (1 st 3 Cycles of chemotherapy)*												Repeat Cycles with chemotherapy*				After chemo to W52	W52-104	Patient end of Study visit**	Survival FU							
Study Week				1		1	1	2	3	4	5	6	7	8	9	10	11	13 17 21	14 18 22	15 19 23	16 20 24	Every 4 weeks**	Every 12 weeks**	W104 or 4 weeks after last TG01 / GM-CSF ^k	Every 6 months and at study end** Thereafter ~every 12 months					
Study Day		-84 to -7	-7	1		3	5	8	15	22	29	36	43	50	57	64	71	Cycle D1	Cycle D8	Cycle D15	Cycle D22									
TG01 / GM-CSF ^a	51 to 59			x		x	x	x	x		x		x		x		x	x		x		x ^l	x ^l							
DTH injection ^b	51 to 59			x				x	x		x		x		x		x					x ^l	x ^e							
Gemcitabine ^c	51 to 59			x				x	x		x	x	x		x	x	x	x	x	x										
5-FU and Leucovorin ^e	51 to 59			x					x		x		x		x		x	x		x										
Informed Consent	60	x																												
Patient eligibility	60	x																												
Demography / Medical History	60		x																											
Resect pancreas	60	x																												
Tumour sample	60	x																												
ECG	61, 68		x	<----- As clinically indicated ----->																										
Physical Exam/ PS	61, 68		x	x							x				x			x					x ^e	x						
Vital Signs	61		x	x		x	x	x	x		x	x	x		x	x	x	x	x	x		x ^f	x	x						
Haematology / Chemistry ^d	61, 68		x	x				x	x		x	x	x		x	x	x	x	x	x		x ^f	x	x						
Pregnancy test	61		x																											
Concurrent illness	61		x																											
DTH assessment ^b	55, 66			x				x	x		x		x		x		x					x ^l	x ^e							
Immunology sample ^d	65, 66			x														x ^l					x ^e	x						
CA19.9 / other biomarkers ^d	67			x							x				x			x					x ^e	x						
Urinalysis	61, 68		x	<----- As clinically indicated ----->																										
CT/MRI / assess disease ^h	61, 66		x	<----- Every 6 months ----->																					x					
Adverse events	67, 71			<----- As clinically indicated ----->																										
Concomitant medications	60, 61		x	<----- As clinically indicated ----->																										
Survival follow-up																													x	

- a: GM-CSF given 10-15 min before TG01
After end of chemotherapy treatment may be given for up to 2 years or until withdrawal of consent, toxicity or the need for additional treatment for pancreatic cancer whichever is the earliest
Patients should be observed for at least 30 minutes after all vaccinations.
- b: DTH injection should be performed 30 minutes before the GM-CSF/TG01 injection Assessment of DTH injection site to be done 48 hours (+/- 4 hours) after each GM-CSF/TG01 injections.
- c: To start within 12 weeks from surgery
- d: Blood samples to be taken prior to all treatments.
- e: At 52 weeks
- f: Every 12 weeks
- g: Given on Day 1 and 2 every 2 weeks. 5-FU/Leucovorin should be used as an alternative if required due to raised ALT.
- h: CT-scan to be done at baseline (if possible), then every 6 months from the start of vaccination (+/- 4 weeks' time window) and at end of the study visit.
- i: at 2nd GM-CSF/TG01 injection after end of chemotherapy (8 weeks after last chemotherapy injection)
- j: at week 13 only (day 1 of cycle 4) prior study treatment administration
- k: For patients who discontinue before the 2 years, a survival follow-up will be performed where possible at week 104.
- l: For all GM-CSF/TG01 administrations after chemotherapy the patients should be give prophylactic treatment (30 minutes before treatment) to prevent possible occurrence of allergic reactions. At visits where the patients will receive a DTH injections (TG01) before the GM-CSF/TG01 administration then the prophylactic treatment should be given 30 minutes prior the DTH injection.

*: +/- 1 day window for visits in the initial treatment period and for other weekly visits (Initial treatment period or chemotherapy treatment period)

** : window of +/- 1 week for 4 weekly injections and 12 weekly injections

Table 3: Schedule of visits – Modified vaccination group

	Page in protocol	Screening		Initial Treatment Period*										Repeat Cycles with chemotherapy*				After chemo to W52 ***	W52-104	Patient end of study visit**	Survival FU
Study Week				1	2	3	4	5	6	7	8	9	10	1 5 9 13 17 21	2 6 10 14 18 22	3 7 11 15 19 23	4 8 12 16 20 24	Every 4 weeks **	Every 12 weeks **	W104 or 4 weeks after last GMCSF/TG01	Every 6 months and at study end** Thereafter ~every 12 months
Study Day		-56 to -7	-7	1	8	15	22	29	36	43	50	57	64	Cycle D1	Cycle D8	Cycle D15	Cycle D22				
GM-CSF /TG01 ^a	51 to 59			x	x	x	x		x				x ^b					x ^c	x		
DTH injection ^d	51 to 59								x		x							x ^e			
Gemcitabine ^f	51 to 59													x	x	x					
5-FU and Leucovorin ^g	51 to 59													x		x					
Informed Consent	60	x																			
Patient eligibility	60	x																			
Demography/Medical history	60		x																		
Resect pancreas	60	x																			
Tumour sample	60	x																			
ECG	61, 68		x	<----- As clinically indicated ----->																	
Physical Exam/ PS	61, 68		x											x				x ^h	X ⁿ	x	
Vital Signs	61		x	x	x	x			x		x		x ⁱ	x	x	x		x ^h	x	x	
Haematology/Chemistry ^j	61, 68		x	x		x			x		x		x ⁱ	x	x	x		x ^h	x	x	
Pregnancy test	61		x																		
Concurrent illness	61		x																		
DTH assessment ^d	55, 66								x		x							x ^e			
Immunology sample ^j	65, 66			x							x							x ^{i, j}	X ⁿ	x	
CA19.9 / other biomarkers ^j	67			x										x				x ^m	X ⁿ	x	
Urinalysis	61, 68		x	<----- As clinically indicated ----->																	
CT/MRI / assess disease ^k	61, 66		x	<----- Every 6 months ----->																x	
Adverse events	67, 71			<----- As clinically indicated ----->																	
Concomitant medications	60, 61		x	<----- As clinically indicated ----->																	
Survival follow-up	51 to 59																				x

- a: Start as soon as possible after surgery. GM-CSF given 15-20 min before TG01. Patients should be observed for at least 30 minutes after each vaccinations
- b: Patients that have not started chemotherapy by week 10 will receive GM-CSF/TG01 4-weekly, starting at week 10 and until start of chemotherapy or week 52 or withdrawal of consent, toxicity or the need for additional treatment for pancreatic cancer whatever comes first.
- c: After end of chemotherapy, GM-CSF/TG01 treatment will be given 4 and 5 weeks after last chemotherapy injection and thereafter every 4 weeks from 8 weeks post-chemotherapy up to 1 year (week 52) or until withdrawal of consent, toxicity or the need for additional treatment for pancreatic cancer whichever is the earliest.
- d: DTH injection should be performed 30 minutes before the GM-CSF injection. Assessment of DTH injection site to be done 48 hours (+/- 4 hours) after the TG01 and GM-CSF injections.
- e: After end of chemotherapy, a DTH injection and DTH assessment will be done at 3rd vaccination post-chemotherapy (8 weeks post chemotherapy). For patients not starting chemotherapy at all, the DTH test and assessment are to be done at week 52
- f: Start preferably 3 weeks after start of vaccination and preferably at Study Day 22, 36 or 50 (once patients are able to receive chemotherapy see repeated cycles) although can start later
- g: Given on Day 1 and 2 every 2 weeks. 5-FU/Leucovorin should be used as an alternative if required due to raised ALT.
- h: Every 12 weeks
- i: When blood samples are to be taken these should be done prior to all treatments.
- J: only 4 weeks after last chemotherapy injection (at 1st post-chemotherapy vaccination)
- k: CT-scan to be done at baseline, then every 6 months from the start of vaccination (+/- 4 weeks' time window) and at end of the study visit. CT scans may be done at other times if clinically indicated
- l: If patient hasn't started chemotherapy
- m: Only for patients not starting chemotherapy at all and to be done prior each vaccination (every 4 weeks)
- n: at week 52 only

*: +/- 1 day window for visits in the initial treatment period and for other weekly visits (Initial treatment period or chemotherapy treatment period)

** : window of +/- 1 week for 4 weekly injections and 12 weekly injections

***: Applies also to patients not starting chemotherapy at all and the period will be from week 10 to week 52

3.2 Rationale for trial design, doses and stop decisions

3.2.1 Trial design

Whilst not registered, gemcitabine is the main chemotherapy used as adjuvant treatment following resection of pancreatic adenocarcinoma. It is rational therefore, to see whether the use of immunotherapy added to this regimen can improve on the disease-free survival and potential overall survival of this condition. However, before this, it is important to assess whether there is any interference with the immune response when TG01 is used concomitantly with gemcitabine.

3.2.2 Rationale for dose

The traditional approach to dose selection for cytotoxic anticancer agents is to escalate the dose until dose 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. TG01 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.

In a clinical study (CTN RAS 98010) a total of 38 pancreatic cancer patients, 13 after tumour resection and 25 with advanced disease, have been treated with TG01 with minimal toxicity and with good immunological outcome. In the resected group, 11 of 11 (100%) evaluable patients demonstrated an immune response (DTH response), and in the advanced disease group 14 of 25 (56%) patients demonstrated a positive DTH response. In this study the immunotherapy dose was 0.7 mg (0.1 mg of each peptide) and 30 µg GM-CSF was used as an immunomodulator (Weden et al., 2011).

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, the clinical development will continue using a total TG01 dose of 0.7 mg (0.1mg each peptide) together with GM-CSF as immunomodulator.

3.2.3 Rationale for GM-CSF (Molgramostim) adjuvant

Peptides are poorly immunogenic by themselves. To induce measurable levels of T-helper type 1 (Th1) or type 2 (Th2) immune responses against peptides, adjuvants are often required (Gupta et al., 1996). Several adjuvants have been evaluated in humans for adjuvant activity when combined with carbohydrate and protein/peptide-based immunotherapy (Gupta et al., 1995; Singh & O'Hagan 1999). However, the only adjuvant licensed for use in human vaccines, aluminium hydroxide (Gupta et al., 1995) is a poor enhancer of the type of immune responses (Th1) that may be required for the efficacy of peptide-based ASCI, and, therefore, could not be selected for TG01 development. Studies in rats show that GM-CSF administered intradermally as a single dose with antigens, compared favourably with complete Freund's adjuvant and aluminium hydroxide in eliciting cellular immunity (Disis et al., 1996).

GM-CSF has a number of biological properties making it a strong candidate to function as an immunomodulator for ASCI. It has been shown that GM-CSF can drive both humoral and cellular immune responses (Disis et al., 1996). Moreover, GM-CSF has been shown to induce anti-tumour immunity that has been associated with the induction of a broader T cell cytokine response (both Th1 and Th2), which has been implicated as important in mediating tumour rejection (Hung et al., 1998; Mach et al., 2000; Soiffer et al., 1998).

GM-CSF was selected as the immunomodulator for the development of TG01 based on its reported potent adjuvant activity when given in combination with protein/peptide antigens (Dranoff et al., 1993; Gjertsen et al., 1995; Hunger et al., 2001). Studies in mice (Dranoff et al., 1993) have shown that T-cell responses could be generated in mice bearing human pancreatic tumour xenografts. Potent anti-tumour activity was shown in patients with metastatic melanoma following injection of autologous melanoma immunotherapy combined with GM-CSF (Leong et al., 1999).

GM-CSF has during recent years been used extensively as an immunomodulator for ASCI in clinical trials. GM-CSF has either been used alone (Gjertsen et al., 2001; Bernhardt et al., 2006, Dutoit et al., 2002; Lomas et al., 2004; Schaed et al., 2002; Disis et al., 1999; Hunger et al., 2001; Brunsvig et al., 2006) or in combination with other adjuvants (Chianese-Bullock et al., 2005), normally in the range of 30-250 µg/injection. The dose to be used in this study is 30 µg which is consistent with a stimulatory effect of low doses of GM-CSF (Parmiani G et al., 2007).

3.2.4 Rationale for dose regimen

ASCI requires a more aggressive and continued treatment than traditional vaccination (prophylaxis) against infectious diseases. In vaccination the antigens used are foreign to the human immune system, the vaccinated subjects are healthy with normal immune functions and the induced immune response is allowed to down-regulate to a memory response ready to be reactivated upon a challenge. In contrast to this, in ASCI the tumour associated antigens (TAA) that are used are "self", or in the case of RAS peptides, slightly altered "self" protein/peptides to the treated subject and consequently immunological tolerance is much more difficult to break in this setting. The treated subjects are cancer patients that normally develop immune suppression and often have a rapid deteriorating immune system and, finally, a prevailing active anticancer immune

response is necessary in order to kill the cancer cells which on their side are continuously counteracting the anti-cancer immune response by inducing immune suppression.

The scenario described above is highly relevant for patients with pancreatic cancer who have a short life expectancy and a rapidly deteriorating immune system. In order to meet the challenges of inducing immune response in a limited time window available, the rapid disease progression and deterioration of the immune system, it is important to use an aggressive treatment regimen in order to induce efficient immune response as fast as possible and to keep the induced anti-cancer immune response in an active state. Whilst, complete resection and cure is the aim of pancreatic surgery, in reality this is rarely the case and the need for a rapid immune response to “mop” up any residual cancer cells add an urgency even in this setting.

In vaccination either subcutaneous or intramuscular administration are normally used, and the vaccine is usually formulated with an adjuvant that provides a depot of antigens as well causing irritation and inflammatory reactions at the site of injection. In order to obtain optimal immunisation with TG01 the intradermal administration route is used. The resident Langerhans cells in the dermis are highly potent antigen presenting cells with strong capacity to endocytose antigens and to elicit subsequent T cell responses.

Intradermal injection is accordingly the preferred route of administration ASCI intended to result in protective T-cell immunity. Due to the architecture (thickness) of the skin only small volumes may be injected at a single site and irritants causing ulceration must be avoided. TG01 is reconstituted in water for injection and administered without any substances that provide a depot effect. The only “pharmacologically active” dose of peptides to reach the lymph nodes is the amount of peptides taken up by Langerhans cells locally before the injected peptides are degraded by tissue proteases. After migrating to the draining lymph nodes the activated Langerhans cells have a very limited life span. Thus each administration is followed by only a short period of expansion of specific T-cells before the stimulus is lost. In the absence of a depot effect and thus a continued release of antigen and stimulation of T-cells, repeated immunizations over an extended time period is required to generate a robust immune response. This will ensure a continued activation and expansion of antigen specific T cells to kill resident tumour cells and to replace T-cells that are tolerised/anergised by the tumour.

The dosing regimen was developed using ASCI as standalone treatment but the rationale behind also applies when combined with chemotherapy. However, it is known that many anti-cancer chemotherapies also act via immunological pathways and, therefore, there is a potential synergy between chemotherapy and active immunotherapy for cancer (Lesterhuis et al., 2011). For adjuvant treatment of pancreatic cancer TG01 will be used in combination with gemcitabine. It has been shown in mice that gemcitabine can modulate antigen-specific anti-tumour immune responses by enhancing cross presentation of tumour antigens to MHC class I and class II-restricted T-cells (Nowak et al., 2002). In other animal studies gemcitabine could counteract immune suppression by depressing myeloid suppressor cells (Suzuki et al., 2005.) and successfully be combined with immunotherapy to yield synergistic anti-tumour effects (Nowak et al., 2003; Broomfield et al., 2005). When combined with gemcitabine, the TG01 treatment regimen is adapted in order to optimize the potential synergistic effects of the two treatments.

Adjuvant gemcitabine treatment of pancreatic cancer is given in cycles of three weeks treatment and one week rest for up to six cycles (ESPAC3), starting within 8 weeks after the resection has been done (Van Laethem et al., 2010; Neoptolemos et al., 2010; Oettle et al., 2007). It is considered to be beneficial for the patients to obtain an anti-cancer immune response as soon as possible after surgery and TG01 treatment will therefore be started as soon as possible but certainly between 1 to 8 weeks after the tumour has been removed. Gemcitabine treatment will be started together with TG01 treatment preferably at least 3 weeks after initiation of TG01 immunotherapy. From when gemcitabine treatment is initiated TG01 will either be administered as booster injections every 2 weeks or will be put on hold until end of chemotherapy. In patients who have not shown recurrence or who had a positive immune response during the study treatment period, further booster injections will be given after gemcitabine has been completed.

The current study started 2 years ago and patients in the main group participating for the whole length of the study (up to 2 years), could receive 26-28 vaccinations with GM-CSF/TG01 as a maximum and an additional 9 injections of TG01 (see tables 1 and 2) for the purpose of detecting an immune response (which is the goal of the TG01 treatment). Vaccination started either before or at the same time as chemotherapy treatment and continued during chemotherapy and post-chemotherapy where possible. In total 19 patients were recruited under this treatment regimen and so far all except one patient have shown a positive immune response during the course of the study. It was also observed that 4 patients receiving this treatment regimen experienced allergic reactions related to TG01 or GM-CSF/TG01 after they received several injections. This type of allergic reactions are not uncommon when using these types of medications and, when they occur, can be usually prevented by using pre-medication with an antihistamine. It is believed that the number of vaccinations could be, in part, responsible for these events and as positive immune responses were clearly seen with the previous vaccination schedule, Targovax believe that the same immune response can be obtained with a reduced number of vaccinations, which will be tested in the proposed modified vaccination group. In addition, vaccinations during chemotherapy with gemcitabine will be reduced. Once an immune responses has been obtained by vaccinating up to 6 weeks and gemcitabine has been started, vaccination will be put on hold until chemotherapy completion. Vaccination will be restarted after chemotherapy has been completed.

3.2.5 Use of Gemcitabine as adjuvant chemotherapy

Gemcitabine has been shown to provide significantly better Disease Free Survival (DFS) versus observation alone with a mean DFS of 13.4 months compared with 6.9 months although there was no difference for overall survival (median OS 22.1 months (Oettle et al., 2007)).

The use of 5-FU and folinic acid or gemcitabine-based chemoradiation has also been tested as adjuvant therapy but show no advantages over gemcitabine alone for either DFS or OS. The DFS for gemcitabine alone ranged from 10.9 months to 14.3 months and median OS from 23 to 24.4 months. The length of treatment ranged from 4-6 cycles (i.e. up to 25 weeks) at a dose of 1000 mg/m² (Neoptolemos et al., 2010; Van Laethem et al., 2010). The start of the gemcitabine adjuvant treatment was up to 8 weeks following surgery.

Therefore, it seems appropriate to use gemcitabine as the primary chemotherapy for adjuvant treatment and provides a reasonable basis on which to compare disease-free and overall survival. However, considering that gemcitabine treatment may result in increased ALT/AST, patients may, in these instances, stop gemcitabine and take 5-FU/Leucovorin and continue GM-CSF/TG01 as planned per protocol or start with 5-FU/Leucovorin if the enzymes are high at the outset.

3.3 Selection of trial population

6-32 patients with histologically or cytologically confirmed diagnosis of resected adenocarcinoma of the pancreas will be enrolled and treated with GM-CSF/TG01 with the intention of combining with gemcitabine as adjuvant chemotherapy.

3.3.1 Inclusion criteria

For inclusion in the trial, patients must fulfil the following protocol entry criteria:

1. Histologically or cytologically confirmed diagnosis of adenocarcinoma of the pancreas
2. Stage I or II disease (clinical stage T1-3, N0-1, M0 by AJCC staging criteria).
3. Successful surgical resection
 - Complete resection (R0) or with microscopic residual disease (R1)
 - Expected to receive gemcitabine monotherapy as adjuvant chemotherapy
4. Laboratory Values:
 - Absolute neutrophil count $\geq 1.5 \times 10^9/l$
 - Platelets $\geq 100 \times 10^9/l$
 - Haemoglobin ≥ 9 g/dl
 - Total bilirubin $\leq 1.5 \times$ UNL
 - Serum creatinine $\leq 1.5 \times$ UNL
 - Albumin ≥ 2.5 g/dl
 - AST or ALT $\leq 5 \times$ UNL
5. 18 years of age or older.
6. ECOG performance status (PS) of 0-1.
7. Life expectancy of at least 6 months
8. Men and women of childbearing potential must be willing to use effective methods of contraception to prevent pregnancy
9. Provide written (signed) informed consent to participate in the trial prior to any trial specific screening procedures

3.3.2 Exclusion criteria

Patients are not eligible for inclusion in this trial if they meet one or more of the following criteria:

1. Has received an investigational drug within 4 weeks prior to Trial drug administration
2. Has received previous therapy for pancreatic cancer including radiation or chemotherapy (except for the primary resection or primary neoadjuvant chemotherapy).
3. 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).
4. Has any other serious illnesses or medical conditions such as, but not limited to:

- Any uncontrolled infection
 - Uncontrolled cardiac failure classification III or IV (NY Heart Association)
 - Uncontrolled systemic and gastro-intestinal inflammatory conditions
 - Bone marrow dysplasia
 - History of auto-immune disease
 - History of adverse reactions to vaccines
5. Known history of positive tests for HIV/AIDS, hepatitis B or C
 6. Pregnant or lactating females or have no pregnancy test at baseline (postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential).
 7. Contraindication to gemcitabine treatment
 8. Have had any other malignancies within last 3 years (except for adequately treated carcinoma of the cervix or basal or squamous cell skin cancer)
 9. Known malignant brain lesion(s)
 10. Are unlikely to start chemotherapy within 12 weeks of surgery (e.g. delayed wound healing, or infection, etc.)
 11. Are not expected to complete 6 cycles of chemotherapy
 12. Are planned to receive yellow fever or other live (attenuated) vaccines during the course of study (see concomitant medication section)

3.3.3 Removal of patients from the trial, therapy or assessment

If a patient has to be withdrawn from the trial, the principal investigator (PI) should be informed immediately. If there is a medical reason for the withdrawal, the patient should be followed until the condition has either resolved itself or is stable and the individual concerned is able to resume care by his/her physician. Details of the reason for withdrawal should be recorded in the patient's Case Report Form.

All patients should continue to be included in the assessments of their safety and efficacy. Patients who withdraw should, if possible, have a follow-up examination (withdrawal visit), including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests. All details of this follow-up examination should be recorded in the patient's medical source documents. Then unless patients withdrew their consent, a survival follow-up visit should be done every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.

3.3.3.1 Patient withdrawal

Participation in the trial is strictly voluntary. Patients are free to discontinue the trial at any time without giving their reason(s). If a patient withdraws from the trial, the Investigators are to be informed immediately.

A patient must be withdrawn from the trial treatment in the event of any of the following:

- withdrawal of the patient's consent
- 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
- recurrence of pancreatic cancer with no immune response

- occurrence of AEs, if discontinuation of trial medication is desired or considered necessary by the Investigator and/or patient (if applicable)
- occurrence of pregnancy
- intake of non-permitted concomitant medication as defined in Section 4.6 where the predefined consequence is withdrawal from the trial
- lack of patient compliance
- protocol violation

If a patient fails to attend scheduled assessments during the course of the trial, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the patient's medical source documents.

All patients who withdraw from the trial for any reason and at any time should have an end of study examination (withdrawal visit). Patients will be examined for any status changes that require further follow-up. Any new medical condition or event occurring during the trial will be followed until the patient is stable and able to resume care by his/her physician.

3.3.3.2 Trial discontinuation

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- occurrence of AEs unknown to date in respect of their nature, severity and duration, or the unexpected incidence of known AEs
- medical or ethical reasons affecting the continued performance of the trial
- difficulties in the recruitment of patients
- cancellation of drug development.

3.3.3.3 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up.

All patients who have new or worsening Common Toxicity Criteria (CTC version 4) grade 3 or 4 laboratory values at the time of discontinuation must have further laboratory tests performed and the results recorded on the appropriate CRF until the laboratory values have returned to 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 patient's medical records.

Laboratory abnormalities should **not** be reported as adverse events unless any criterion for an AE is fulfilled i.e. that it is clinically significant and because it is detrimental to the patient, the laboratory abnormality causes study drug dose adjustment, leads to patient's discontinuation from the study, or the investigator insists the abnormality should be reported as an AE. Laboratory abnormalities should not be reported as separate adverse events if they are part of an overall diagnosis (e.g. fever and leucocytosis for pneumonia).

At discontinuation all on-going study-related toxicities and SAEs must be followed until resolution, unless in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

After discontinuation from treatment, patients must be followed up for all existing and new AEs for 28 calendar days after the last dose of study drug. All new AEs occurring during that period must be recorded (if SAEs they must be reported to [REDACTED] within 24 hours (Fax Number: [REDACTED]) and followed up for resolution as above. Life-threatening or fatal events occurring prior to document recurrence should be reported to the Medical Monitor by calling [REDACTED] within 2 hours of knowledge of the event.

Should protocolled dosing be stopped during the study, the principal investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the CRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation and also course, treatment and outcome after discontinuation. They will also immediately inform the CRA of the discontinuation. Any SAE should be communicated to [REDACTED] according to the procedures defined in Section 7.3.

3.4 Time schedule

Screening must be completed within the 56 days prior to the start of treatment for the main group and the modified vaccination group and within 84 days for the concomitant group. Patients will be required to attend the clinic for the administration and evaluation of their therapy (See Section 3.1). For each administration of study drug, patients will be observed for at least 30 minutes after each injection of TG01. Hospitalisation for administrative reasons will be at the investigator's discretion, in accordance with hospital standard procedures and will not be considered as a serious adverse event.

Safety will be monitored for each patient throughout the trial until their end of study visit which will be 28 days after their last GM-CSF/TG01 or chemotherapy dose, whichever is appropriate.

For all patients, where possible, a survival follow-up will be performed every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.

4. TRIAL TREATMENT

4.1 Identity of the investigational product

TG01 is a sterile lyophilisate consisting of a mixture of seven peptides. The finished product is a white powder for injection, consisting only of the active substances containing 2.1 mg of peptides (individual peptides comprising 0.3 mg each). The lyophilisate is to be reconstituted with sterile water for injection before use.

GM-CSF is provided as a lyophilised powder containing 0.1 mg of active substance for reconstitution in sterile water for injection to be given via intradermal injection.

Gemcitabine is provided as a lyophilised powder (vials of 200 mg and 1 g) for reconstitution in saline to be given via intravenous injection. To be reconstituted according to Prescribing Information for gemcitabine.

5-FU is provided as a solution for intravenous injection (vials of 500mg in 10 mL). To be administered according to the Prescribing Information for 5-FU.

Leucovorin is provided as a solution for intravenous injection (10mg/ml). To be administered according to Prescribing Information for Leucovorin.

All handling of the Investigational Medicinal Product at the supply company and at site should be in compliance with normal handling of sterile products for injection and should follow the to the current Good Manufacturing Practice (GMP) guidelines.

Further descriptive information on the products can be found in the IB.

4.1.1 Packaging and labelling of the investigational product

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

4.1.1.1 TG01

TG01 will be packaged and labelled by [REDACTED], a specialised pharmaceutical clinical supply company located in [REDACTED], in accordance with 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 a box containing a defined number of vials.

TG01 will be shipped to the investigational sites under controlled, frozen (-20 °C) conditions.

4.1.1.2 GM-CSF

GM-CSF will be package and labelled by [REDACTED], a specialised pharmaceutical clinical supply company located in [REDACTED], in accordance with 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 a box containing “a defined number of vials”.

GM-CSF will be shipped to the investigational site(s) under controlled, refrigerated conditions (2 -8°C).

4.1.1.3 Chemotherapy

Commercially available chemotherapy (gemcitabine or 5-FU and Leucovorin) will be used.

4.1.2 Storage, issue, and return of investigational product

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. A copy of the signed receipt will be kept in the trial files.

TG01 must be kept frozen at -20 °C and GM-CSF must be kept at 2-8 °C during storage prior to reconstitution. After reconstitution the materials can be kept at room temperature for 6 hours at all sites with the exception of GM-CSF in the UK where the drug is to be kept refrigerated at 2-8°C for 6 hours. All study drugs are to be stored safely and separately from other drugs. The trial medication may not be used for any purpose other than the present trial, since the insurance coverage shall otherwise become null and void. 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. 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.

4.2 Assignment of patients to treatment

Patients are to be registered and assigned to treatment after written informed consent has been obtained and all pre-trial evaluations have been completed. Patient eligibility should be documented on the patient eligibility CRF page.

4.3 Preparation of trial treatment

4.3.1 TG01

TG01 is provided in 2R glass vials containing 2.1 mg of TG01 and the content of one vial of TG01 shall be dissolved in 0.3 mL of sterile water for injection (7 mg/mL). The solution is to be used within 6 hours after reconstitution.

4.3.2 GM-CSF

GM-CSF is provided in vials containing 0.1 mg and the content of one vial shall be dissolved in 0.33 mL of sterile water for injection (0.30 mg/mL). The solution is to be used within 6 hours after reconstitution.

4.3.3 Chemotherapy

Gemcitabine will be administered at a dose of 1000 mg/m². The drug will be provided in vials of 200 mg and 1 g for reconstitution in saline to be given via intravenous injection. If gemcitabine is replaced by 5-FU and Leucovorin:

- 5-FU will be administered at 500mg/m²
 - Leucovorin will be administered at 60mg/m² or 100mg
- 5-FU/Leucovorin will be prepared in accordance with the standard procedure at the institution.

4.3.4 DTH

The content of one vial of TG01 shall be dissolved in 0.3 mL sterile water for injection. The solution is to be used within 6 hours after reconstitution.

4.4 Dosage and administration of trial treatment

4.4.1 GM-CSF/TG01 dose and administration

Phase I and phase II part - main group: GM-CSF/TG01 will be given on days 1, 3, 5, 8, 15, 22 and every 2 weeks until end of chemotherapy (with day 1 defined as the first day of TG01 treatment which should be 1-8 weeks after surgery). For those patients who do not receive chemotherapy vaccination will continue as above until week 10 and then 4-weekly.

Phase II part – concomitant treatment group: GM-CSF/TG01 will be given on days 1, 3, 5, 8, 15 and every 2 weeks until end of chemotherapy (with day 1 defined as the first day of GM-CSF/TG01 treatment which should be 9-12 weeks after surgery).

Phase II part – modified vaccination group: GM-CSF/TG01 will be given on days 1, 8, 15, 22 and 36 then if chemotherapy hasn't started, 4-weekly until the start of chemotherapy at which point vaccination will be put on hold until the end of chemotherapy treatment. Patients who do not start chemotherapy at all will continue to receive 4-weekly vaccinations from week 10 to week 52.

Main group and concomitant group: After the end of chemotherapy, in patients who have not shown recurrence during the study treatment period, further booster injections will be given every 4 weeks until week 52 and then every 12 weeks for up to 2 years or until withdrawal of consent or toxicity whichever is the earliest. In patients who recur and a positive immune response has been seen during the treatment period, further booster injections should be given every 4 weeks until week 52 and then every 12 weeks for up to 2 years or until withdrawal of consent or toxicity whichever is the earliest. For all these GM-CSF/TG01 booster injections the patients should be given prophylactic treatment, 30 minutes prior to the GM-CSF injection (see section 4.5.3).

Modified vaccination group: after the end of chemotherapy, GM-CSF/TG01 will be given 4 weeks and 5 weeks after end of chemotherapy and then every 4 weeks from week 8 post-chemotherapy until week 52 and then every 12 weeks for up to 2 years or until withdrawal of consent or toxicity whichever is the earliest. In patients who recur and a positive immune response has been seen during the treatment period, further booster injections should be given as per schedule for up to 2 years or until withdrawal of consent or toxicity whichever is the earliest. No prophylactic treatment will be required unless an allergic reaction occurs and further vaccinations will be given.

The TG01 dose is 0.70 mg (0.10 mL injection of a TG01 solution at 7 mg/mL) reconstituted in water for injection GM-CSF dose is 0.03 mg (- 0.10 mL injection of a GM-CSF solution at 0.3 mg/mL) reconstituted in water for injection

Both study drugs will be intradermal injections into the back of the upper arm with GM-CSF administered 10-15 min before the injection of TG01. Patients should be observed for at least 30 minutes after all vaccinations.

4.4.2 Chemotherapy

Phase I and phase II part - main group and modified vaccination group: Patients will receive chemotherapy starting at least 3 weeks after initiation of GM-CSF/TG01 (Day 22, 36 or 50 of the initial treatment period) and in the **main group** chemotherapy should not start later than 12 weeks from the date of surgery; the day of the first dose will be considered Day 1 of the chemotherapy treatment period.

In part II, patients for whom chemotherapy timing cannot be assured will start vaccination as soon as the vaccination schedule can be adhered to and will receive chemotherapy or not according to their needs.

Phase II part – concomitant group: patients who for medical reasons cannot start vaccination early will start chemotherapy at the same time as GM-CSF/TG01 and not later than 12 weeks from the date of surgery; the day of the first dose will be considered Day 1 of the chemotherapy treatment period.

Gemcitabine will be given as 1000 mg/m² iv over 30 minutes on days 1, 8 and 15 of a four week cycle for 6 cycles in total.

If 5-FU/leucovorin needs to be substituted this will be given as 500 mg/m² iv on days 1 and 2 every 2 weeks of a four week cycle for 6 cycles in total.

Leucovorin will be given prior 5-FU as 60 mg/m² or 100 mg iv on days 1 and 2 every 2 weeks of a four week cycle for 6 cycles in total.

4.4.3 DTH

Phase I and phase II part - main group: During the initial period, TG01 will be given on days 1, 8, 15, 22, 36, 50, and 64 in the lower area of the contralateral arm. TG01 will then be administered at the 2nd GM-CSF/TG01 injection after the end of chemotherapy (8 weeks after the last chemotherapy injection) for patients receiving chemotherapy and at week 52 for all patients. At post-chemotherapy visits prophylactic treatment should be given 30 minutes prior the DTH injection (see section 4.5.3).

Phase II part – concomitant group: During the initial treatment period, TG01 will be given on days 1, 8, 15, 29, 43, 57, and 71 in the lower area of the contralateral arm. TG01 will then be administered at the 2nd GM-CSF/TG01 injection after the end of chemotherapy (8 weeks after the last chemotherapy injection) and at week 52. At post-chemotherapy visits prophylactic treatment should be given 30 minutes prior the DTH injection (see section 4.5.3).

Phase II part – Modified vaccination group: During the initial period, TG01 will be given on days 36 and 50 in the lower area of the contralateral arm. TG01 will then be administered at the 3rd GM-CSF/TG01 injection after the end of chemotherapy (8 weeks after the last chemotherapy injection). For patients not receiving chemotherapy an additional TG01 injection will be given at week 52.

The DTH-test dose must be prepared on the day of treatment and is to be given 30 minutes before GM-CSF/TG01 injection (GM-CSF is to be administered 10-15 min before the injection of TG01 in the main group and in the concomitant group and 15-20 min before the injection of TG01 in the modified vaccination group).

DTH dose: 0.10 mL of TG01 at 7 mg/mL water for injection solution must be prepared for intradermal injection in a sterile syringe.

4.4.4 Chemotherapy dosing criteria

Gemcitabine:

Before the administration of gemcitabine at the start of each new treatment cycle patients must be assessed to ensure that they satisfy the gemcitabine prescribing information of the country where the study is conducted or should follow the below criteria if no instructions are available.

- Granulocytes count $\geq 1.5 \times 10^9/L$ for 1st cycle and $\geq 1 \times 10^9/L$ for following cycles
- platelets $> 100 \times 10^9/L$
- Laboratory evaluation of renal and hepatic function, including serum creatinine should be within 1.5 x UNL

5-FU and Leucovorin: Dosing criteria should follow the standard procedure at the institution

4.5 Management of Toxicity

4.5.1 Anticipated toxicity and management

TG01 or its individual peptides have been given only to patients with pancreatic or colorectal cancer. Therefore, the majority of adverse events and serious adverse events have been related to progression of their disease or concomitant medications. Several cases of local reactions of erythema and induration have been reported and more recently four patients experienced allergic reactions related to TG01 or TG01/GMCSF. Two of them experienced a serious adverse event of anaphylaxis soon after TG01 administration considered to be related to the GM-CSF/TG01 injections or TG01 alone. The third patient experienced on 2 occasions symptoms of an allergic reaction approximately 10 min after injections (GM-CSF/TG01). The last patient experienced dizziness, lightheaded, puffiness of both eyes following GM-CSF/TG01 before starting gemcitabine treatment. The mechanism for the anaphylactic reactions occurring so long after the start of vaccination, but following the course of gemcitabine, and its similarity to the two other cases where gemcitabine has been given for at least 3-4 cycles, might suggest some association as yet unexplained.

In addition flu-like symptoms (including fever), headaches, urticaria and oedema may occur. Back pain, nausea and diarrhoea have also been reported as treatment related and there were 2 related serious adverse events of arthritis and hypoglycaemia. It is difficult to dissociate abnormal (Grade 3/4) laboratory toxicities from the patients' underlying disease or medications and in study 98010, which uses all of the peptides of TG01, there were 3 events of granulocytopenia, raised alkaline phosphatase and raised gamma-GT. However, there were only 13 patients in this category so carefully monitoring of haematology and biochemistry is required.

GM-CSF is generally well tolerated and, with the low dose anticipated may have few if any adverse reactions. However, in previous studies the most common adverse events are: transient myalgia, weakness, mild fatigue, rashes, and mild erythema at the site of injection.

Gemcitabine: Most frequent toxicities reported with gemcitabine given as single agent are myelosuppression, nausea and vomiting, transient elevations of one or both serum transaminases, proteinuria and haematuria and a few cases of haemolytic uraemic syndrome (HUS), fever frequently associated with other flu-like symptoms, rash, dyspnoea, oedema, flu-like symptoms with or without fever, infection, alopecia and paresthesias.

5-FU: most frequent toxicities reported with 5-FU are stomatitis, oesopharyngitis, diarrhoea, anorexia, nausea and emesis, alopecia, dermatitis and leucopenia.

Leucovorin: most frequent toxicities reported with Leucovorin are diarrhoea, stomatitis, myelosuppression, skin rash, hives, pruritus and wheezing (although rare).

4.5.2 Chemotherapy dose interruption/reduction

Gemcitabine

Institutions should follow the manufacturer's instructions for dosing modification for the country in which the study is being conducted.

If gemcitabine is delayed, GM-CSF/TG01 should be continued as planned.

If gemcitabine treatment is stopped, GM-CSF/TG01 may continue as described in section 3.1.

If no instructions are available, the following guidelines can be followed:

Table 4: Gemcitabine dose delay/reduction guidelines

Absolute granulocyte count (x 10 ⁶ /L)		Platelet count (x 10 ⁶ /L)	% of full dose
≥1000	And	≥100,000	100
500-999	Or	50,000-99,999	75
<500	Or	<50,000	Hold

5-FU and Leucovorin

Institutions should follow the manufacturer's instructions for dosing modification for the country in which the study is being conducted.

If 5-FU and Leucovorin are delayed, GM-CSF/TG01 should be continued as planned.

If 5-FU and Leucovorin treatment is stopped, GM-CSF/TG01 may continue as described in section 3.1.

If no instructions are available, the standard procedure at the institution for reduction of 5-FU/Leucovorin should be followed

4.5.3 GM-CSF/TG01 dose interruption

If a patient experiences GM-CSF or TG01 related toxicity on the days of the scheduled GM-CSF/TG01 injections, GM-CSF/TG01 should be delayed until toxicity resolved to CTC grade 1. The patient should then restart at the next planned visit. Chemotherapy should be continued as planned as long as chemotherapy prescribing information requirements are fulfilled.

Management of TG01 or GM-CSF related reactions:

- **All groups: 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 TG01 administrations they should be pre-medicated with intravenous antihistamine treatment (e.g. chlorpheniramine or dexchlorpheniramine) 30 minutes before either the DTH injection (TG01 alone) when done before vaccination or before vaccination (i.e. before the GM-CSF injection which is followed by the TG01 10-15 minutes later in the main group or concomitant group or 15-20 minutes later in the modified vaccination group)
- **Main group and concomitant group ONLY: For patients who have completed/finished chemotherapy**– All TG01 administrations should be preceded by intravenous antihistamine treatment as above
- **All groups: 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
- **All groups:** Where a DTH injection is being performed the TG01 DTH dose should be administered **30 minutes** before the GM-CSF/TG01 administration and patients should be observed for at least 30 minutes after ALL GM-CSF/TG01 administration
- **All groups: In patients who have not had prophylaxis**
 - If after the TG01 DTH dose the patient exhibits a Grade 1 or 2 allergic reaction then the GM-CSF/TG01 administrations should be delayed and the patient given intravenous antihistamine treatment as above
 - If a Grade 3 or 4 reaction occurs then no more vaccinations should be given and the patient withdrawn from TG01 treatment; if the patient is still receiving chemotherapy then this should continue per schedule.
- **All groups: In patients who have had prophylaxis**
 - If after the DTH dose the patient exhibits a Grade 1 reaction then the GM-CSF/TG01 administrations should only be given if the investigator believes it is reasonable to do so based on the nature of the reaction
 - If a Grade ≥ 2 reaction occurs then no more vaccinations should be given and the patient withdrawn from TG01 treatment (and continue chemotherapy if this has not been completed)
- **All groups:** Patients who are to receive no more vaccinations due to an allergic reaction but have exhibited a positive immune response may continue in the study until completion or earlier if the investigator feels that this is appropriate
- **All groups:** Precautions should be in place in case of anaphylaxis

4.6 Concomitant medication

No systemic anti-cancer therapy other than gemcitabine or 5-FU/Leucovorin is to be used during the trial before recurrence of the disease. After recurrence, for patients who have an immune response, the standard of care can be used according to the investigational site's usual practise.

Other vaccination must not be administered during the Initial treatment period (until week 11 for the main group, week 13 for the concomitant group and week 8 for the modified vaccination group) and should be avoided if possible for the rest of the study duration.

Vaccination with yellow fever or live (attenuated) vaccines is prohibited until at least 3 months after the last chemotherapy administration.

Any agent with a known effect on the immune system should be excluded before recurrence, 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 TG01 and other agents have been conducted.

4.7 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 (Section 4.6).

5. TRIAL MEASUREMENTS AND ENDPOINTS

5.1 Primary endpoint

Safety

- Adverse events
- Laboratory assessments

Immune response by week 11 or 12 (main group) or 13 (concomitant group) or 8 (modified vaccination group), at end of the treatment period with chemotherapy and at end of study assessed by

- DTH responses
- Proliferative T-cell responses

5.2 Secondary endpoints

Efficacy at 2 years

- Disease-free survival
- Overall survival

5.3 Exploratory endpoints

- Relationship between KRAS status in resected primary tumour and recurrence survival outcomes (including disease recurrence and overall survival)
- CA19-9 levels

5.4 Screening assessments

5.4.1 Informed consent

The Investigator must inform the patient verbally about the content of the trial and its risks and benefits, as outlined in the information for patients within the informed consent document. The patient should then be given sufficient time to read the information for patients and consider participation. If the patient chooses to participate, the patient and Investigator must both sign the Informed Consent Form. One copy will be given to the patient and the original must be documented in the medical source documents. In this study, the informed consent will have to be signed after surgery but before treatment start.

5.4.2 Patient eligibility

For trial entry, all patients must fulfil all the inclusion criteria, described under Section 3.3.1. No patient with any exclusion criterion from the list described in Section 3.3.2 may participate. To assure compliance with the entry criteria, all the assessments described in Sections 5.4.3 to 5.4.5 must be completed at screening to determine the patients' eligibility for entry into the trial.

5.4.3 Demographic data, medical history

A medical history (for details see below), including demographics, and physical examination of the patient must be completed during the 7 days prior to GM-CSF/TG01 1st dose.

Data to be collected at the screening examination are as listed below:

- Medical History of pancreatic cancer
 - date of initial diagnosis
 - stage of disease at diagnosis
 - Date(s) of surgery and extent of resection (R0 or R1)
- Concomitant non-malignant diseases and treatments
- All concomitant medications
- Medications taken within the 4 weeks prior to enrolment
- Patients' procreative potential and contraceptive use must be documented. For childbearing potential/fertile women, a pregnancy test is to be done within 7 days prior to the start of treatment and results are to be documented (serum or urine testing is acceptable).

5.4.4 Special examinations

- Tumour samples for KRAS status determination will be collected at surgery for analysis at the local laboratory
- ECG within 7 days of start of Study Drugs (as detailed in section 5.9.3) and then if clinically indicated
- CT-scan after surgery

A report of the examinations is to be made available in the patient's source documents for the trial.

5.4.5 Physical examination

A full physical examination will be performed and must include a complete, organ-oriented physical examination of the patient (i.e. head and neck, chest, abdomen, superficially the limbs, rudimentary neurological tests such as reflexes and sensation). The physical examination findings and relevant parameters are to be documented in the medical source documents.

This examination will also include performance status and vital signs (weight, height, heart rate and blood pressure, and body temperature).

Any new conditions reported during the trial will be recorded on the AE forms. Only those findings that are in addition to the condition being treated will be recorded as AEs. Conditions that are considered by the investigator to be unequivocally disease-related will not be recorded as AEs.

5.4.6 Laboratory safety measurements

Routine haematology, biochemistry and urine assessments will be performed at the local laboratory at the trial centre within 7 days prior to the start of treatment.

5.5 Assessments during treatment phase

Initial Treatment Period with GM-CSF /TG01 +/- chemotherapy

Main group: Initial Treatment Period (up to week 11) +/- chemotherapy for patients starting TG01 vaccination first (timings based on start of GM-CSF/TG01 treatment) – Table 1:

- GM-CSF/TG01 to start as soon as possible after the surgical resection. Day 1 will be the first day of GM-CSF/TG01 treatment with chemotherapy commencing a minimum on day 22 (3 weeks after the first TG01 treatment) but may also be started at day 36 or 50 (or later) of GM-CSF/TG01 treatment or may not be started at all. GM-CSF/TG01 treatment will be administered on days 1, 3, 5, 8, 15, and 22 and then 2-weekly until the end of chemotherapy treatment. Patients who do not start chemotherapy at all can move to a 4-weekly vaccination from vaccination week 10 to week 52.
- If given, Gemcitabine will be administered on cycle day 1, 8 and 15 of a four week cycle for 6 cycles in total. 5-FU and Leucovorin will be administered on cycle day 1, 2, 15 and 16 of a four week cycle for 6 cycles
- DTH application on days 1, 8 15, 22 36, 50 and 64. DTH is assessed 48 h \pm 4 h after each injection
- Haematology and blood chemistry at days 1, 8, 22, 36, 50 and 64 taken prior to injection of GM-CSF/TG01 and at days 1, 8 and 15 of each Gemcitabine cycle prior to injection of study treatments. Key laboratory values in accordance with the Prescribing Information for chemotherapy should be available prior to chemotherapy dosing. For patients who do not start chemotherapy at all, haematology and blood chemistry should be taken at days 1, 8, 22, 36, 50 and 64 and then every 12 weeks
- Urinalysis as clinically indicated
- Vital signs, concomitant medications and adverse events at each visit

- Physical exam and performance status before the start of each chemotherapy cycle. For patients who do not start chemotherapy at all, these assessments should be done every 12 weeks
- Blood sampling for immunology – samples taken prior to GM-CSF/TG01 injection on day 1 and day 71 (or 78)
- Blood sampling for CA19.9 will be taken prior GM-CSF/ TG01 injection on day 1 and prior chemotherapy day 1 of each cycle. For patients who do not start chemotherapy at all, these assessments should be done on day 1 and prior every 4-weekly vaccination cycle
- A further 10 ml sample (5 ml serum; 5 ml plasma) will be taken and stored for potential analysis of additional biomarkers on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy at all, these assessments should be done on day 1 and prior every 4-weekly vaccination cycle
- CT scan every 6 months from start of vaccination and at any time point if indicated

Phase II part – **concomitant treatment group**: Initial Treatment Period (up to week 13) +/- chemotherapy for patients starting TG01 vaccination and chemotherapy at the same time (Table 2):

- GM-CSF/TG01 will start within 9-12 weeks of the surgical resection. Day 1 will be the first day of GM-CSF/TG01 treatment. GM-CSF/TG01 treatments will be administered on days 1, 3, 5, 8, 15 and then 2-weekly until the end of chemotherapy treatment.
- Chemotherapy will start at the same time as GM-CSF/TG01 and no later than 12 weeks from surgery. Gemcitabine will be administered on cycle day 1, 8 and 15 of a four week cycle for 6 cycles in total. 5-FU and Leucovorin will be administered on cycle day 1, 2, 15 and 16 of a four week cycle for 6 cycles
- DTH application on days 1, 8 15, 29, 43, 57 and 71. DTH is assessed 48 h \pm 4 h after each injection
- Haematology and blood chemistry at days 1, 8 and 15 of each Gemcitabine cycle prior to injection of study treatments. Key laboratory values in accordance with the Prescribing Information for chemotherapy should be available prior to chemotherapy dosing
- Urinalysis as clinically indicated
- Vital signs, concomitant medications and adverse events at each visit
- Physical exam and performance status before the start of each chemotherapy cycle
- Blood sampling for immunology – samples taken prior to GM-CSF/TG01 injection on day 1 and week 13
- Blood sampling for CA19.9 will be taken on day 1 of each chemotherapy cycle prior GM-CSF/TG01 administration
- A further 10 ml sample (5 ml serum; 5 ml plasma) will be taken and stored for potential analysis of additional biomarkers on day 1 of each chemotherapy cycle prior GM-CSF/TG01 administration
- CT scan every 6 months from start of vaccination and at any time point if indicated

Phase II – modified vaccination group: Initial Treatment Period (up to week 8) +/- chemotherapy for patients starting TG01 vaccination first (timings based on start of GM-CSF/TG01 treatment) - Table 3.

- GM-CSF/TG01 will start as soon as possible after surgical resection. Day 1 will be the first day of TG01 treatment. GM-CSF/TG01 will be administered on Days 1, 8, 15, 22 and 36 then if chemotherapy hasn't started vaccination will be given 4-weekly until the start of chemotherapy at which point vaccination will be put on hold until the end of chemotherapy treatment. Patients who do not start chemotherapy at all will continue to receive 4-weekly vaccinations from week 10 to week 52.
- Chemotherapy will commence at least 3 weeks after start of GM-CSF/TG01. Patients can however start chemotherapy later or not start at all if more appropriate. For patients receiving chemotherapy, 6 cycles of chemotherapy will be given. Note that chemotherapy will not be delayed if it is considered important to start within 3 weeks of the start of vaccinations.
- DTH skin test injections on days 36 and 50. DTH reaction is assessed 48 h \pm 4 h after each injection
- Haematology and blood chemistry at days 1, 8, 22, 36, 50, and 64 taken prior to injection of GM-CSF/TG01 and Days 1, 8 and 15 of each gemcitabine cycle. **Key laboratory values in accordance with the Prescribing Information for chemotherapy should be available prior to chemotherapy dosing.** For patients who do not start chemotherapy at all, haematology and blood chemistry should be taken at days 1, 8, 22, 36, 50 and 64 and then every 12 weeks
- Urinalysis as clinically indicated
- Vital signs, concomitant medications and adverse events at each visit.
- Physical examination and Performance Status before the start of each gemcitabine cycle. For patients who do not start chemotherapy, these assessments should be done every 12 weeks.
- Blood sampling for immunology – samples taken prior to GM-CSF/TG01 injection on day 1 and at week 8
- Blood sampling for CA19.9 on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy, these assessments should be done on Day 1 and prior every 4-weekly vaccination cycle
- A further 10 ml sample (5 ml serum; 5 ml plasma) will be taken and stored for potential analysis of additional biomarkers on day 1 prior to GM-CSF/TG01, prior chemotherapy 1st administration and monthly thereafter until end of chemotherapy. For patients who do not start chemotherapy, these assessments should be done on Day 1 and prior every 4-weekly vaccination cycle
- CT scan every 6 months from the start of vaccination and at any other time point if indicated

After the end of chemotherapy or from week 10 for patients who do not get chemotherapy:

Main group and concomitant group:

- GM-CSF/TG01 every 4 weeks until 52 weeks and then every 12 weeks for up to 2 years. For all these subsequent GM-CSF /TG01 administrations the patients should be given prophylactic treatment (30 minutes before treatment) to prevent possible occurrence of allergic reactions.

- DTH skin test injections at the 2nd GM-CSF/TG01 injection after end of chemotherapy (8 weeks after last chemotherapy injection) and at week 52. DTH reaction is to be assessed 48 h \pm 4 h after TG01 injection. For patients who do not start chemotherapy at all, these assessments should be done at week 52 only
- Immunology blood samples – samples taken at week 52 prior GM-CSF/TG01 injection
- CA19.9 and additional biomarkers blood samples – samples taken at week 52 prior GM-CSF/TG01 injection. For patients not starting chemotherapy, samples should be taken prior every 4-weekly cycle and at week 52
- Physical examination and performance status at 52 weeks. For patients who do not start chemotherapy, these assessments should be done every 12 weeks and at week 52
- Vital signs, haematology and biochemistry at 12 weekly intervals
- Concomitant medications and adverse events at each visit
- CT scan every 6 months from start of vaccination and at any time point if indicated

Modified vaccination group:

- GM-CSF/TG01 will be given 4 weeks and 5 weeks after end of chemotherapy and then every 4 weeks from week 8 post-chemotherapy until week 52 and then every 12 weeks until week 104 (2 years). Patients who do not start chemotherapy at all will receive 4-weekly vaccinations from week 10 to week 52 and then every 12 weeks until week 104 (2 years).
- DTH skin test at 3rd vaccination post-chemotherapy (8 weeks post-chemotherapy). The DTH reaction is to be assessed 48 h \pm 4 h after TG01 injection. For patients not starting chemotherapy at all, the DTH test and assessment are to be done at week 52.
- Blood sampling for immunology – sample to be collected 4 weeks after the last chemotherapy injection (1st vaccination injection) and at week 52
- Blood sampling for CA19.9 and additional biomarkers – samples to be taken prior to GM-CSF/TG01 injection at week 52. For patients not starting chemotherapy, samples should be taken prior every 4-weekly vaccination cycle and at week 52
- Physical examination and performance status to be taken at week 52. For patients who do not start chemotherapy, these assessments should be done every 12 weeks and at week 52
- Vital signs, haematology and biochemistry every 12 weeks
- Concomitant medications and adverse events at each visit
- CT scan every 6 months from the start of vaccination and at any other time point if indicated

End of Study Visit (104 weeks or 4 weeks after last GM-CSF /TG01 injection if patient is to be discontinued)

- Haematology and blood chemistry
- Physical exam and performance status
- Vital signs, concomitant medications and adverse events
- Blood sampling for immunology, CA19.9 and additional biomarkers taken prior to GM-CSF/TG01 injection

- CT-scan

For all patients where possible, a survival follow-up will continue to be performed every 6 months after the initial 2 years of study period and until the last remaining patient in the modified cohort reaches the 2 years study period or withdraws consent or experiences toxicity, whichever is the earliest. Thereafter, a survival follow-up will continue to be performed approximately every 12 months until end of life.

5.6 Immunological effect

An immune responder is defined as having a positive DTH and/or a positive T-cell test from a blood sample at least once by the end of the initial treatment period (week 11 in main group, week 13 in the concomitant group and week 8 in the modified vaccination group) (see below):

T-cell Assay

Patients will have a blood sample taken prior to GM-CSF/TG01 for further testing of immune response, at:

- Day 1
- Week 11 (main group) or week 13 (concomitant group) or week 8 (modified vaccination group)
- 4 weeks after end of chemotherapy
- Week 52
- End of study

All samples will be processed and stored under appropriate conditions until being analysed. Blood samples from each time point will be analysed for TG01 specific T-cell responses by proliferation assays. Specific T-cell responses will be considered positive if the stimulation index (SI) is ≥ 2 .

Delayed Type Hypersensitivity (DTH)

It is performed in order to demonstrate whether an immune response has been elicited.

Administration of TG01 only (without GM-CSF or preceded by GM-CSF administration) must be injected intradermally in the lower area of the contralateral arm acting as a Delayed Type Hypersensitivity (DTH) test.

Phase I part and phase II part – main group: the DTH test is administered on days 1, 8, 15, 22, 36, 50, 64, at the 2nd GM-CSF/TG01 injection after the end of the chemotherapy (8 weeks after the last chemotherapy injection) and at week 52. For patients not receiving chemotherapy at all, the DTH test is administered on days 1, 8, 15, 22, 36, 50, 64 and at week 52.

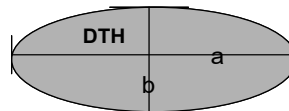
Phase II part – concomitant group: the DTH test is administered on days 1, 8, 15, 29, 43, 57, 71, at the 2nd GM-CSF/TG01 injection after the end of the chemotherapy (8 weeks after the last chemotherapy injection) and at week 52.

Phase II part – modified vaccination group: the DTH test is administered on days 36 and 50, at the 3rd GM-CSF/TG01 injection after the end of the chemotherapy (8 weeks after the last chemotherapy injection) and at week 52. For patients not starting chemotherapy at all, the DTH test and assessment are to be done on days 36 and 50 and at week 52.

The DTH skin reaction assessment is to be performed 48 hours (+/- 4 hours) after each administration. The DTH-test will be considered positive if the area of the skin reaction has an average diameter* of $\geq 5\text{mm}$ at the 48 hours (+/- 4 hours) assessment.

Figure 6: DTH Skin Reaction Registration (induration and erythema)

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



5.7 CT-scan

An abdominal CT or MRI scan should be performed for full tumour assessment at baseline, every 6 months from the start of vaccination and at the last or end of study visit. Additional CT-scans should also be done if indicated during the study period.

5.8 Efficacy measurements and endpoints

5.8.1 Immunology response

Response by week 11 or 12 (main group) or by week 13 (concomitant group) or by week 8 (modified vaccination group) assessed by:

- DTH responses
- Proliferative T-cell responses

Response at end of chemotherapy treatment assessed by:

- DTH responses
- Proliferative T-cell responses

Response at week 52 assessed by:

- DTH responses
- Proliferative T-cell responses

Response at end of study assessed by:

- Proliferative T-cell responses

5.8.2 Disease-free survival

- Time from randomisation to 1st disease progression or death from any cause

Note that although scanning at regular intervals during the study is not mandated it is expected that a CT scan will be performed every 6 months from the start of vaccination and if there is clinical evidence of disease recurrence

- Number of patients alive and disease free at 1 and 2 years

5.8.3 Overall survival

- Time from randomisation to death due to any cause
- Number of patients alive at 1 and 2 years

5.8.4 KRAS status expression

Relationship between KRAS status and recurrence

5.8.5 CA19.9 levels

Level of CA19-9 during treatment period, at week 52 and at end of the study.

5.8.6 Other markers levels

Level of other biomarkers during treatment period, at week 52 and at end of the study.

5.9 Safety measurements and endpoints

5.9.1 Adverse events

5.9.1.1 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given in section 7 of this protocol. It is extremely important that all staff involved in the trial are familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

5.9.2 Laboratory safety measurements and variables

5.9.2.1 Methods of assessment

Routine haematology, biochemistry and urinalysis assessments will be performed at the laboratory local to the trial centre.

The following routine laboratory parameters will be investigated (see section 9.7 for the total volume of blood samples to be collected):

Table 5: Summary of required laboratory assessments

Chemistry	Haematology	Clotting Screen	Urinalysis
Alkaline Phosphate	Red blood cell (RBC) count	INR	Blood
ALT (SGPT)	Haemoglobin		Proteins
AST (SGOT)	Haematocrit		Glucose
Total Protein	White blood cell (WBC) count		White cells
Albumin	Neutrophils		
Bilirubin	Lymphocytes		
Lactate dehydrogenase (LDH)	Monocytes		
Blood urea nitrogen (BUN) or Uric Acid	Eosinophils		
Creatinine	Basophils		
Sodium	Platelet count		
Potassium			
Creatinine kinase (CK)			

5.9.2.2 Calculation or derivation of endpoint

Section 7 provides details on how AEs based on laboratory tests will be recorded and reported.

Laboratory test results will be graded according to NCI-CTC version 4.0.

5.9.3 ECG

ECG will be evaluated locally. Any clinically significant abnormal findings observed and recorded during the treatment period will be recorded as AEs. The same method of assessment should be used throughout.

5.9.4 Performance status

Performance status will be evaluated locally using the ECOG scale:

Grade	ECOG
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

6. ANALYSIS OF TRIAL DATA

6.1 Study Endpoints

6.1.1 Primary Endpoint

The primary safety endpoint is the assessment of adverse events and laboratory values during the study period.

The primary efficacy endpoint is immune response by week 11 or 12 (main group) or by week 13 (concomitant group) or by week 8 (modified vaccination group), at end of the treatment period with chemotherapy and at week 52.

6.1.2 Secondary Endpoints

The secondary target variables for this trial are:

Efficacy

- Time from randomisation to first disease progression or death from any cause
- Time from randomisation to death

6.1.3 Exploratory Endpoints

- Relationship between KRAS status in resected primary tumour and recurrence survival outcomes (including disease recurrence and overall survival)
- CA19-9 levels

6.2 Definitions of evaluability

The definitions of study populations are as follows:

Population	Definition
All treated patients (ATT)/safety	This will comprise all patients who received at least one dose of Investigational pharmaceutical product (IMP)
Immune	This will comprise patients who provided at least one set of T cell and/or DTH response results
Modified Immune	This will comprise all patients in the Immune population who have received at least one cycle of gemcitabine or 5-FU/leucovorin

Patients who withdrew from study before completing 1 cycle of gemcitabine may be replaced.

6.3 Analytical methods

Endpoints will be analysed as detailed in the sections below:

6.3.1 Primary endpoints

Summary measures:

6.3.1.1 Nature, incidence and severity of adverse events

Adverse events will be summarised by counts and proportions (percentages) of patients reporting an AE expressed as a percentage of all patients. All premature terminations will be summarised by the primary reason for trial withdrawal; ITT population.

6.3.1.2 Laboratory assessments

Summary measures: Standard summary statistics; ITT population.
Listings will highlight assessments of clinical significance.

6.3.1.3 Incidence of and reasons for Study Drug dose interruptions, Study Drug dose reductions and withdrawals

Summary measures: Counts and proportions; ITT population.

6.3.1.4 Study Drug exposure

Summary measures: Standard summary statistics; ITT population.
Listings will highlight assessments of clinical significance.

6.3.1.5 Immune response

Summary measures: DTH test results, T-cells assay; Per Protocol population and Immune population. The data will be summarised.

6.3.2 **Secondary endpoints**

6.3.2.1 Disease-free survival

Summary measures: Median time to progression or death. Proportion alive and disease-free at 1 and 2 years (Median and proportion calculated by Kaplan-Meier, ITT population).

6.3.2.2 Overall survival

Summary measures: Median time to death. Proportion alive at 1 and 2 years. (Median and proportion calculated by Kaplan-Meier, ITT population).

6.3.2.3 CA19-9 Evaluation

Summary measures: Changes over time (trend and absolute changes); ITT population.

6.3.2.4 Other biomarkers

Summary measures: Changes over time (trend and absolute changes); ITT population.

6.4 **Sample size and power**

No formal sample size has been calculated. 6-32 patients are deemed sufficient to assess the safety and immune response in this pilot study and given an early indication of efficacy in terms of DFS and OS based on historical controls.

7. **DRUG SAFETY**

7.1 **Definitions of adverse events and serious adverse events**

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

7.1.1 **Adverse events**

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/TG01 or chemotherapy (gemcitabine or 5-FU and Leucovorin)) 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, even if no trial treatment has been administered or recently administered. A grading severity scale is provided for each AE term. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 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.

7.1.2 Serious adverse events

A serious AEs (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 hospitalisation
- 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 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?' (see APPENDIX II for guidelines on interpretation of causality).

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]

[REDACTED]

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

7.2 Recording of adverse events

For the purpose of this trial, any detrimental change in a patient's condition, subsequent to their entering 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 in 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 anew 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 National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 and recorded on the appropriate CRF page.

Laboratory/vital signs abnormalities should **not** be reported as adverse events unless any criterion for an AE is fulfilled i.e. that it is clinically significant and because it is detrimental to the patient, the abnormality causes study drug dose adjustment, leads to patient's discontinuation from the study, or the investigator insists the abnormality should be reported as an AE. Laboratory/vital signs abnormalities should not be reported as separate adverse events if they are part of an overall diagnosis

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 7.1.2. 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.

7.2.1 Exposure to GM-CSF/TG01 or chemotherapy during pregnancy/lactation

In principle, pregnancy and lactation are exclusion criteria and pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under trial may have interfered with the effectiveness of a contraceptive medication. In the event of a pregnancy occurring during the course of the trial, the patient must be withdrawn from trial medication immediately and the pregnancy notified to [REDACTED] and the sponsor without delay. The patient must be followed-up during the entire course of the pregnancy and lactation period. Perinatal and neonatal outcomes must be recorded even if completely normal and without AEs.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs (See Section 8.3 below). Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to [REDACTED], on the 'pregnancy outcomes report form'.

7.3 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 [REDACTED]

- Patient identifier – patient number, investigator
- Details of the event or outcome (see section 7.1.2)

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 by day 1 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.

7.4 Death

All deaths occurring within the trial period or within 28 days of the last dose of Study Drug (TG01 and GMCF or chemotherapy (gemcitabine or 5-FU/Leucovorin)) must be reported to the safety group, for the purpose of SAE reporting. However, deaths due unequivocally to disease recurrence/progression are not SAEs. Any deaths occurring more than 28 days after the last dose of Study Drug (TG01 and GMCF or chemotherapy) will not be reported to the regulatory authorities, for the purposes of safety reporting.

7.5 Procedures to be followed in the event of abnormal laboratory test values

The severity grading used for laboratory measurements will be the NCI-CTC, version 4.0 grading for laboratory parameters. Laboratory parameters not rated by the NCI-CTC, version 4.0, scoring will not be graded. The AEs based on laboratory tests will be recorded and reported as described in Section 7.2.

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up until the test values have returned to the normal or baseline range, and/or an adequate explanation of the abnormality is found.

If a clear explanation is established it should be recorded in the patient's medical source documents.

7.6 Overdosing with the trial medication

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. For the purposes of this trial, any dose administered to a patient that exceeds the planned protocol dose should be reported as an overdose. It must be reported as an SAE irrespective of outcome and even if no toxic effects were observed.

There is no clinically proven antidote available for TG01, GM-CSF or gemcitabine.

The expected manifestations of overdose are likely to be:

TG01

Significant toxicities have not been seen to date and the mode of action of TG01 makes it unlikely that an overdose will cause additional toxicity

GM-CSF

The dose of GM-CSF used is very low and overdose symptoms are likely to mimic the toxicities of doses more commonly used to support neutropenia such as bone and musculoskeletal pain

Gemcitabine: Myelosuppression, paraesthesia, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m² was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a Phase 1 study. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and should receive supportive therapy, as necessary.

5-FU: most frequent toxicities reported with 5-FU were stomatitis, oesopharyngitis, diarrhoea, anorexia, nausea and emesis, alopecia, dermatitis and leucopenia.

Leucovorin: most frequent toxicities reported with Leucovorin were diarrhoea, stomatitis, myelosuppression, skin rash, hives, pruritus and wheezing (although rare).

8. RESPONSIBILITIES OF THE INVESTIGATORS

The Investigators shall be responsible for ensuring that the trial is performed in accordance with the protocol and the Declaration of Helsinki (July 1999), as well as with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) approved July 1996 and applicable regulatory requirements. These documents state that the informed consent of the patients is an essential precondition for participation in the clinical trial.

8.1 Patient information

An unconditional prerequisite for participation of a patient in the trial is the patient's written consent after having been informed of the following:

- that the trial involves research
- the purpose of the trial
- the trial treatment(s)
- the trial procedures to be followed, including all invasive procedures
- the patient's responsibilities
- those aspects of the trial that are experimental (e.g. novel or non-validated measurements, which are additional to normal therapeutic assessment.)
- the reasonably foreseeable risks or inconveniences to the patient and, when applicable, to an embryo, foetus, or nursing infant
- the reasonably expected benefits (when there is no intended clinical benefit to the patient, the patient should be made aware of this)

- the alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks
- the compensation and/or treatment available to the patient in the event of trial-related injury
- that the patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient is otherwise entitled
- that the monitor(s), the auditor(s), the Independent Ethics Committee (IEC), and the regulatory authority(ies) will be granted direct access to the patient's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access
- that records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available even if the results of the trial are published
- that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue to participate in the trial
- the person(s) to contact for further information regarding the trial and the rights of trial patients, and whom to contact in the event of trial-related injury
- the foreseeable circumstances and/or reasons under which the patient's participation in the trial may be terminated
- the expected duration of the patient's participation in the trial
- the approximate number of patients involved in the trial
- for women, the warning that clinical studies may not be carried out in pregnant women and that pregnancy should therefore be avoided. If pregnancy occurs, the investigator must be notified immediately
- insurance coverage
- mentioning that the patient may undertake additional medical treatment at any time during the clinical trial only with the express permission of the Investigators (unless indicated in an emergency) (note condition of insurance coverage in APPENDIX III)
- warning that the patient may not have taken part in any other clinical trial or used any other unlicensed medication during the past 28 days
- mention that any change in any concomitant medication must be reported to the Investigator immediately
- permitted and non-permitted concomitant medication and dietary aspects.

The information should be given to the patient both verbally and in writing. The wording must be chosen in such a way that the content is fully and readily understandable for

laypersons. Patients must be given sufficient time to consider their participation in the trial.

8.2 Patient consent

The consent of the patient to participate in the trial has to be given in writing prior to participation in the trial. It must be signed and personally dated by the patient and by the Investigator/person designated by the Investigator to conduct the informed consent discussion.

The signed and dated declaration of informed consent will remain at the Investigators' site and must be safely archived by the Investigators so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and consent should be provided to the patient prior to participation and a copy maintained in the patient's source documents if there is a separate archive file for the informed consent documents for the trial.

8.3 Ethics review

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.

8.4 Source data and patient files

The Investigators have to keep a written or electronic patient file for every patient participating in the trial. This patient file should contain the available demographic and medical information of the patient, in particular the following: name, date of birth, sex, height, weight, patient history, concomitant diseases and concomitant medication (including changes during the trial), statement of entry into the trial, trial identification, the date of informed consent, all trial visit dates, predefined performed examinations and clinical findings, observed AEs (if applicable), and reason for withdrawal from the trial if applicable. It should be possible to verify the inclusion and exclusion criteria for the trial from the available data in this file.

It must be possible to identify each patient by using this patient file.

Additionally, any other documents with source data, especially original print-outs of data that were generated by technical equipment, have to be filed. All these documents have to bear at least the patient identification number and the printing date printed by the recording device, to indicate to which patient and to which trial procedure the document belongs.

Print-outs of computerised patient files must be signed and dated by the Investigators, countersigned by the monitor and kept with the Investigators' copies of the CRF, as a

source document. Data are to be recorded directly onto the CRFs (i.e. there is to be no prior written or electronic record of data).

8.5 Training of staff

The principal investigator will maintain a record of all individuals involved in the trial (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the trial is given to all these staff, and that they will receive any new information of relevance to the performance of this trial.

8.6 Trial agreements

The principal investigator at each centre 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.

8.7 Confidentiality

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.

9. TRIAL MANAGEMENT

9.1 Monitoring

Before the initiation of the trial, a representative of Targovax will visit the investigational site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) (and other personnel involved with the trial) their responsibilities with regard to protocol adherence, and the responsibilities of Targovax or its representatives

During the trial, a CRA representing Targovax will have regular contacts with the investigational site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patients' records at the hospital or practice, and other records relevant to the trial). This will require direct access to all original records for each patient (e.g. clinic charts)

The monitor or another Targovax representative will be available between visits if the investigator(s) or other staff at the centre need information and advice.

The monitoring of the study will be conducted by a Targovax representative who has appropriate expertise in monitoring clinical trials such as this to ICH GCP standards.

9.2 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.

9.3 Case report form handling

The main objective is to obtain those data required by the trial protocol in a complete, accurate, legible and timely fashion. The data in the CRFs should be consistent with the relevant source documents.

The data recorded during the course of this trial must be documented in the CRFs and must be forwarded to the nominated Data Management Group, for processing and evaluation on behalf of Targovax. All data must be stored in an anonymous form in accordance with the data-protection regulations.

The Investigators must ensure that the CRFs forwarded to Data Management and any other associated documents, contain no mention of any patient names.

The CRFs must be filled in completely and legibly (with either black or blue ballpoint pen, acceptable for use on official documents). Any amendments and corrections necessary must be undertaken and countersigned by the Investigators, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids (e.g. Tipp-Ex). The Investigators must state their reasons for the correction of important data.

In the case of missing data/remarks, the entry spaces provided for in the CRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

The CRFs must be suitable for submission to the regulatory authorities.

The nominated Data Management Group is [REDACTED], with headquarters at [REDACTED] and will have the appropriate experience to undertake the data management and statistical activities for this study to ICH GCP standards.

9.4 Amendments to the trial protocol

Changes in the trial protocol must take the form of written trial-protocol amendments. These will require the approval of all signatories of the final protocol.

Any amendments to the protocol which affect the patient, e.g. changes in procedures/assessments or matters relating to patient safety, require a favourable opinion approval from the Ethics Committee for the trial centre(s) concerned, prior to implementation. Changes of a purely administrative nature should be notified to the committee(s), but do not require formal approval. Any amendment affecting the patient requires further informed consent from each patient before implementation.

9.5 Deviations from the trial protocol

Deviations from the trial protocol, especially the prescription of doses not scheduled in the trial protocol, other modes of administration, other indications, and longer treatment periods are not permissible (except in an emergency).

9.6 Trial report and publication policy

After the conclusion of the trial, a report will be written with the co-operation of the Investigators and in conjunction with Targovax, which will include a descriptive statistical analysis and an appraisal of the results from a medical viewpoint. This report will be based on the items listed in this trial protocol. Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentation, etc.) by the Investigators, requires the approval of Targovax.

9.7 Volume of blood sampling and handling of biological samples

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 6: Volume of blood to be drawn from each patient in the study

Assessment		Sample volume (ml)	No. of samples	Total volume (ml)
Immunology		60	5	300
CA19.9		5	9	45
Other analysis		10	9	90
Safety	Clinical chemistry	5	23-31	115-155
	Haematology	5	23-31	115-155
Total				665-745 ml

10. REFERENCES

1. Bernhardt SL, Gjertsen MK, Trachsel S, Møller M, Eriksen JA, Meo M, Buanes T and Gaudernack G. (2006) Telomerase peptide vaccination of patients with non-resectable pancreatic cancer: a dose escalating phase I/II study. *British Journal of Cancer*; 95: 1474 – 1482
2. Broomfield S, Currie A, van der Most RG, Brown M, van BI, Robinson BW et al., (2005) Partial, but not complete, tumor-debulking surgery promotes protective antitumor memory when combined with chemotherapy and adjuvant immunotherapy. *Cancer Res*; 65: 7580–7584
3. Brunsvig PF, Aamdal S, Gjertsen MK, Kvalheim G, Markowski-Grimsrud CJ, Sve I, Dyrhaug M, Trachsel S, Moller M, Eriksen JA, Gaudernack G. (2006) Telomerase peptide vaccination: a phase I/II study in patients with non-small cell lung cancer. *Cancer Immunol Immunother*; 55(12):1553-1564
4. Capella G., Cronauer-Mitra S., Peinado M. A., Perucho M. (1991) Frequency and spectrum of mutations at codons 12 and 13 of the c-K-RAS gene in human tumors. *Environmental Health Perspectives*; 93: 125-131
5. Chianese-Bullock KA, Pressley J, Garbee C et al., (2005) MAGE-A1-, MAGE-A10-, and gp100-derived peptides are immunogenic when combined with granulocyte-macrophage colony-stimulating factor and montanide ISA-51 adjuvant and administered as part of a multi-peptide vaccine for melanoma. *J Immunol*; 174:3080-6
6. Disis ML, Grabstein KH, Sleath PR et al., (1999) Generation of immunity to the HER-2/neu oncogenic protein in patients with breast and ovarian cancer using a peptide-based vaccine. *Clin Cancer Res*; 5:1289-97
7. Disis ML, Bernhard H, Shiota FM et al., (1996). Granulocyte-macrophage colony-stimulating factor: an effective adjuvant for protein and peptide-based vaccines. *Blood*; 88:202-10
8. Dranoff G, Jaffee E, Lazenby A, Golumbek P, Levitsky H, Brose K, Jackson V, Hamada H, Pardoll D, Mulligan RC. (1993) Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. *Proc Natl Acad Sci*; 90: 3539-3543
9. Dutoit V, Taub RN, Papadopoulos KP et al., (2002) Multi-peptide CD8(+) T cell response to a NY-ESO-1 peptide vaccine results in imprecise tumor targeting. *J Clin Invest*; 110:1813-22

10. Fossum B., Gedde-Dahl T. III, Hansen T., Eriksen J. A., Thorsby E., Gaudernack G. (1993). Overlapping epitopes encompassing a point mutation (12 Gly-->Arg) in p21 RAS can be recognized by HLA-DR, -DP and -DQ restricted T cells. *Eur. J. Immunol.*; 23: 2687-2691
11. Fossum B., Gedde-Dahl T. III, Breivik J., Eriksen J. A., Spurkland A., Thorsby E., Gaudernack G. (1994) p21-RAS-peptide-specific T-cell responses in a patient with colorectal cancer. CD4+ and CD8+ T cells recognize a peptide corresponding to a common mutation (13Gly-->Asp). *Int. J. Cancer.*; 56: 40-45
12. Gedde-Dahl T. III., Eriksen J. A., Thorsby E., Gaudernack G. (1992). T-cell responses against products of oncogenes: generation and characterization of human T-cell clones specific for p21 RAS-derived synthetic peptides. *Hum. Immunol.* 33: 266-274
13. Gedde-Dahl T. III, Nilsen E., Thorsby E., Gaudernack G. (1994) Growth inhibition of a colonic adenocarcinoma cell line (HT29) by T cells specific for mutant p21 RAS. *Cancer Immunol. Immunother.*; 38: 127-134
14. Gjertsen MK, et al., (1995) Vaccination with mutant ras peptides and induction of T-cell responsiveness in pancreatic carcinoma patients carrying the corresponding RAS mutation. *The Lancet*: 346: 1399-1400
15. Gjertsen M.K., Buanes T., Roseland A.R., Bakka A., Gladhaug I., Søreide O., Eriksen J.A., Møller M., Baksaas I., Lothe R.A., Sæterdal I., Gaudernack G. (2001) Intradermal RAS peptide vaccination with granulocyte-macrophage colony-stimulating factor as adjuvant: clinical and immunological responses in patients with pancreatic adenocarcinoma. *Int. J. Cancer.* , 92: 441-445
16. Gupta RK, Siber GR (1995). Adjuvants for human vaccines--current status, problems and future prospects. *Vaccine*;13:1263-76
17. Gupta RK, Rost BE, Relyveld E et al., (1995). Adjuvant properties of aluminum and calcium compounds. *Pharm Biotechnol*; 6:229-48
18. Gupta RK, Griffin P Jr, Chang AC, Rivera R, Anderson R, Rost B, Cecchini D, Nicholson M, Siber GR. (1996) The role of adjuvants and delivery systems in modulation of immune response to vaccines. *Adv Exp Med Biol*; 105-13
19. Hung K, Hayashi R, Lafond-Walker A et al., (1998). The central role of CD4(+) T cells in the antitumor immune response. *J Exp Med*;188:2357-68
20. Hunger RE, Brand CU, Streit M et al., (2001). Successful induction of immune responses against mutant ras in melanoma patients using intradermal injection of peptides and GM-CSF as adjuvant. *Exp Dermatol*;10:161-7
21. Leong SP, Enders-Zohr P, Zhou YM et al., (1999). Recombinant human granulocyte macrophage-colony stimulating factor (rhGM-CSF) and autologous melanoma

vaccine mediate tumor regression in patients with metastatic melanoma. J Immunother;22:166-74

22. Lesterhuis WJ, Haanen JBAG and Punt CJA (2011). Cancer immunotherapy-revisited. Nature reviews drug discovery,; vol 10: 591-600
23. Lomas M, Liauw W, Packham D et al., (2004). Phase I clinical trial of a human idiotypic p53 vaccine in patients with advanced malignancy. Ann Oncol;15:324-9
24. Mach N, Gillessen S, Wilson SB et al., (2000). Differences in dendritic cells stimulated in vivo by tumors engineered to secrete granulocyte-macrophage colony-stimulating factor or Flt3-ligand. Cancer Res;60:3239-46
25. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, et al., (2010) Adjuvant Chemotherapy With Fluorouracil Plus Folinic Acid vs Gemcitabine Following Pancreatic Cancer Resection. A Randomized Controlled Trial. JAMA; 304: 1073-1081
26. Neuhaus P, Reiss H, Post S, Gellert K, et al., (2008) CONKO-001: Final results of the randomized, prospective, multicenter phase III trial of adjuvant chemotherapy with Gemcitabine versus observation in patients with resected pancreatic cancer (PC). J Clin Oncol Meeting Abstracts (2008) Volume: 26, Issue: 15_suppl, Pages: LBA4504
27. Nowak AK, Robinson BW, Lake RA. (2002) Gemcitabine exerts a selective effect on the humoral immune response: implications for combination chemo-immunotherapy. Cancer Res; 62: 2353–2358
28. Nowak AK, Robinson BW, Lake RA. (2003). Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. Cancer Res 63:4490-4496, 2003
29. Oettle H et al., (2007) Adjuvant Chemotherapy With Gemcitabine vs Observation in Patients Undergoing Curative-Intent Resection of Pancreatic Cancer A Randomized Controlled Trial .JAMA. 297: 267-277
30. Parmiani G et al., (2007) Opposite immune functions of GM-CSF administered as vaccine adjuvant in cancer patients Annals of Oncology; 18: 226 - 232
31. Peace D et al., (1991) T Cell recognition of transforming proteins encoded by mutated ras proto-oncogenes. J Immunol. 146:2059-2065
32. Schaed SG, Klimek VM, Panageas KS et al., (2002). T-cell responses against tyrosinase 368-376(370D) peptide in HLA*A0201+ melanoma patients: randomized trial comparing incomplete Freund's adjuvant, granulocyte macrophage colony-stimulating factor, and QS-21 as immunological adjuvants. Clin Cancer Res;8:967-72

33. Singh M, O'Hagan D. (1999) Advances in vaccine adjuvants. *Nat Biotechnol*; 17:1075-81
34. Soiffer R, Lynch T, Mihm M et al., (1998) Vaccination with irradiated autologous melanoma cells engineered to secrete human granulocyte-macrophage colony-stimulating factor generates potent antitumor immunity in patients with metastatic melanoma. *Proc Natl Acad Sci U S A*;95:13141-6
35. Suzuki E, Kapoor V, Jassar AS, Kaiser LR, Albelda SM. (2005) Gemcitabine selectively eliminates splenic Gr-1⁺/CD11b⁺ myeloid suppressor cells in tumor-bearing animals and enhances antitumor immune activity. *Clin Cancer Res*; 11: 6713–6721.
36. Van Laethem J-L et al., (2010) Adjuvant Gemcitabine alone versus Gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomised EORTC-40013-22012/FFCD-9203/GERCOR Phase II study. *J Clin Onc*. 24 (29): 4450-4456
37. Weden et al., (2011). Long Term Follow-up of Resected Pancreatic Cancer Patients Following Vaccination Against Mutant K-RAS. *International Journal of Cancer*: in press
38. Yamada A et al., (2006). Nonmutated self-antigen-derived cancer vaccine peptides elicit an IgE-independent but mast cell-dependent immediate-type skin reaction without systemic anaphylaxis. *J Immunol*: 176:857-863

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: PATIENT INSURANCE AND INDEMNITY

Patients will be covered by an insurance set with Legemiddelansvarsforeningen. A certificate of insurance can be provided upon request.