CONFIDENTIAL

CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Phase III, open-label, multicentre, randomised trial to establish safety and efficacy of an EGF cancer vaccine in inoperable, stage IV biomarker positive, wild type EGF-R NSCLC patients eligible to receive standard treatment and supportive care
PROTOCOL NUMBER:	BV-NSCLC-002
EUDRACT NUMBER:	2013-005335-25
DRUG:	Epidermal growth factor (EGF) conjugated cancer vaccine
SPONSOR:	Bioven (Europe) Ltd. Registered office: Cruickshank Building North Aberdeen Biotechnology Craibstone Aberdeen AB12 9TR United Kingdom
CO-ORDINATING INVESTIGATOR:	Dr. Marianne Nicolson Aberdeen Royal Infirmary Foresterhill Aberdeen AB25 2ZN United Kingdom
CONTRACT RESEARCH ORGANISATION:	IndiPharm, Inc 701 Lee Road Suite 210 Wayne, Pennsylvania 19087 United States

VERSION TABLE

Final Version 1	27-Jan-2014
Final Version 1.1	11-Feb-2014

STATEMENT OF CONFIDENTIALITY

The information contained herein is expressly subject to the terms and conditions of the Confidentiality Agreement dated 28 October 2009 by and between IndiPharm and Bioven.

SIGNATURE PAGE

This Protocol was subjected to critical review. The information it contains is consistent with the current risk/benefit evaluation of the test preparation as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

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This Protocol has been written in accordance with current ICH-GCP guidelines

TABLE OF CONTENTS

1. GLOSSARY

ADR	Adverse drug reaction
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC 5	Target area under the concentration-time curve of 5 mg/mL·min
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CRO	Contract Research Organisation
DSMB	Data safety monitoring board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	^{51}Cr-ethylenediamine tetraacetic acid
EGF	Epidermal growth factor
EGF-R	Epidermal growth factor receptor
ELISA	Enzyme linked immunosorbent assay
EC	European Commission
EU	European Union
EW	Early Withdrawal
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma glutamyl transferase
GM-CSF	Granulocyte-macrophage colony stimulating factor
GMP	Good Manufacturing Practice
GP	General practitioner
HIV	Human immunodeficiency virus
hu-rEGF	Human recombinant epidermal growth factor
ICF	Informed consent form
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IRP	Independent review panel
ITT	Intention-to-Treat
KRAS	Kirsten ras sarcoma viral oncogene
LDH	Lactate dehydrogenase
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCS	Mental component summary
MCV	Mean corpuscular volume
MREC	Multicentre Research Ethics Committee
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung carcinoma
ORR	Overall response rate
OS	Overall survival
OSR	Overall survival rate
PIS	Patient Information Sheet
PR	Partial response
PCS	Physical component summary
PD	Pharmacodynamics
PFS	Progression-free survival
PP	Per Protocol
QA	Quality assurance
QoL	Quality of life
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation; Stable disease
SmPC	Summary of product characteristics
SUSAR	Suspected unsuspected serious adverse event
SOP	Standard operating procedure
TMF	Trial master file
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America

WBC	White blood cell (count)
WMA	World Medical Association

2. PROTOCOL SYNOPSIS

Title	A Phase III, open-label, multicentre, randomised trial to establish safety and efficacy of an EGF cancer vaccine in inoperable, stage IV(TMN 7th edition) biomarker positive, wild type EGF-R, NSCLC patients eligible to receive standard treatment and supportive care.
Protocol Number	BV-NSCLC-002
EudraCT Number	2013-005335-25
Investigational Product	Epidermal growth factor (EGF) cancer vaccine
Coordinating Investigator:	Dr. Marianne Nicolson Aberdeen Royal Infirmary, Foresterhill, Aberdeen, AB25 2ZN, United Kingdom (UK)
Number of Centres & Countries	Approximately 65 centres in 14 countries (Australia, Czech Republic, Germany, Hungary, India, Malaysia, Philippines, Poland, Spain, Thailand, Ukraine, United Kingdom [UK], United States of America (USA) and Vietnam.
Phase	Phase III
Indication	Non-small cell lung carcinoma (NSCLC)
Study Design	This is a Phase III, open-label, multicentre, randomised trial. Screening: Patients will attend the clinic to undergo screening procedures at Visit 1. Randomisation: Once Stage IV NSCLC (TNM 7th edition 2010) has been confirmed (histologically or cytologically) and in accordance with the inclusion/exclusion criteria, eligible patients with serum EGF concentration above threshold level of 250 pg/ml and wild type EGF-R will be randomised to an active vaccination group or non-vaccination group in a 1:1 ratio. Patients will also be stratified by ECOG performance status (0 vs. 1) and histological subtype (squamous vs. non-squamous) to ensure equal distribution of these potentially influential factors. All patients will undergo study assessments (Visit 2a). Patients randomised to the active vaccination group will receive a low dose of cyclophosphamide (200 mg/m^2 body surface area [BSA], intravenously). Initial Vaccination Phase: Patients in the active vaccination group only will receive their first vaccination (Visit 2b) 3 days after Visit 2a and a second vaccination (Visit 2c) 14 days later. First-Line Chemotherapy: All patients enrolled in the trial will commence first-line chemotherapy (Visit 3a), as per normal standards of clinical care (i.e. by using a platinum doublet chemotherapy). For non-vaccinated patients this start date should be within 10 days of Visit 2a (Randomisation). For patients in the active vaccine group this start date should be 7 days (max. 10 days) after Visit 2c. Pemetrexed is permitted as maintenance therapy after first-line chemotherapy in those patients who have not progressed on initial platinum-based combination chemotherapy (whether or not containing pemetrexed, as

	per local guidelines). No other maintenance therapy is permitted. Assessments during chemotherapy (Visits 3a, 3b, 3c, etc) will be performed at the start of every cycle of chemotherapy except for CT/MRI scans which will be performed at the end of each cycle at applicable visits. Vaccinated patients will in addition attend additional visit days (Visit 3b, Day-2 and Visit 3c, Day -2) for EGF vaccine administration. These additional visits will occur 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b and 3c). No vaccination will be given before Cycles 1, 4, 5, and 6 of chemotherapy (Visits 3a, 3d, 3e, and 3f). Post First-Line Chemotherapy, Pre-Progression Phase: For all patients in both groups, Visit 4a will begin 9 weeks after the last platinum-based chemotherapy visit and will continue every 8 weeks (Visits 4b, 4c, etc) until progression or withdrawal from the study. Patients in the active vaccination group will receive the vaccine **at a reduced dose** until disease progression. Serum EGF will be measured at each visit on all patients. Upon central review of the EGF data, visits (for all patients in both treatment groups) may be changed to a 6-week vaccination schedule if serum EGF increases above the baseline level established by primary vaccination. Patients in both groups will be followed up for disease progression according to RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1). At the end of every 2 cycles of chemotherapy, at the first visit of the Post First-Line platinum-based Chemotherapy Pre-Progression Phase, and every 8 weeks thereafter, disease stage and progression will be assessed per protocol in both groups according to the same methodology as used to determine disease stage and tumour size at time of Screening. These will include chest and upper abdomen Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans. A blinded independent review panel (IRP) will review all scans used in the tumour assessment for this study. Post-Progression Follow-up: For all patients, visits (5a, 5b, etc) will begin once progression is confirmed radiologically. Only data relating to adverse events (AEs) (for 30 days from the date of progression or withdrawal from the study), concomitant medications (oncology related therapies only) and survival status will continue to be collected every 12 weeks until death or withdrawal from the study. For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.
Primary Objective	• To assess overall survival (OS) of an EGF cancer vaccine in inoperable, stage IV biomarker positive, wild type EGF-R, NSCLC patients when compared to the control group receiving best treatment and supportive care.

Secondary Objectives	• To assess progression-free survival (PFS), survival rate, time to progression (TTP), response rate (RECIST criteria) and quality of life (QoL). • To establish the safety of an EGF cancer vaccine in inoperable, stage IV NSCLC patients.
Exploratory Objectives	• To explore the pharmacodynamics (PD) of the EGF cancer vaccine (including serum EGF and anti-EGF antibody titres). • To assess effect of KRAS and ALK rearrangements on efficacy of EGF vaccine
Study Duration	Patients will continue to receive study vaccine up until the point of disease progression. Thereafter patients will enter a follow up phase and will not receive further study vaccine or any further study specific procedures. Patients will remain in the study until 24 months after last patient has been randomised, or earlier if all patients have completed or withdrawn from the study prior to this time point.
Sample Size	The sample size is based on the following assumptions: • 15-month recruitment period • 24 month follow-up period from last patient recruited • Hazard ratio of control versus vaccine of 1.409 (corresponding to a median overall survival after randomisation of 11 months versus 15.5 months [an extension of 4.5 months]). • 1:1 ratio of active versus control. • Interim analysis once 150 patients have reached 12 months after randomisation Based on these assumptions a two-sided log rank test with 80% power needs in total 267 events (deaths) and 167 patients in each treatment group to show a 5% significance. Assuming a drop-out rate of 20%, approximately 418 patients need to be randomised into the study (with approximately 1393 patients to be screened [assuming a 70% screening failure rate]).
Principal Selection Criteria	Patients are eligible to be included in the study if they: 1. Are aged 18 or older. 2. Have serum EGF concentration >250 pg/ml determined from sample taken at screening. 3. Have wild type EGF-R sequence. 4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 5. Have adequate bone marrow, liver and renal function, as assessed by the Investigator. A sample taken at Screening should confirm that: • White blood cell (WBC) count ≥ 3000 per µL • Platelet count ≥ 100,000 per µL • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (or ≤ 5 x ULN when liver metastases are present)

	• Total bilirubin ≤ 1.5 x ULN • Serum creatinine ≤ 1.5 x ULN 6. Have histologically and/or cytologically confirmed diagnosis of NSCLC, corresponding to locally and regionally advanced, inoperable disease (Stage IV [as defined by the American Joint Committee on Cancer staging system- TNM 7th edition 2010]), excluding brain metastases. 7. Are eligible to receive first-line chemotherapy (without concurrent radiotherapy to thorax measurable lesions or consolidation radiotherapy). 8. Agree to use double-barrier contraception (males and females alike [if applicable]). A negative pregnancy test must be documented at Screening for females of childbearing potential. Note: Females of childbearing potential are defined as those women with less than 2 years after last menstruation and not surgically sterile, while post-menopausal refers to those women with at least 2 years from last menstruation. 9. Have signed a voluntary written informed consent form (ICF). Patients should be cooperative, willing and able to participate and adhere to the Protocol requirements, including their availability for the follow-up. Patients will be ineligible if one or more of the following statements are applicable: 1. Patient has no measurable disease (as defined by RECIST criteria, version 1.1). 2. Patient has EGF-R mutation. 3. Patient has EGF serum concentration below required threshold. 4. Patient is a candidate for concurrent chemo-radiotherapy or post chemo thoracic radiotherapy. 5. Patient has a history of known or suspected central nervous system (CNS) metastases. 6. Patient has a history of primary malignancy (except resected non-melanoma skin cancer or curatively treated carcinoma in situ of the cervix), unless in complete remission and off all chemotherapy and/or radiotherapy for that disease for a minimum of 5 years. Any palliative radiotherapy to alleviate pain in bone metastases is permitted. 7. Patient is taking immunosuppressant drugs such as azathioprine, tacrolimus, cyclosporine, etc. Use is not permitted within 1 month before Screening. 8. Patient is taking any other immunotherapy. 9. Patient has primary or secondary immunodeficiencies (e.g. documented Human Immunodeficiency Virus [HIV]). 10. Patient has autoimmune disease. 11. Patient has undergone splenectomy. 12. Patient is taking oral, intramuscular or intravenous corticosteroids. Use is not permitted within 1 month before Screening. Inhaled corticosteroids to treat respiratory

	insufficiency (e.g. chronic obstructive pulmonary disease [COPD]), or topical steroids are permitted. 13. Patient has neurotoxicity (Grade ≥2). 14. Patient has diarrhoea (Grade ≥2). 15. Patient has received other vaccines (with the exception of the influenza vaccine), within 1 month before Screening. 16. Patient has a history of any severe or life-threatening hypersensitivity reaction. 17. Patient has an unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, serious cardiac arrhythmia requiring medication, hepatic, renal and metabolic disease). 18. Patient has recent history (within 6 months before Screening) of chronic alcohol or drug abuse which may compromise the patient's safety or ability to participate in study activities. 19. Patient has a history of psychiatric disorder that prevents patients from providing informed consent or following Protocol instructions. 20. Patient is currently enrolled in an investigational device or drug trial, or <1 month since completing an investigational device or drug trial. 21. Female patients who are pregnant or lactating. 22. Patient has any other factor that in the opinion of the Investigator (or designee) would make the patient unsafe or unsuitable for the study.
Investigational Product	
Formulation	The active component of the vaccine is human recombinant EGF (hu-rEGF). The P64K carrier protein from *N.meningitidis* plays a role in overcoming immunological tolerance to self proteins, in this particular case, the human EGF. Both biological compounds are recombinant compounds produced in Yeast and *E.coli* cells, respectively. Prior to vaccination, the active chemical conjugate (hu-rEGF-rP64K) will be mixed with the adjuvant (Montanide ISA 51 VG [Seppic, France]). Both components (conjugate and adjuvant) are in one dose presentations.
Dosage	The dosage of conjugate is 1 mg total protein per mL. 0.8 mL of this active component will be added to the same volume (0.8 mL) of adjuvant. 1.2 mL of the 1.6 mL conjugate-adjuvant mix will be extracted from the vial for vaccination. The dosage of active component is 0.6 mg.
Administration	Eligible patients randomised to the active vaccine group will receive the study vaccine according to the Schedule of Assessments. The patient will be injected at four sites (i.e. four injections – the deltoid muscle of both arms and the gluteus muscle of both legs) at each timepoint. The overall dose per timepoint will be 4.8 mL.

	Vaccinations during the Post First-Line Chemotherapy, Pre-Progression Phase (Visits 4a, 4b, 4c, etc) will be administered at **a reduced dose** i.e. patients will receive only 2 injections per timepoint (2.4 mL) instead of 4 injections per timepoint (4.8 mL). Patients will be injected at two sites (i.e. an injection in the deltoid muscle of both arms).
Reference Therapy	Patients randomised to the non-vaccination arm will be treated as per the normal standard of care.
Visit Schedule	Screening: Visit 1 Randomisation: Visit 2a: (within 28 days from Visit 1) including administration of cyclophosphamide for patients randomised to active vaccine group Initial Vaccination Phase (active vaccination group only): Visit 2b: (+3 days from Visit 2a) First dose of study vaccine Visit 2c: (+14 days from Visit 2b) Second dose of study vaccine First-Line Chemotherapy: Visit 3a: Control group: within 10 days from Visit 2a Active vaccine group: 7 days [max. 10] from Visit 2c Visits (3b, 3c, etc) will occur at the start of each chemotherapy cycle. Vaccinated patients will in addition attend a Visit 3b, Day-2 and Visit 3c, Day-2 for EGF vaccine administration 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b and 3c). Post First-Line Chemotherapy, Pre-Progression Phase: Visit 4a: (+9 weeks from last first-line chemotherapy visit) Note: Patients receiving platinum based doublet chemotherapy and not eligible to receive maintenance pemetrexed will attend Visit 4a, 9 weeks after their last first-line chemotherapy visit. For patients that are eligible for pemetrexed maintenance therapy, Visit 4a should take place 9 weeks after Visit 3d (4th first-line chemotherapy cycle visit) in addition to ongoing 3-weekly maintenance pemetrexed cycles. Visits (4b, 4c, etc) will continue every **8 weeks** until progression or withdrawal from the study. Vaccinations will be administered **at a reduced dose** in the active vaccine group only. Post-Progression Follow-Up: Visits (5a, 5b, etc) will occur every **12 weeks** once progression is observed. Visits will continue until death or withdrawal from the study.
Criteria for Evaluation Primary endpoints	• Overall survival.
Secondary endpoints	• Progression-free survival. • Survival rate. • Time to progression.

	• Response rate (RECIST criteria, version 1.1). • Quality of Life – SF-36 v2 questionnaire. • Safety (including AEs, laboratory evaluation, vital signs, physical examination).
Exploratory endpoints	• PD (including serum EGF and anti-EGF antibody titres). • KRAS and ALK rearrangements
Statistical Methods	The primary endpoint for this trial is to compare overall survival between active and control, defined as the time from randomisation to death from any cause. The survival distribution will be summarised using the Kaplan-Meier method together with 95% confidence intervals (CIs). Progression-free survival (PFS), defined as the time from randomisation to objective tumour progression or death (whichever occurs first), and time to progression (TTP), defined as the time from randomisation to first documented disease progression, will be described using the same method as the primary endpoint. Overall response rate (ORR), defined as the percentage of patients with a complete response (CR) or partial response (PR), as assessed by RECIST or those having died. ORR will be described using frequency tables together with the two-sided 95% Pearson-Clopper CIs. An interim analysis (without locking the database) will be performed once 150 patients have reached 12 months after randomisation. In addition, the number of events (deaths) that occur will be tracked. Summary statistics will be presented for continuous/quantitative variables, by way of number of patients (n), mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of qualitative variables. Percentages will be calculated using the total patients per treatment.

3. BACKGROUND INFORMATION

3.1 NAME AND DESCRIPTION OF THE INVESTIGATIONAL PRODUCT(S)

Lung cancer is the most common cancer globally, accounting for 1.2 million new cases annually. Approximately 80-85% of all lung cancer cases are non-small cell lung cancer (NSCLC). Lung cancer is one of the most difficult cancers to treat as a high proportion of patients have advanced stage disease at diagnosis; therefore it has one of the lowest survival rates of any cancer. The highest recorded 5-year patient survival rates (14%) are observed in the USA. In Europe, the 5-year overall survival (OS) rate is 8%, similar to that of the developing world.

Surgical resection remains the primary and most effective modality for early disease, however, only a quarter of patients undergo successful resection, with a recurrence rate of 50%. Therapeutic approaches in advanced disease involve chemotherapy and/or radiotherapy; however this is associated with relatively poor results. For the vast majority of patients current treatment modalities are not effective. The median survival time for patients with Stage IV NSCLC treated with platinum-based chemotherapy combination regimens remains less than 12 months [1]. A variety of novel approaches are under investigation to improve the medical management of this disease including targeting the Epidermal Growth Factor Receptor (EGF-R) signalling pathway as it plays a central role in the regulation of cell growth, proliferation, differentiation and survival in normal and malignant cells.

The EGF-R belongs to a super-family of receptors with intrinsic tyrosine kinase activity. It is a 170 kD transmembrane protein with an extracellular ligand binding domain and an intracellular tyrosine kinase moiety. One of its ligands is the Epidermal Growth Factor (EGF); a 53 amino acid polypeptide that, upon binding to the receptor, dimerisation of the EGF-R occurs and multiple cell processes are regulated such as proliferation, differentiation, angiogenesis, transformation and apoptosis. EGF-R targeted treatments have shown great promise as anti-tumoural agents based on the following clinical observations:

i. Tumours of epithelial origin i.e. most solid tumours, e.g. lung, ovary, breast, prostate, head and neck over-express the EGF-R, reportedly up to 20-fold above normal levels.

ii. This over-expression of EGF-R is directly correlated with unfavourable prognosis, earlier relapse following surgery and higher rate of metastases.

Marketing authorisation in the European Union (EU) and USA has been granted for small molecule drugs that block the active site of tyrosine kinase and prevent signal transduction, such as gefitinib (Iressa®), erlotinib (Tarceva®), Crizotinib (Xalkori) and recently Afatinib approved in USA for treatment of advanced NSCLC. The EGF-R is also a therapeutic target for several monoclonal antibodies such as cetuximab (Erbitux®). The Sponsor's approach is to target the ligand of the EGF-R.

The product under clinical development, hu-rEGF-rP64k-Montanide ISA 51 VG, is a conjugated recombinant EGF vaccine with recombinant EGF as the active moiety and P64k as a carrier protein. At the time of administration to patients the conjugate is mixed with Montanide ISA 51 VG, a known mineral oil based adjuvant. This vaccine is under investigation for complementing or even replacing current therapeutic approaches for treatment of NSCLC.

3.2 NON-CLINICAL FINDINGS

Experiments in animal models provided impetus for clinical trials of EGF-R inhibitors in cancer patients. In previous studies, it has been shown that immunisation with autologous EGF in mice and monkeys provoked an antibody response [2]. It was also shown that mice with antibody titres against self-EGF had better survival when transplanted with an EGF-R expressing tumour [2, 3].

Further details can be found in the Investigator's Brochure [4].

3.3 CLINICAL FINDINGS

The clinical experience with the EGF vaccine began in 1995. Currently, several pilot clinical trials and Phase II randomised trials have been completed; with more than 100 advanced NSCLC patients receiving the EGF vaccine. The pilot clinical trials demonstrated that the EGF vaccine is safe and immunogenic, able to induce anti-EGF antibody response, and a decrease in serum EGF concentrations. The immunogenicity of the vaccine depends on the adjuvant, the dose, and schedule. It was demonstrated that increasing the EGF vaccine dose improved anti-EGF antibody titres. No significant toxicity was seen after vaccination [5, 6, 7 and 8].

A recently completed randomised Phase II trial validated the data obtained in the pilot trials. Comparison of immunised patients with a control, unvaccinated group demonstrated a good anti-EGF antibody response in 51.3% of vaccinated patients and in none of the control group [7]. Serum EGF concentration showed a major decrease in 64.3% of vaccinated patients. Good antibody response patients survived significantly more than those with poor antibody response. Also, patients whose serum EGF dropped below 168 pg/mL survived significantly more than the rest [7]. There was a trend to an increased survival for vaccinated patients compared with controls. The survival advantage for vaccinated patients compared with controls was statistically significant in the subgroup of patients with age younger than 60 years [7].

Over 500 patients have now been treated with the EGF vaccine. Further details can be found in the Investigator's Brochure [4].

3.4 POTENTIAL RISKS AND BENEFITS

<u>EGF Cancer Vaccine</u>

Current therapeutic approaches in advanced disease involve platinum-based chemotherapy, however the median survival time remains <12 months. The critical analyses of the above data indicate that advanced stage NSCLC patients vaccinated with the conjugated EGF vaccine according to the Vaccine-Chemotherapy-Vaccine schedule, survive significantly longer than non-vaccinated subjects. The safety of the vaccine has been established in clinical trials with more than 500 patients administered more than 10,000 doses. The most commonly reported adverse events (AEs) experienced were pain at the injection site, fever, headache, vomiting, chills, flushing, anorexia, cramps, hot flushes, hypertension (high blood pressure), hypotension (low blood pressure) and swelling at the injection site. The data generated to date indicate clinical efficacy, a good safety profile, and a positive risk/benefit assessment for the vaccine. The proposed study should further optimise the schedule of vaccine administration with respect to the immunological response.

Cyclophosphamide

Cyclophosphamide is a widely studied anti-cancer drug and is frequently used in combination chemotherapy regimens involving other cytotoxic drugs [9]. Its immunomodulating effects have significant dose-and therapeutic schedule-related repercussions. This pre-treatment was introduced to disrupt immunologic tolerance to EGF and to induce immunogenicity toward this human molecule from the first dose [10]. The benefits of a low dose of cyclophosphamide (200 mg/m^2 of body surface area [BSA]) administered 3 days before vaccine treatment onset have been described in the literature [11, 12].

3.5 TREATMENT

The active component of the vaccine is human recombinant EGF (hu-rEGF). The P64K carrier protein from *N.meningitidis* plays a role in overcoming immunological tolerance to self proteins, in this particular case, the human EGF. Both biological compounds are recombinant compounds produced in Yeast and *E.coli* cells, respectively.

Prior to vaccination, the active chemical conjugate (hu-rEGF-rP64K) will be mixed with the adjuvant (Montanide ISA 51 VG [Seppic, France]) to enhance the response to the vaccine. Both components (conjugate and adjuvant) are in one dose presentations.

The dosage of conjugate is 1 mg total protein per mL. 0.8 mL of this active component will be added to the same volume (0.8 mL) of adjuvant. 1.2 mL of the 1.6 mL conjugate-adjuvant mix will be extracted from the vial for vaccination.

Eligible patients randomised to the active vaccine group will receive the study vaccine according to the schedule outlined in Sections 5.2.1 and 5.4 and Table 2.

The patient will be injected at four sites (i.e. four injections – the deltoid muscle of both arms and the gluteus muscle of both legs) at each timepoint. The overall dose per timepoint will be 4.8 mL.

Vaccinations during the Post First-Line Chemotherapy, Pre-Progression Phase (Visits 4a, 4b, 4c, etc) will be administered at **a reduced dose** i.e. patients will receive only 2 injections per timepoint (2.4 mL) instead of 4 injections per timepoint (4.8 mL). Patients will be injected at two sites (an injection in the deltoid muscle of both arms).

If any of these injection sites cannot be used for any reason, alternative intramuscular injection site(s) can be used.

3.6 CONDUCT OF STUDY

This clinical study will be conducted in compliance to this Protocol, the guidelines of the World Medical Association Declaration of Helsinki, the guidelines of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), designated standard operating procedures (SOPs), and with local laws and regulations in the country of conduct.

3.7 POPULATION

Male or female patients, aged 18 years upwards, with proven locally and regionally advanced, inoperable NSCLC Stage IV, with wild-type EGF-R; serum EGF concentration >250 pg/ml, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;

adequate bone marrow, liver and renal function; who are eligible to receive first-line chemotherapy (without concurrent thoracic or consolidation radiotherapy).

Study centres will be selected for inclusion into this study that use the standard of care treatment regimens described in Section 7.6 of this Protocol.

4. STUDY OBJECTIVES AND PURPOSE

4.1 OBJECTIVES

The primary objective of this study is:

- To assess overall survival (OS) of an EGF cancer vaccine in inoperable, stage IV biomarker positive, wild type EGF-R, NSCLC patients when compared to the control group receiving best treatment and supportive care.

The secondary objectives of this study are:

- To assess progression-free survival (PFS), survival rate, time to progression (TTP), response rate (Response Evaluation Criteria In Solid Tumours [RECIST] criteria) and quality of life (QoL).
- To establish the safety of an EGF cancer vaccine in inoperable, stage IV NSCLC patients.

The exploratory objectives * of this study are:

- To explore the pharmacodynamics (PD) of the EGF cancer vaccine (including serum EGF and anti-EGF antibody titres).
- To assess effect of KRAS and ALK rearrangements on efficacy of EGF vaccine

Note: * The results for these exploratory endpoints will be reported separately from the main Clinical Study Report (CSR).

4.2 RATIONALE

The study vaccine is postulated to activate the immune system to generate an anti-EGF antibody response. The antibodies bind to circulating EGF and thereby prevent binding to EGF-R and subsequent activation, inhibiting the downstream signalling pathways [4]. This vaccine-based strategy has been shown to complement chemotherapy in prolonging survival of Stage IV NSCLC patients in Phase I and II clinical trials and has received marketing authorisation in Cuba as CIMAvax® for treatment of advanced NSCLC. The same vaccine has also received authorisation in Peru.

Pre-treatment with cyclophosphamide has been shown to disrupt immunologic tolerance to EGF and to induce immunogenicity toward this human molecule from the first dose [10]. Only patients in the active vaccine group will receive a single, low dose of cyclophosphamide at Randomisation (Visit 2a) i.e. 3 days prior to administration of the first vaccination (Visit 2b).

5. INVESTIGATIONAL PLAN

5.1 ENDPOINTS

5.1.1 Primary Endpoints

- Overall survival.

5.1.2 Secondary Endpoints

- Progression-free survival.
- Survival rate.
- Time to progression.
- Response rate (RECIST criteria, version 1.1).
- Quality of Life – SF-36 v2 questionnaire.
- Safety (including AEs, laboratory evaluation, vital signs, physical examination).

5.1.3 Exploratory Endpoints

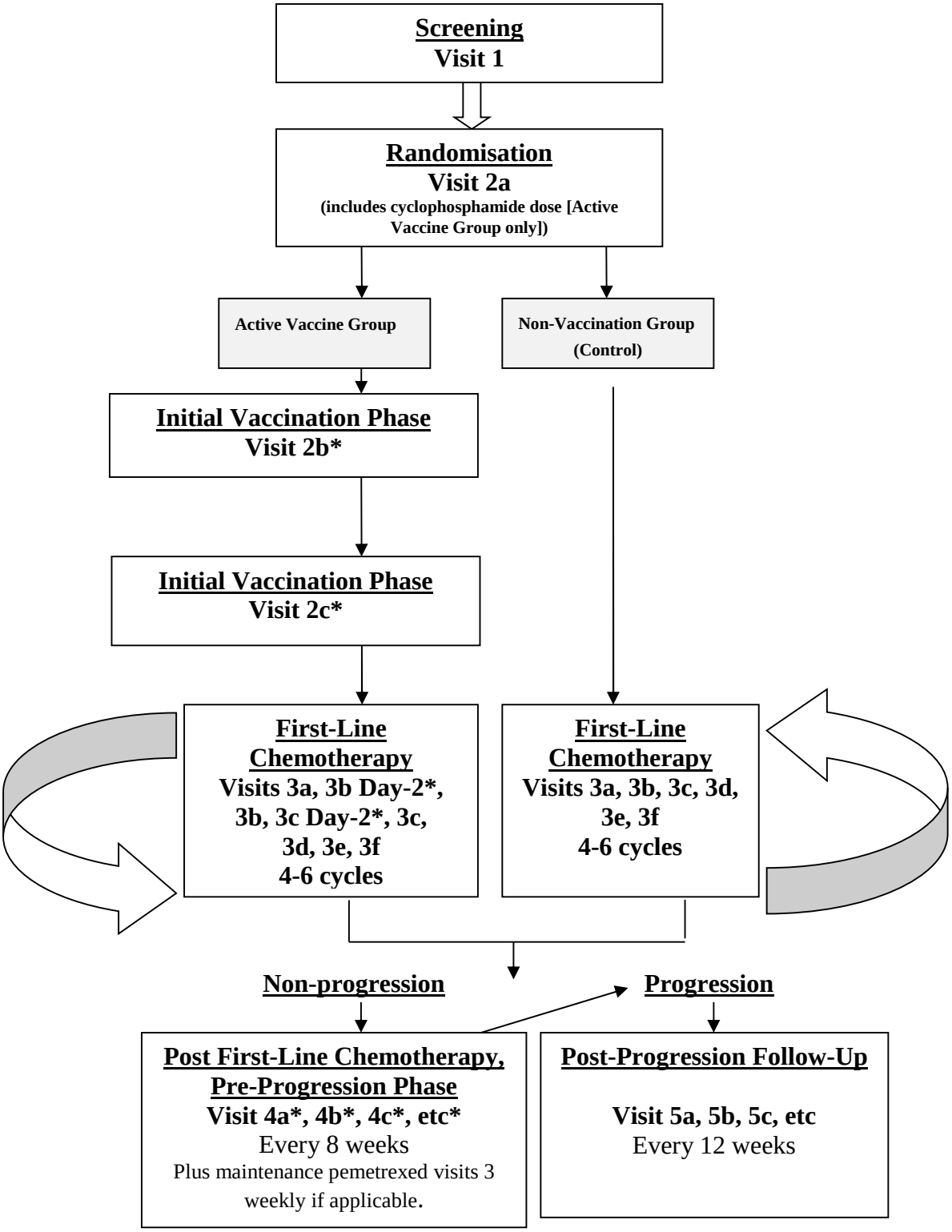
- PD (including serum EGF and anti-EGF antibody titres).
- KRAS and ALK rearrangements

5.2 OVERALL STUDY DESIGN AND PLAN

This is a Phase III, open-label, multicentre, randomised trial to be conducted in approximately 65 centres in 14 countries (Australia, Czech Republic, Germany, Hungary, India, Malaysia, Philippines, Poland, Spain, Thailand, Ukraine, United Kingdom [UK],,United States of America (USA) and Vietnam

A schematic diagram of the study design is shown in Figure 1. The Schedule of Assessments is presented in Table 2.

Figure 1. Schematic Diagram: Phase III, NSCLC EGF Vaccine Trial



*: Study vaccine administered to patients in the Active Vaccine Group only.
Note: First-line chemotherapy should be stopped at disease progression, after a maximum of 6 cycles or after 4 cycles in patients not responding to treatment. Maintenance pemetrexed may be delivered 3-weekly as per standard practice to patients with response or stable disease following at least 4 cycles of combination platinum-based chemotherapy.
Note: Following chemotherapy, patients who have not progressed will enter the Post First-Line Chemotherapy, Pre-Progression Phase.

An example of the scheduled visits is shown in **Table 1**.

Table 1. Schedule of Study Visits

	VISIT	ACTIVE VACCINE GROUP	CONTROL GROUP
Screening	1	Day 0	Day 0
Randomisation	2a	Up to Day 28	Up to Day 28
Initial Vaccination Phase	2b	* Day 31	-
Initial Vaccination Phase	2c	* Day 45	-
First-Line Chemotherapy - Cycle 1	3a	Day 52	Day 38
First-Line Chemotherapy - Cycle 2	3b		
Vaccine Administration Day	3b, Day-2	*Day 71	-
Chemotherapy Assessments	3b	Day 73	Day 59
First-Line Chemotherapy - Cycle 3	3c		
Vaccine Administration Day	3c, Day-2	*Day 92	-
Chemotherapy Assessments	3c	Day 94	Day 80
First-Line Chemotherapy - Cycle 4 [1, 2, 6]	3d	Day 115	Day 101
First-Line Chemotherapy - Cycle 5 [2]	3e	Day 136	Day 122
First-Line Chemotherapy - Cycle 6 [2]	3f	Day 157	Day 143
Post First-Line Chemotherapy, Pre-Progression Phase [3]	4a	* Day 220	Day 206
Post First-Line Chemotherapy, Pre-Progression Phase [4]	4b, 4c, etc	* +8 weeks	+ 8 weeks
Post-Progression Follow-Up Phase [5]	5a, 5b, etc	+12 weeks	+ 12 weeks

*: Study vaccine administered to patients in the Active Vaccine Group only. The vaccination administration day is an additional visit where vaccination group patients attend for study vaccination.

Assumes: 1 cycle = 21 days = 3 weeks

1: Non-responding patients as evidenced by RECIST will stop after 4 cycles and will enter the Follow-Up Phase.
2: Non-progressing patients will enter the Post First-Line Chemotherapy, Pre-Progression Phase after 4-6 cycles (maintenance pemetrexed is allowed)
3: The Post First-Line Chemotherapy, Pre-Progression Phase will start 9 weeks (63 days) after the last first-line chemotherapy visit (3b-3f).
4: Visits will continue every 8 weeks until progression, death or withdrawal from the study.
5: Patients who progress will enter the Post-Progression Follow-Up Phase and the study vaccine will be stopped.
6: Patients who are to be switched to maintenance pemetrexed should receive 4 cycles of platinum chemotherapy (whether or not containing pemetrexed, as per local guidance) before entering the Post-First-Line Chemotherapy Pre-Progression Phase.

Screening: Patients will attend the clinic to undergo screening procedures at Visit 1.

Patients will undergo a screening/baseline scan within 28 days prior to their first chemotherapy treatment. Scans should not be older than 4 weeks prior to the first study chemotherapy administration. In case of older assessments (i.e. scans performed more than 4 weeks prior to treatment start) a repeat imaging assessment should be performed during the Screening or Initial Vaccination Period and evaluated according to RECIST criteria (version 1.1). Patients EGF-R mutation status should be determined if this is not already known prior to screening visit. Analysis of biopsy should be performed locally or by an accredited centre in line with local practice.

Randomisation: Once inclusion/exclusion criteria have been verified, eligible patients will be randomised to an active vaccination group or non-vaccination group in a 1:1 ratio. Patients will also be stratified by ECOG performance status (0 vs. 1), and histological subtype (squamous vs. non-squamous) to ensure equal distribution of these potentially influential factors.

All patients will undergo study assessments (Visit 2a) within 28 days of Visit 1. Patients randomised to the active vaccination group will receive a low dose of cyclophosphamide (200 mg/m^2 BSA, intravenously).

Initial Vaccination Phase: Patients in the active vaccination group only will receive their first vaccination (Visit 2b) 3 days after Visit 2a and a second vaccination (Visit 2c) 14 days later. Study vaccine will be administered as one full dose at four injection points (1.2 mL per point).

Patients should be monitored in the clinic for at least 3 hours following their first four vaccinations (Visits 2b, 2c, 3b, Day-2 and 3c, Day-2).

First-Line Chemotherapy: All patients enrolled in the trial will commence first-line chemotherapy (Visit 3a), as per normal standards of clinical care (i.e. by using a platinum doublet chemotherapy). For non-vaccinated patients this start date should be within 10 days of Visit 2a. For vaccinated patients this start date should be 7 days (max. 10 days) after Visit 2c.

Assessments during chemotherapy (Visits 3a, 3b, 3c, etc) will be performed at the start of every cycle of chemotherapy except for CT/MRI scans which will be performed at the end of each cycle at applicable visits.

Vaccinated patients will in addition attend Visit 3b, Day-2 and Visit 3c, Day-2 for vaccine administration 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b and 3c). No vaccination will be given before Cycles 1, 4, 5, and 6 of chemotherapy (Visits 3a, 3d, 3e, and 3f).

Note: Non-responding patients as evaluated by RECIST will stop chemotherapy after 4 cycles and should enter the Follow-Up phase.

Post First-Line Chemotherapy, Pre-Progression Phase: Visit 4a will begin 9 weeks after the last chemotherapy visit. Vaccinations will be administered **at a reduced dose** in the active vaccine group only. Visits (Visit 4b, 4c, etc) will continue every **8 weeks** until progression or withdrawal from the study, at which point vaccinations will stop. Maintenance pemetrexed may be delivered to non-progressing patients at 3-weekly intervals according to local practice.

Note: In the event the patient cannot further tolerate chemotherapy, then study vaccinations can start after completing at least two cycles of chemotherapy. If two cycles of

chemotherapy cannot be tolerated, the patient should be withdrawn from the study. Patients who are to be treated with maintenance pemetrexed should not have progressed after receiving four cycles of platinum-based first-line chemotherapy.

Note: Patients receiving platinum based doublet chemotherapy who are not eligible to receive maintenance pemetrexed will attend Visit 4a, 9 weeks after their last first-line chemotherapy cycle.

For patients that are eligible for pemetrexed maintenance therapy, Visit 4a should take place 9 weeks after Visit 3d (4th first-line chemotherapy cycle) in parallel to ongoing 3-weekly maintenance pemetrexed cycles.

Maintenance Pemetrexed Visits

The unscheduled eCRF visit should be used to capture data from patients who receive pemetrexed as maintenance therapy. Vital signs, physical examination, laboratory evaluation (biochemistry, haematology and urinalysis), adverse events and pemetrexed administration should be recorded at a minimum.

At applicable visits, serum EGF will be measured. Upon central review of the EGF data, visits (for all patients in both treatment groups) may be changed to a **6-week** vaccination schedule if serum EGF increases above the baseline level established by primary vaccination.

Patients will be followed up for disease progression according to RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1). At the end of every 2 cycles of chemotherapy, at the first visit of the Post First-Line Chemotherapy, Pre-Progression Phase, and every 8 weeks thereafter, disease stage and progression will be assessed per protocol according to the same methodology as used to determine disease stage and tumour size at time of Screening. These will include chest and upper abdomen Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans, brain CT or MRI (only in case of suspected brain metastases), and/or bone scans with confirmatory X-ray if needed (in case of suspected bone metastases). A blinded independent review panel (IRP) will review all scans used in the tumour assessment for this study for consistency.

Post-Progression Follow-up: For all patients, visits (5a, 5b, etc) will occur every **12 weeks** once progression is observed. Only data relating to AEs (for 30 days from the date of progression or withdrawal from the study), concomitant medications (oncology related therapies only) and survival status will continue to be collected until death or withdrawal from the study.

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

Unscheduled Visits: Unscheduled visits can be performed when deemed necessary by the Investigator. Data from unscheduled visits should be recorded in the eCRF. The unscheduled visit should also be used to capture data from patients who receive pemetrexed as maintenance therapy as detailed above.

5.2.1 Study Procedures

The Schedule of Assessments is provided in Table 2.

Table 2. Schedule of Assessments

Study Assessment	Screening	Randomisation	Initial Vaccination Phase		First-Line Chemotherapy [1]						Post First-Line Chemotherapy, Pre-Progression Phase [2, 19]			Additional maintenance pemetrexed visits [19]	Post-Progression Follow-Up [10]	EW Visit
					3a	3b	3b	3c	3c	3d, 3e, 3f.						
Visit	1	2a	2b	2c		3b, Day-2[1a]		3c, Day-2[1a]			4a	4b, 4c, etc		Unscheduled	5a, 5b, 5c, etc	EW
Day/Week (since previous visit)	0	within 28 days	+3 days	+14 days	7 [max. 10] days from V2c or within 10 days of V2a						+9 wks	+8 wks [3]	[6 wks] [3]	+3 weeks	+12 wks	
Window (days)	-	-	+2	±2	-	±1	-	±1			±3	±3	±3	±1	±3	
Informed Consent (prior to any study procedures)	X															
Inclusion/Exclusion Criteria	X	X														
Demographics and Baseline Characteristics[17]	X															
Randomisation		X														
Medical History	X															
ECOG Performance Status	X	X			X		X		X	X	X	X	X			X
CT or MRI Scan [4, 5] (for tumour assessment)	X	(X) [4, 5]	(X) [4, 5]	(X) [4, 5]			X [4]			X [4]	X	X	X			X
RECIST Criteria (version 1.1) [4]	X	(X) [4, 5]	(X) [4, 5]	(X) [4, 5]			X [4]			X [4]	X	X	X			X
Electrocardiogram (ECG) (12-lead) [13]	X															X
Weight	X	X			X		X		X	X	X	X	X			X
Pregnancy Test (if applicable)	X[18]	X			X		X		X	X	X	X	X			X
Physical Examination	X	X			X		X		X	X	X	X	X	X		X
Laboratory Evaluation (haem., biochem., urinaly.)	X	X			X		X[15]		X[15]	X	X	X	X	X		X
Vital Signs (blood pressure, pulse rate, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Prior/Concomitant Medications	X[17]	X	X	X	X		X		X	X	X	X	X		X [11]	X
Progression/Survival Status			X	X	X		X		X	X	X	X	X		X	X
Quality of Life (SF-36 v2) Questionnaire		X	X	X	X		X		X	X	X	X	X			X
Pharmacodynamic Blood Sampling [6]	X[6,]	X [6]		X [6]	X [6]		X [6]		X [6]	X [6]	X [6]	(X) [6]	(X) [6]			X[6]
Cyclophosphamide (active group only) [7]		X [7]														
Vaccination (active group only) [9]			X	X		X		X			X [2]	X [2]	X [2]			
Injection Site Reactions (active group only)			X[8]	X[8]		X[8]		X[8]			X	X	X			X

Chemotherapy					X		X		X	X						
Adverse Event / Toxicity Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X [12]	X
Collect biopsy sample (for local EGF-R mutation analysis) [14]	X															
Collect biopsy sample (for central KRAS and ALK analysis)[16]		X														

1: Assessments during the First-Line Chemotherapy Phase will be performed at the start of every cycle of chemotherapy (Day 1). CT/MRI scans will be performed at end of every 2 cycles of chemotherapy.

1a: This visit is the 'EGF vaccination administration visit' and only applies to vaccinated patients

2: Vaccinations during the Post First-Line Chemotherapy, Pre-Progression Phase will continue every 2 months until progression, withdrawal from the study, or death. Patients will receive a reduced dose (i.e. 2 injections per timepoint instead of 4 injections per timepoint).

3: If serum EGF increases from the EGF baseline established by primary vaccination during the Post First-Line Chemotherapy, Pre-Progression Phase, the **8-week** vaccination schedule may be changed to a 6-**week** vaccination and visit schedule.

4: A CT or MRI scan (to assess NSCLC disease stage according to RECIST criteria) will be performed at Screening (Visit 1), at the end of every 2 cycles of chemotherapy (i.e. Cycles 2, 4, 6), and at each visit during the Post First-Line Chemotherapy, Pre-Progression Phase (i.e. every 8 weeks). Bone and brain scans will be performed if bone/brain metastases are suspected.

5: Patients will undergo a screening/baseline scan within 28 days prior to their first chemotherapy treatment. Scans should not be older than 4 weeks prior to the first study chemotherapy administration. In case of older assessments (i.e. scans performed more than 4 weeks prior to treatment start) a repeat baseline imaging assessment should be performed during the screening period or initial vaccination phase and evaluated according to RECIST criteria (version 1.1).

6: Blood samples will be analysed for serum EGF concentration at Screening, Randomisation (Visit 2a), after the end of the Initial Vaccination Phase (Visit 2c), at **each** First-Line Chemotherapy visit, at **each** Post First-Line Chemotherapy, Pre Progression Phase visit, and at the EW visit (if applicable). Anti-EGF antibody titre will be collected at the Randomisation visit (Visit 2a), the first Chemotherapy visit (Visit 3a), at **each** Post First-Line Chemotherapy, Pre Progression Phase visit, and at the EW visit (if applicable). Anti-EGF samples collected during the Post First-Line Chemotherapy, Pre-Progression Phase will only be analysed from the first and last visits in this phase. Blood samples for all patients in the active vaccine group but only 40% of patients in the control group will be analysed. For EGF concentration measurement 2 aliquots will be collected at applicable visits.

7: Cyclophosphamide (200 mg/m^2 BSA) administered to active vaccination group patients only at Randomisation (Visit 2a) i.e. 3 days before the first vaccination (Visit 2b).

8: Patients should be monitored in the clinic for at least 3 hours following their first four vaccinations (Visits 2b, 2c, 3b, Day-2 and 3c, Day-2). At following vaccination visits the monitoring may be reduced to 1 hour assuming no previous adverse reactions have been observed.

9: Vaccinations will be administered in the active group only, 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b, Day-2 and 3c, Day-2).

10: Follow-up visits will begin once progression has been observed and will continue every 3 months until death or withdrawal from the study.

11: Oncology specific medications only.

12: 30 days after progression or withdrawal from the study.

13: ECG may be taken at additional visits if clinically indicated.

14: A sample of the biopsy collected will be prepared for EGF-R mutation assessment by local laboratory or other accredited centre.

15: Laboratory evaluations for vaccinated patients at Visits 3b and 3c can occur on either day (vaccine administration day -2, or chemotherapy day) at the discretion of the Investigator.

16. A sample of biopsy (ideally from same biopsy taken for EGF-R mutation analysis) will be prepared for KRAS and ALK rearrangement assessment and sent to the central lab for assessment.

17. Prior medications to be recorded if taken within one month of screening.

18. Serum pregnancy test should be taken at screening; all other pregnancy tests can be performed on urine sample

19. Maintenance pemetrexed should be recorded on unscheduled visit page of the eCRF. Vital signs, physical examination, laboratory evaluation (biochemistry, haematology, urinalysis), adverse events and pemetrexed administration should be recorded at a minimum.

SCREENING:

Visit 1

- Informed consent.
- Patient eligibility (inclusion/exclusion criteria).
- Blood sample for PD assessment (serum EGF concentration). Sample to be analysed locally.
- Biopsy sample to confirm EGF-R mutation status (to be evaluated locally or at accredited centre in line with local practice), if not already determined). Note, biopsy can be stored and also used for KRAS and ALK sample at Visit 2.
- Demographics and baseline characteristics (age, race, height, smoking status).
- Medical history.
- ECOG performance status (see Appendix 3)
- CT or MRI scan * to assess NSCLC disease stage according to RECIST criteria.

  * Patients will undergo a screening/baseline scan within 28 days prior to their first chemotherapy treatment. Scans should not be older than 4 weeks prior to the first study chemotherapy administration. In case of older assessments (i.e. scans performed more than 4 weeks prior to treatment start) a repeat imaging assessment should be performed during the Screening or Initial Vaccination Period and evaluated according to RECIST criteria (version 1.1).
- 12-lead ECG.
- Weight.
- Serum pregnancy test (for females of childbearing potential).
- Physical examination.
- Laboratory evaluation (haematology, biochemistry, urinalysis).
- Vital signs (blood pressure, pulse rate, temperature).
- Prior (or current) medications taken within 1 month of screening.

RANDOMISATION:

Visit 2a (within 28 days of Screening)

- Patient eligibility confirmed.
- Randomisation (1:1 ratio).
- ECOG performance status.
- Biopsy sample prepared for KRAS and ALK rearrangement evaluation (to be evaluated by central lab). Note, sample from same biopsy taken at screening should ideally be used.
- CT or MRI scan. *

  * Patients will undergo a screening/baseline scan within 28 days prior to their first chemotherapy treatment. Scans should not be older than 4 weeks prior to the first study chemotherapy administration. In case of older assessments (i.e. scans

performed more than 4 weeks prior to treatment start) a repeat imaging assessment should be performed during the Screening or Initial Vaccination Period and evaluated according to RECIST criteria (version 1.1).

- Weight.
- Urine pregnancy test (for females of childbearing potential).
- Physical examination.
- Laboratory evaluation (haematology, biochemistry and urinalysis).
- Vital signs (blood pressure, pulse rate, temperature).
- Prior/concomitant medications.
- QoL (SF-36) questionnaire.
- Blood samples for PD assessment (serum EGF and anti-EGF antibody titre analysis) by central laboratory.
- Cyclophosphamide (200 mg/m^2 BSA) administered to **active vaccine group patients only**.
- AEs / toxicity assessment.

INITIAL VACCINATION PHASE - Active Vaccine Group only:

Visit 2b (+3 days from Visit 2a [+2 days window])

- Vital signs (blood pressure, pulse rate, temperature).
- Concomitant medications.
- Progression/survival status.
- QoL (SF-36) questionnaire.
- Vaccination.
- Injection site reaction(s) assessments
- AEs / toxicity assessment.

  * Check that baseline CT scan was performed within 28 days or repeat.

Visit 2c (+14 days from Visit 2b [±2 days window])

- Vital signs (blood pressure, pulse rate, temperature).
- Concomitant medications.
- Progression/survival status.
- QoL (SF-36) questionnaire.
- Blood sample for PD assessment (serum EGF concentration only) by central laboratory.
- Vaccination.
- Injection site reaction(s) assessments.
- AEs / toxicity assessment.

  * Check that baseline CT scan was performed within 28 days or repeat.

FIRST-LINE CHEMOTHERAPY:

Visits 3a, 3b, 3c, etc

All patients will undergo assessments at the start of each cycle of chemotherapy (i.e. Visit 3a = Cycle 1; Visit 3b = Cycle 2; Visit 3c = Cycle 3; etc).

Vaccinated patients will in addition attend a Visit 3b, Day-2 and Visit 3c, Day-2 for EGF vaccine administration 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b and 3c).

- **Control group: Visit 3a: Within 10 days from Visit 2a**
- **Active vaccine group: Visit 3a: +7 days (max. 10 days) from Visit 2c**

Note: Study vaccine will be administered to patients in the active vaccination group only at Visit 3b, Day-2 and Visit 3c, Day-2, 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b and 3c).

Visit 3b, Day-2 and 3c, Day-2 – EGF Vaccine Administration

- [Vaccination - see above].
- Vital signs (blood pressure, pulse rate, temperature).
- Injection site reaction(s) assessments.
- AEs / toxicity assessment.

Visits 3a, 3b, 3c, 3d, 3e and 3f

- [CT or MRI scan to assess NSCLC disease stage according to RECIST criteria at the end of every two cycles of chemotherapy i.e. end of Cycles 2, 4, and 6 (Visits 3b, 3d, and 3f)].
- ECOG performance status.
- Weight.
- Urine pregnancy test (for females of childbearing potential).
- Physical examination.
- Laboratory evaluation (haematology, biochemistry, urinalysis).
- Vital signs (blood pressure, pulse rate, temperature).
- Concomitant medications.
- Progression/survival status.
- QoL (SF-36) questionnaire.
- Blood sample(s) for PD assessment (serum EGF and anti-EGF antibody titre analysis at Visit 3a; serum EGF concentration only at subsequent First-Line Chemotherapy visits).
- Chemotherapy as per normal standards of care.
- AEs / toxicity assessment.

POST FIRST-LINE CHEMOTHERAPY, PRE-PROGRESSION PHASE:

Visit 4a: (9 weeks from last chemotherapy visit [±3 days window])

- ECOG performance status.
- CT or MRI scan to assess NSCLC disease stage according to RECIST criteria.
- Weight.
- Urine pregnancy test (for females of childbearing potential).
- Physical examination.
- Laboratory tests (haematology, biochemistry, urinalysis).
- Vital signs (blood pressure, pulse rate, temperature).
- Concomitant medications.
- Progression/survival status.
- QoL (SF-36) questionnaire.
- Blood sample(s) for PD assessment (serum EGF and anti-EGF antibody titre analysis)
- Vaccination (active vaccine group only) at **reduced dose** (see Sections 7.3 and 7.4).
- Injection site reactions.
- AEs / toxicity assessment.

Visit 4b, 4c, etc: (every 8 weeks [±3 days window])

Vaccinations during the Post First-Line Chemotherapy, Pre-Progression Phase will continue every **8 weeks** until progression or withdrawal from the study.

Assessments will be as per Visit 4a.

Note: If serum EGF increases from the EGF baseline established by primary vaccination during the Post First-Line Chemotherapy, Pre-Progression Phase, the 8-week vaccination schedule may be changed to a **6-week** vaccination schedule. This visit schedule will be used for patients in both treatment groups. Assessments will remain as described above.

Maintenance Pemetrexed Visits (every 3 weeks).

To be performed in addition to Visit 4a, 4b 4c etc if patient is to additionally receive maintenance pemetrexed

- Physical examination.
- Laboratory tests (haematology, biochemistry, urinalysis).
- Vital signs (blood pressure, pulse rate, temperature).
- AEs / toxicity assessment.

POST-PROGRESSION FOLLOW-UP:

Visits 5a, 5b, 5c, etc: (every 12 weeks [±3 days window])

For all patients, follow-up visits will begin once progression is observed.

Data collected at these follow-up visits will include:

- AEs / toxicity assessment (for 30 days after progression or withdrawal from the study).
- Concomitant medications (oncology related therapies only).
- Survival status.

Assessments will continue every 12 weeks until death or withdrawal from the study.

5.3 RANDOMISATION AND BLINDING

Eligible patients will be randomised to an active vaccination group or non-vaccination group in a 1:1 ratio.

To ensure equal distribution of potentially influential factors in the two study arms, patients will be stratified at randomisation according to the following parameters:

- ECOG performance status (0 versus 1)
- Histological subtype (squamous versus non-squamous)

IndiPharm will provide the randomisation schedule.

Randomisation will be controlled by the Interactive Response System.

This is an open-label trial and therefore blinding is not necessary.

5.4 STUDY TREATMENT

5.4.1 Identity of Investigational Product

EGF Vaccine

The EGF Vaccine is an active immunotherapy approach for the treatment of advanced NSCLC. The product will be used in adjunct with chemotherapy.

The vaccine is composed of human recombinant EGF (hu-rEGF) produced in yeast, and chemically conjugated to the P64K *Neisseria meningitides* recombinant protein produced in *Escherichia coli*. For protein conjugation, glutaraldehyde (0.05%) is added to the protein mixture allowing the reaction for 1 hour; then, the conjugated moiety is purified by ultrafiltration/diafiltration and sterile filtered. The conjugate is then mixed with an adjuvant (Montanide ISA 51 VG [Seppic, France]) to form water in oil emulsion immediately before injection. The study vaccine should be mixed (hu-rEGF-rP64K + adjuvant) by the Investigator (or designee) within 24 hours of administration.

The EGF vaccine is produced in the Centre of Molecular Immunology, Havana, Cuba, in manufacturing facilities equivalent to European Medicines Agency Good Manufacturing Practice (GMP) standards.

The dosage of conjugate is 1 mg total protein per mL. 0.8 mL of this active component will be added to the same volume (0.8 mL) of adjuvant.

A volume of 1.2 mL of the 1.6 mL conjugate-adjuvant mix will be extracted from the vial for vaccination. The dosage of active component per single injection is 0.6 mg. At visits where 4 injections are given, the total dose of active component is 2.4 mg. At visits where 2 injections are given, the total dose of active component is 1.2 mg.

Cyclophosphamide

Cyclophosphamide is reported to modulate the immune system in hosts. Recent studies show selective suppression by cyclophosphamide of CD4+, CD25+ naturally occurring regulatory T cells, which are widely believed to play a role in immune tolerance. Furthermore, previous reports showed that cyclophosphamide pre-treatment before vaccination increased antibody responses, which was explained by its effect on suppressor T cells. The benefits of a low dose of cyclophosphamide (200 mg/m^2 of BSA) administered 3 days before vaccine treatment onset have been described in the literature [11, 12].

5.4.2 Packaging and Labelling

The manufacture, filling, and final product testing of the rEGF-rP64k conjugate will be performed by the Centre of Molecular Immunology, Havana, Cuba.

Labelling and packaging of the study vaccine (and cyclophosphamide) will be conducted by Biotec Services International Ltd., UK.

Vaccine and adjuvant will be labelled in accordance with national regulations. The label will contain the information as required by the relevant regulatory and national requirements.

Labelling will be performed according to Annex 13 of the GMP guidelines of the European Commission (EC), ICH-GCP guidelines, and local law.

5.4.3 Storage

The study vaccine supplied is to be used exclusively in the clinical study according to the instructions of this Protocol.

The Investigator (or designee e.g. Pharmacy) must confirm the receipt of the study medication with his/her signature. A copy of this receipt must be kept by the Investigator and another copy will be retained by IndiPharm.

The purified rEGF-rP64K conjugate should be stored at 2-8ºC (36-46°F), in accordance with the study vaccine label.

Study medication must be stored in securely locked areas not generally accessible until administered to the patients. The key to the storage area is to be kept by the Investigator (or other person responsible for the study medication). The store will be accessible only to those persons authorised by the Investigator to dispense/administer the study vaccine.

5.4.4 Destruction of Surplus Medication

All surplus study drug will be sent to Biotec Services International Ltd., UK for destruction following authorisation from IndiPharm and the Sponsor.

5.5 DURATION OF STUDY PARTICIPATION

Patients will continue to receive study vaccine up until the point of disease progression. Thereafter patients will enter a follow up phase and will not receive further study vaccine or any further study specific procedures. Patients will remain in the study until 267 events (deaths) have occurred. Non-progressing patients may continue to receive the study vaccine after the end of the study, if the Investigator deems it clinically beneficial for the patient.

5.6 DISCONTINUATION CRITERIA

The discontinuation criteria for individual patients, parts of study and the entire study are presented in Sections 6.3 to 6.5.

5.7 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Investigator, or an approved representative, should maintain records of the product's delivery to the study centre, the inventory at the centre, the administration to each patient, and will ensure that all investigational products are stored in a secure, limited access area. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and study patients. A temperature log should also be kept. Investigators should maintain records that document adequately that the patients were administered the doses specified by the Protocol and reconcile all investigational product(s) received from the Sponsor.

To ensure adequate records, all study treatments will be accounted for on an ongoing basis throughout the study in drug accountability forms at the study centre. Records will be kept in accordance with the applicable regulatory requirements and the Investigator will ensure that that study medication is dispensed only by qualified site staff. These records will be independently monitored by a IndiPharm monitor.

5.8 CODE BREAKS

This is an open label study and therefore there are no blinding procedures.

5.9 SOURCE DATA

Source documents (including all demographic and medical information, electronic case report forms [eCRFs], diaries, questionnaires, and a copy of the signed informed consent form [ICF] indicating the study number and title) for each patient in the study will be maintained by the Investigator or designee (generally in the patient's files), and all information in the eCRFs must be traceable to the source documents.

All data should be recorded directly into the patient's medical record (or patient diaries or questionnaires) as source data. It will be confirmed at the Trial Initiation Monitoring Visit which documents will be considered as source data for each Investigator centre. These will be documented and reviewed by the monitor at each monitoring visit.

Source documents must be available to document the existence of the patient and substantiate the integrity of study data collected.

5.10 Discussion of Study Design, Including the Choice of Control Groups

Patients will provide written informed consent and will be screened at Visit 1, prior to any study specific procedures being performed. Male and female patients aged 18 upwards are eligible for inclusion. Potential patients will be tested at screening for serum EGF concentration, and those with EGF concentration measured locally (or via other accredited centre) at ≤250 pg/ml will be excluded. Data from an ongoing clinical trial, EC_081, suggest that the higher the EGF titre at enrolment, the more significant the survival benefit with treatment with the vaccine appears to be. Preliminary results suggest that without treatment with the vaccine, those patients with high EGF titres have the shortest overall survival time. This may be the result of EGF-R/EGF being the most important or sole driver of disease in these patients. Enrolment of only those patients with a high EGF concentration may therefore lead to superior survival benefit.

Patients with EGF-R mutation should be excluded, as this subpopulation of NSCLC patients may be treated with drugs licensed for this specific condition.

Patients will return to the clinic within 28 days from Visit 1 for randomisation to treatment, assuming all eligibility criteria have been met. Scans should not be older than 4 weeks prior to the first study chemotherapy administration. In case of older assessments (i.e. scans performed more than 4 weeks prior to treatment start) a repeat imaging assessment should be performed during the Screening or Initial Vaccination Period and evaluated according to RECIST criteria (version 1.1).

Eligible patients will be randomised (1:1 ratio) at this visit and will undergo study assessments (Visit 2a). Patients randomised to the active vaccine will receive a low dose of cyclophosphamide (200 mg/m^2 BSA) to induce immunogenicity towards EGF [4]. Cyclophosphamide may have side-effects (for example, nausea, vomiting, diarrhoea, alopecia, etc) which the patient will be informed of via the Patient Information Sheet and in consultation with the Investigator.

Vaccinations will be administered as one full dose at four injection points (1.2 mL per point). Patients in the active vaccine group will attend the clinic for their first vaccination (Visit 2b), 3 days after Visit 2a. A second vaccination will be administered at Visit 2c, 14 days after Visit 2b. Patients will then begin first-line chemotherapy (Visit 3a) between 7 and 10 days after Visit 2c. The vaccine is administered before chemotherapy with the aim to induce a better antibody response to EGF and to decrease the serum EGF level [4]. The second vaccination should be given 7 days [maximum 10 days] prior to the commencement of chemotherapy to allow this immunological response to occur [4].

Patients in the (control) non-vaccination group will begin first-line chemotherapy (Visit 3a) as soon as possible and within 10 days of Visit 2a.

Chemotherapy regimens and the care administered to all patients enrolled in the study will be as per standard clinical care. In active vaccine group patients, the study vaccine will be administered 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b, Day -2 and 3c, Day -2). No study vaccine will be administered before Cycles 1, 4, 5 or 6 (Visits 3a, 3d, 3e or 3f). If chemotherapy is planned to be delayed (for example, due to low white cell counts/platelets) the study vaccine administration should also be delayed. If the study vaccine is administered but then chemotherapy is delayed, patients will continue in the protocol as normal. The patient will not be withdrawn for this reason.

Nine weeks after the last combination chemotherapy visit, all patients will enter the Post First-Line Chemotherapy, Pre-Progression Phase (Visit 4a) even if maintenance pemetrexed is to be delivered. Patients in the active vaccine group will receive the study vaccine **at a reduced dose** each visit, which will be followed by measurement of serum EGF.

In order to initiate immune response to human "self" protein, the initial vaccination regimen will consist of four vaccinations - two prior to initiation of chemotherapy and two during the initial cycles of chemotherapy. As chemotherapy has a strong negative impact on rapidly dividing cells including immune cells, the capacity of these cells to respond to vaccination decreases progressively with each new chemotherapy cycle, thus making vaccination no longer relevant. Vaccinations will therefore only be administered in conjunction with the second and third cycles of chemotherapy to further complete and strengthen the immunological responses induced by vaccinations prior to chemotherapy. Vaccination will not be administered during cycle 1, or during cycles 4, 5 or 6 when the immune system will be significantly depressed. After chemotherapy, when the patient enters the 'Post First-line Chemotherapy, Pre-Progression Phase' vaccinations will be resumed and those vaccinations will boost or maintain immunological level. To boost previously produced immune responses, lower vaccine doses are generally used, hence only two injections of vaccine will be administrated at each time point during this phase.

The Post First-Line Chemotherapy, Pre Progression Phase will continue (Visits 4b, 4c, etc) every **8 weeks** until progression or withdrawal from the study. Upon central review of the EGF data, visits may be changed to a **6-week** vaccination schedule for all patients if serum EGF increases above the baseline level established by primary vaccination.

Follow-up visits (Visits 5a, 5b, etc) will begin once progression is observed. Patients will not undergo any further study specific procedures and the study vaccine will be stopped in the active vaccine group. Only data relating to AEs, concomitant medications (oncology related therapy only) and survival status will continue to be collected every **12 weeks** until death or withdrawal from the study.

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

6. SELECTION AND WITHDRAWAL OF PATIENTS

For both the study vaccine and cyclophosphamide there are no gender-specific side-effects known or to be expected. Thus, male and female patients may be included in the study.

6.1 PATIENT INCLUSION CRITERIA

Patients are eligible to be included in the study if they:

1. Are aged 18 years upwards.
2. Have serum EGF concentration > 250pg/ml determined from sample taken at screening.
3. Have wild type EGF-R sequence.
4. Have an ECOG performance status of 0 or 1.
5. Have adequate bone marrow, liver and renal function, as assessed by the Investigator. A sample taken at Screening should confirm that:
    - White blood cell (WBC) count ≥ 3000 per µL
    - Platelet count ≥ 100,000 per µL
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (or ≤ 5 x ULN when liver metastases are present)
    - Total bilirubin ≤ 1.5 x ULN
    - Serum creatinine ≤ 1.5 x ULN
6. Have histologically and/or cytologically confirmed diagnosis of NSCLC, corresponding to locally and regionally advanced, inoperable disease Stage IV [as defined by the American Joint Committee on Cancer staging system [13]), excluding brain metastases.
7. Are eligible to receive first-line chemotherapy (without concurrent radiotherapy to thorax measurable lesions or consolidation radiotherapy).
8. Agree to use double-barrier contraception (males and females alike [if applicable]). A negative pregnancy test must be documented at Screening for females of childbearing potential.

    Note: Females of childbearing potential are defined as those women with less than 2 years after last menstruation and not surgically sterile, while post-menopausal refers to those women with at least 2 years from last menstruation.
9. Have signed a voluntary written ICF. Patients should be cooperative, willing and able to participate and adhere to the Protocol requirements, including their availability for the follow-up.

6.2 PATIENT EXCLUSION CRITERIA

Patients will be ineligible if one or more of the following statements are applicable:

1. Patient has no measurable disease (as defined by RECIST criteria, version 1.1).
2. Patient has EGF-R mutation sequence.

3. Patient has EGF serum level below the required threshold.
4. Patient is a candidate for concurrent chemo-radiotherapy or post chemo thoracic radiotherapy.
5. Patient has a history of known or suspected central nervous system (CNS) metastases.
6. Patient has a history of primary malignancy (except resected non-melanoma skin cancer or curatively treated carcinoma in situ of the cervix), unless in complete remission and off all chemotherapy and/or radiotherapy for that disease for a minimum of 5 years. Any palliative radiotherapy to alleviate pain in bone metastases is permitted.
7. Patient is taking immunosuppressant drugs such as azathioprine, tacrolimus, cyclosporine, etc. Use is not permitted within 1 month before Screening.
8. Patient is taking any other immunotherapy.
9. Patient has primary or secondary immunodeficiencies (e.g. documented HIV).
10. Patient has autoimmune disease.
11. Patient has undergone splenectomy.
12. Patient is taking oral, intramuscular or intravenous corticosteroids. Use is not permitted within 1 month before Screening. Inhaled corticosteroids to treat respiratory insufficiency (e.g. chronic obstructive pulmonary disease [COPD]), or topical steroids are permitted.
13. Patient has neurotoxicity (Grade ≥2).
14. Patient has diarrhoea (Grade ≥2).
15. Patient has received other vaccines (with the exception of the influenza vaccine), within 1 month before Screening.
16. Patient has a history of any severe or life-threatening hypersensitivity reaction.
17. Patient has an unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, serious cardiac arrhythmia requiring medication, hepatic, renal and metabolic disease).
18. Patient has recent history (within 6 months before Screening) of chronic alcohol or drug abuse which may compromise the patient's safety or ability to participate in study activities.
19. Patient has a history of psychiatric disorder that prevents patients from providing informed consent or following Protocol instructions.
20. Patient is currently enrolled in an investigational device or drug trial, or <1 month since completing an investigational device or drug trial.
21. Female patients who are pregnant or lactating.
22. Patient has any other factor that in the opinion of the Investigator (or designee) would make the patient unsafe or unsuitable for the study.

6.3 PATIENT WITHDRAWAL CRITERIA

6.3.1 Removal of Patients from Therapy or Assessment

The patient will be advised in the ICF that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's, the contract research organisation's (CRO), or the Sponsor's discretion at any time.

If a patient is withdrawn from the study before disease progression, they will be asked to attend the Early Withdrawal (EW) visit (see **Table 2** for procedures and assessments).

Patients in the active vaccine group will continue to receive vaccinations until progression, withdrawal from the study, or death.

In the event that the patient drops out of the study or is withdrawn from the study, the end of study/discontinuation page in the patient's eCRF should be completed. On the end of study/discontinuation page the Investigator (or designee) should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal. Withdrawn patients will not be replaced. Disease progression is not considered to be a reason for withdrawal from the study as patients should continue to be followed in the follow-up phase to allow overall survival to be evaluated.

The following are reasons for patient dropout/withdrawal:

Withdrawn by the Investigator due to:

- Adverse event.
- Patient showing clinical or radiological progression during the Initial Vaccination Phase (i.e. Visits 2b and 2c), prior to commencement of chemotherapy.
- Protocol violation or non-compliance with the Protocol (e.g., missed vaccinations, <2 cycles of chemotherapy completed).
- Administration of a prohibited medication or radiotherapy to any area other than bone.
- Pregnancy.
- Clinically significant abnormal laboratory value(s) that Investigator considers to warrant patient withdrawal.
- Toxicity.
- Other.

The patient requested withdrawal due to:

- An AE for which the Investigator did not consider removal from the study necessary.
- Withdrawal of consent.
- Other.

Other:

- Sponsor/CRO requested patient to be withdrawn (e.g. protocol violation).
- Lost to follow-up.
- Administrative problems.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. All attempts to make contact with the patient should be documented in source notes.

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

6.3.1.1 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be assembled and will be responsible for monitoring the safety of the patients in the study. The DSMB will consist of at least two clinicians and one statistician with expertise in oncology trials. The DSMB will make recommendations to the Sponsor regarding the conduct of the study, including possible early discontinuation for safety reasons. The DSMB will operate according to a charter signed by all members, which will detail the objectives and the proposed meeting times of the committee.

6.3.2 Pregnancy

6.3.2.1 Female Patients Pregnancy

Patients who become pregnant during the study should discontinue the study immediately.

Patients should be instructed to notify the Investigator if it is determined after completion of the study that they became pregnant during the treatment phase of the study.

Whenever possible a pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to IndiPharm and/or the Sponsor after delivery and at important developmental milestones during the first year.

6.3.2.2 Male Patients' Partners Pregnancy

Male patients should be instructed to use adequate contraception whilst taking part in the study.

Male patients should be instructed to notify the Investigator if it is determined that during the study or after completion of the study that their partner became pregnant during the treatment phase of the study.

Whenever possible any pregnancy should be followed to term, any premature terminations reported, and the status of the mother and child should be reported to IndiPharm and/or the Sponsor after delivery and at important developmental milestones during the first year.

6.4 PREMATURE TERMINATION OF STUDY IN A STUDY CENTRE

The Sponsor reserves the right to discontinue the study at any time. The reasons will be discussed with the Investigator. A study site may also be discontinued by the Sponsor for significant deviations from the Protocol or due to difficulties experienced in running the study at that centre.

The Sponsor may terminate this study in one particular or several study centre(s) for one of the following reasons:

- Non-compliance with GCP and/or regulatory requirements.
- Centre cannot recruit an adequate number of patients.

- False documentation in the eCRF, either deliberately or due to carelessness.
- Inadequate co-operation with the Sponsor or its representatives.
- The Investigator requests closure of his/her study centre.

If the study is prematurely terminated in one or more study centres, Investigators must inform their patients and take care of appropriate follow-up and further treatment of the patients. Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) and regulatory authorities will be informed about reason and time of termination according to the applicable laws and regulations.

6.5 TERMINATION OF STUDY

6.5.1 Regular Termination of Study

End of study will be 24 months after recruitment of the last patient, or earlier if all patients have completed or withdrawn from the study prior to this time point.

Within 90 days of the end of a clinical study, the Sponsor (or CRO) will notify IECs and regulatory authorities about the regular termination of the study as required according to national laws and regulations. If the study has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

6.5.2 Premature Termination of Study

The study may be terminated prematurely for any reason and at any time by the Sponsor, IECs, regulatory authorities, respective steering committees or the Co-ordinating Investigator. A decision to prematurely terminate the study is binding to all Investigators of all study centres. IECs and regulatory authorities will be informed about reason and time of termination according to the applicable laws and regulations.

If the study is terminated prematurely, Investigators must inform their patients and take care of appropriate follow-up and further treatment of the patients.

6.6 FURTHER TREATMENT AFTER THE END OF THE STUDY

For patients who leave the study or when the study ends, normal standards of care, according to local practice, will continue as necessary.

7. TREATMENT OF PATIENTS

7.1 TREATMENTS ADMINISTERED

7.1.1 Investigational Product

Prior to vaccination, the active chemical conjugate (hu-rEGF-rP64K) will be mixed with the adjuvant (Montanide ISA 51 VG [Seppic, France]) by the Investigator (or designee) at the study site.

The dosage of conjugate is 1 mg total protein per mL. 0.8 mL of this active component will be added to the same volume (0.8 mL) of adjuvant.

A volume of 1.2 mL of the 1.6 mL conjugate-adjuvant mix will be extracted from the vial for vaccination. The dosage of active component per single injection is 0.6 mg. At visits where 4 injections are given, the total dose of active component is 2.4 mg.

Mixing instructions are provided in separate guidelines (see Section 7.3 for a summary). Once mixed, the vaccine/adjuvant combination is stable for 24 hours and should be stored at a temperature of 2-8°C.

Both components (conjugate and adjuvant) are in one dose presentations.

Batch number(s) and expiry date(s) will be documented in the Trial Master File (TMF) and in the final CSR.

7.1.2 Control group

Patients randomised to the non-vaccination arm will be treated as per the normal standard of care at that centre. Centres will be selected for participation in this study that utilise the Protocol specified standard of care treatment regimens.

7.2 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Eligible patients will be randomised to the active vaccine group or the non-vaccination group in a 1:1 ratio. Randomisation will be controlled using an Interactive Response System.

7.3 SELECTION OF DOSES IN THE STUDY

Cyclophosphamide

A low dose of cyclophosphamide (200 mg/m^2 BSA, intravenously) will be given to patients in the active vaccine group only at Randomisation (Visit 2a) i.e. 3 days before the first vaccination.

Further information on cyclophosphamide is provided in Section 5.4.1.

EGF Vaccine

The EGF vaccine is a therapeutic cancer vaccine composed of hu-rEGF conjugated to the carrier protein, r-P64K, and emulsified with the adjuvant Montanide ISA 51 VG, just prior to administration to patients.

In previous trials, one trial (IICRD EC-056) used a single 1.2 mL injection (0.6 mg active component) administered only after completion of chemotherapy, whilst trial PCT5-IICRD EC-062 used a split-dose regimen, with four injections per time point; two vaccinations

before chemotherapy and then monthly vaccinations after chemotherapy (0.6 mg active component per single injection, 2.4 mg total active component total in four injections) [4].

The Investigator (or designee) is responsible for the dispensing of the study vaccine according to the study schedule.

Mixing instructions are summarised below. Further details are provided in separate guidelines:

- Check that both vials are within the expiry date stated on the label and that the product has been stored at a temperature of 2-8°C.
- To prepare the emulsion:
    - Load the syringe supplied with 0.8 mL of EGF cancer vaccine.
    - Dispense the EGF cancer vaccine into the vial containing the adjuvant, so that they are mixed in equal parts (i.e. 0.8 mL of EGF cancer vaccine + 0.8 mL of Montanide ISA 51 VG).
    - Emulsify the contents of the two vials by injection/ejection of the contents of the vial containing the mixture of EGF vaccine and adjuvant with the sterile syringe supplied.
    - Perform the injection/ejection of the mixture between 6 and 10 times to ensure the formation of a stable emulsion.
- Draw 1.2 mL of the final emulsion from the vial to the syringe intended for vaccine administration.
- Administer the emulsion to one injection site (gluteus or deltoid region).
- If applicable, the above steps should be repeated until a total of four injections (to gluteal and deltoid regions) have been administered. This step is not required during the Post First-Line Chemotherapy, Pre-Progression Phase*.

Note: If one of the four injections sites (i.e. deltoid muscle of both arms and the gluteus muscle of both legs) is unsuitable for injection, an alternative intramuscular injection site must be identified by the Investigator.

***Note:** Vaccinations during the Post First-Line Chemotherapy, Pre-Progression Phase (Visits 4a, 4b, 4c, etc) will be administered **at a reduced dose** i.e. patients will receive only 2 injections per timepoint (2.4 mL, 1.2 mg active component) instead of 4 injections per timepoint (4.8 mL, 2.4 mg active component). Patients will be injected at two sites (i.e. an injection in the deltoid muscle of both arms).

7.4 Selection and Timing of Dose for Each Patient

The immunisation schedule is as follows:

<u>Randomisation</u> (Visit 2a): within 28 days from Screening

- Cyclophosphamide (200 mg/m^2 BSA, intravenously) for patients randomised to the active vaccination group.

<u>Initial Vaccination Phase</u>

- **Visit 2b** (+3 days from Visit 2a): First dose of study vaccine

- **Visit 2c** (+14 days from Visit 2b): Second dose of study vaccine

First-Line Chemotherapy

Study vaccinations will continue in the active vaccine group, administered at Visits 3b, Day-2 and 3c, Day-2, 2 days (±1) before Cycles 2 and 3 of chemotherapy (Visits 3b and 3c). No vaccination will be given before Cycles 1, 4, 5, and 6 of chemotherapy (Visits 3a, 3d, 3e, and 3f).

Note: If the study vaccine is administered (i.e. 1-3 days before chemotherapy), but then chemotherapy is delayed, patients will continue in the protocol as normal. The patient will not be withdrawn for this reason.

Post First-Line Chemotherapy, Pre-Progression Phase

For all patients, the Post First-Line Chemotherapy, Pre-Progression Phase (Visit 4a) will start 9 weeks after the last chemotherapy visit. Visits will continue every 8 weeks (Visits 4b, 4c, etc) unless a 6-week vaccination schedule is required (see Section 7.5). Maintenance pemetrexed in non-progressing patients may be delivered 3-weekly according to local practice.

Patients in the active vaccine group will receive the study vaccine **at a reduced dose** at each visit during the Post First-Line Chemotherapy, Pre-Progression Phase until progression or withdrawal from the study, at which point vaccinations will stop.

Patients will receive only 2 injections per timepoint instead of 4 injections per timepoint.

Note: The rationale for the reduction in dose during the Post First-Line Chemotherapy, Pre-Progression Phase is described in Section 5.10.

7.5 DOSE ADJUSTMENT CRITERIA

The frequency of vaccinations may be adjusted as follows:

Post First-Line Chemotherapy, Pre Progression Phase

Vaccinations will be administered to the active group every **8 weeks** until progression or withdrawal from the study. Each vaccination will be followed by measurement of serum EGF. Upon central review of the EGF data, visits (for all patients) may be changed to a 6-**week** vaccination schedule if serum EGF increases above the baseline level established by primary vaccination.

Dose Delays

Chemotherapy or the study vaccine will not be administered in case of bone marrow toxicity of grade >2, i.e. neutrophils < 1000 per µL. In this case the study vaccine and chemotherapy will be restarted once the bone marrow toxicity is grade 2 or below with a maximum interruption between chemotherapy cycles of 3 weeks. If the patient continues to have a bone marrow toxicity of grade >2 after 3 weeks, the patient should be withdrawn from the study (and the study vaccine stopped if in the active vaccine group).

If chemotherapy is planned to be delayed (for example, due to low white cell counts/platelets) the study vaccine administration should also be delayed. If the study vaccine is administered but then chemotherapy is delayed, patients will continue in the protocol as normal. The patient will not be withdrawn for this reason.

7.6 CONCOMITANT MEDICATION

7.6.1 Concomitant Medication

7.6.1.1 Chemotherapy and Biological Therapy

All eligible patients will commence first-line platinum based chemotherapy as per the normal standard of care (Visit 3a). Standard of care treatment should consist of a platinum based two drug combination of cytotoxic drugs. Moreover, pemetrexed chemotherapy can be administered according label in late stage non squamous disease. Patients.

If platinum based chemotherapy is planned to be delayed (for example, due to low white cell counts/platelets), the study vaccine should also be delayed so that study vaccine is always given 2 days (±1) before chemotherapy (**Note:** Applicable to Cycles 2 and 3 only).

If the study vaccine is administered but then platinum chemotherapy is delayed, patients will continue in the protocol as normal. The patient will not be withdrawn for this reason.

First-line chemotherapy should be stopped at disease progression or after 4 cycles in patients not responding to treatment. The two drug cytotoxic combinations should be administered for no more than 6 cycles.

The first drug in the platinum combination should be carboplatin or cisplatin. The choice of a second drug in the platinum-based doublet can include the following: docetaxel, gemcitabine, paclitaxel, pemetrexed, or vinorelbine. These chemotherapy regimens must have a minimum dose of 75 mg/m^2 every 3 weeks for cisplatin and the AUC 5 calculated from EDTA for carboplatin as preferred method. Other methods for carboplatin dose calculation (e.g. Cockroft-Gault formula) are acceptable, if standard procedure at the site.

The use of maintenance chemotherapy or targeted agent is NOT PERMITTED in this study, EXCEPT FOR the use of maintenance pemetrexed in patients whose disease has not progressed after four cycles of initial platinum-based combination chemotherapy (whether or not containing pemetrexed, as per local guidelines).

Second and third-line chemotherapy will be administered after disease progression and termination of study vaccinations as per the normal standard of care.

<u>Biological agents</u>

The use of targeted agents such as bevacizumab, erlotinib, cetuximab, and gefitinib as first-line treatment is not allowed in this Protocol.

7.6.1.2 Cyclophosphamide

Patients in the active vaccine group only will receive a single, low dose of cyclophosphamide (200 mg/m^2 BSA, intravenously) at Randomisation (Visit 2a) i.e. 3 days prior to administration of the first dose of study vaccine. Patients should be well hydrated prior to receiving cyclophosphamide to help prevent cystitis or other urinary tract infections.

7.6.2 Prohibited Medications/Therapy

Prohibited medications must be stopped at least 1 month before Screening. These medications are not permitted at any point during the course of this study (including the Initial Vaccination Phase and the Post First-Line Chemotherapy, Pre-Progression Phase):

- All immunosuppressant drugs such as azathioprine, tacrolimus, cyclosporine, etc.

- Oral, intramuscular and intravenous corticosteroids, with the exception of corticosteroids given in association with other drugs to control the chemotherapy induced emesis (e.g. dexamethasone in association with 5HT3 antagonists or dexamethasone administered to patients treated with pemetrexed in accordance with pemetrexed prescribing information).
- Chemotherapeutic agents other than those utilised as first-line treatments for NSCLC and specified in the Protocol (see Section 7.6.1.1).
- Any other type of immunotherapy against cancer.
- Targeting therapies for NSCLC such as bevacizumab, erlotinib, cetuximab and gefitinib as first-line therapy.
- Concomitant radiotherapy, except palliative radiotherapy to alleviate pain in bone metastases.
- Any other investigational drugs.

7.6.3 Permitted Medications/Therapy

All other supportive therapies are permitted during the study.

For clarification, the following are permitted:

- Inhaled corticosteroids to treat respiratory insufficiency, COPD, etc, or topical steroids.
- Growth factors such as G-CSF (granulocyte-colony stimulating factor), GM-CSF (granulocyte-macrophage colony stimulating factor).
- Transfusion of blood products.
- Antibiotics, anti-emetics, analgesics, anti-diarrheals.
- Targeting therapies for NSCLC such as bevacizumab, erlotinib, cetuximab and gefitinib as 2nd and/or 3rd line therapies after progression.
- Maintenance pemetrexed: Pemetrexed is permitted as maintenance therapy after first-line chemotherapy in those patients who have not progressed on initial platinum-based combination chemotherapy (whether or not containing pemetrexed, as per local guidelines).

7.7 ASSESSMENT OF COMPLIANCE

Injections will be administered by the Investigator (or designee) and therefore there will be no need to monitor patient compliance.

Details of each study vaccine (including date and time of the injections, and site of administration) will be recorded for each patient in the eCRF.

8. ASSESSMENT OF EFFICACY

8.1 EFFICACY PARAMETERS

8.1.1 Primary Efficacy Variable

Overall Survival (OS)

A CT or MRI scan (to assess NSCLC disease stage according to RECIST criteria [Appendix 4]) will be performed at Screening (Visit 1), at the end of every 2 cycles of chemotherapy (i.e. Cycles 2, 4, 6), and at each visit during the Post First-Line Chemotherapy, Pre-Progression Phase (i.e. every 8 weeks).

Note: A scan may be repeated at Randomisation (Visit 2a) or during the Initial Vaccination Phase if the Screening scan is older than 28 days.

The baseline reading will be the latest scan performed at Screening, Randomisation or during Initial Vaccination Phase.

OS is defined as the time from randomisation to death due to any cause.

8.1.2 Secondary Efficacy Variables

Progression-Free Survival (PFS)

PFS is defined as the time from randomisation to objective tumour progression or death (whichever occurs first). Progression includes radiological or clinical progression, withdrawal due to progression, and death due to any cause. If a patient has no event, the PFS is censored at the last contact.

Survival Rate

Survival rates will be assessed at 12 and 24 months after randomisation

Time to Progression (TTP)

TTP is defined as the time from randomisation to observed tumour progression, censoring for death without progression.

Response Rate (RECIST criteria)

Further details on the RECIST response criteria (version 1.1) are provided in Appendix 4.

A guideline describing a standard approach to solid tumour assessment and definitions for objective measurement of change in tumour size in cancer clinical trials can be found at the following website: http://www.eortc.be/recist/

Quality of Life (QoL) – SF-36 v2 Questionnaire

The SF-36 is a 36-item, short-form health survey [15] and a sample copy is provided in Appendix 2 of this Protocol. Patients will be assessed using the SF-36 at Randomisation (Visit 2a) and at subsequent visits (shown in Table 2) until disease progression.

The SF-36 data will be completed on paper. The SF-36 data will then be entered into the eCRF and the source (paper) copy will be filed at the site.

8.1.3 Exploratory Variables

Pharmacodynamics

Blood samples will be collected and analysed for:

- Serum EGF concentration.
- Anti-EGF antibody titres.

Blood samples will be measured for EGF concentration at Screening (Visit 1), Randomisation (Visit 2a), after the end of the Initial Vaccination Phase (Visit 2c), at each Chemotherapy visit, at each Post First-Line Chemotherapy, Pre-Progression Phase visit, and at the EW visit (if applicable).

Anti-EGF will be measured at the Randomisation visit (Visit 2a), the first Chemotherapy visit (Visit 3a), each visit during the Post First-Line Chemotherapy, Pre-Progression Phase, and at the EW visit (if applicable). Only anti-EGF samples collected at the first and last Post First-Line Chemotherapy visits will be analysed, even though it will be necessary to collect at each visit in this phase as the last visit in this phase will not always be known in advance.

Blood samples for all patients in the active vaccine group but only 40% of patients in the control group will be analysed. For measurement of EGF concentration 2 aliquots will be collected at the applicable visits but the total volume from each patient will not increase.

The analysis will be performed by the central laboratory for all visits, except for the EGF sample taken at screening which will be analysed locally (or at an accredited centre in line with local practice) for the evaluation of EGF level related to eligibility criteria.

KRAS and ALK rearrangements

For the analysis of KRAS and ALK rearrangements, a formalin-fixed, paraffin embedded (FFPE) sample of the biopsy tumour tissue, ideally taken from biopsy obtained at disease diagnosis will be prepared and shipped for central analysis.

A total of 4 FFPE slides are required for the EGFR, KRAS and ALK testing. They should contain at least a total 2 mm^2 of tumor tissue (that can be spread in different areas). If the slides contain much less tumor infiltration than that, the number of slides should be increased accordingly. The thickness should ideally be 4 micrometers.

The 4 FFPE slides should be as follows

-1 slide stained with H&E for pathological evaluation

-1 unstained slide for ALK testing by IHC (initial screening procedure)

-1 unstained slide for ALK testing by FISH (in the case of patients positive for IHC)

-1 unstained slide, mounted on a penmembrane, for EGFR and KRAS testing.

8.1.4 Assessing, Recording and Analysing Efficacy Parameters

The methodology used to determine disease stage and tumour size will include chest and upper abdomen CT or MRI scans, brain CT or MRI (only in case of suspected brain metastases), and/or bone scans with confirmatory X-rays if needed (only in case of suspected bone metastases). CT scans are the preferred method. The same method of assessment and

the same technique **must** be used to characterise each identified and reported lesion at enrolment and subsequent assessment.

In addition to the Investigator's assessment, a blinded independent review panel (IRP) will review all initial disease staging and response data prior to reporting of the trial. The IRP will consist of (at least) two radiologists who are not affiliated to the study or to the Sponsor, to provide an independent assessment of tumour response. Both the IRP and the Investigator's opinions of tumour response will be databased and reported. Detailed procedures for independent review will be described separately from this Protocol, and finalised before the first IRP meeting.

Results of the IRP will not routinely be communicated to Investigators, and the management of patients will be based solely upon the results of tumour assessment conducted at the Investigator's site.

Measurement of EGF concentration in serum will be performed using a commercially available kit (Quantikine Human EGF Kit; R&D Systems, Minneapolis, MN, USA). Briefly, the assay employs the quantitative sandwich enzyme immunoassay technique, in which an anti-EGF monoclonal antibody is precoated onto a microplate. After adding the standard calibration curve and the patients' samples, an enzyme-linked polyclonal antibody specific for EGF is added to the wells. After a washing step, a substrate solution is added to the wells and the intensity of the colour is measured. The minimum detectable level of EGF in serum is 78 pg/mL [6]. These commercial kits will be supplied to all centres for determination of serum EGF concentration at screening. Identical kits will be used by the central laboratory for analysis of EGF at scheduled study visits.

Anti-EGF antibody titres will be measured through an enzyme linked immunosorbent assay (ELISA). Patients will be classified as having a good antibody response if they reach anti-EGF antibody titres ≥1:4000 and at least four times their pre-vaccination values. This good antibody response criterion was established arbitrarily in 1998 and has been used repeatedly to optimise the vaccine composition and schedule [4, 6, 7 and 8].

8.2 APPROPRIATENESS OF MEASUREMENTS

Radiology

The RECIST guidelines for the evaluation of objective tumour response are widely accepted and established international guidelines [14]. A summary of the major changes between RECIST versions 1.0 and version 1.1 is also presented [14].

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours in the chest/abdomen.

Although lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung, only CT or MRI scans are to be used in this study.

Quality of Life

The SF-36 has 36 questions that measure the following 8 dimensions: physical functioning, physical role limitations, bodily pain, social functioning, general mental health, social role limitations, vitality, and general health perceptions [15]. It may be self-administered or used

in personal/telephone interviews. It takes 5 to 10 minutes to complete. Two summary scores can be calculated, one for the physical component summary (PCS) and one for the mental component summary (MCS) scores. Along with body mass index (BMI), the SF-36 will provide a measure of general physical health.

9. ASSESSMENT OF SAFETY

9.1 SAFETY PARAMETERS

9.1.1 Adverse Events

9.1.1.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence, in a subject or clinical investigation patient administered with a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

9.1.1.2 Adverse Drug Reaction

In the pre-approval clinical experience with a new investigational product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions (ADRs). The phrase 'response to an investigational product' means that a causal relationship between an investigational product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed investigational products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

9.1.1.3 Relationship of Adverse Events

Assessment of causality of AEs to the study vaccine, cyclophosphamide and chemotherapy:

Not related: An AE for which there is no reasonable temporal association between its onset and administration of the study vaccine, cyclophosphamide or chemotherapy or that can reasonably be explained by other factors, including underlying disease, complications, concomitant drugs or concurrent treatment.

Note: Even if the Investigator feels there was no relationship to the study vaccine, cyclophosphamide or chemotherapy, the AE experience is to be reported.

Unlikely to be related: A clinical event, including laboratory test abnormality, with a temporal relationship to administration of study vaccine, cyclophosphamide or chemotherapy which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possibly related: An AE for which there is a reasonable temporal association between its onset and administration of the study vaccine (including the course of treatment after withdrawal of the study vaccine), cyclophosphamide or chemotherapy for which other causal factors may not be excluded.

Probably related: An AE for which there is a reasonable temporal association between its onset and administration of the study vaccine, cyclophosphamide or chemotherapy including the course after withdrawal of the study vaccine, and which is more likely to be explained by the administration of study vaccine, cyclophosphamide or chemotherapy than by any other cause (e.g. underlying disease, complications, concomitant drugs or concurrent treatment).

Definitely related: An AE that is judged as undeniably related to administration of the study vaccine, cyclophosphamide or chemotherapy. Factors taken into consideration when a definite relationship is assigned include whether the AE:

- Followed a clear temporal sequence from administration of the study vaccine, cyclophosphamide or chemotherapy.
- Could not be possibly explained by the known characteristics of the patient's clinical state, environmental or toxic factors, other modes of therapy administered to the patient.
- Disappeared or decreased on cessation or reduction in dose of the study vaccine, cyclophosphamide or chemotherapy.
- Reappeared or worsened when the study vaccine, cyclophosphamide or chemotherapy was re-administered.
- Followed a response pattern known to be associated with administration of the study vaccine, cyclophosphamide or chemotherapy.

9.1.1.4 Intensity of Adverse Events

All AEs (or toxicities) encountered during the study will be evaluated according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0 [16] grading system (0-5), where applicable.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling limiting self care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

9.1.1.5 Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent, if, and only if, first onset or worsening is after first administration of the study vaccine, cyclophosphamide or chemotherapy.

9.1.1.6 Serious Adverse Events

A serious adverse event (SAE) is one that suggests a significant hazard, contraindication, side-effect, or precaution. With respect to human clinical experience, this includes any event that:

- Results in death.
- Is life-threatening.*
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Other medically important condition.

* Life-threatening in the definition of a SAE or adverse reaction refers to an event in which the patient *was at risk of death at the time of event*; it does not refer to an event, which hypothetically might have caused death if it were more severe.

All of the above criteria apply to the case as a whole and should not be confused with the outcomes of individual reactions/events. More than one of the above criteria can be applicable to the one event.

9.1.1.7 Suspected Unexpected Serious Adverse Reaction

A suspected, unexpected serious adverse reaction (**SUSAR**) is defined as a suspected adverse reaction related to the study vaccine which occurs during the study, and that is both unexpected (i.e., not previously identified in nature, severity, or degree of incidence based upon the current Investigator's Brochure [4] and the Summary of Product Characteristics [SmPC]) and serious.

The term "expected" in pharmacovigilance is not used to describe an event which might be anticipated from knowledge of the pharmacological properties of a substance. An event is also not to be described as "expected", merely because it was foreseeable due to the health status (e.g. age, medical history) of the study patient. It refers strictly to the event being mentioned or listed in the Investigator's Brochure.

All SAEs, whether or not deemed drug-related or expected, must be reported to IPM Pharmacovigilance. This is done by completion of the SAE report form within 24 hours of knowledge of the SAE onset. In the event of an electronic system failure, the SAE should be reported to Pharmacovigilance by portal in the format detailed by the SAE Reporting Form (see Section 9.4).

Note: Disease progression/death due to disease progression will not be captured as an AE or SAE if the disease progression/death is expected as normal course of the disease. However if the disease progression was faster than expected then an AE or SAE will be reported.

9.1.1.8 Significant Adverse Events

Other significant AEs are defined as marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug or significant additional concomitant therapy.

9.1.2 Laboratory Evaluation

The analysis of clinical laboratory parameters (haematology, biochemistry and urinalysis) will be performed by the local laboratory. Blood samples will be taken using a direct venepuncture.

Treatment-emergent clinically significant laboratory abnormalities should be recorded as AEs.

9.1.2.1 Haematology

A blood sample will be collected and the following parameters will be measured:

Haematocrit, haemoglobin, red blood cell (RBC) count, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), leukocytes, lymphocytes, monocytes, eosinophils, neutrophils, basophils, platelet count.

9.1.2.2 Biochemistry

A blood sample will be collected and the following parameters will be measured:

ALT, AST, calcium, chloride, cholesterol, creatinine, gamma glutamyl transferase (GGT), glucose, lactate dehydrogenase, (LDH), potassium, total bilirubin, total protein, sodium, and urea.

9.1.2.3 Urinalysis

A urine sample (approximately 20 mL) will be collected and the following parameters will be measured:

pH, protein, glucose, bilirubin, ketones, blood, urobilinogen, leukocytes, and specific gravity.

If the sample is positive for blood, protein or leukocytes, microscopy should be performed.

9.1.3 Other Parameters Specific to Study Design

9.1.3.1 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be assessed in the clinic (prior to administration of the study vaccine, if applicable).

The patient must have been in the clinic for at least 10 minutes prior to vital signs assessments. With the patient in the supine position for at least 5 minutes, systolic and diastolic blood pressure and heart rate will be measured using standard equipment.

Treatment-emergent clinically significant changes in vital signs should be recorded as AEs.

9.1.3.2 Injection Site Reactions

Patients should be monitored in the clinic for at least 3 hours following their first four vaccinations (Visits 2b, 2c, 3b, Day-2 and 3c, Day-2). At following vaccination visits the monitoring may be reduced to 1 hour assuming no previous adverse reactions have been observed.

Injection sites will also be assessed for any significant reactions to previous injections.

Patients will be given a diary card after each injection and will be given instructions on how to assess any injection site reaction. The diary should be completed for 5 consecutive days starting the day following the injection.

The diary will comprise an assessment of (limb) tenderness, redness and hardness rated on a 4-point scale from 0 to 3 with associated definitions as follows:

Grades for tenderness

0 = No tenderness.

1 = Tenderness when the limb is pressed lightly.

2 = Tenderness when the limb is moved.

3 = Tenderness at rest which prevents normal use of the limb.

Grades for redness and hardness

0 = No redness or hardness.

1 = Mild redness or hardness which is measurable but ≤ 30 mm in any one diameter.

2 = Moderate redness or hardness measuring > 30 mm and < 120 mm in any one diameter.

3 = Severe redness or hardness measuring ≥ 120 mm in any one diameter or any reaction accompanied by a marked limitation in motion in the limb or marked axillary node tenderness.

Diary cards will be returned by the patient at their next visit to the clinic and this data will be entered into the eCRF.

Note: The Investigator will be instructed to use their best judgement as to whether any injection site reaction should be recorded as an AE and make their decision using the criteria and guidelines provided above.

Note: If any of the four injections sites (i.e. deltoid muscle of both arms and the gluteus muscle of both legs) are unsuitable for injection, an alternative intramuscular injection site must be identified by the Investigator.

9.1.3.3 Physical Examination

A physical examination of the major body systems will be conducted by the Investigator (or a medically qualified member of the study staff).

Data will be entered into the eCRF and any treatment-emergent clinically significant physical examination abnormalities should be recorded as AEs.

9.1.3.4 Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening only (and at an Early Withdrawal visit, if applicable). An ECG may be performed at other visits if clinically indicated.

The results will be reviewed by the Investigator and recorded in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant. A description should be given for any clinically significant abnormality. Any treatment-emergent abnormal and clinically significant ECGs findings should be recorded as AEs.

9.1.3.5 Pregnancy Tests

Pregnancy tests will be conducted for all females of child-bearing potential at Screening and at subsequent visits according to the Schedule of Assessments in Table 2.

A serum pregnancy test will be conducted at Screening and urine pregnancy tests will be conducted at all other scheduled visits. All pregnancy tests will be analysed locally.

The sample must be negative for the patient to enter or continue in the study.

9.1.3.6 Prior/Concomitant Medications

Prior medications (i.e. those taken within 1 month before exposure to the study vaccine) will be recorded at Visit 1 (Screening) and Visit 2a (Randomisation).

Patients will be asked if they have taken any concomitant medication (i.e. all medications taken during the study, including those started before but ongoing at first dose) at each subsequent visit.

Any changes in concomitant medication since the previous visit will also be recorded on the patient's eCRF.

9.2 Assessing, Recording and Analysing Safety Parameters

AEs will be recorded on the patient's eCRF from the time of informed consent (Screening [Visit 1]). See Section 9.4 for further details.

Blood and urine samples for safety laboratory assessments will be taken according to the study procedures described in Section 9.1.2. Sampling dates and times will be recorded in the patient's eCRF. The samples will be analysed locally and results reported to the Investigators for clinical assessment. Results will also be exported to the database.

Vital signs, ECG and physical examination assessments will be performed on-site according to the study procedures described in Section 9.1.3. The results will be recorded in the eCRF with relevant printouts to be filed with the patient's notes.

Injection site reactions will be recorded in the eCRF of patients in the active vaccine group following the first vaccination at Visit 2b and at each subsequent visit involving vaccination.

9.3 Appropriateness of Measurements

All laboratory (haematology, biochemistry, urinalysis) and other assessments (pregnancy tests, vital signs, ECG, physical examination) are regarded as standard, i.e. are widely used and generally recognised as reliable, accurate and relevant.

The maximum volume of blood collected per patient at a visit will be 14 mL. Details are shown in Table 3. Some of the assessments shown below will not be collected at all visits (see Table 2 for the Schedule of Assessments).

Table 3. Maximum volume of blood collected at a single visit

Assessment	Volume (mL)
Serum pregnancy test [1, 2]	3.5
Haematology	2
Biochemistry	3.5
PD sampling	5
- Serum EGF concentration	
- Anti-EGF antibody titre	
TOTAL	**14**

1: Performed at Screening only.
2: Females of childbearing potential only.

9.4 RECORDING AND REPORTING ADVERSE EVENT/INTERCURRENT ILLNESSES

It is the responsibility of the Investigator to document all AEs that occur during the study from patient entry. An AE includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes whether associated with the study vaccine, cyclophosphamide or chemotherapy and whether or not considered related to the vaccine, cyclophosphamide or chemotherapy. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or drug interaction. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

Patient entry into the study is defined as the time at which informed consent is obtained (this must be before any Protocol-specific diagnostic procedures or interventions). All subsequent AEs after the ICF is signed must be reported regardless of whether or not they are considered drug related.

AEs will be elicited by asking the patient a non-leading question, for example "Have you experienced or are you experiencing any new or changed symptoms since we last asked/since your last visit?" AEs should be reported on the appropriate page of the eCRF.

Each AE will be assigned a CTCAE severity/intensity category as described in Section 9.1.1.4. Further details can be found at the following website:

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

If there is a change in severity of an AE, it must be recorded as a separate event.

Every effort should be made by the Investigator to explain each AE and assess its relationship, if any, to study drug treatment. Causality should be assessed using the categories as described in Section 9.1.1.3.

The Investigator must report in detail all adverse signs and symptoms which are either volunteered by patients or observed during or following the course of administration of the study vaccine, cyclophosphamide or chemotherapy on the appropriate eCRF page.

In the event of a SAE/SUSAR, the Investigator will notify IndiPharm immediately (within 24 hours):

SAE CONTACT DETAILS: Angela K. Pitwood
Vice President
IPM Safety Services
701 Lee Road
Suite 210
Wayne, Pennsylvania 19087
United States
Tel.: +610-230-0619
Fax: +484-840-5592

The IEC must be informed if the serious or unexpected adverse reaction, in the opinion of the Sponsor or the Investigator, is likely to affect the safety of the patients or the conduct of the study.

The Investigators participating in the study will also be notified of the SUSARs.

9.5 ADVERSE EVENT FOLLOW-UP PROCEDURES

All SAEs will be followed to resolution. All non-serious AEs will be followed until the event has resolved (disappeared) or until they have stabilised, and the relationship to study medication is clarified.

9.6 REPORTING AND RECORDING OVERDOSE

Drug overdose is the accidental or intentional use of any IP (study vaccine or cyclophosphamide) or chemotherapy in an amount higher than the dose specified. An overdose or incorrect administration of chemotherapy or IP is not an AE unless it results in untoward medical effects.

Any chemotherapy or IP overdose or incorrect administration should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study drug or IP should be recorded on the Adverse Event eCRF. If the associated AE fulfils serious criteria, the event should be reported in accordance with SAE reporting requirements; (see Section9.4).

10. STATISTICS

10.1 STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a more technical and detailed description (including templates for Tables, Listings, and Figures) of the planned statistical summaries. The SAP will be finalised before initiating any statistical analysis.

Unless otherwise stated tabulation of summary statistics and data analysis will be performed using SAS® Version 9 or later.

10.1.1 Methods of Analysis

Primary endpoint

The primary efficacy variable is overall survival, defined as the time from randomisation to the date of death due to any cause. Patients without death date will be censored at the date the patient was last known to be alive.

Secondary endpoints

PFS is defined as the length of time between randomisation and the date of the first occurrence of disease progression or death. Patients who stop treatment with the study drug and receive alternate therapy prior to documentation of disease progression will be censored on the date of last tumour assessment before starting the alternative therapy. Patients who did not undergo a post-baseline disease assessment but are known to be alive will be censored at the time of randomisation. If a patient has no event, the PFS is censored at the last contact.

TTP is defined as the time from randomisation to first documented disease progression (using Investigator assessments of disease progression by RECIST). Patients who are withdrawn from the study without documented progression and for whom eCRF evidence exists, or patients without an event, will be censored at the date of the last tumour assessment when the patient was known to be progression free. Patients without post-randomisation tumour assessments but who are known to be alive will be censored at the time of randomisation.

Overall response rate (ORR) is defined as the percentage of patients with a complete response (CR) or partial response (PR) as assessed by RECIST. A responder is defined as a patient experiencing either a CR or PR by these criteria.

Survival rates: 12- month and 24 month survival rates are defined as the percentage of patients that are alive at 12 months and 24 months, respectively, from randomisation

Quality of life: QoL will be assessed using the SF-36 questionnaire. The standard algorithm for analysing this questionnaire will be used.

Exploratory endpoints

These will be analysed outside of the main clinical study report.

Statistical Model

Analyses of the primary and secondary efficacy endpoints will be performed on the intent-to-treat (ITT) population. The primary variable will be analysed both in the ITT and in the PP analysis sets.

The primary efficacy analysis will compare OS between the treatment arms at a 5% significance level.

OS, PFS and TTP will be summarised by Kaplan-Meier curves. Median survival estimates as well as associated 95% CIs will be reported for each treatment group. The differences between the two treatment groups will be tested with a two-sided stratified log-rank test.

For analysis of ORR as well as 12-month and 24-month survival rates, summary tables will be generated, presenting the number and proportion of responders in each treatment group, together with point estimates and two-sided 95% Pearson-Clopper CIs. Chi-square tests will be used to assess for differences between the two treatment groups.

Logistic regression analyses will be performed to assess the influence of baseline covariates in an exploratory manner. If deemed to affect the primary efficacy endpoint, the primary summaries may be presented by each of these factors individually. The factors to be explored will include:

- ECOG performance status (0 versus 1)
- Histological subtype (squamous versus non-squamous)

Furthermore, for the primary endpoint, OS, a Cox regression model will be used to estimate the hazard ratio.

No adjustments will be made for multiplicity of testing for the secondary endpoints.

Summary statistics will be presented for continuous/quantitative variables, by way of number of patients (n), mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of qualitative variables. Percentages will be calculated using the total patients per treatment.

All patient data will be presented in separate data listings.

Safety endpoints

All safety parameters will be analysed using the Safety analysis set.

The assessment of safety will be based on the frequency of AEs, on changes in laboratory values and vital signs parameters. All safety variables will be summarised using descriptive statistics.

Adverse Events

Summary statistics will be presented descriptively for the following safety endpoints by treatment group:

- Adverse Events - the number of AEs, the proportion of patients having at least one AE and AEs by coded terms will be presented.
- Related Adverse Events - the number of related AEs, the proportion of patients having at least one related AE and related AEs by coded terms will be presented. Related

AEs are defined as events that are definitely, probably or possibly related to study drug or with an unknown relationship.

- Serious Adverse Events - the number of SAEs, the proportion of patients having at least one SAE and SAEs by coded terms will be presented.
- Adverse Events leading to withdrawal or death - the number of AEs, the proportion of patients having at least one AE and AEs by coded terms will be presented.

Note: Only treatment-emergent AEs (commencing after exposure to study medication) will be included in the AE summaries. Non treatment-emergent AEs (starting prior to exposure to study medication) will be included in the patient listings and not included in the above summaries.

Injection Site Reactions

The frequency of injection site reactions will be summarised. In addition, the subset of reactions which are not mild or moderate will be presented.

Laboratory Tests

Laboratory parameters will be summarised by presenting laboratory shift tables; abnormal values will be flagged in data listings.

Vital Signs

Vital signs data will be summarised by presenting summary statistics of actual values and change from baseline values by visit.

Other Safety Parameters

All other safety parameters will be summarised using descriptive statistics.

Note: Visit window will be defined in the SAP if applicable

10.1.2 Interim Analysis

An interim analysis (without locking the database) will be performed once 150 patients have reached 12 months after randomisation. In addition, the number of events (deaths) that occur will be tracked in order to estimate the study end date. Based on the efficacy assessment the assumptions for sample size calculation will be reassessed using an O'Brien-Fleming-type error spending approach.

In addition, a DSMB analysis will be performed (see Section 6.3.1.1).

10.2 SAMPLE SIZE

The sample size is based on the following assumptions:

- 15-month recruitment period
- 24- month follow-up period from last patient recruited
- Hazard ratio of control versus vaccine of 1.409 (corresponding to a median overall survival after randomisation of 11 months versus 15.5 months [an extension of 4.5 months]).
- 1:1 ratio of active versus control.

- Interim analysis once 150 patients have reached 12 months after randomisation using an O'Brien-Fleming-type error spending approach.

Based on these assumptions a two-sided log rank test with 80% power needs in total 267 events (deaths) and 167 patients in each treatment group to show a 5% significance.

Assuming a drop-out rate of 20%, approximately 418 patients need to be randomised into the study (with approximately 1393 patients to be screened [assuming a 70% screening failure rate]).

10.3 LEVEL OF SIGNIFICANCE

All tests for the secondary endpoints will be performed using a two-sided α level of 5%.

10.4 CRITERIA FOR THE TERMINATION OF THE STUDY

No statistical stopping rules will be formulated for this study.

10.5 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED AND SPURIOUS DATA

Missing, unused and spurious data will be treated as such.

10.6 DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

Any deviations from the original statistical plan as described in this Protocol will be agreed by the Sponsor and the CRO and documented and justified in a Protocol Amendment, the final SAP or the CSR, as appropriate.

10.7 PATIENT SELECTION FOR ANALYSES

The definitions of the analysis sets for the different types of analyses are in line with the ICH E9 guidelines.

Three analysis sets will be defined:

- Safety analysis set: All randomised patients and patients in the active vaccine group who receive at least one dose of the study vaccine. Patients will be analysed according to the first dose received during the study.
- ITT analysis set: All randomised patients and patients in the active vaccine group who receive at least one dose of the study vaccine. Patients will be kept in their respective randomised treatment groups for the purposes of analysis.
- Per Protocol (PP) analysis set: all patients from the ITT analysis set without any major protocol deviations (e.g. incorrect randomisation, poor compliance, absence of baseline measurement of the primary variable, prohibited concomitant medications etc).

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The clinical monitor(s) should be given direct access to primary patient data (i.e. source data) which supports the data on the eCRFs for the study, i.e., general practice charts, hospital notes, appointment books, original laboratory records, patient diaries and questionnaires, etc. Because this enters into the realm of patient confidentiality, this fact must be included in the Informed Consent Form (ICF) that the patient signs. Other authorised persons such as auditors may need to have direct access to this source data.

11.1 SOURCE DATA

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

11.2 SOURCE DOCUMENTS

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries and questionnaires or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

11.3 DIRECT ACCESS

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g. domestic and foreign regulatory authorities, Sponsor/CRO monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

An independent audit at the study site may take place at any time during or after the study. The independent audit may be carried by the CRO's Quality Assurance (QA) Department, the QA department of the Sponsor, or a regulatory authority.

12.1 QUALITY CONTROL

Quality Control is defined as the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

12.2 QUALITY ASSURANCE

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with GCP and the applicable regulatory requirements.

12.2.1 Inspection

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsor's and/or CRO's facilities, or at any other establishments deemed appropriate by the regulatory authorities.

12.2.2 Audit

An Audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the Protocol, designated SOPs, GCP and the applicable regulatory requirements.

13. ETHICS

13.1 ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in compliance to this Protocol, and in accordance with the provisions of the guidelines of the World Medical Association Declaration of Helsinki, the guidelines of ICH-GCP (CPMP/ICH/135/95), designated SOPs, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

In addition, this study will be undertaken in accordance with the Protocol and GCP on the conducting and monitoring of clinical studies. The IEC/IRB must be constituted according to the local laws/guidelines.

13.2 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE APPROVAL

Before initiating a study, the Investigator should have written and dated approval/favourable opinion from the relevant IRB/IEC for the study Protocol (and any amendments), written ICF, consent form updates, patient recruitment procedures (e.g. advertisements), and any other written information to be provided to patients. Approval will be indicated in writing with reference to the final Protocol number and date. Details of the IRB/IECs constitution including names of its members and what function they perform on the committee (e.g. chairman, specialist, lay-member) should be made available to the CRO.

During the study the Investigator should provide to the IRB/IEC all documents that are subject to review.

Each participating centre will submit the Protocol to the local IRB/IEC and their written unconditional approval obtained and submitted to the sponsor before the start of the study.

The Sponsor will ensure an Investigator's Brochure is available and will supply the Investigator with the Investigator's Brochure and Protocol for the Investigator to submit to the local IRB/IEC for the Protocol's review and approval. Verification of the IRB/IECs unconditional approval of the Protocol will be transmitted to the Sponsor prior to the start of the study. This approval must refer to the study by exact Protocol title and number, identify the documents reviewed and state the date of review.

The IRB/IEC must be informed by the Investigator of all subsequent Protocol amendments and of unexpected serious adverse experiences occurring during the study, which are likely to affect the safety of the patients or the conduct of the study. Approval for such changes must be transmitted in writing to the Sponsor by the Investigator.

The Investigator should provide the IRB/IEC with all relevant amendments or updates of the Protocol and Investigator's Brochure. Also, the Investigator should provide written reports to the IRB/IEC annually or more frequently if requested on any change significantly affecting the conduct of the study and/or increasing risk to the patients. A final report of study outcome, if required, should also be submitted by the Investigator to the IRB/IEC.

13.3 INFORMED CONSENT

The principles of informed consent in the Declaration of Helsinki (Appendix 1) should be implemented in this clinical study before Protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed

appropriate by the IRB/IEC. Patients, their relatives, or if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The Investigator will explain the nature, purpose and risks of the study and provide the patient with a copy of the Patient Information Sheet. The patient will be given sufficient time to consider the study's implications before deciding whether to participate.

Consent forms must be in a language fully comprehensible to the prospective patient. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC and signed by the patient and the Investigator obtaining the consent. The informed consent form will also be annotated with the study patient number.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. Consent must be documented by the patient's dated signature. The signature confirms the consent is based on information that has been understood. Each patient's signed ICF must be kept on file by the Investigator for possible inspection by regulatory authorities and the Sponsor.

Should there be any amendments to the Final Protocol, such that would directly affect the patient's participation in the study e.g. a change in any procedure, the ICF must be amended to incorporate this modification and the patient must agree to sign this amended ICF indicating that they re-consent to participate in the study.

Patients will be instructed that they are free to obtain further information from the Investigator at any time and that they are free to withdraw their consent/assent and discontinue participation in the project at any time without prejudice.

The prospective patient will also be advised that access to medical records would be required and his/her general practitioner (GP) will be informed of the patient's participation in this study.

13.4 MODIFICATION OF PROTOCOL

The Investigator or the CRO should not implement any deviation from, or changes of, the Protocol without agreement by the Sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment. The only exceptions are where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor[s], change of telephone number[s]).

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed Protocol amendment(s) should be submitted:

a) to the IRB/IEC for review and approval/favourable opinion,

b) to the Sponsor for agreement and, if required,

c) to the regulatory authority(ies).

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the Sponsor and the Co-ordinating Investigator. The CRO will ensure that the Investigators submit necessary Protocol amendments to the appropriate IRB/IEC.

All agreed Protocol amendments must be clearly documented using standard procedures as defined by the Sponsor, and must be signed and dated by the Sponsor and the Investigator.

14. DATA HANDLING AND RECORD KEEPING

14.1 COMPLETION OF ELECTRONIC CASE REPORT FORMS

Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them and when the data should be documented.

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs to record (according to the eCRF Completion Guidelines) all observations and other data pertinent to the clinical trial obtained during study visits. All eCRFs should be fully completed to ensure accurate data interpretation.

The computerised handling of the data after receipt of the eCRFs may generate additional requests via electronic queries to which the Investigator is obliged to respond by confirming or modifying the data questioned. These requests with their responses will be appended to the eCRFs held by the Investigator and Sponsor.

14.2 ARCHIVING

According to ICH-GCP, the documents which should be archived are 'essential documents' which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced.

Source documentation must also be archived. This may include observations and source data contained in medical records (certified copies or originals are acceptable for archiving purposes), data collection forms or eCRFs and research related records held in support departments. All hard copies of source documents must be retained. If electronic records of documents exist these must be backed up and retained with the hard copies.

Essential documents should be retained until at least 2 years after the last approval of all outstanding marketing application(s) in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Essential documents may need to be retained for a longer period than determined in ICH-GCP depending on local regulations. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained.

15. FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed with each Investigator and will be documented in a separate financial agreement that will be signed by the Investigator and the CRO, prior to the study commencing.

The Sponsor has insurance coverage for study related medicine-induced injury and other liabilities incurred during clinical studies which will provide compensation for any study related injury according to local laws and regulations.

16. PUBLICATION POLICY

Any data, records or other information arising out of the performance of this study shall not be used for the commercial benefit of the Investigator.

It is intended that the results of the study may be published as scientific literature. Results may also be used in submission to regulatory authorities. The following conditions are to protect commercial confidential materials (patents, etc), not to restrict publication.

The Investigator agrees that the Sponsor shall have the right to the first publication of the results of the study which is intended to be a joint, multi-centre publication of the study results made by the Sponsor in conjunction with the Investigators and institutions from all appropriate sites contributing data, analysis and comments. Notwithstanding the foregoing, following the first publication, the Investigator may publish data or results from the study; provided, however, that the Investigator submits the proposed publication to Sponsor for review at least sixty (60) days prior to the date of the proposed publication. The Sponsor shall have the right to remove from the proposed publication any information that is considered confidential and/or proprietary. In the event that such publication may affect the patentability of any invention to which the Sponsor has rights, the Sponsor shall have the right to request an additional delay to the proposed disclosure of no more than ninety (90) days so as to allow the Sponsor to preserve its intellectual property.

In the event a multi-centre publication is not submitted within twelve (12) months after conclusion, abandonment or termination of the study at all sites, or if the Sponsor confirms there will be no multi-centre study publication (whichever comes first), the Investigator may publish the study results subject to the Sponsor's rights as set forth herein. The Investigator agrees not to publish any study related material other than in accordance with this section.

17. CONTRACT RESEARCH ORGANISATION (CRO) SPECIFIC ADMINISTRATIVE PROCEDURES

17.1 STUDY PERSONNEL

Prior to the start of the study, each Investigator must supply the CRO with the names and *curricula vitae* of the clinically responsible Co-Investigators of the study and the names of other possible participants and their professional backgrounds (e.g. medical doctor, nurse, etc).

17.2 STUDY MONITORING

The Sponsor and the CRO are responsible for ensuring the proper conduct of the study with regards to Protocol adherence and validity of the data recorded on the eCRFs. The CRO has therefore assigned both a physician and a clinical monitor to the study. Their duties are to aid the Investigator and at the same time, the CRO, in the maintenance of complete, legible, organised and easily retrievable data. In addition, a clinical monitor will explain, interpret and ensure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of a pharmaceutical product and ensure an understanding of the Protocol, reporting responsibilities and the validity of the data.

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data entered to the eCRFs and in all required reports. Data entered to the eCRF, which are derived from source documents, should be consistent with the source documents (or the discrepancies should be explained).

17.2.1 Return of Case Report Forms

Before acceptance, the clinical monitor will review the eCRFs for completeness and adherence to the Protocol.

17.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Prior to shipment of investigational product, the following documents must be submitted/returned to the CRO by the Investigator:

- Signed final version of the Protocol (three copies will be sent to the Investigator for signing: one to be returned to the CRO, one to be returned to the Sponsor and one to be retained in the Investigator's files)
- Signed, initialled and dated (within the last 12 months) *curriculum vitae* of the Investigator(s) (and other relevant staff, if required).
- Signed and dated form FDA 1572 (if applicable).
- Copy of the letter or notice from the IRB/IEC approving the final version of this Protocol and Patient Information Sheet and ICF.
- Signed MREC Annex D (if applicable).
- Approved PIS/ICF Approval Form.
- Sample Drug dispensing record.

- Written approval to proceed with designated Investigator/site from the Sponsor (if necessary).
- Written national regulatory approval.
- Written insurance statement.
- Signed Investigator Financial Agreement.

18. REFERENCES

1. Neninger E, Verdecia BG, Crombet T, Viada C, Pereda S, Leonard I, et al., Combining an EGF based cancer vaccine with chemotherapy in advanced non-small cell lung cancer. J. Immunother. 2009; 32: 92-99.
2. Gonzalez G, Sanchez B, Suarez E, et al. Induction of immune recognition of self epidermal growth factor (EGF): effect on EGF-biodistribution and tumour growth. Vaccine Res 1996; 5: 233–244.
3. Gonzalez G, Pardo OL, Sanchez B, et al. Induction of immune recognition of self-epidermal growth factor II: characterization of the antibody response and the use of a fusion protein. Vaccine Res 1997; 6: 91–100.
4. Investigator's Brochure, Epidermal growth factor (EGF) cancer vaccine. Version 4.
5. Gonzalez G, Crombet T, Torres F, Catala M, et al. Epidermal growth factor-based cancer vaccine for non-small-cell lung cancer therapy. Ann Oncol. 2003; 14(3): 461-6.
6. Ramos TC, Vinageras EN, Ferrer MC, Verdecia BG, et al. Treatment of NSCLC patients with an EGF-based cancer vaccine: report of a Phase I trial. Cancer Biol Ther. 2006; 5(2): 145-9.
7. Neninger Vinageras E, de la Torre A, Osorio Rodríguez M, Catalá Ferrer M, et al. Phase II randomized controlled trial of an epidermal growth factor vaccine in advanced non-small-cell lung cancer. J Clin Oncol. 2008; 26(9): 1452-8.
8. González G, Crombet T, Neninger E, Viada C, Lage A. Therapeutic vaccination with epidermal growth factor (EGF) in advanced lung cancer: analysis of pooled data from three clinical trials. Hum Vaccin. 2007; 3(1): 8-13.
9. Summary of Product Characteristics (SmPC): Cyclophosphamide. 04 Feb 2010. Pharmacia Limited, UK.
10. Rodríguez PC, Rodríguez G, González G, Lage A. Clinical development and perspectives of CIMAvax EGF, Cuban vaccine for non-small-cell lung cancer therapy. MEDICC Rev. 2010; 12(1): 17-23.
11. Gonzalez G, Crombet T, Torres F, Catala M, Alfonso L, Osorio M, Neninger E, Garcia B, Mulet A, Perez R, Lage R. Epidermal growth factor-based cancer vaccine for non-small-cell lung cancer therapy. Ann Oncol. 2003; 14(3): 461-6.
12. González G, Crombet T, Neninger E, Viada C, Lage A. Therapeutic vaccination with epidermal growth factor (EGF) in advanced lung cancer: analysis of pooled data from three clinical trials. Hum Vaccin. 2007; 3(1): 8-13.
13. American Joint Committee on Cancer (AJCC), Cancer Staging Handbook. 7th ed. New York: Springer.
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228-47.

15. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992; 30: 473-483.

16. Cancer Therapy Evaluation Program, Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0, DCTD, NHI, DHHS, 28 May 2009.

    http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-014_QuickReference_5x7.pdf

17. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5: 649-655.

18. Linardou H, Dahabreh IJ, Kanaloupiti D, et al. Assessment of somatic k-ras mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. Lancet Oncology. 2008; 9: 962-972.

19. Vinageras EN, Torre A, Rodriguez MO, Ferrer MC, Bravo I, Pino MM, Abreu DA, Brooks SA, Rives R, Carrillo, C, Duenas MG, Viada C, Verdecia BG, Ramos TC, Marinello GG, Davila AL: Phase II Randomized Controlled Trial of an Epidermal Growth Factor in Advanced Non-Small-Cell Lung cancer. Journal of Clinical Oncology. 2008; 26: 1452-1457

19. APPENDICES

Appendix 1 **World Medical Association Declaration of Helsinki**

Appendix 2 **Sample Quality of Life Questionnaire – SF-36 v2**

Appendix 3 **Eastern Cooperative Oncology Group (ECOG) Performance Status**

Appendix 4 **RECIST Criteria (Version 1.1)**

Appendix 5 **Study Acknowledgement / Protocol Signature Page**

Appendix 1

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964 and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989 and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association (WMA) binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor,

permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

7. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
8. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
9. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
10. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix 2

SAMPLE QUALITY OF LIFE QUESTIONNAIRE – SF-36 v2

Adobe Acrobat Document

Appendix 3

ECOG PERFORMANCE STATUS*

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol. [17]

Appendix 4

RECIST CRITERIA (Version 1.1)

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Measurability of tumour at baseline

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measureable).
- 20 mm by chest X-ray.

Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Methods of Assessment

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested.

CT, MRI: **Only CT and MRI scans will be acceptable for the purposes of this study.** CT is the best currently available and reproducible method to measure lesions selected for response assessment. CT scan slice thickness should be 5 mm or less. MRI is also acceptable in certain situations (e.g. for body scans).

[Chest X-ray]: Chest CT is preferred over chest X-ray since CT is more sensitive than X-ray, particularly in identifying new lesions.

[Ultrasound] is not useful in assessment of lesion size and should not be used as a method of measurement.

The use of *endoscopy* and *laparoscopy* for objective tumour evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measureable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as **target lesions** and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterise the objective tumour regression in the measureable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent' or in rare cases 'unequivocal progression'.

Response Criteria

Response will be evaluated using the RECIST criteria. Detailed are provided in Tables A4.1, A4.2 and A4.3.

Table A4.1: Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
* Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table A4.2: Evaluation of Non-Target Lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
* Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
* Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table A4.3 : Time Point Response: Patients with Target (± non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	Non-CR/Non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any response	PD	Yes or No	**PD**
Any response	Any	Yes	**PD**

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR.

Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories: 1) CR, 2) PR, 3) SD, 4) PD, 5) Inevaluable for response: specify reasons (for example: early death from malignant disease; early death from toxicity; tumour assessments not repeated/incomplete; other [specify]).

All of the subjects who met the eligibility criteria and received at least one full course (21 days) should be included in the main analysis of the response rate. Subjects in response categories 4-5 should be considered as failing to respond to treatment (disease progression).

Appendix 5

STUDY ACKNOWLEDGEMENT / PROTOCOL SIGNATURE PAGE

Investigator's Statement:

I have read and understand the foregoing Protocol entitled "A Phase III, open-label, multicentre, randomised trial to establish safety and efficacy of an EGF cancer vaccine in inoperable, stage IVbiomarker positive, wild type EGF-R NSCLC patients eligible to receive standard treatment and supportive care", Protocol number **BV-NSCLC-002**, and agree to conduct the Study, in compliance with Good Clinical Practice (CPMP/ICH/135/95), designated Standard Operating Procedures, National Laws and regulations of the countries conducting the study and within the principles of the Declaration of Helsinki as outlined herein.