AstraZeneca

Amended Clinical Study Protocol	
Drug Substance	ZD6474
Study Code	D4200C00057
Edition Number	4
Date	[redacted]

A Phase III, Randomised, Double-Blind, Multi-Centre Parallel-Group Study to Assess the Efficacy of ZD6474 (ZACTIMA™) Versus Erlotinib (TARCEVA®) in Patients With Locally Advanced or Metastatic (Stage IIIB – IV) Non-Small Cell Lung Cancer (NSCLC) after Failure of at least One Prior Cytotoxic Chemotherapy

Sponsor: AstraZeneca[redacted]

AstraZeneca Research and Development site representative

[redacted]

The following Amendment(s) and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		
2	[redacted]		
3.1	[redacted]		
4	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	[redacted]		

[redacted]

PROTOCOL SYNOPSIS

A Phase III, Randomised, Double-Blind, Multi-Centre, Parallel-Group Study to Assess the Efficacy of ZD6474 (ZACTIMA™) Versus Erlotinib (TARCEVA®) in Patients With Locally Advanced or Metastatic (Stage IIIB – IV) Non-Small Cell Lung Cancer (NSCLC) after Failure of at least One Prior Cytotoxic Chemotherapy

International Co-ordinating Investigator

[redacted]

Study centre(s) and number of patients planned

This phase III multi-centre study will be conducted in a minimum of 1150 patients (575 per arm) with locally advanced or metastatic (IIIb-IV) non-small cell lung cancer (NSCLC) after failure of at least 1 but not more than 2 previous cytotoxic chemotherapy regimens. It is planned that approximately 160 investigator sites in 22 countries will participate in the study and that each site will recruit between 5-25 patients.

Study period		**Phase of development**
Estimated date of first patient enrolled	[redacted]	III
Estimated date of last patient completed	[redacted]	

Objectives

The primary objective of this study is to demonstrate an improvement in Progression Free Survival (PFS) for ZD6474 (ZACTIMA™) Versus Erlotinib (Tarceva®) in patients with locally advanced or metastatic NSCLC after failure of at least one but no more than two, prior cytotoxic chemotherapy regimens. Eligible patients must have a documented history of progressive disease or unacceptable toxicity either during or after treatment with prior cytotoxic chemotherapy treatment for the disease.

The secondary objectives of the study are:

1. To demonstrate an improvement in overall survival (OS) for ZD6474 compared with Erlotinib

2. To demonstrate an improvement in the objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) for ZD6474 compared with Erlotinib

3. To demonstrate an improvement in the time-to-deterioration of pain, dyspnoea, cough in patients treated with ZD6474, compared with Erlotinib, based on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) plus lung cancer module (QLQ-LC13)

4. To study the safety and tolerability of ZD6474 compared with Erlotinib

5. To investigate the population pharmacokinetics (PK) of ZD6474 and assess the relationship between PK and QTc, measures of safety and efficacy and pharmacodynamic (PD) biomarkers.

6. To investigate plasma levels of the N-desmethyl and N-oxide metabolites of ZD6474 in this patient population

The exploratory objectives of the study are to:

1. To investigate the correlation of epidermal growth factor receptor (EGFR) expression, amplification and mutations and other related biomarker status with efficacy in archival tumour samples in those patients where such tumour material is available

2. To collect a genetic blood sample for DNA extraction and storage

3. To investigate in blood plasma samples, the correlation of levels of circulating protein biomarkers with efficacy

4. To investigate the effect on health-related quality of life (HRQOL)/symptoms of ZD6474 compared with Erlotinib based on EORTC QLQ-C30 plus lung cancer module QLQ-LC13

5. To investigate patient health status index during the period of treatment with investigational therapy by assessment of the EuroQoL 5 Dimension Instrument (EQ5D)

6. To investigate the time to deterioration in patient World Health Organisation Performance Status (TDPS) during the period of treatment with investigational therapy

7. To investigate changes in patient weight

8. To investigate EGFR mutational status and mutational status of other candidate genes in cell-free circulating tumour DNA found in plasma.

Study design

This is a parallel group, international, randomised, double-blind, double-dummy, comparator, multi-centre study design to assess whether ZD6474 (300 mg daily) confers an advantage in terms of PFS compared with Erlotinib (150 mg daily) in patients with locally advanced or metastatic NSCLC who have received prior cytotoxic chemotherapy treatment.

Patients will be randomised in a 1:1 ratio to receive either ZD6474 300 mg plus placebo or Erlotinib 150 mg plus placebo as a once daily oral dose, to be taken at least 1 hour prior to or 2 hours after intake of food, from Day 1.

Patients will continue to receive study treatment until progression of their disease is determined according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, providing they do not meet any other withdrawal or discontinuation criteria.

Radiological evaluation using RECIST will be performed at screening and every 4 weeks during the study until week 16 and every 8 weeks thereafter. It is important to follow the assessment schedule as closely as possible. Patients will be evaluated until objective progression, and then be followed up for survival unless they withdraw consent. If a patient discontinues study medication prior to objective disease progression they should continue to be assessed regularly, as per the protocol schedule, until disease progression and then followed up for survival, unless they withdraw consent.

The safety data from all patients will be assessed on an ongoing basis. Patients who experience Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicity (section 3.2.2) that is considered related to ZD6474/Erlotinib will have their study medication stopped until resolution of the toxicity. When the toxicity has recovered as described in Section 3.2.2 the patient may restart treatment with a reduced dose of ZD6474/Erlotinib in a blinded manner, according to the dose reduction plan outlined in section 3.4.2.2. The study assessments should be continued as outlined in the study plan. If the patient has been off study medication for greater than 3 weeks due to toxicity, the patient must be permanently discontinued from ZD6474/Erlotinib and will be followed for objective progression and survival, unless they withdraw consent.

In order to obtain a sub-group of 200 patients for the ZD6474 population-PK analysis, blood samples will be obtained from approx 400 patients randomised into the study.

Every attempt will be made to obtain archived tumour samples from all patients enrolled on the study, although tissue collection will not be mandatory.

Target patient population

Male or female patients aged 18 years or older with histologically or cytologically confirmed locally advanced or metastatic (Stage IIIB-IV) NSCLC after failure of at least one, but not more than two, prior cytotoxic chemotherapy regimens (either radiological documentation of disease progression or due to toxicity) and who have a performance status of 0 to 2 (WHO 1981).

Investigational product, dosage and mode of administration

ZD6474 or matching placebo (300 mg in tablet form) will be dosed orally, once daily, preferably at the same time each morning, 1 hour prior to intake of food or 2 hours after intake of food.

Comparator, dosage and mode of administration

In addition to ZD6474 or matching placebo described above, patients will receive Erlotinib or matching placebo (150 mg in tablet form) which will also be dosed orally, once daily, and is to be taken at the same time as ZD6474 or matching placebo.

Duration of treatment

ZD6474/Erlotinib will be administered once daily from Day 1. Patients may continue to receive study treatment as long as they are benefiting from treatment (in the Investigator's opinion) and they do not meet any other withdrawal or discontinuation criteria. Once a patient progresses on ZD6474/Erlotinib, according to RECIST criteria, the patient will stop receiving study medication. Patients will be evaluated until objective progression is documented and will then be followed up for survival, unless they withdraw consent. Blinded ZD6474/Erlotinib should not be combined with any other anti-cancer therapies.

Outcome variables

Efficacy

- Primary outcome variable:
  - PFS
- Secondary outcome variables:
  - OS
  - ORR, DCR and DOR
  - Time to deterioration of pain, dyspnoea and cough (TDS)
- Exploratory outcome variable:
  - HRQOL/symptoms as measured by the EORTC QLQ-C30 plus lung cancer module QLQ-LC13

Safety

- Incidence and type of adverse events (AEs), clinically significant laboratory or vital sign abnormalities, and electrocardiographic (ECG) changes

Patient reported outcomes (PROs)

- HRQOL/symptoms as measured by the EORTC QLQ-C30 plus lung cancer module QLQ-LC13

Health economics

- EQ5D questionnaire

Other measures of patient benefit

- World Health Organisation Performance Status (WHO PS)
- TDPS
- Weight

Pharmacokinetic

- To investigate the population-PK in this patient population and investigate correlations between exposure (area under the curve at steady state [AUC_{ss}]), maximum concentration at steady state($C_{ss,max}$), and total body clearance of drug from plasma after an oral dose (CL/F) with Aes, QTc and efficacy (PFS, OS, and ORR) and PD Biomarkers for ZD6474

Pharmacodynamic

- Plasma vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor 2 (VEGFR2) and basic fibroblast growth factor (bFGF)
- Expression levels of EGFR in archival tumour samples
- EGFR gene amplification
- To investigate EGFR mutational status and mutational status of other candidate genes in cell-free circulating tumour DNA found in plasma.

Genetics

- Mutational status of target EGFR and pathway related genes

Statistical methods

The primary analysis population will comprise all patients. A nominal 2-sided significance level of 5% will be used for all analyses, except for the primary endpoint of PFS and the secondary endpoint of overall survival where the nominal significance level will be adjusted to approximately 4.88% to allow for a single interim analysis.

In order to detect a 25% prolongation of overall Progression-Free Survival (PFS) with >90% power at the 2-sided 4.88% significance level, a minimum of 1110 progression events were

required. Assuming median PFS of 2.2 months for Erlotinib, a non-linear recruitment period of 15 months and minimum follow-up of 7 months, a minimum of 1150 patients will be randomised. This equates to a 2-week improvement in the median time to progression; i.e. a 2.75-month median PFS on the ZD6474 arm. The estimate of median PFS for Erlotinib has been taken from a randomised, placebo-controlled, phase III Erlotinib study (Shepherd et al 2005).

The analysis of OS will be conducted at the time of analysis of the primary endpoint of PFS. Assuming median OS of 6.7 months for Erlotinib (Shepherd et al 2005), it is estimated that 769 events (deaths) will have occurred at this time, in which case the power to detect a 25% prolongation of survival would be 87%. This equates to a 7-week improvement in the median OS; i.e. an 8.375-month median OS on the ZD6474 arm.

PFS and OS will be analyzed using a log-rank test. ORR and DCR will be analyzed using logistic regression.

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs and ECG changes, which will be collected for all patients. AEs (both in terms of Medical dictionary for regulatory activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient and summarized by treatment group.

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

LIST OF APPENDICES

LIST OF SUPPLEMENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 4.7.1.1)
ADME	Absorption/Distribution/Metabolism/Excretion
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
APTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
Assessment	An observation made on a variable involving a subjective judgement
AST	Aspartate aminotransferase
AUC	Area under plasma concentration-time curve from zero to infinity
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
bFGF	Basic fibroblast growth factor
BP	Blood pressure
BUN	Blood urea nitrogen
°C	Degree Centigrade
C_{max}	Maximum concentration
$C_{ss, max}$	Maximum steady state plasma concentration
CI	Confidence Interval
CL/F	Total body clearance of drug from plasma after an oral dose
CR	Complete response (RECIST criteria)
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events (National Institutes of Health, National Cancer Institute, Version 3.0)
DCR	Disease control rate
DMPK	Drug Metabolism Pharmacokinetics
DNA	Deoxyribonucleic Acid
DOR	Duration of response
ECG	Electrocardiogram

Abbreviation or special term	Explanation
eCRF	electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ5D	EuroQoL 5 Dimension Instrument
FISH	Fluorescence in situ hybridisation
GCP	Good Clinical Practice
HR	Hazard ratio
HRQOL	Health-related quality of life
IB	Investigator's Brochure
IC_{50}	Inhibitory concentration
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
INR	International normalized ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
KDR	Kinase insert domain receptor
LBBB	Left bundle branch block
LD	Longest diameter
LDH	Lactate dehydrogenase
LIMS	Laboratory Information Management System
Measurement	An observation made on a variable using a measurement device.
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of mercury
MRI	Magnetic Resonance Imaging
msec	Millisecond
MTD	Maximum tolerated dose
NCI	National Cancer Institute

Abbreviation or special term	Explanation
nM	Nanomolar
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1).
ORR	Objective response rate
OS	Overall survival (defined as time to death)
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.
Parameter	A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients.
PD	Progressive disease (RECIST criteria)
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial response (RECIST criteria)
Principal Investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a Principal Investigator.
PRO	Patient Reported Outcome
PSI	Pulmonary Symptom Index
PT	Prothrombin time
PVC	Premature ventricular contraction
QoL	Quality of Life
QLQ	Quality of Life Questionnaire
QT	The interval between Q and T on ECG
QTc	QT interval corrected for heart rate by the Bazett's method
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 4.7.1.1).
SAP	Statistical Analysis Plan
SD	Stable disease (RECIST criteria)
SDT	Study Delivery Team

Abbreviation or special term	Explanation
SDV	Source Data Verification
SMQ	Special MedDRA Query
SNP	Single nucleotide polymorphism
SVC	Superior vena cava
$t_{½}$	Terminal half-life
TDPS	Time to deterioration in patient WHO PS
TDS	Time to deterioration of disease-related symptoms (pain, dyspnoea, cough)
TKI	Tyrosine kinase inhibitor
TTD	Time to death
TTP	Time to progression
ULRR	Upper limit of reference range
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VEGFR-2	Vascular endothelial growth factor receptor-2
VEGFR-3	Vascular endothelial growth factor receptor-3
Vss/F	Volume of distribution (apparent) at steady state after an oral dose
WBC	White blood count
WBDC	Web-based data capture
WHO	World Health Organization
WHO PS	World Health Organization Performance Status

1. INTRODUCTION

Investigators should be familiar with the ZACTIMA™ (ZD6474) Investigator's Brochure (IB).

1.1 Background

Tumour angiogenesis

Therapies that inhibit the growth of new blood vessels, so called angiogenesis inhibitors, offer considerable promise as anticancer agents. The link between angiogenesis and tumour progression and spread was first established some 30 years ago by Judah Folkman (Folkman 1971). Folkman noted that without new blood vessels, many tumours only grow to a few millimeters in size. He also found that while a tumour may remain small, its cells continue to proliferate, a situation brought about by a balance between cell rate of proliferation and

apoptosis (programmed cell death). These observations led to the concept of an "angiogenic switch", a complex process by which a tumour mass expands and overtakes the rate of internal apoptosis by developing blood vessels, thereby changing into an angiogenic phenotype. Evidence has emerged that suggests this change is a result of a shift in net balance of stimulators and inhibitors of angiogenesis within the tumour microenvironment in which the inhibitors are down regulated(Hanahan and Folkman 1996). It is now recognized that the growth of most solid tumours and the formation of metastases are dependent on this process.

VEGF has been shown to play a pivotal role in tumour angiogenesis (Stacker and Achen 1999). VEGF is a mitogen for vascular endothelial cells derived from arteries, veins, and lymphatics and induces a strong angiogenic response in a variety of in vivo models; it also functions as a survival factor for endothelial cells (Leung et al 1989, Ferrara 1999). In addition, it has been proposed that a major function of VEGF is the induction of plasma protein leakage because of its ability to induce vascular leakage (Dvorak et al 1995). Other properties of VEGF include promotion of monocyte chemotaxis, inhibition of functional maturation of dendritic cells, and vasodilatation (Ferrara 1999). The discovery of VEGF was followed by the identification of specific VEGF receptors (VEGFR) that constituted a new subfamily of tyrosine-kinase receptors, vascular endothelial growth factor receptor 1 (VEGFR-1) (fms-like tyrosine kinase [Flt-1]) and VEGFR-2 (kinase insert domain-containing receptor [KDR]) (Neufeld et al 1999). Of the two receptors originally identified on endothelial cells, only signalling of VEGFR-2 was sufficient to induce endothelial cell proliferation and vascular permeability (Ferrara and Gerber 2003). Vascular endothelial growth factor receptor 3 (VEGFR-3) (fms-like tyrosine kinase 4 [Flt-4]) was recently identified and appears to be primarily associated with lymphangiogenesis (Paavonen et al 2000). Most solid tumours express high levels of VEGF, and the VEGF receptors appear predominantly in endothelial cells of vessels surrounding or penetrating the malignant tissue (Siemeister et al 1998). Interestingly, a correlation between VEGF expression and prognosis has been noted for several cancers (Gasparini et al 1997,Maeda et al 1996) Increased levels of VEGF expression in non-small cell lung cancer (NSCLC) cells are associated with poor prognosis, local invasion, advanced stage, and lymph node involvement (Niklinska et al 2001, Shou et al 2001). The importance of VEGF in tumour angiogenesis was revealed in experiments of abrogation of VEGF activity by neutralizing antibodies or by the introduction of dominant negative VEGF receptors into endothelial cells of associated blood vessels. This resulted in inhibition of associated growth and in associated regression (Kim et al 1993, Millauer et al 1994).

1.1.1 ZD6474

1.1.1.1 Background

ZD6474 is an inhibitor of the tyrosine kinase domain of the VEGF receptor-2 (KDR or VEGFR-2). ZD6474 also inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase, though at an inhibitory concentration (IC_{50}) of 500 nano-molar (nM), which was higher than that for VEGFR-2 (40nM) (Ciardiello et al 2003, Wedge et al 2002).

It is expected that this molecule may be beneficial in a broad range of human malignancies, and perhaps other diseases, that are dependent upon VEGF-mediated angiogenesis. ZD6474 has shown excellent reversible inhibition of associated cell growth in a broad range of pre-clinical models, including lung cancer xenografts. Regression of some established tumours in animals were observed following oral administration. Two Phase I studies of patients with advanced solid tumours were conducted in the West and in Japan, which demonstrated a maximum tolerated dose (MTD) of 300 mg, with common adverse events (AEs) including diarrhoea, rash, and asymptomatic QTc prolongation. Furthermore, in the Japanese study four out of nine patients with NSCLC exhibited an objective response to ZD6474 according to RECIST.

Subsequently, 2 randomised Phase II studies (6474IL/0003 and 6474IL/0006) were performed in patients with NSCLC refractory to first-line therapy. Study 6474IL/0003 randomised patients to receive ZD6474 or gefitinib (IRESSA®), and following progression, patients could switch to the alternate treatment. The results of this study demonstrated a statistically significant improvement in time to progression (TTP) in patients initially randomised to ZD6474, compared to those randomised to gefitinib.

Study 6474IL/0006 randomised patients to docetaxel in combination with placebo, ZD6474 100 mg, or ZD6474 300 mg. The results of this study demonstrated that ZD6474 combined with docetaxel prolonged PFS in patients with NSCLC.

However, in studies 6474IL/0003 and 6474IL/0006 progression advantages were not reflected in a corresponding advantage in Overall Survival (OS). OS was not the primary endpoint in either study and therefore neither study had sufficient statistical power to detect improvements. Differences between randomised treatment groups in the usage of subsequent anti-cancer therapy may be part of the explanation for the lack of improvement in OS in these studies, particularly given the protocol-specified switch to the alternative randomised treatment in Study 6474IL/0003. In addition, the possibility of an efficacy disadvantage associated with stopping ZD6474 treatment cannot be ruled out.

1.1.1.2 Summary of adverse events (AEs) in ZD6474 studies

The most common AEs associated with ZD6474 in the phase I and other monotherapy studies included rash, diarrhoea and asymptomatic QTc prolongation. In Study 6474IL/0003, patients with advanced or metastatic NSCLC were enrolled after failure of prior platinum-based chemotherapy. The study was conducted in 2 parts. In Part A, patients were randomised to 1 of 2 double-blind treatment arms 300 mg ZD6474 or 250 mg gefitinib. In Part B patients received the alternate study treatment to that given in Part A. The median duration of therapy for each arm (in Part A) was ZD6474 56.0 days and gefitinib 57.0 days. More patients discontinued therapy as a result of adverse events for those who received ZD6474 (22.9%) compared to those who received gefitinib (10.6%).

The most frequent adverse events observed in this study were similar to those observed in previous studies of ZD6474 or gefitinib. The most frequent adverse events for ZD6474 (Part A) were diarrhoea (55.4%), fatigue (36.1%), rash (27.7%), and nausea (24.1%). The most

frequent adverse events for gefitinib were diarrhoea (41.2%), fatigue (31.8%), nausea (29.4%), and anorexia (24.7%).

Approximately 10% of patients who received ZD6474 had an adverse event of hypertension. The majority were CTC grade 1 or 2, three were CTC grade 3, and none were CTC grade 4. There were no serious adverse events (SAEs) of hypertension. The median increase in systolic blood pressure for patients who received ZD6474 was 10 mmHg; the median increase in diastolic blood pressure was 6 mmHg.

An increased incidence of SAEs was noted in patients who received ZD6474 compared to those who received gefitinib (44.6% vs. 35.3%). Cardiac disorders (6.0% vs. 1.2%), gastrointestinal disorders (6% vs. 2.4% and mainly diarrhoea), and respiratory disorders (13.3% vs. 8.2%) did occur more frequently in patients receiving ZD6474. The cardiac events included a variety of terms without any apparent pattern. Respiratory events were primarily those which would be anticipated in patients with advanced lung cancer. Three patients receiving ZD6474 developed pulmonary embolism and 3 patients developed interstitial lung disease, but cases were confounded by such factors as smoking, reduced mobility, infection, lung cancer progression and previous chemotherapy or radiation therapy. One patient in each arm developed a serious skin disorder. One patient who received ZD6474 developed a haematologic event, as did 2 patients who received gefitinib. No patients who received ZD6474 developed serious hepatotoxicity.

At the time of data cut-off [redacted], 49.4% of patients in the ZD6474 arm and 42.4% of patients in the gefitinib arm had died. The primary cause of death was disease progression. Other causes of death for the ZD6474 arm included acute respiratory distress syndrome (ARDS) (n=1), choking (n=1), interstitial lung disease (n=1), large intestine perforation (n=1), and sepsis (n=1). Other causes of death for the gefitinib arm included arterial haemorrhage (n=1), pneumonia (n=1), and respiratory failure (n=2).

Thirteen adverse events on study were followed by an outcome of death, 7 in the ZD6474 arm (ARDS, pneumonia, pneumonitis, dyspnoea, interstitial lung disease, respiratory failure and carcinomatous meningitis) and 6 in the gefitinib arm (breathlessness, bone pain, cellulitis, acute respiratory failure (2 cases) and pleural effusion).

Recognizing that QT prolongation might result in a variety of adverse events, AstraZeneca utilized the broad special Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for QT prolongation. The terms queried included electrocardiogram QT corrected interval prolonged, electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, long QT syndrome, long QT syndrome congenital, Torsades de Pointes, ventricular tachycardia, cardiac death, sudden cardiac death, sudden death, cardiac arrest, cardiac fibrillation, cardiorespiratory arrest, ECG repolarization abnormality, ECG J wave abnormality, ECG U wave abnormality, loss of consciousness, syncope, syncope vasovagal, ventricular arrhythmia, ventricular fibrillation, and ventricular flutter.

For ZD6474, the only event that was actually reported was electrocardiogram QT corrected interval prolonged. This was reported in 18 patients in Part A taking ZD6474 and 7 patients

in Part B taking ZD6474. Three patients taking gefitinib (all in Part A of the study) reported electrocardiogram QT corrected interval prolonged. In addition, 1 patient taking gefitinib reported syncope in Part B of the study.

There were 12 patients with confirmed QTc prolongation in Study 6474IL/0003, according to the protocol defined-criteria. Of these, 6 occurred in the first 28 days, and 2 in the following 28 days. The remaining 4 occurred sporadically, with the longest time to occurrence 323 days. There were 3 events of CTC grade 1 reversible dizziness in patients with a confirmed QTc prolongation occurring within the first 4 weeks; all 3 events also occurred within the first 4 weeks of therapy. Patients with dizziness had other events that might have caused dizziness and the events were not well correlated in time with the actual QT prolongation. There were no other potentially relevant adverse events in patients with confirmed QTc prolongation within the first 4 weeks, and no relevant adverse events in patients whose first confirmed QTc prolongation occurred more than 4 weeks after randomisation.

In Study 6474IL/0006, patients with advanced or metastatic NSCLC were enrolled after failure of prior platinum-based chemotherapy. Patients were randomised to treatment with a standard dose of docetaxel and either placebo or 100 mg of ZD6474 or 300 mg of ZD6474. The median duration of therapy for each arm (docetaxel/placebo, docetaxel /ZD6474 100 mg, and docetaxel /ZD6474 300 mg) was 64 days, 127days, and 61.5 days, respectively. More patients discontinued therapy as a result of AEs for those who received 300 mg ZD6474 (25%) compared to those who received 100 mg (11.9%) or placebo (12.2%).

The AE profile was similar for all three treatment arms, although somewhat higher frequencies were observed for the 100 mg ZD6474 arm compared with placebo, and for the 300 mg ZD6474 arm compared with 100 mg ZD6474.

The most frequent AEs observed in this study were similar to those observed in prior studies for ZD6474 or reported for docetaxel in the literature. The most common AEs and their frequencies as reported in the 300 mg ZD6474, 100 mg ZD6474 and placebo arms, respectively, were diarrhoea (50.0%, 38.1%, 24.4%), fatigue (45.5%, 40.5%, 26.8%), neutropenia (31.8%, 26.2%, 19.5%) and nausea (29.5%, 26.2%, 17.1%). Rash was observed in 15.9%, 16.7% and 9.8% of patients in the three arms respectively.

1.1.2 Erlotinib TARCEVA® (Roche Products Limited)

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer after failure of at least one prior chemotherapy regimen. At a dose of 150 mg, Erlotinib has been shown to have a significant beneficial effect on overall survival compared with placebo .

In a randomised, double-blind, placebo controlled study involving 731 patients with locally advanced or metastatic NSCLC , having failed at least one prior chemotherapy regimen (the BR.21 study), patients were randomised 2:1 to receive Erlotinib 150 mg or placebo orally once daily. Study endpoints included overall survival, progression free survival (PFS), response rate, duration of response, time to deterioration of lung cancer related symptoms

(cough, dyspnoea and pain), and safety. The primary endpoint was survival.(Roche Products Limited 2005)

Results showed that the median overall survival was 6.7 months in the Erlotinib group (95 % CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95 % CI, 4.1 to 6.3 months).The median PFS was 9.7 weeks in the Erlotinib group (95 % CI, 8.4 to 12.4 weeks) compared with 8.0 weeks in the placebo group (95 % CI, 7.9 to 8.1 weeks).

Rash (75 %) and diarrhoea (54 %) were the most commonly reported adverse drug reactions (ADRs). Most were Grade 1/2 in severity and manageable without intervention. Grade 3/4 rash and diarrhoea occurred in 9 % and 6 %, respectively in Erlotinib treated patients and each resulted in study discontinuation in 1 % of patients. Dose reduction for rash and diarrhoea was needed in 6 % and 1 % of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhoea was 12 days (Roche Products Limited 2005)

Erlotinib resulted in symptom benefits by significantly prolonging time to deterioration in cough dyspnoea and pain, versus placebo.

1.2 Rationale

The outlook for patients with refractory advanced NSCLC is poor, with a median survival of approximately 6 months after failure of first line treatment.

There are now several reports on the use of novel targeted therapies with unique mechanisms of action, which have provided proof of the concept in the clinical trials leading to market. Bevacizumab (Avastin ®), an anti-VEGF recombinant humanized monoclonal antibody, showed improved efficacy in stage IIIb/IV NSCLC when combined with paclitaxel/ carboplatin (Sandler et al 2005) and in advanced colorectal cancer (CRC) when combined with Irinotecan/5 Fluorouracil/Leucovorin (Hurwitz et al 2004). Agents such as EGFR-tyrosine kinase inhibitors (TKIs) (e.g. Erlotinib), and anti-EGFR monoclonal antibodies (mAbs) (e.g. Erbitux) have shown efficacy in refractory NSCLC and refractory CRC, respectively.

Combination therapies have been reported with these novel agents. Herbst et al 2005 reported on a Phase I/II trial of Bevacizumab and Erlotinib in patients with NSCLC having shown an increased response rate and PFS, suggesting that EGFR and VEGFR blockade may have significant activity in NSCLC even without chemotherapy.

ZD6474 has both EGFR & VEGFR TKI activity. Hence, ZD6474 may have potential utility as a novel agent containing both EGFR and VEGF inhibition in one compound.

In a Japanese Phase I study with doses ranging from 100 mg to 400 mg, objective tumour response was seen from 4 of 9 patients with NSCLC. In a Phase II study (6474IL/0006), ZD6474 combined with docetaxel showed prolonged PFS in patients with NSCLC compared to docetaxel alone. In a second phase II study (6474IL/0003), ZD6474 alone prolonged PFS

compared to the EGFR inhibitor gefitinib, suggesting that the combination of EGFR and VEGFR inhibition in ZD6474 offers superior efficacy to an EGFR inhibitor alone.

Erlotinib is an EGFR inhibitor currently indicated for the treatment of patients with NSCLC after failure of at least one prior chemotherapy regimen. The current study will compare the efficacy of ZD6474, as assessed by the primary endpoint of PFS, to Erlotinib in this patient population. ZD6474 has the potential to offer superior efficacy to Erlotinib in NSCLC because of the combination of VEGFR and EGFR inhibition, as suggested by the phase II study 6474IL/0003 in which ZD6474 had superior PFS to gefitinib. In the phase II studies, 300mg has been tolerated, with the most common toxicities being rash and diarrhoea. These side effects are also seen with Erlotinib, and with each agent these adverse events can be managed with symptomatic treatment or with dose reduction. Although QTc prolongation is also seen with ZD6474, this has been asymptomatic and can be managed with dose reduction.

The dose of ZD6474 in this study was selected following review of the efficacy, safety and pharmacokinetic (PK) data to date. In study 6474IL/0003, the 300 mg dose demonstrated superior efficacy to gefitinib with an acceptable safety profile.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to demonstrate an improvement in Progression Free Survival (PFS) for ZD6474 compared with Erlotinib in patients with locally advanced or metastatic NSCLC after failure of at least one but no more than two, prior cytotoxic chemotherapy regimens. Eligible patients must have a documented history of progressive disease or unacceptable toxicity either during or after treatment with prior cytotoxic chemotherapy treatment for the disease.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To demonstrate an improvement in overall survival for ZD6474 compared with Erlotinib

2. To demonstrate an improvement in the ORR, DCR, and DOR for ZD6474 compared with Erlotinib

3. To demonstrate an improvement in the time-to-deterioration of pain, dyspnoea, cough in patients treated with ZD6474, compared with Erlotinib, based on the EORTC QLQ-C30 plus lung cancer module QLQ-LC13

4. To study the safety and tolerability of ZD6474 compared with Erlotinib

5. To investigate the population pharmacokinetics (PK) of ZD6474 and assess the relationship between PK and QTc, measures of safety and efficacy and pharmacodynamic (PD) biomarkers

6. To investigate plasma levels of the N-desmethyl and N-oxide metabolites of ZD6474 in this patient population.

2.3 Exploratory objectives

The exploratory objectives of the study are to:

1. To investigate the correlation of epidermal growth factor receptor (EGFR) expression, amplification and mutations and other related biomarker status with efficacy in archival tumour samples in those patients where such tumour material is available

2. To collect a genetic blood sample for DNA extraction and storage

3. To investigate in blood plasma samples, the correlation of levels of circulating protein biomarkers with efficacy

4. To investigate the effect on health-related quality of life (HRQOL)/symptoms of ZD6474 compared with Erlotinib based on the EORTC QLQ-C30 plus lung cancer module QLQ-LC13

5. To investigate patient health status index during the period of treatment with investigational therapy by assessment of the EuroQoL 5 Dimension Instrument (EQ5D)

6. To investigate the time to deterioration in patient WHO PS during the period of treatment with investigational therapy

7. To investigate changes in patient weight

8. To investigate EGFR mutational status and mutational status of other candidate genes in cell-free circulating tumour DNA found in plasma

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This is a parallel group, international, randomised, double-blind, double-dummy, comparator, multi-centre study design to assess whether ZD6474 (300 mg daily) confers an advantage in terms of PFS compared with Erlotinib (150 mg daily) in patients with locally advanced or

metastatic NSCLC who have received prior cytotoxic chemotherapy treatment. It is planned that 1150 patients will be randomised into the study in approx 160 investigator sites across 22 countries and that each site will recruit between 5-25 patients. EU Directive implementing countries will recruit 395 patients (40 in France, 70 in Italy, 30 in the Netherlands, 30 in Spain, 50 in the UK, 55 in Germany, 50 in Norway, 30 in Denmark, 40 in Sweden). The final number of subjects randomised was 1243.

Patients will be randomised in a 1:1 ratio to receive either ZD6474 300 mg plus placebo or Erlotinib 150 mg plus placebo as a once daily oral dose from Day 1.

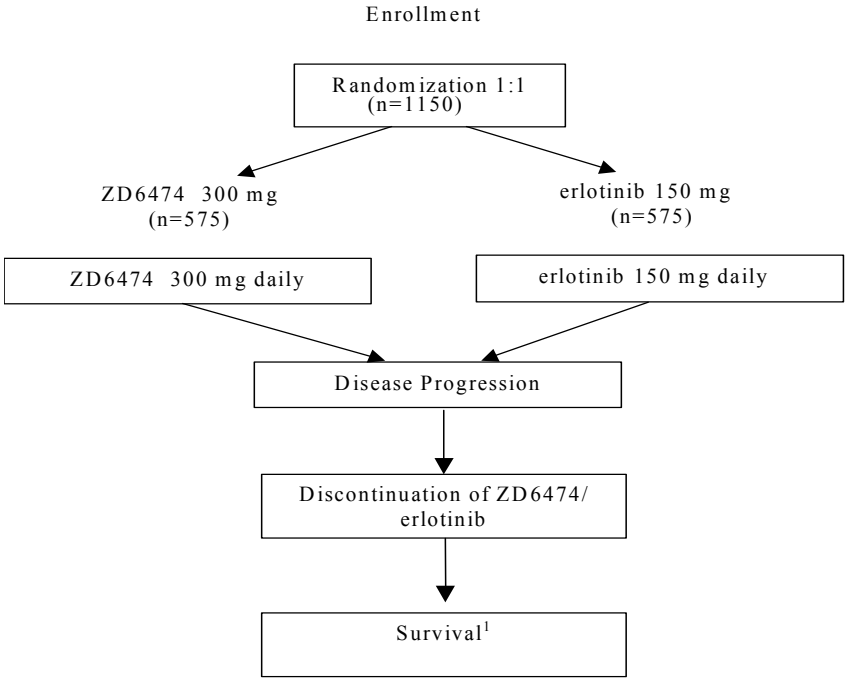
Patients will continue to receive study treatment until progression of their disease is determined according to RECIST criteria. Once a patient progresses on ZD6474/Erlotinib, study treatment will stop.

Radiological evaluation using RECIST will be performed at screening and every 4 weeks during the study until week 16 and every 8 weeks thereafter. It is important to follow the assessment schedule as closely as possible. Patients will be evaluated until objective progression and then be followed up for survival unless they withdraw consent. If a patient discontinues study medication prior to objective disease progression they should continue to be assessed regularly, as per the protocol schedule, until disease progression and then followed up for survival, unless they withdraw consent.

The safety data from all patients will be assessed on an ongoing basis. Patients who experience CTCAE grade 3 or 4 toxicity (Section 3.2.2) that is considered related to ZD6474/Erlotinib will have their study medication stopped until resolution of the toxicity. When the toxicity has recovered as described in Section 3.2.2, the patient may restart treatment, but at a reduced dose only. This will be in a blinded manner according to the dose reduction plan in section 3.4.2.2 . The study assessments should be continued as outlined in the study plan. If the patient has been off study medication for greater than 3 weeks due to toxicity, the patient must be permanently discontinued from ZD6474/Erlotinib and will be followed for objective progression and survival, unless they withdraw consent.

In order to obtain a sub-group of 200 patients for the ZD6474 population-PK analysis, blood samples will be obtained from approx 400 patients randomised into the study.

Figure 1 Study flow chart



[1] Primary analysis will be conducted after approximately 1110 PFS events. Patients will be evaluated until objective disease progression and will then be followed up for survival unless they withdraw consent. If a patient discontinues study medication prior to objective disease progression they should continue to be assessed regularly, as per the protocol schedule, until disease progression and then followed up for survival, unless they withdraw consent.

Table 1 Study plan – Screening and study treatment period

Visit	**1 (screening)**		**2**	**3**	**4**	**5[(a)]**	**6**	**7**	**8[(a)]**
Week	**0**		**0**	**1**	**2**	**4**	**8**	**12**	**16+**
Day	**-21-0**	**-7-0**	**1**	**8**	**15**	**29**	**57**	**85**	**113+**
Visit window	**0**	**0**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**
Written Informed consent	X								
Medical history	X								
Demography	X								
Physical examination (b)		X				X	X	X	X
Height		X							
Weight / Vital signs (c)		X	X	X	X	X	X	X	X

Table 1 Study plan – Screening and study treatment period

Visit	1 (screening)		2	3	4	5[a]	6	7	8[a]
Week	0		0	1	2	4	8	12	16+
Day	-21-0	-7-0	1	8	15	29	57	85	113+
12-lead ECG [d]	X[d]		X	X	X	X	X	X[d]	
Pregnancy test[e]		X							
Haematology / clinical chemistry & urinalysis [f]	X		X[f]	X	X	X	X	X	X
Genetic blood sample (optional) [g]			X						
Archival tumour sample (optional) [h]			X						
WHO Performance Status		X	X	X	X	X	X	X	X
Tumour assessment according to RECIST [i]	X					X	X	X	X[i]
EORTC QLQ-C30 plus LC-13[j]		X				X	X	X	X
EQ5D[j]		X				X	X	X	X
Record prior anti cancer therapy		X							
Inclusion /Exclusion criteria [k]	X[k]		X[k]						
Randomisation			X						
Study Medication Dispensing			X			X	X	X	X
PK Assessments [l]				X	X	X	X	X[l]	
Blood sampling for plasma biomarkers			X	X	X	X	X	X	X
Cell-free tumour DNA[m] optional			X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X
Adverse event review [n]	X[n]		X	X	X	X	X	X	X
Historical tumour biomarker status [o]			X						

- Assessments and treatment should be carried out as specified in the study plan. If the scheduled study day falls on a weekend or holiday, at Visit 3 onwards, the visit/assessments may be delayed or advanced by ±3 days
- Please note that Visit at which the Patient discontinues study medication is always the Discontinuation of study medication visit detailed on Table 2. For example, if the patient attends for Visit 4 and it is decided that study medication is discontinued, the Discontinuation visit and scheduled procedures are carried out instead of Visit 4. If a subject discontinues between visits, the next scheduled Visit will be the discontinuation visit.

(a) From Visit 5 (Week 4, Day 29), subsequent visits will be scheduled every 4 weeks. All assessments marked in Visit 8+ in Table 1 should take place at each of these 4 weekly visits (apart from RECIST, see comment i.)

(b) Please note that any clinically significant new findings or aggravated pre-existing conditions found at Physical examination should be recorded as AEs.
(c) Weight and Vital signs to be recorded as scheduled, vital signs include blood pressure (BP), pulse, and temperature. BP and pulse should be taken after patient has been resting for 5 minutes and before any blood sampling.
(d) 12-lead ECG must be performed at screening (Visit 1), (within 21 days before the first dose). The screening QTc must be < 480 msec (or ≤460 msec for patients currently taking medications described in Table 2 of Appendix D). Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility.
At Visit 2 (day 1), 3 x 12-lead ECGs are performed prior to first dosing to obtain baseline QTc. Baseline QTc will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another). When possible, ECGs should be performed at the same time throughout the study (performed 4-8 hours after the patient takes their oral medication) at the scheduled visits. See Section 3.2.2.1 for more information on ECG's. Following Visit 7 (day 85) ECG's are performed every 3 months until discontinuation of study medication. If QTc prolongation occurs at one of the usual assessment times, or at any other time, please refer to Section 3.2.2.1 for further details.
Patients who are receiving one of the drugs listed in Appendix D, Table 2, at the time of study entry must have an additional ECG obtained 4-8 hours after the first dose of study medication.
(e) Females of childbearing potential only must have a negative pregnancy test within 3 days before Day 1
(f) Haematology / Clinical chemistry & urinalysis need only be assessed at visit 2 (day 1) if the screening assessments were more than 7 days before
(g) Optional 10 mL blood sample for retrospective genotyping analysis can occur at Visit 2 or any subsequent visits. Sample to be taken pre-dose if patient has provided consent.
(h) Every attempt to obtain archival paraffin-embedded tumour sections will be collected if a patient has provided consent.
(i) RECIST assessments to be performed at screening and every 4 weeks during the study until objective disease progression up to week 16 and every 8 weeks thereafter. Patients who discontinue study medication prior to objective disease progression should continue to be evaluated for progression every 8 weeks according to the study plan unless the patient withdraws consent. Scans performed for RECIST will be expected to cover chest and abdomen. Pelvis will be included if clinically indicated. For ad hoc additional scans performed for new/worsening symptoms (e.g. brain MRI) please refer to section 4.6.3.1
(j) Quality of life and disease-related symptom assessments are to be administered at screening (within 7 days before the first dose of study medication on Day 1), every 4 weeks thereafter, at discontinuation of study treatment and at the 30-day follow-up visit. These assessments should be completed before the results of patients tumour assessments are given to them.
(k) Eligibility (inclusion/exclusion) criteria must be confirmed prior to commencing treatment on Day 1
(l) Blood samples for PK will be collected on Day 8 (Week 1), Day 15 (Week 2), Day 29 (Week 4), Day 57 (Week 8) & Day 85 (Week 12) and every 3 months thereafter until discontinuation of study medication, from approx 400 patients randomised into the study. Samples should be collected as close to or at the same time as the ECG is performed (approximately 4-8 hours after the patient takes their study medication on the assessment days).
(m) Providing the patient has given consent. Any remaining plasma from the plasma biomarker sample will be used for the cell-free tumour DNA analysis
(n) All adverse events that occur after the patient consent should be recorded
(o) Information can be collected at Visit 2 or any subsequent visits.

Table 2 Study plan – Discontinuation of Study Medication, Follow-up & Survival

Visit	Discontinuation of study medication	30 day follow-up	60 day follow-up(a)	Survival(g)
Physical examination (b)	X	X		

Table 2 Study plan – Discontinuation of Study Medication, Follow-up & Survival

Visit	Discontinuation of study medication	30 day follow-up	60 day follow-up(a)	Survival(g)
Weight	X	X		
Vital signs (c)	X	X		
12-lead ECG	X			
Haematology	X			
Clinical chemistry	X			
Urinalysis	X			
WHO Performance Status	X	X		
RECIST (d)	X			
EORTC QLQ-C30 plus LC13(e)	X	X		
EQ5D(e)	X	X		
PK Assessments	X			
Blood sampling for plasma biomarkers	X			
Subsequent cancer therapy (f)	X	X	X	X
Survival (g)			X	X
Adverse event review	X	X	X	
Concomitant medication	X	X	X	

(a) The 60-day follow-up visit may be conducted via telephone contact.
(b) Physical exam, any clinically significant new findings or aggravated pre-existing conditions should be recorded as AEs.
(c) Vital signs include blood pressure (BP), pulse, and temperature. BP and pulse should be taken after patient has been resting for 5 minutes and before any blood sampling.
(d) Patients who discontinue study medication prior to objective disease progression should continue to be evaluated for objective progression by RECIST every 8 weeks according to the protocol schedule, unless the patient withdraws consent. Scans performed for RECIST will be expected to cover chest and abdomen. Pelvis will be included if clinically indicated. For ad hoc additional scans performed for new/worsening symptoms (e.g. brain MRI) please refer to section 4.6.3.1
(e) Quality of life questionnaires are to be administered at discontinuation of study medication and at the 30-day follow-up visit. The questionnaires should be completed before the patient is given results of their associated assessments.
(f) Details of the first and subsequent cancer therapies after discontinuation of study medication will be collected, unless the patient withdraws consent.

(g) Assessments for survival **must** be made at the 60 day follow-up visit and then every 8 weeks, unless the patient withdraws consent. Survival information may be obtained via telephone, or as appropriate by contact with patient, patient's family or current treating physician.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

A randomised, double- blind, Phase III comparator study will be appropriate to assess whether ZD6474 confers a longer PFS benefit when compared with Erlotinib in patients with refractory, advanced NSCLC. The population for this study will consist of patients who failed at least one, but no more than two, prior cytotoxic chemotherapy regimens, and for whom Erlotinib is therefore an appropriate therapeutic option (2nd or 3rd line patients). The study is based on the results of a randomised, double-blind, phase II study in 2nd and 3rd-line NSCLC (study 6474IL/0003), which compared ZD6474 300 mg to gefitinib. In this study, ZD6474 provided superior efficacy when compared to gefitinib. The median PFS for patients who received ZD6474 was 11 weeks, compared to 8 weeks for gefitinib, with 2–sided p=0.025. In addition to the advantage of PFS, patients who received ZD6474 had a higher response rate (8% vs. 1%) and disease control rate at 8 weeks (45% vs 34%) compared to patients who received gefitinib. While a disadvantage in overall survival was seen for patients who were initially randomised to ZD6474, this difference was not statistically significant, and was likely to be confounded, in part, by the design of the study, which allowed patients to switch-over to the opposite treatment at the time of disease progression. Common AEs experienced by patients who received ZD6474 included rash, diarrhoea, and asymptomatic QTc prolongation. These were managed with symptomatic treatment or with dose reduction. Therefore, the dose of ZD6474 to be studied in this study will be 300mg, as was used in the previous phase II study.

Erlotinib is an appropriate comparator in this patient population, as it is an accepted and approved agent for the 2nd and 3rd line treatment of NSCLC. By blinding patients and investigators, and assessing tumour measurements on a fixed and frequent schedule, the risk of bias that could affect the interpretation of the PFS endpoint should be reduced.

3.2.2 Risk/benefit and ethical assessment

A previous phase II study, 6474IL/0003, showed a statistically significant advantage in PFS for ZD6474 compared to gefitinib, an EGFR inhibitor. Therefore, the current study, which compares the efficacy of ZD6474 to the EGFR inhibitor Erlotinib, is appropriate. Erlotinib is a widely accepted and approved standard of care for patients with NSCLC, so it is ethical to conduct this study with a primary objective to demonstrate an advantage in PFS for ZD6474 over Erlotinib. In study 6474IL/0003, the side effects of ZD6474 could be managed with symptomatic treatment or with dose reduction, and the management of toxicity is outlined in the following sections.

All toxicities will be graded according to the National Cancer Institute (NCI) CTCAE, Version 3. Management of toxicities including dose modifications are detailed below and summarized in Table 3.

3.2.2.1 QTc prolongation

Patients will have ECGs performed to monitor the QTc interval (using Bazett's correction).

The screening QTc must be <480 msec. Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility. Patients who are receiving a drug that has arisk of QTc prolongation (see Appendix D, Table 2) are excluded if QTc is ≥ 460 msec. Baseline QTc will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1.

For this study QTc prolongation is defined as:

A single QTc value of ≥550 msec or an increase of ≥100 msec from baseline;

OR

Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second QTc being the mean of 3 consecutive ECGs):

- A QTc interval ≥500 msec, but <550 msec;

OR

An increase of ≥60 msec, but <100 msec from baseline QTc to a QTc value ≥480 msec

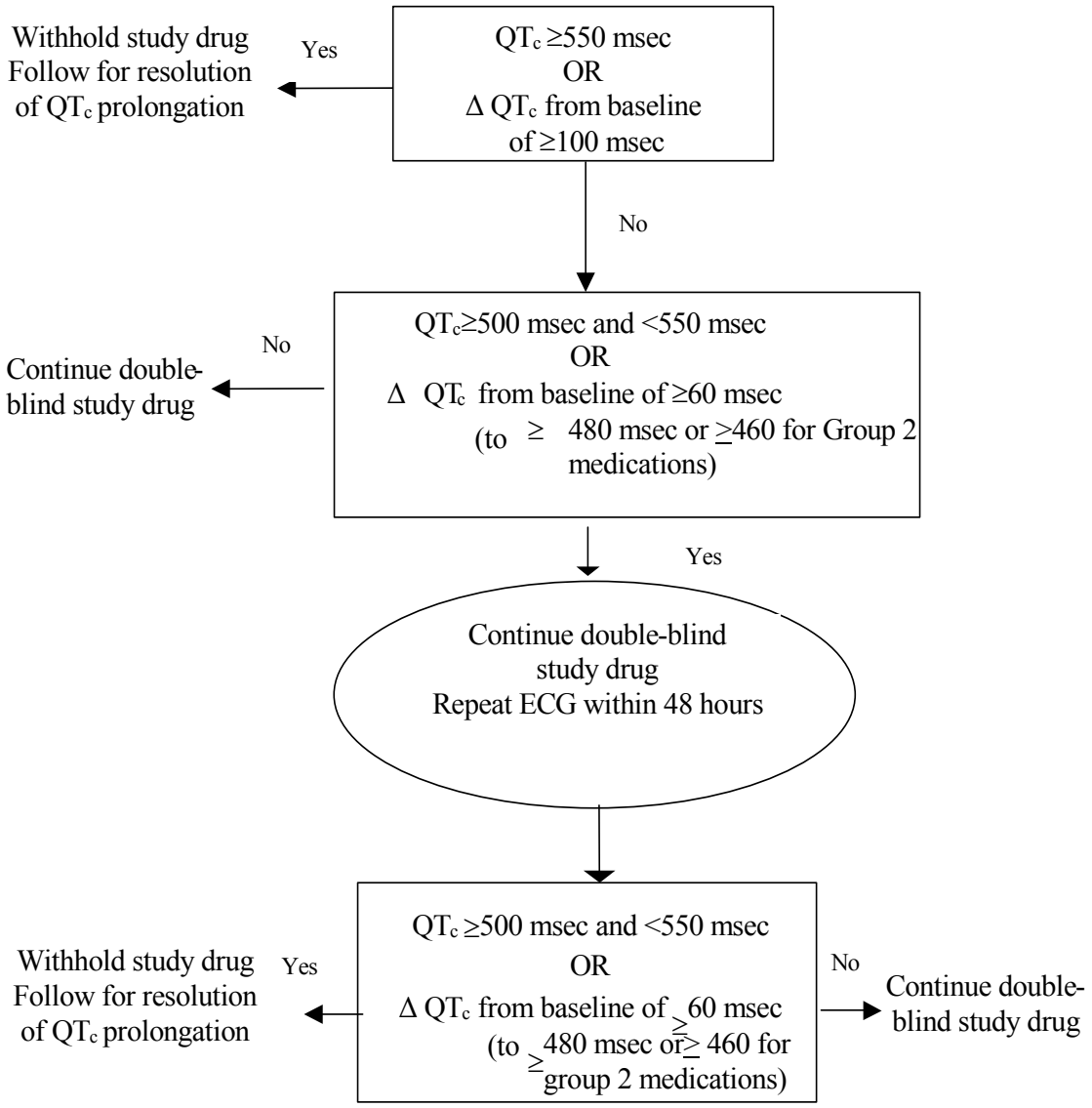
Patients who are receiving one of the drugs listed in Appendix D, Table 2, at the time of study entry must have an additional ECG obtained 4-8 hours after the first dose of study medication.

Management of patients with QTc prolongation

Figure 2 summarizes the management of QTc prolongation for this study.

For a single QTc value of ≥550 msec or an increase of ≥100 msec from baseline, study medication must be withheld. ECGs and electrolytes should be followed 3 times a week until QTc falls below 480 msec or baseline, whichever is higher. ZD6474/Erlotinib treatment may be resumed at a lower dose after the QTc recovers to <480 msec or baseline.

Figure 2 Flow chart detailing management of QTc prolongation



For a QTc interval ≥500 msec, but <550 msec, or an increase of ≥60 msec but <100 msec from baseline QTc to a QTc value ≥480 msec (≥460 msec for group 2 medications), ZD6474/Erlotinib may be continued but a repeat ECG (in triplicate) must be obtained within 48 hours. If QTc prolongation is confirmed, ZD6474/Erlotinib should be withheld. ECGs and electrolytes should be checked 3 times a week until QTc falls below 480 msec (or ≤460 msec for group 2 medications) or baseline, whichever is higher. ZD6474/Erlotinib treatment may be resumed at a lower dose after the QTc recovers to <480 msec (or ≤460 msec for group 2 medications) or baseline. If the patient does not meet the criteria for QTc prolongation at the repeat ECG then the patient should continue treatment with double blind study medication and resume the ECG schedule as outlined in the Study Plan.

If ZD6474/Erlotinib is restarted after the QTc prolongation has resolved, ECGs should be performed 1, 2, 4, 8, 12 weeks and every 3 months after study medication is restarted. The

reduced dose is 200 mg ZD6474 or 100 mg Erlotinib initially. If the patient experiences QTc prolongation on the 200 mg ZD6474 or 100 mg Erlotinib dose they can be given 100 mg ZD6474 or 50 mg Erlotinib, on resolution of the QTc prolongation. If ZD6474/Erlotinib must be withheld for >3 weeks to allow for QTc prolongation to recover < 480 msec (or ≤460 msec for group 2 medications) or baseline, the patient will not be restarted on study medication. If QTc prolongation recurs after all dose reductions as detailed, the patient will permanently discontinue treatment with study medication.

3.2.2.2 Gastrointestinal toxicity

Nausea, vomiting, or both may be controlled with antiemetic therapy.

Diarrhoea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation. No dose modifications will be made because of grade 1 or 2 diarrhoea.

If CTCAE grade 3 or 4 diarrhoea develops, ZD6474/Erlotinib, should be withheld until diarrhoea resolves to CTCAE grade 1 or baseline. Patients who are clinically unstable because of diarrhoea or other intercurrent medical illness must be admitted and evaluated using telemetry and serum electrolytes until clinically stable. Upon recovery from >CTCAE grade 3 gastrointestinal toxicity (despite prophylactic measures), study treatment may resume at a permanently reduced dose of 200 mg ZD6474 or 100 mg Erlotinib initially. If the patient experiences toxicity on the 200 mg ZD6474 or 100 mg Erlotinib dose they can be given 100 mg ZD6474 or 50 mg Erlotinib, on resolution of toxicity. If >CTCAE grade 3 diarrhoea recurs after the final dose reduction, the patient will permanently discontinue treatment with study medication. If ZD6474/Erlotinib must be withheld for >3 weeks for resolution of diarrhoea, the patient will permanently discontinue treatment with study medication.

3.2.2.3 Cutaneous toxicity

It is strongly recommended that all patients follow a program of sun protective measures while receiving study medication and for 3-4 weeks after discontinuing study medication. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash, and to minimize the requirement for dose reduction of study therapy.

If a patient develops a skin rash, the following actions are recommended to the Investigator for the management of this reaction:

- A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams, either topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.

- The rash should be graded as soon as possible according to the CTCAE cutaneous toxicity criteria.

- If a rash of CTCAE grade 2 or higher is detected, immediate symptomatic treatment should be provided.

- If a rash of CTCAE grade 3 or higher is detected, ZD6474/Erlotinib should be withheld until recovery to CTCAE grade 1 or below. Study medication may then be resumed at a permanently reduced dose of 200 mg ZD6474 or 100 mg Erlotinib initially. If the patient experiences toxicity on the 200 mg ZD6474 or 100 mg Erlotinib dose they can be given 100 mg ZD6474 or 50 mg Erlotinib on resolution of the toxicity.

If severe cutaneous toxicity recurs after the final dose reduction, the patient will permanently discontinue study medication. If ZD6474/Erlotinib must be withheld for >3 weeks due to cutaneous toxicity, the patient will permanently discontinue treatment with study medication.

3.2.2.4 Other toxicity

In case of acute development of new or progressive, unexplained pulmonary symptoms such as dyspnoea, cough and fever, study treatment should be interrupted and permanently discontinued if Interstitial Lung Disease (ILD) is diagnosed.

If any other CTCAE grade 3 or 4 toxicity that is not outlined in Sections 3.2.2.1 to 3.2.2.3 develops and is attributable to either ZD6474/Erlotinib, study medication should be withheld until the toxicity resolves to CTCAE grade 1 or baseline. Upon recovery, treatment may resume at a permanently reduced dose of 200mg ZD6474 or 100 mg Erlotinib. If the patient experiences toxicity on the 200 mg ZD6474 or 100 mg Erlotinib dose they can be given 100 mg ZD6474 or 50 mg Erlotinib, on resolution of toxicity. If CTC grade 3 or 4 toxicity recurs after this final dose reduction, the patient must permanently discontinue study treatment.

Patients who develop CTCAE grade 3 hypertension may continue on study therapy if blood pressure is controlled on antihypertensive medication. Antihypertensive medication known to potentially prolong QTc interval should not be given while the patient is in the study. (please refer to Appendix D of the study protocol for a list of these). If blood pressure cannot be stabilized with increased antihypertensive medication, study medication must be discontinued and cannot be resumed until blood pressure is controlled to baseline level. Patients with CTCAE grade 4 hypertension should discontinue study medication and cannot resume therapy until blood pressure is controlled to baseline level.

If ZD6474 /Erlotinib must be withheld for >3 weeks for resolution of toxicity, the patient will permanently discontinue treatment with study medication.

Table 3 Summary of guidance on the management of toxicity for ZD6474 /Erlotinib

Toxicity	ZD6474 (300 mg)/Erlotinib (150 mg)
QTc value ≥550 msec or prolonged ≥100 msec from baseline	Withhold study medication; if QTc recovers to <480 msec (or ≤460 msec for group 2 medications) or baseline, then reduce dose to 200 mg ZD6474 or 100 mg Erlotinib initially. If toxicity recurs, reduce dose to 100 mg ZD6474 or 50 mg Erlotinib on resolution. If QTc does not recover to <480 msec (or ≤460 msec for group 2 medications) or baseline within 3 weeks, patient will permanently discontinue ZD6474/Erlotinib.
QTc value ≥500 msec and <550 msec or prolonged ≥60 msec but < 100 msec from baseline	Continue dosing; repeat ECG (in triplicate) within 48 hours; if repeat ECG meets criteria, withhold study medication; then if QTc recovers to <480 msec (or ≤460 msec for group 2 medications) or baseline, reduce dose to 200 mg ZD6474 or 100 mg Erlotinib initially. If toxicity recurs, reduce dose to 100 mg ZD6474 or 50 mg Erlotinib on resolution. If QTc does not recover to <480 msec (or ≤460 msec for group 2 medications) or baseline within 3 weeks, patient must permanently discontinue treatment with study medication. Or, if the repeat ECG does not meet criteria, patient should continue study medication.
Grade 3 or 4 diarrhoea	Withhold study medication until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 200 mg ZD6474 or 100 mg Erlotinib, initially. If toxicity recurs, reduce dose to 100 mg ZD6474 or 50 mg Erlotinib on resolution. If severe diarrhoea recurs after the final dose reduction, patient must permanently discontinue study medication. If ZD6474 /Erlotinib must be withheld for >3 weeks patient must permanently discontinue treatment with study medication
Grade 3 or 4 cutaneous toxicity	Withhold study medication until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 200 mg ZD6474 or 100 mg Erlotinib, initially. If toxicity recurs, reduce dose to 100 mg ZD6474 or 50 mg Erlotinib on resolution. If severe cutaneous toxicity recurs after the final dose reduction, patient must permanently discontinue study medication. If ZD6474 /Erlotinib must be withheld for >3 weeks patient must permanently discontinue treatment with study medication.

Table 3 Summary of guidance on the management of toxicity for ZD6474 /Erlotinib

Toxicity	ZD6474 (300 mg)/Erlotinib (150 mg)
Grade 3 or 4 hypertension	CTCAE grade 3 hypertension: continue on study therapy if blood pressure is controlled on antihypertensive medication. If blood pressure cannot be stabilized with increased antihypertensive medication, study medication must be withheld and cannot be resumed until blood pressure is controlled to baseline level. CTCAE grade 4 hypertension: study medication should be withheld and cannot be resumed until blood pressure is controlled to baseline level. If ZD6474 /Erlotinib must be withheld for >3 weeks patient must permanently discontinue treatment with study medication.
Other grade 3 or 4 toxicity	Withhold study medication until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 200 mg ZD6474 or 100 mg Erlotinib. If toxicity recurs, reduce dose to 100 mg ZD6474 or 50 mg Erlotinib on resolution. If ZD6474 /Erlotinib must be withheld for >3 weeks patient must permanently discontinue treatment with study medication.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled eg, patient screening log. This information is necessary to establish that the patient population was selected without bias.

3.3.2 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

1. Provision of informed consent

2. Female or male aged 18 years and over

3. Histologic or cytologic confirmation of locally advanced or metastatic NSCLC (IIIB-IV). Sputum cytology alone is not acceptable. Cytology specimens obtained by brushing, washing, or needle aspiration are acceptable.

4. Failure of at least one, but no more than two, prior cytotoxic chemotherapy regimens (either radiological documentation of disease progression or due to toxicity).

5. WHO Performance status 0 – 2

6. One or more measurable lesions at least 10 mm in the longest diameter (LD) by spiral CT scan or 20 mm with conventional techniques according to RECIST criteria

7. Negative pregnancy test for women of childbearing potential

8. Life expectancy of 12 weeks or longer.

9. Able to read and write

For inclusion in the genetic research part of the study, patients must fulfil the following criterion:

Provision of informed consent for genetic research and tissue sampling

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Mixed small cell and non small-cell lung cancer histology

2. Prior treatment with EGFR TKIs or VEGFR TKIs (prior treatment with cetuximab [Erbitux] or bevacizumab [Avastin] is permitted)

3. Chemotherapy or other systemic anti-cancer therapy within 4 weeks before the start of study therapy (6 weeks for nitrosoureas, mitomycin and suramin)

4. Radiation therapy within 4 weeks before the start of study therapy, not including local palliative radiation.

5. Major surgery within 4 weeks, or incompletely healed surgical incision before starting study therapy

6. Any unresolved toxicity > CTCAE grade 2 from previous anti-cancer therapy

7. Serum bilirubin greater than 1.5x upper limit of reference range (ULRR)

8. Serum creatinine clearance ≤30 ml/min (calculated by Cockcroft-Gault formula) See Appendix G.

9. ALT or AST > 2.5 x ULRR if no demonstrable liver metastases, or > 5 x ULRR if judged by the Investigator to be related to liver metastases

10. Alkaline phosphatase (ALP) > 2.5 x ULRR if no demonstrable liver metastases, or > 5 x ULRR if judged by the Investigator to be related to liver metastases

11. Significant cardiovascular event (e.g. myocardial infarction, superior vena cava [SVC] syndrome, New York Heart Association [NYHA] classification of heart disease (see appendix I) ≥2 within 3 months before entry, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia

12. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation), which is symptomatic or requires treatment (CTCAE grade 3 or 4) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation, controlled on medication, is not excluded.

13. Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age

14. QT prolongation with other medications that required discontinuation of that medication

15. Presence of left bundle branch block (LBBB)

16. QTc with Bazett's correction unmeasurable or ≥ 480 msec or greater on screening ECG. (Note: If a patient has QTc ≥480 msec on screening ECG, the screen ECG may be repeated twice [at least 24 hours apart]. The average QTc from the three screening ECGs must be <480 msec in order for the patient to be eligible for the study). Patients who are receiving a drug that has a risk of QTc prolongation (see Appendix D, Table 2) are excluded if QTc is ≥ 460 msec.

17. Potassium <4.0 mmol/L despite supplementation; serum calcium (or ionized or adjusted for albumin), or magnesium out of normal range despite supplementation

18. Women who are pregnant or breast feeding

19. Concomitant medications that may cause QTc prolongation or induce Torsades de Pointes (see appendix D). Drugs listed in Appendix D, Table 2, that in the Investigator's opinion cannot be discontinued, are allowed.

20. Concomitant medications that are potent inhibitors (ketoconazole, itraconazole, atazanavir, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO) and voriconazole) or inducers (rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital and St. John's Wort) of CYP3A4 function

21. Brain metastases or spinal cord compression, unless treated at least 4 weeks before entry, and stable without steroid treatment for 10 days

22. Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 millimeter of mercury [mmHg] or diastolic blood pressure greater than 100 mmHg)

23. Previous or current malignancies of other histologies within the last 5 years, with the exception of in situ carcinoma of the cervix and adequately treated basal cell or squamous cell carcinoma of the skin

24. Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol

25. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren syndrome, severe exposure keratopathy or any other disorder likely to increase the risk of corneal epithelial lesion such as bullous keratopathy, aniridia, severe chemical burns or neutrophilic keratitis

26. Previous randomisation of treatment in the present study or other ZD6474 studies

27. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site)

28. Receipt of any investigational agents within 30 days prior to starting study treatment

3.3.4 Restrictions

1. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment.

2. Due to the experimental nature of ZD6474, female patients must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception defined as barrier method in conjunction with spermicide. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception or intrauterine device are allowed. Male patients must be surgically sterile or using an acceptable method of contraception (defined as barrier method in conjunction with spermicide) during their participation in this study.

3. It is strongly recommended that all patients follow a program of sun protective measures while receiving study medication and for 3-4 weeks after discontinuing study medication:

   – Avoiding direct sunlight

- Covering sun exposed skin with clothing (long trousers, long sleeve shirts and hats)

- Using a SPF 45 or higher sunblock

4. Patients who are still smoking should be encouraged to stop smoking as plasma concentrations of erlotinib could be reduced otherwise.

3.3.5 Discontinuation of subjects from treatment or assessment

3.3.5.1 Criteria for Discontinuation

Patients will be considered to have withdrawn from the study only in the event of death, loss to follow-up, or withdrawal of informed consent. No data will be collected after the date of withdrawal of informed consent.

Patients may withdraw consent at any time without prejudice to further treatment.

3.3.5.2 Procedures for discontinuation

Procedures for withdrawal from study

The reason for withdrawal from the study should be recorded on the appropriate eCRF(s). The investigator should immediately notify AstraZeneca of a patient's withdrawal from the study.

Discontinuation of study treatment

Discontinuation from study treatment is when a patient no longer receives study medication but continues to be followed up for objective disease progression and / or survival.

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuation of study treatment are:

- Voluntary discontinuation by the patient who is at any time free to withdraw from study treatment, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Dose delay or interruption of more than 3 weeks
- Disease progression

Procedures for discontinuation of study treatment

Patients who discontinue study treatment should always be asked about the reason(s) for their discontinuation and the presence of any AEs. If possible, they should be seen and assessed by

an investigator(s). AEs are to be followed up; questionnaires (e.g., for patient reported outcomes) and investigational products should be returned by the patient. The discontinuation visit should take place as soon as possible after the last dose of ZD6474 /Erlotinib.

If a patient discontinues study medication prior to objective disease progression they should continue to be followed for objective disease progression as per the protocol schedule in addition to the above.

All patients randomised will be followed up for survival status following objective disease progression unless they withdraw consent.

Survival status should be collected by telephone contact with the patient, patient's family, or by contact with the patient's current physician. The date and details of the first and subsequent therapies for cancer after discontinuation of treatment will be collected and the best response recorded.

All ongoing study-related toxicities and SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. All new study-related AEs and all SAEs occurring up to 60 days after the last dose of ZD6474 /Erlotinib must be reported to AstraZeneca and must be followed until resolution where possible.

All patients who have any CTCAE grade 3 or 4 laboratory values at the time of discontinuation of study medication must be followed up until they have returned to CTCAE grade 1 or baseline, unless the values are not likely to improve because of the underlying disease.

3.3.5.3 Procedures for handling incorrect enrolled patients

Patients not meeting the inclusion/exclusion criteria for a study should, under no circumstances, be enrolled into the study - there can be no exceptions to this rule. However, incorrectly enrolled or randomised patients may continue to receive study treatment and assessments if, in the opinion of the investigator and/or study team physician, this is not considered to involve any risk or discomfort to the patient

3.3.5.4 Procedures for discontinuation from genetic aspects of the study

A patient may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment. See Appendix J for details.

3.4 Treatments

Additional packaging details for this clinical study material are described in the Clinical Supply Action Plan on file with AstraZeneca Investigational Products Section.

3.4.1 Identity of investigational product and comparators

Descriptive information for ZD6474 can be found in the IB. ZD6474 and matching placebo will be supplied as white film-coated tablets. Erlotinib and matching placebo will be supplied as white film coated tablets. The formulation numbers and descriptions are provided below:

Table 4 Formulation numbers of ZD6474 and Erlotinib

Tablet strength (mg)	Formulation number
Erlotinib 25 mg tablet	F13448
Erlotinib 100 mg tablet	F13449
Erlotinib 150 mg tablet	F13450
ZD6474 100 mg tablet	F013025
ZD6474 300 mg tablet	F013383
Placebo to match Erlotinib 25 mg tablet	F13451
Placebo to match Erlotinib 100 mg tablet	F13452
Placebo to match Erlotinib 150 mg tablet	F13453
Placebo to match ZD6474 100 mg tablet	F013044
Placebo to match ZD6474 300 mg tablet	F013385

AstraZeneca Pharmaceuticals Investigational Products will pack the study medication. Study medication will be packed into white high-density polythene (HDPE) bottles with child resistant, tamper evident closures. Study medication must be kept out of the reach of children. Patients will be supplied with sufficient medication for each visit. There will be sufficient tablets in the bottle to cover the visit window.

3.4.2 Doses and treatment regimens

3.4.2.1 ZD6474 or Erlotinib regimen – standard dosing

Patients will be given single oral doses of ZD6474 300 mg plus placebo, or Erlotinib 150 mg plus placebo daily. ZD6474 or Erlotinib tablets (or matching placebos) must be taken whole and they must not be broken or crushed or dissolved. Tablets must be taken preferably at the same time each morning, at least 1 hour prior to or 2 hours after, intake of food.

Patients may continue to receive blinded ZD6474 /Erlotinib as long as in the Investigator's opinion they are benefiting from treatment and they do not meet any other withdrawal or discontinuation criteria.

Patients randomised in the study at the standard dose will be dispensed 2 bottles of blinded tablets every 4 weeks. The 2 bottles will either contain ZD6474 300 mg and placebo to Erlotinib, or Erlotinib 150 mg tablets and placebo to ZD6474 as determined by the randomisation scheme. Patients will take 1 tablet from each bottle per day at the same time of

day each morning. On Day 1 patients must wait to take their ZD6474 /Erlotinib tablets until after the baseline blood samples have been collected.

3.4.2.2 ZD6474 / Erlotinib dose reduction

There will be no intra-patient dose escalation in this study. Patients who have toxicity related to ZD6474 /Erlotinib may have their dose reduced and up to 2 dose reductions are allowed. (see Section 3.2.2 for guidance on management of toxicity). Table 5 summarizes study medication dispensing information in relation to toxicity management. Dose reduction within each treatment arm will be managed in a blinded manner.

Table 5 Dispensing for dose reduction

Dose	ZD6474 + Placebo to match Erlotinib			Erlotinib + Placebo to match ZD6474		
	Bottle 1	**Bottle 2**	**Bottle 3**	**Bottle 1**	**Bottle 2**	**Bottle 3**
Standard dose (2 tablets daily)	ZD6474 (Active) 1 x 300 mg tablet	Erlotinib (Placebo) 1 x 150 mg tablet	N/A	ZD6474 (Placebo) 1 x 300 mg tablet	Erlotinib (Active) 1 x 150 mg tablet	N/A
1st dose reduction (3 tablets daily)	ZD6474 (Active) 1 x 100 mg tablet	ZD6474 (Active) 1 x 100 mg tablet	Erlotinib (Placebo) 1 x 100 mg tablet	ZD6474 (Placebo) 1 x 100 mg tablet	ZD6474 (Placebo) 1 x 100 mg tablet	Erlotinib (Active) 1 x 100 mg tablet
2nd dose reduction (3 tablets daily)	ZD6474 (Active) 1 x 100 mg tablet	Erlotinib (Placebo) 1 x 25 mg tablet	Erlotinib (Placebo) 1 x 25 mg tablet	ZD6474 (Placebo) 1 x 100 mg tablet	Erlotinib (Active) 1 x 25 mg tablet	Erlotinib (Active) 1 x 25 mg tablet

3.4.2.3 Missed or forgotten doses

If the patient inadvertently does not take the dose in the morning, he or she may take that day's dose any time up to 10 p.m. that same day. However, if a patient misses taking their scheduled dose and is unable to take the missed dose on the same day, he or she must take the next scheduled dose and the missed dose will not be made up. The missed dose must be documented on the appropriate CRF. The dose of study treatment may be repeated if vomiting occurs within 30 minutes of taking the study treatment. Tablets must be taken at least 1 hour prior to or 2 hours after, intake of food.

3.4.3 Labelling

Information on the bottle labels will indicate the study number, unique medication identification number, blinded contents, caution, and storage conditions and will have blank

spaces for the E-code and date of dispensing (to be written in by the site personnel at the centre at the time of dispensing). Dosing instructions will be included on the label.

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational product bottle label.

3.4.5 Accountability

The study treatment(s) must be used only as directed in the protocol. Records of overall dispensing and returns will be maintained by each centre, separately from the CRFs recording the treatment dispensed to individual patients.

Patients must return all unused medication and empty containers to the Investigator, who will retain these until they are collected by AstraZeneca authorized personnel, along with any study medication not dispensed.

The Investigator must maintain accurate records accounting for the receipt of the investigational products and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the person to whom the drug was dispensed, the quantity and date of dispensing, and any unused drug returned to the Investigator. This record is in addition to any drug accountability information recorded on the eCRFs. At the termination of the study or at the request of the sponsor, the Investigator must send any unused supplies for destruction in liaison with their AstraZeneca monitor.

3.5 Method of assigning patients to treatment groups

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (e.g., the first patient screened at centre number 0001 would be assigned the E-code E0001001 the second patient screened would be E0001002 and so on). This number is the patient's unique identifier and is used to identify the patient on the eCRFs. For this study, an Interactive Voice Response System (IVRS) system will be used. All screened patients are assigned an E-code irrespective of whether or not they are subsequently randomised to receive study treatment.

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as patients are eligible for randomisation. When a patient is entered into screening, the Investigator should contact the Centralized Registration/Randomisation Centre by telephone to register the patient. Patients will be randomised in a 1:1 ratio If a patient withdraws from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study.

The actual treatment given to individual patients will be determined by a randomisation scheme. The randomisation scheme will be generated by biostatistics and produced by a

computer software program that incorporates a standard procedure for generating random numbers. The randomisation scheme will be stratified by centre.

Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the Centralized Registration/Randomisation Centre by telephone for the issue of a patient randomisation number and allocation of randomised therapy. Patients will be identified to the Centralized Registration/Randomisation Centre using patient initials, E-code, and date of birth. The Centralized Registration/Randomisation Centre will inform the Investigator of the patient randomisation number and medication packs to be allocated. The patient randomisation number will correspond to either ZD6474 or Erlotinib.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

Study medication will be labeled using a unique material identification number which is linked to the randomisation scheme. The Centralized Registration/ Randomisation Centre will assign the bottles of study material to be dispensed to each patient. The active and placebo tablets within each treatment arm will be identical and presented in the same packaging to ensure blinding of the medication.

3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists at the study centre. The patient's randomisation code break will be available through the Centralized Registration/Randomisation Centre.

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Patients should be given relevant contact numbers by their Investigator at the start of their participation in case they experience AEs or toxicity and are being evaluated outside of the investigative site.

Treatment codes will not be broken for the planned final analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.6.3 Methods for breaking the blind for monitoring of the safety

An Independent Data Monitoring Committee (IDMC) will be in place before the start of the study to monitor emerging toxicity. See Section 6.6 for more information. The IDMC will review the data in an unblinded manner midway through the study, when 555 progression events have occurred.

The blind should be maintained for personnel at AstraZeneca, such as biometrics personnel, who are responsible for analysis and interpretation of the results at the study's conclusion.

3.7 Pre-study, concomitant and post-study treatment(s)

3.7.1 Treatment for cancer

No additional systemic treatment known to have an effect on NSCLC may be used during the study prior to disease progression, except:

- Palliative radiotherapy for painful bony metastases.
- Bisphosphonates for treatment of bone pain or hypercalcaemia.
- Palliative thoracic radiotherapy

Currently, limited information is available regarding the safety and therapeutic benefit of the combination of ZD6474 and radiotherapy. Thus, the investigator may use his/her own discretion of whether to stop or continue ZD6474 during the radiation therapy ensuring careful safety monitoring. Any lesions which have been patiented to palliative radiotherapy will not be further considered evaluable unless evidence of disease progression has occurred based on RECIST criteria (Section 4.6.3.1).

After disease progression, patients may be treated at the discretion of the treating physician.

If the patient discontinues from study medication, the names and dates of the first and subsequent therapies for cancer, after study medication withdrawal will be collected.

3.7.2 Other concomitant treatment

Supportive care measures and symptomatic treatment for any treatment-associated toxicity may be instituted once the first signs of toxicity occur.

Concomitant use of the known potent inducers or inhibitors of CYP3A4: rifampicin, phenytoin, carbamazepine, barbiturates, St John's Wort, ketoconazole, itraconazole, atanazavir, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO) and voriconazole are not allowed within 2 weeks of study or during the study.

Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (see Appendix D, Table 1) are not allowed within 2 weeks of starting study medication or during study. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

Drugs with a possible risk of Torsades de Pointes (see Appendix D, Table 2) are not allowed within 2 weeks of study entry but may be allowed during study (see next paragraph).

The following medications can be taken by patients, but require additional monitoring:

- Co-administration of drugs that in some reports might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes (see Appendix D, Table 2) should be avoided if possible. However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored including regular checks of QTc and electrolytes. If a patient is receiving one of the medications in this group prior to study entry, and it cannot be discontinued before study entry, then the screening QTc must be ≤460msec, and an additional ECG must be obtained 4-8 hours after the first dose of study medication. Patients who are taking one of the drugs in this group whilst in the study, the ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the patient remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no QTc prolongation has been noted during 4 weeks of co-administration of a drug from Appendix D, Table 2. The electrolytes should be maintained within the normal range using supplements if necessary.

- Warfarin is allowed in therapeutic and low-doses and these patients should be monitored regularly for changes in their International Normalized Ratio (INR), at the discretion of the Investigator.

- Use of NSAIDs (Non-steroidal anti-flammatory drugs) is permitted at the discretion of the investigator; some patients treated with Erlotinib have developed gastrointestinal bleeding sometimes associated with concomitant use of NSAIDs or warfarin.

- Caution should be exercised when administering inhibitors of P-glycoprotein e.g. verapamil, cyclosporine as this may cause altered distribution or elimination of erlotinib. Also caution should be exercised when combining antacids, proton pump inhibitors or H2 antagonists as the effects on absorption of erlotinib have not been studied as absorption maybe impaired leading to lower plasma levels.

Other medications, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator(s). The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF.

3.8 Treatment compliance

It is the Investigator or institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure the following:

- Deliveries of such products from AstraZeneca are correctly received by a responsible person (e.g. a pharmacist)

- Such deliveries are recorded

- Study treatments are handled and stored safely and properly

- Study treatments are only dispensed to study patients in accordance with the protocol
- Any unused products are returned for destruction in liaison with the AstraZeneca project team.
- At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist.

Patients should be given clear instructions on how and when to take their study treatment. Their tablet returns should be counted to check for compliance. Discrepancies between the number of tablets returned and the expected number of tablets returned should be discussed with the patient and the reasons for non-compliance documented.

If the patient is not compliant after counseling on the importance of taking study medication as instructed, the investigator may withdraw the patient from study treatment.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

Table 6 shows the relationship between the objectives and outcome variables for this study.

Table 6 Objectives and outcome variables

Objective	Variable(s)
Primary	
To demonstrate an improvement in PFS for ZD6474 compared with Erlotinib in patients with locally advanced or metastatic NSCLC after failure of at least one but no more than two, prior cytotoxic chemotherapy regimens.	PFS
Secondary	
To demonstrate an improvement in overall survival for ZD6474 compared with Erlotinib	Overall survival

Table 6 Objectives and outcome variables

Objective	Variable(s)
To demonstrate an improvement in the overall ORR (CR + PR), DCR (CR + PR + SD) and DOR for ZD6474 compared with Erlotinib using modified RECIST (Therasse et al 2000)	ORR by RECIST, DCR and DOR
To demonstrate an improvement in time to deterioration of pain, dyspnoea, cough in patients treated with ZD6474 compared with Erlotinib, based on the EORTC QLQ-C30 plus lung cancer module (QLQ-LC13)	TDS (Pain, Dyspnoea, cough)
To study the safety and tolerability of ZD6474 compared with Erlotinib in patients with locally advanced or metastatic NSCLC after failure of at least one but no more than two, prior cytotoxic chemotherapy regimens	Incidence, CTCAE grade and type of AEs, clinically significant laboratory abnormalities or changes in vital signs, and ECG changes
To investigate the population PK of ZD6474 and assess the PK-QTc, PK-safety and PK-efficacy, and PD biomarker relationships	ZD6474:AUCss, Css, max, CL/F, Vss/F, individual predicted plasma concentrations.AEs, PFS, OS, ORR, DCR, DOR and PD biomarkers for ZD6474
To investigate plasma levels of the N-desmethyl and N-oxide metabolites of ZD6474 in this patient population	Plasma levels of the N-desmethyl and N-oxide metabolites to ZD6474, accumulation ratio and ratio of ZD6474
Exploratory	
To investigate the correlation of EGFR expression, amplification and mutations and other related biomarker status with efficacy, in archival tumour samples, in those patients where such tumour material is available	EGFR mutational status (EGFR sequence), EGFR protein expression (% of tumour cells positive for membranous staining by IHC) and FISH category
To collect a genetic blood sample for DNA extraction and storage	
To investigate in blood plasma samples, the correlation of levels of circulating protein biomarkers with efficacy	Levels of soluble VEGF, VEGFR, bFGF and other biomarkers to assess surrogate markers of tumour angiogenesis

Table 6 Objectives and outcome variables

Objective	Variable(s)
To investigate the effect on HRQOL/symptoms of ZD6474 compared with Erlotinib based on the EORTC QLQ-C30 plus lung cancer module QLQ-LC13	EORTC QLQ-C30 plus QLQ-LC13 questionnaire
To investigate health status index during the period of treatment with investigational therapy	EQ5D
To investigate the time to deterioration in patient WHO Performance Status during the period of treatment with investigational therapy (pre and post progression)	WHO PS and TDPS
To investigate changes in patient weight	Weight
To investigate EGFR mutational status and mutational status of other candidate genes in cell-free circulating tumour DNA found in plasma	

4.1 Primary variable

The primary outcome variable of this study is PFS, which is defined as the number of days from randomisation to objective disease progression (see Section 6 for Statistical methods and determination of sample size). Further detail is given in Section 4.6.

4.2 Screening and demographic measurements

Before entering the study, patients will be assessed to ensure that they meet eligibility criteria (see Sections 3.3.2 and 3.3.3). Patients who do not meet these criteria must not be allowed to enter the study.

The following must be assessed within 3 weeks before the first dose of study medication is administered:

- Provision of written informed consent
- Demography (date of birth, sex, race etc)
- Radiological and clinical tumour assessment (per RECIST) Note – baseline RECIST assessments may be made up to 4 weeks before the first dose of study medication)

- Medical history, including all previous but now resolved significant medical conditions; additional data includes detailed smoking history, date of diagnosis, chemotherapy and other anti-cancer therapy history, tumour stage and number of organs involved, histologic type, collection of historical tumour biomarker status (EGFR mutation, EGFR protein expression, EGFR gene amplification and k-ras mutation, where available), prior radiation and radiation site, oncology surgical history, reason for withdrawal from prior therapy and most recent date of disease progression

- 12-lead ECG

- Full haematology, clinical chemistry and urinalysis testing

- Eligibility (inclusion/exclusion) criteria

The following must be assessed within 7 days before the first dose of study medication is administered:

- Physical examination, including measurement of height and weight

- Vital signs: resting blood pressure and pulse measurement, recording of body temperature

- WHO PS

- EORTC QLQ-C30 plus lung cancer module QLQ-LC13

- EQ5D

- Review of all concomitant medication & prior anti cancer therapy

The following must be assessed within 3 days before the first dose of study medication is administered:

- Urine pregnancy test in women of childbearing potential

Eligibility (inclusion/exclusion) criteria must be confirmed prior to commencing treatment on Day 1.

4.3 Patient-Reported Outcomes (PROs)

The methods for collecting PRO data are presented below.

4.3.1 EORTC QLQ-C30 and QLQ-LC13

4.3.1.1 Methods of assessment

Patient-reported outcomes will be assessed using the EORTC QLQ-C30 plus QLQ-LC13 questionnaire (Appendix F). The questionnaire has been designed for assessing HRQOL in lung cancer patients participating in international clinical trials.

HRQOL is important in NSCLC because the underlying disease can have a significant impact on patient well-being (Kosmidis 1996) and family functioning (Sarna et al 2002). Therefore, a well-validated questionnaire for measuring HRQOL/symptoms in this patient population is needed, and, as this will be a multinational study, cultural and linguistic adaptation will also be essential.

The EORTC QLQ-C30 (Aaronson et al 1993) and Lung Cancer Module QLQ-LC13 (Bergman et al 1994) meets the requirements for this study and are commonly employed in lung cancer clinical trials (Earle 2004). In fact, the EORTC QLQ-C30 is the most commonly used cancer-specific HRQOL tool in oncology (Garratt et al 2002). It is also one of the most commonly used tools in NSCLC along with the EORTC QLQ-LC13 scale (Bottomley et al 2003). These tools have undergone extensive testing and validation and have undergone detailed cross-cultural testing and validation (Cull et al 2002). The tools will be assessed at the times indicated in the study plan. Both questionnaires are designed for completion by the patient.

4.3.1.2 Derivation or calculation of variable

The EORTC QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) and perceived financial impact of the disease.

The EORTC QLQ-LC13 includes questions assessing lung cancer-associated symptoms (cough, haemoptysis, dyspnoea and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia) and pain medication. The lung cancer module incorporates one multi-item scale to assess dyspnoea, and the remainder are single items.

Each item/scale of the EORTC QLQ-C30 core questionnaire and the QLQ-LC13 lung cancer module constitutes a separate variable for analysis although, for assessing pain, dyspnoea and cough, a specific combination of questions are used as described in 4.3.2.1. Raw scores for each item/scale can be transformed to a 0 to 100 scale, as described in the EORTC QOL Scoring Manual (Fayers et al 2001). Missing data will also be handled according to the methods described in the EORTC QOL Scoring Manual.

4.3.2 Time to deterioration of pain, dyspnoea and cough

Patients with NSCLC commonly present with problems such as persistent pain, dyspnoea, and cough. Therefore, the primary analysis of the PRO assessment (and a secondary objective of the trial) will involve comparing times to deterioration of the disease-related symptoms of pain, dyspnoea and cough between the treatment arms.

4.3.2.1 Methods of assessment

Pain will be assessed using questions 9 and 19 of the QLQ-C30. Dyspnoea will be assessed using question 8 of the QLQ-C30 and questions 3, 4 & 5 of the QLQ-LC13 (or, equivalently, questions 33, 34 & 35 of the combined QLQ-C30 and QLQ-LC13 questionnaires). Cough will be assessed using question 1 of the QLQ-LC13 (or, equivalently, question 31 of the combined QLQ-C30 and QLQ-LC13 questionnaires).

4.3.2.2 Derivation or calculation of variable

Times to deterioration of pain, dyspnoea, and cough will be defined as the time when a sustained clinically important deterioration in the scores for these symptoms has been recorded. A sustained clinically important deterioration will be defined as an increase in scores from baseline of >=10 points (Osoba et al 1998), which is confirmed at the next completed assessment.

Patients without a baseline assessment will be excluded from the analysis.

Patients, who progress or die before the symptom has shown a clinically important deterioration, will be defined as deteriorating at the time of progression or death, as appropriate.

Patients who do not experience either documented deterioration in the symptom, or disease progression, or death, will be treated as censored observations at the time of the last symptom assessment.

Further details of the analysis will be presented prospectively in the Statistical Analysis Plan.

4.3.3 Analysis of HRQOL/symptoms

4.3.3.1 Methods of assessment

In addition to questions relating to pain, dyspnoea and cough, the EORTC QLQ-C30 core questionnaire and the QLQ-LC13 module also contains a number of other items/scales referring to global health status/QOL, functioning, and symptoms.

Each of these items/scales will be analysed separately in an exploratory analysis. The questions relating to these items/scales are described in the EORTC QOL Scoring Manual.

4.3.3.2 Derivation or calculation of variable

The analyses of HRQOL/symptoms will involve comparisons of the times to deterioration of the scales/items of the EORTC QLQ-C30 and QLQ-LC13 questionnaires between the

treatment arms, and comparisons of the changes in these scales/items over time. The scoring of the items/scales will be as described in the EORTC QOL Scoring Manual. A sustained clinically important deterioration/improvement in these items/scales will be defined as an increase in scores from baseline of >=10 points (Osoba et al 1998), which is confirmed at the next completion assessment.

Patients without a baseline assessment will be excluded from the analysis. Patients who progress or die before HRQOL/symptoms deteriorate by the values specified above, will be defined as deteriorating at the time of progression or death, as appropriate.

Patients who do not experience either documented deterioration in HRQOL/symptoms, or disease progression, or death, will be treated as censored observations at the time of the last HRQOL/symptom assessment.

Further details of the analysis will be presented prospectively in the Statistical Analysis Plan.

4.3.4 Administration of PRO questionnaires

EORTC QLQ-C30 and QLQ-LC13 questionnaires should be completed by the patients at baseline and at the times indicated in the study plan, before assessments, and before imparting any news about the status of the disease. Patients should be allowed to complete the questionnaires in their own time, and without help from relatives or clinic staff. A form will be completed by the clinic staff to indicate if a questionnaire has been completed at each QoL visit, and if not, the reason will be recorded.

Each centre must allocate responsibility for completion of the EORTC QLQ-C30 and QLQ-LC13 questionnaires to a specific individual (i.e. a Research Nurse). The AstraZeneca Study Delivery Team will provide training for relevant personnel in the administration of the EORTC QLQ-C30 and QLQ-LC13 questionnaires. It is also important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection (Fayers and Machin 2000, Young et al 2002)

The instructions for completion of the EORTC QLQ-C30 plus QLQ-LC13 questionnaire are:

- Provide the patient with the information sheets.
- The patient must complete it in private in his or her own time.
- The patient must complete it before any investigations or discussions about their disease with the clinic staff.

Help should not be given from relatives or clinical staff unless the patient is incapable of completing the questionnaire. In this case, the patient can receive help from a study nurse in understanding the instructions and completing the questions. However, under no circumstances should help in interpreting the questions or in selecting responses be provided.

The questionnaire will be administered in all countries for which a validated questionnaire is available.

4.4 Health Economic measurements and variables

The methods for collecting Health Economic data are presented below.

4.4.1 EQ5D

4.4.1.1 Methods of assessment

Utilities for the estimation of quality-adjusted life years will be derived from the EQ-5D (Appendix H). The EQ-5D descriptive system is a standardized instrument for use in the measurement of health outcome, applicable to a wide range of health conditions and treatment (The EuroQoL Group 1990). In particular, the EQ-5D offers a single index of patients' health status that can be used to estimate quality-adjusted life years, which are commonly used in cost-effectiveness assessments. The instrument is extensively validated and is available in several languages for use in multinational studies. The EQ5D instrument will be administered in all countries for which a validated questionnaire is available.

4.4.1.2 Derivation or calculation of outcome variable

The EQ-5D comprises 5 questions with 3 levels of response that generate a number of unique health states. Each health state corresponds to a combination of 1 level from each of 5 dimensions. For each health state there exists a corresponding valuation. The valuation is obtained by converting the health states into a weighted health status index by applying scores from the appropriate available 'value sets'. This valuation will be used for health economic assessments. The EQ-5D will be self-administered along with the EORTC QLQ-C30 plus QLQ-LC13 questionnaire.

4.5 Pharmacokinetic measurements and variables

Table 7 shows the relationship between the PK endpoints and analysis of this study and the study objectives

Table 7 PK endpoints related to each objective

Objective	Variable(s)
To investigate the population pharmacokinetics (pop-PK) of ZD6474 and to assess the PK-QTc, PK-safety and PK-efficacy relationships	**PK** Individual predicted plasma concentrations, AUC_{ss}, $C_{ss,max}$, CL/F, Vss/F **Safety** AEs, QTc **Efficacy** PFS, OS and ORR PD Biomarkers for ZD6474
To investigate plasma levels of the N-desmethyl and N-oxide metabolites of ZD6474in this patient population	Accumulation ratio and ratio to ZD6474

The methods for collection of biological samples and derivation of pharmacokinetic variables are presented below in Sections 4.5.1 and 4.5.2.

4.5.1 Collection of biological samples

A volume of 6mls of venous blood will be taken at the sampling times shown in the study plan, into tubes containing lithium heparin anticoagulant and thoroughly mixed. The blood samples will then be centrifuged within 15 minutes of collection by spinning at 1000 g for 10 minutes. The plasma should be taken off immediately and stored in a plain tube at -20 ºC before transportation to the central holding laboratory. The date and the time of collection will be recorded on the appropriate eCRF. Further details on collection, labelling, and shipping are in the central laboratory manual.

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters

A validated high performance liquid chromatography method with tandem mass spectrometric detection will be used to measure the plasma concentration of ZD6474 and the N-desmethyl and N-oxide metabolites.

The PK data will be analyzed using non-linear mixed effects models (Beal and Sheiner 1988-1998). The PK structural models will be developed in addition to inter- and intra-individual variance models. Assumptions of the pharmacokinetics will be based on previous data and the exact nature of the structural, inter-individual variance and intra-individual variance models will be based on examination of the diagnostic scatter plots (predicted versus observed concentrations, weighted residual versus predicted concentrations, weighted residuals versus time, final parameter estimates, standard error of the parameter estimates, estimated objective function and structure of the variance/covariance matrix). If data from the study proves limited and is identified as insufficient to define the pharmacokinetics (large standard errors, non-identifiable PK profile), additional data will be included from previous clinical studies. Depending on the definition of the PK model parameter, estimates for all patients will be calculated using Bayesian based methodology. Parameters will include plasma drug clearance, estimated maximum drug concentration, half-life, and volumes of distribution.

Once the PK model is defined, covariates (including age, weight, race, gender, etc) will be added in a step-wise manner, and the statistical significance tested via a relevant change in the objective function, depending on the statistical significance level. The clinical relevance of all covariates included in the model will be explored and discussed, through simulation.

With the derivation of the parameters, estimates and accurate predictions of the plasma concentration, modelling of the pharmacodynamics, QTc, AEs, and efficacy end points will then be undertaken. In a similar manner to the pharmacokinetics model, accuracy will be undertaken through diagnostic plots.

A PK analysis plan will be prepared prior to the commencement of this analysis.

4.5.2.1 N-desmethyl and N-oxide metabolites

In the first 40 patients on ZD6474 that attain 6 months on study and are included in the PK sub analysis group, the plasma levels of the N-desmethyl and N-oxide metabolites of ZD6474 will be determined. This will be in the samples taken during weeks 1, 12 and at 6 months. Accumulation ratios will be determined at week 12 and at 6 months from the week 12 and 6 month concentrations divided by the week 1 concentration. The ratio of each metabolite to ZD6474 will be determined by dividing the ZD6474 concentration by that for each metabolite for the weeks 1 and 12 and 6 month samples.

Individual plasma concentrations, accumulation ratios and ratios of ZD6474 to metabolites will be listed and summarized by sample time.

4.6 Efficacy and pharmacodynamic measurement and variables

4.6.1 Progression-free survival (PFS)

4.6.1.1 Methods of assessment

PFS is determined using data from RECIST assessments performed at baseline, during treatment and during the follow-up period.

4.6.1.2 Derivation or calculation of outcome variable

PFS will be defined from the date of randomisation to the date of objective progression or death (by any cause in the absence of progression). Patients who have not progressed or died at the time of statistical analysis will be censored at the time of their latest objective associated assessment. This includes patients who are lost to follow-up or have withdrawn consent. For patients lost to follow-up without having progressed, if it can be established that death occurred within a further 3 months this will be considered an event, otherwise the patient will be censored for PFS at the time of their last associated assessment date.

4.6.2 Overall survival (OS)

4.6.2.1 Methods of assessment

Patients's survival status throughout the course of the study will be used to determine OS.

4.6.2.2 Derivation or calculation of outcome variable

OS is calculated from the date of randomisation to the date of death. Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

4.6.3 Objective response, disease control and duration of response

4.6.3.1 Methods of assessment

The RECIST criteria will be used to perform the objective tumour assessments and determine a patient's PFS and best overall objective tumour response; details are given in Appendix E.

Baseline radiological tumour assessments should be performed ideally no more than 3 weeks, but definitely no more than 4 weeks before the start of study treatment and at all time points defined in the study plan.

Previously irradiated lesions will not be considered measurable.

All measurable lesions, up to a maximum of 10 lesions and representative of all involved organs (maximum of 5 lesions per organ), 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 (LD)) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease.

All other lesions (or sites of disease) 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 "present with progression".

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the eCRF in the same order as they were recorded at screening. Details of any new lesions will also be collected.

Any lesions that have been patiented to local/regional radiotherapy for symptom control (palliative radiotherapy), during the course of the study, will be excluded from the assessments of ORR, DCR and DOR, as these will not be considered evaluable, unless evidence of disease progression has occurred based on RECIST criteria. Those lesions identified as having progressed, based on RECIST criteria, will still be included in the assessment of PFS.

A patient is determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions or the appearance of one or more new lesions (see Appendix E). Progression of target lesions is defined as at least a 20% increase in the sum of the LD of target lesions taking as references the smallest sum of LD recorded. Death will be regarded as a progression event in those patients who die before documented disease progression. Unequivocal malignant disease identified on additional anatomical imaging e.g.

CT or MRI or bone scan confirmed by x-ray, prompted by symptoms is considered disease progression and should be recorded as new lesions. If the Investigator is in doubt as to whether progression has occurred, particularly with respect to non-target lesions and the appearance of a new lesion then it is advisable to pursue treatment for 4 additional weeks (and then repeat the RECIST assessment to confirm progression).

Categorization of the objective tumour response assessments will be based on the RECIST criteria for target and non-target lesions. Response will be assigned as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) at each scheduled visit by the Investigator. For the purposes of analysis the sponsor will determine visit and overall response using the lesion assessments recorded on the eCRF.

It is important to follow the assessment schedule as closely as possible as PFS is the primary endpoint and biases in analysis can occur if 1 treatment group is examined more often or sooner than the other. If an unscheduled radiological and clinical tumour assessment is performed, and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan). This is in order to minimize any unintentional bias caused by some patients being monitored at a different frequency than other patients.

Patients who discontinue study treatment prior to disease progression will continue to have objective tumour assessments every 4 weeks (every 8 weeks after the first 16 weeks of treatment), or as clinically indicated until progression is documented unless the patient withdraws consent.

After disease progression, patients should be followed up for survival every 8 weeks, as outlined in the study plan, unless the patient withdraws consent.

Adherence to the study plan should be observed whenever possible.

For patients with objective response of CR or PR, confirmation of response by repeat imaging should be performed at the next schedule imaging visit at 4 weeks (no earlier than 4 weeks [every 8 weeks after the first 16 weeks of treatment]) following date of response.

4.6.3.2 Derivation or calculation of outcome variable

The overall best ORR will be calculated as the percentage of patients with CR or PR. The DCR will be calculated as the percentage of patients with CR or PR or SD $\geq$ 8 weeks.

DOR will be calculated for those patients who have a best response of CR or PR only. DOR will be defined in two ways:

- from date of randomisation until the date of documented disease progression or death from any cause in the absence of documented progression, and
- from the date of first documentation of response until date of documented disease progression or death from any cause in the absence of documented progression.

4.6.4 Pharmacodynamic biomarker measurements and variables

Blood plasma samples will be collected as outlined in the study plan and assessed for pharmacodynamic biomarkers. Archival tumour samples will be collected from consenting patients and assessed for pharmacodynamic biomarkers. Pharmacodynamic biomarkers will be investigated for possible correlation with clinical outcomes (OS, response, and PFS) and for the effects of the study medication.

Since this is a rapidly evolving and complex area of investigation, and as yet not completely understood, pharmacodynamic biomarker data obtained in this study will not be definitive, but may generate hypotheses that are likely to require further testing in additional clinical studies.

4.6.4.1 Methods of assessment

Plasma samples

Plasma will be prepared from venous blood (10 mL) collected as detailed in the study plan. Plasma protein levels of VEGF, bFGF and VEGFR2 will be determined. If the current assays become more sensitive, we will investigate other potential protein biomarkers associated with tumour angiogenesis in these plasma samples (see central laboratory manual for further details regarding sample collection, preparation and shipment). Tumours shed cell-free DNA that can be detected in blood plasma, in consenting patients, cell-free tumour DNA will be analysed from plasma for mutations in EGFR and other candidate genes.

Archival tumour samples

In patients where samples are available, archival, paraffin-embedded tumour samples (derived from resection, biopsy or archival fixed cell blocks from cytology samples) should be collected for consenting patients for analysis of (i) EGFR expression, and related signal transduction, proliferation and apoptosis markers, (ii) EGFR amplification, (iii) analysis of mutation status of the EGFR gene, and (iv) expression profiles predictive of sensitivity to EGFR signalling inhibitors in pre-clinical studies (see central laboratory manual for further details regarding sample collection, preparation and shipment). EGFR amplification will be classified according to the six FISH categories defined by Cappuzzo et al 2005). Patients with FISH categories 1-4 will be classified as FISH-negative, whereas patients with FISH categories 5 and 6 will be classified as FISH positive (see Table 8).

Table 8 Classification of FISH status

	FISH[a] Category	EGFR gene copy number
FISH-negative	1. (Disomy)	≤2 copies in >90% of cells
	2. (Low trisomy)	3 copies in ≥10% but <40% of cells
	3. (High trisomy)	3 copies in ≥40% of cells
	4. (Low polysomy)	≥4 copies in ≥10% but <40% of cells
FISH-positive	5. (High polysomy)	≥4 copies in ≥40% of cells
	6. (Gene amplification)	Ratio of EGFR gene to chromosome of ≥2 or ≥15 copies of EGFR per cell in ≥10% of cells

(a) Fluorescence in situ hybridization (FISH) has been used to measure the copy number of the EGFR gene in tumour samples from patients with NSCLC who were treated on studies with Erlotinib or gefitinib. Patients can be divided into those that are "FISH-negative", defined as FISH categories 1, 2, 3 and 4, or "FISH-positive", defined FISH categories 5 and 6 (Cappuzzo et al 2005). Patients should be classified into the highest qualifying FISH category

Genetics

Refer to Appendix J for details.

4.6.4.2 Derivation or calculation of outcome variable

Appropriate summaries of plasma and tumour sample correlates will be produced.

4.6.5 Time to deterioration in patient WHO Performance Status (TDPS)

4.6.5.1 Methods of assessment

WHO PS is recorded according to the study plan (see Table 1).

4.6.5.2 Derivation or calculation of variable

Baseline WHO PS is defined as the measurement recorded closest to, but not subsequent to, the first dose of ZD6474 /Erlotinib. At a given time point, deterioration in WHO PS is considered to be ≥1 change from baseline score.

TDPS is defined as the interval from the date of randomisation to the first assessment of 'deterioration'.

If a deterioration of WHO PS has not been observed at the time of analysis, TDPS will be censored as of the last non-missing WHO PS assessment date.

4.7 Safety measurements and variables

The methods for collecting safety data are described below.

4.7.1 Adverse events

4.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

All AEs will be graded according to the NCI CTCAE, Version 3.0.

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

For the purposes of this study, any detrimental change in a patient's condition subsequent to them entering the study and during the 60-day follow-up period should be considered an AE.

When there is a deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration should be considered a lack of efficacy. Signs and symptoms unequivocally due to disease progression are therefore not considered AEs

Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product or Erlotinib, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

Any event or hospitalization that is unequivocally due to progression of disease must not be reported as an SAE.

The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?" For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

SAEs will be collected from the time of informed consent and will be followed up until resolution or up to 60 days after administration of the last dose of study treatment.

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

AEs and SAEs will be collected throughout the study and will be recorded from the time of informed consent and followed up to resolution or for 60 days after the last administration of study medication.

All AEs will be recorded on the eCRFs provided. A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment, other treatment given, and follow-up tests) and outcome, should be provided along with the Investigator's assessment of causality (the relationship to the study treatment). AEs will also be graded according to the NCI CTCAE, Version 3.0, and changes tracked on the relevant eCRF.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE (see Appendix B for guidelines on interpretation of causality).

(a) Subjective symptomology

All signs and symptoms, including those spontaneously reported by the patient, or obtained as a result of open questions such as "Have you had any health problems since your previous visit?" will be recorded in the patients' medical notes, assessed by the investigator and reported on the patients' eCRF as an AE if appropriate.

(b) Abnormal laboratory values/vital signs/ECGs

The reporting of laboratory/vital sign/ECG abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:

- Any criterion for an SAE is fulfilled
- The laboratory/vital signs abnormality causes the patient to discontinue from the study treatment
- The laboratory/vital signs abnormality causes the patient to interrupt the study treatment
- The laboratory/vital signs abnormality causes the patient to modify the dose of study treatment
- The investigator believes that the abnormality should be reported as an AE

If an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign should be considered additional information that must be collected on the relevant eCRF. AEs will be coded using the MedDRA (Medical Dictionary for Regulatory Activities).

A vendor to be selected by AstraZeneca will evaluate ECGs centrally, and results will be communicated to each site within 24-48 hours. If a QTc prolongation is recorded, the vendor will inform the Investigator and AstraZeneca within 24 hrs. Any clinically significant abnormal findings and QTc prolongations during the treatment period will be recorded as AEs.

(c) Disease progression

Any event that is **unequivocally** due to disease progression should not be reported as an AE.

(d) Lack of efficacy

When there is deterioration in the condition for which the study treatment is being used (i.e., NSCLC), there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the study treatment contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

(e) New cancers

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this clinical study.

(f) Deaths

For all deaths that occur within the study period or for 60 days after the last administration of ZD6474 or Erlotinib, **except those that are unequivocally due to disease progression**, an AE form and an SAE form should be completed, detailing the AE that resulted in the death (Please note that death is an outcome, not an event). The SAE must be reported to the study monitor within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Death as a result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented on the relevant eCRF, but should not be reported as an AE.

The investigator must continue to follow all patients for survival beyond the 60-day period after the administration of last dose of study treatment and collect information around the death on the appropriate eCRF.

(g) Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs and managed accordingly.

(h) Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it.

SAE information will be entered and submitted into the Web Based Data Capture (WBDC) system on the relevant eCRF modules. An automated email alert will be sent to the designated AstraZeneca representative who will work with the investigator to ensure that all the necessary information is available in the system within the required time frames, but taking advantage of the time allocated in those timelines. The AstraZeneca representative will notify the appropriate AstraZeneca Drug Safety department through the WBDC system via email that a completed electronic SAE module and relevant information from other appropriate eCRF modules are available in the WBDC system. If the system is unavailable, the investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as the system becomes available again.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If follow-up indicates a change in the SAE from serious to fatal or life threatening, this information needs to be available in the WBDC system within 1 calendar day.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that becomes serious but which is not fatal or life-threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by Day 1 for all fatal and life-threatening cases and by Day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca (see section 8.1).

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of assessment

Routine haematology, clinical chemistry and urinalysis assessments will be conducted by a central laboratory service provider. Urinary pregnancy testing will be performed using kits provided by the central laboratory service provider.

All patients who have any CTCAE grade 3 or 4 laboratory values at the time of discontinuation of study medication must be followed up until they have returned to CTCAE grade 1 or baseline, unless the values are not likely to improve because of the underlying disease. Additional samples may be taken, as clinically indicated.

The following laboratory parameters will be investigated Table 9. See Table 10 for total volume of blood samples to be collected.

Table 9 Laboratory safety variables

Type of assessment	Variables
Haematology	Haemoglobin, platelet count, WBC[a], APTT[b], INR[b] PT[b]
Clinical chemistry	
Hepatic function	ALP, ALT, AST, total bilirubin
Renal function	BUN, creatinine
Other	Albumin, inorganic phosphate, magnesium, potassium, sodium, calcium, chloride, bicarbonate, total protein, glucose, LDH, TSH, amylase, lipase
Urinalysis	Proteins, blood, glucose

a total, with manual or automated differentiation
b at screening only, unless patient is on anticoagulation therapy and requires additional evaluation

4.7.2.2 Derivation or calculation of outcome variables

Section 4.7.1.2 provides details on how AEs based on laboratory tests will be recorded and reported.

4.7.3 12-lead ECG, Vital signs and physical examination

4.7.3.1 12 lead ECG- methods of assessment

Patients will have 12-lead ECGs performed to monitor the QTc interval (using Bazett's correction). The screening ECG assessment must be performed within 21 days of planned first dosing on Day 1. Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility. The screening QTc must be <480 msec. Patients who are receiving a drug that has a risk of QTc prolongation (see Appendix D, Table 2) are excluded if QTc is ≥ 460 msec.

Baseline QTc will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1.

When possible ECGs should be performed at the same time throughout the study, approximately 4-8 hours after the patient takes their study medication on Days 8 (Week 1), 15

(Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and every 3 months thereafter until discontinuation of study medication. An additional ECG must be performed at the discontinuation visit. In the event of QTc prolongation, the QTc will be re-evaluated within 48 hours with 3 consecutive ECGs (within 5-10 minutes of one another). The criteria for QTc prolongation are:

- A single QTc value of ≥550 msec, or an increase of ≥100 msec from baseline;

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs)):

- A QTc interval of ≥500 msec, but <550 msec;

OR

- An increase of ≥60 msec, but <100 msec from baseline QTc, to a value ≥480 msec

Patients who are receiving one of the drugs listed in Appendix D, Table 2, at the time of study entry must have an additional ECG obtained 4-8 hours after the first dose of study medication.

In the event of a QTc prolongation see Section 3.2.2.1.

PK samples will be taken as close to or at the same time as the ECG's. The time of each visit does not have to be exactly the same; only the assessment i.e., ECG and PK sample at a particular visit needs to be taken at approximately the same time. Whenever possible the assessments should be carried out at the same time of day.

A vendor to be selected by AstraZeneca will evaluate ECGs and provide standardized equipment for recording of ECGs. A cardiologist at the vendor will review all ECGs for the presence of QTc prolongation or other abnormalities, in particular any changes in the T wave morphology that would suggest a higher likelihood for the development of any arrhythmia. Any clinically significant abnormal findings or QTc prolongations during the study period will be recorded as AEs.

4.7.3.2 12-lead ECG derivation or calculation of outcome variables

The following parameters will be recorded for each ECG: date and time of ECG, heart rate (beats/min), QRS (ms), PR (ms), QT (ms), QTcB (ms), QTcF (ms), sinus rhythm (yes/no) and overall evaluation (normal/abnormal).

4.7.3.3 Vital signs and physical examinations - methods of assessment

Full physical examinations will be performed including height (screening only), weight, blood pressure, pulse, and temperature at the screening visit and as outlined in the study plan. Blood pressure should be measured after the patient has been resting for 5 minutes.

Performance status will be assessed using the WHO criteria (Appendix C) at Screening, Baseline and as outlined in the study plan. The same observer should assess performance status each time.

4.7.3.4 Vital signs and physical examinations derivation or calculation of outcome variables

Any new conditions reported during the study will be recorded on the AE forms. Only those findings that are in addition to the condition being treated will be recorded as AEs, see Section 4.7.1.2. for reporting of AEs. Conditions that are considered by the investigator to be unequivocally disease-related will not be recorded as AEs.

4.7.4 Other safety measurements and variables (not applicable)

4.8 Volume of blood sampling and handling of biological samples

Full details of sample handling will be detailed in a separate laboratory manual. The total volume of blood that will be drawn from each patient in this study is as follows:

Table 10 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples [a]	Total volume (mL) [b]
Pharmacodynamic biomarkers	VEGF, bFGF and VEGFR-2	10	8	80
Pharmacokinetic[c]	ZD6474	6	6	36
Safety	Clinical chemistry	6[d]	9	54
	Haematology	4.5[d]	9	41
Genetics (optional)	DNA storage	10	1	10
Total		26.5 – 36.5	33	221 mL

a Additional samples may be collected if required (e.g., for repeat safety assessments).
b These volumes are based on a patient completing up to Day 113 and the Discontinuation visit
c Any remaining material from plasma samples already being collected for analysis of circulating proteins, will be analysed additionally for mutational status of candidate genes in circulating tumour DNA.
d PK sampling will be conducted on 400 patients
e Assumed volumes for central laboratory

If in the opinion of the treating physician there is a need for additional blood sampling, this may be undertaken as clinically indicated.

4.8.1 Analysis of biological samples

4.8.1.1 Clinical chemistry samples

The analyte stability limits defined by the central laboratory vendor will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory vendor will not analyze

samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory vendor may be amended in accordance with its Standard Operating Procedures. The central laboratory vendor will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If the central laboratory vendor chooses to sub-contract the analytical work to another laboratory, the central laboratory vendor must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analyzed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

4.8.1.2 Pharmacokinetic samples

The long-term stability of the analyte(s) should be documented in method validation produced by AstraZeneca DMPK. Results from analyses of samples stored longer than the time period for which stability has been demonstrated should not be reported unless complementary analyte(s) stability data is acquired and amended to the relevant method validation report. Stability of ZD6474has been documented for 12 months in work done by AstraZeneca. Samples stored for longer than 12 months will not be analyzed.

4.9 Genetic measurements and co-variables

Refer to Appendix J for details.

5. DATA MANAGEMENT

AstraZeneca R&D will coordinate data management activities. The Study Data Management Plan will describe the methods used to collect, check, and process clinical data in greater detail. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered reviewed, edited and Source Data Verification (SDV) performed, the principal investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. After eCRF lock, AstraZeneca will perform final validation checks, including central consistency checks. Prior to study closure a copy of the eCRF will be archived at the study site.

Data from any third party vendors (e.g. laboratory, ECG, IVRS) will be returned to AstraZeneca directly as Statistical Analysis Software (SAS) datasets. The data provided will be reconciled against the clinical study database on an ongoing basis to ensure consistency and accuracy. All discrepancies will be queried within the WBDC system and any required amendments will be made to the appropriate dataset.

The PK data (plasma concentrations) will be fully validated on an ongoing basis during study conduct by the DMPK Delivery Manager at AstraZeneca. Once Clean File has been declared the PK data will be sent in the form of a protected Excel spreadsheet directly to the study team programmer for loading into AstraZeneca's statistical analysis software (SAS). Unblinded PK data will not be accessed by AstraZeneca staff affiliated with the conduct of the study prior to Clean File.

The Study Delivery Team at AstraZeneca R&D will document the date of clean file and database lock. Following Clean File, required amendments to the database due to critical errors will only be allowed with the appropriate supporting documentation. Non-critical errors will not result in amendments to the database but will be captured via the appropriate documentation.

Concomitant medications will be coded using the AZ Drug Dictionary (AZDD). AEs, medical and surgical histories will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). As new versions of the AZDD and MedDRA are released, version control will be implemented according to the study specific coding guidelines.

5.1 Reporting of genotypic results

Refer to Appendix J for details.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data.

6.2 Description of outcome variables in relation to objectives and hypotheses

Please refer to Table 6 for a description of the relationship between specific study objectives and outcome variables.

6.3 Description of analysis sets

Efficacy data from this study will be analyzed on an intention-to-treat (ITT) basis using randomised treatment. There will be one primary analysis population comprising all patients.

In addition, a per protocol analysis excluding significant protocol deviators will be carried out for the primary analysis of PFS and OS.

The safety data for this study will be summarized using treatment received. The analysis population will consist of all patients who received at least one dose of ZD6474 /Erlotinib

6.4 Method of statistical analysis

6.4.1 PFS, OS, TDS, TDPS and ORR

At the time of the final analysis of the primary endpoint of PFS, the secondary endpoint of OS will also be analyzed.

The analyses for PFS, OS, TDS, and TDPS will be performed using the log-rank test (unadjusted model with treatment factor only) in the ITT population.

For PFS, OS, TDS, and TDPS, a Cox's proportional hazards regression model will also be performed as a secondary analysis. The model will allow for the effect of treatment and will also include terms for tumour stage, number of organs involved, prior Avastin failures, histology, smoking history, gender, ethnic origin, EGFR expression, EGFR amplification and EGFR mutation status. The conclusion will be based on the unadjusted analysis, which is considered as primary. If the unadjusted analysis and the adjusted analysis yield different results, the consequences of the covariate adjustment will be explored.

A global test for the presence of the treatment by baseline covariate interactions will be performed at the 1% level of significance by including all the 2-way treatment by baseline covariate interactions in the model. The assumptions of proportionality will also be investigated with a time-dependent exploratory variable, which is defined as treatment *{log(time to event)}. If the p-value from the Wald Chi-squared statistic for this variable is less than 5% there is evidence of a departure from the adjusted model assumptions. In this case, the reason will be explored and reported in the statistical text.

The comparison of treatments will be estimated using the HR together with the corresponding two-sided 95% confidence interval (CI) and p-value.

In addition, subgroup analyses will be performed on PFS and OS. The subgroups to be explored will be the same factors included as covariates in adjusted Cox's proportional hazard model, as described above.

PFS, OS, TDS, and TDPS will be summarized using Kaplan-Meier methods. Kaplan-Meier plots and Kaplan-Meier estimates of median time to event will be presented by randomised treatment group.

The primary analysis of ORR will be analyzed using logistic regression including treatment factor only. A secondary analysis will also be performed where the logistic regression model will allow for the effect of treatment and will also include terms for tumour stage, number of organs involved, prior Avastin failures, histology, smoking history, gender, ethnic origin,

EGFR expression, EGFR amplification and EGFR mutation status. The conclusion will be based on the unadjusted analysis, which is considered as primary. If the unadjusted analysis and the adjusted analysis yield different results, the consequences of the covariate adjustment will be explored. The results of the analyses will be presented in terms of odds ratios together with associated CIs and 2-sided p-values. The estimates of the differences in the response rates and the corresponding 2-sided 95% CIs will also be presented.

6.4.2 Symptoms and Quality of Life

The statistical analysis of QoL assessments will use data from the EORTC QLQ-C30 plus QLQ-LC13 questionnaire. Data will be summarized over time in terms of mean, median, standard deviation, minimum and maximum and number of patients for each treatment group. Graphical displays will also be presented. The analysis of time to deterioration of pain, dyspnoea and cough (TDS) will be analysed as described in Section 6.4.1. Times to deterioration of the other scales/items of the QLQ-C30 and QLQ-LC13 will be analysed in a similar way to TDS.

For EORTC QLQ-C30 plus QLQ-LC13 scores, a mixed model using the repeated measures approach will be fitted to the data. The analysis will include all non-missing visit scores and the model will include terms for treatment, baseline score, time of assessment, tumour stage, number of organs involved, prior Avastin failures, histology, smoking history, gender, ethnic origin, EGFR expression, EGFR amplification and EGFR mutation status. The results of the analyses will be presented in terms of adjusted means for each treatment, estimated effect for the treatment comparison, associated CI and p-value. In addition, summary tables will be produced to investigate the relationship between TDS and duration of PFS.

The proportion of patients deteriorating with no change or improving for pain dyspnoea and cough, the total score and each domain will be summarised by treatment group and visit.

6.4.3 WHO performance status

WHO PS scores will be summarized over time for each treatment group using appropriate summary statistics. In addition, summary tables will be produced to investigate the relationship between TDPS and duration of PFS.

6.4.4 Safety and tolerability

Safety and tolerability data will be presented by treatment received. Appropriate summaries of these data will be presented. Safety and tolerability will be assessed in terms of AEs, laboratory data, ECG data, vital signs and weight, which will be collected for all subjects. AEs (both in terms of MedDRA preferred terms and CTCAE grade), laboratory data, ECG data, vital signs data and weight will be listed individually by subject and summarised by treatment received. For patients who have a dose modification, all AE data (due to toxicity or otherwise) will be assigned to the initial treatment received group. ECG changes will be summarized for each treatment group.

Vital signs data will be listed for each patient and changes in vital signs will be summarized for each treatment group.

6.4.5 Pharmacokinetics

Please see Section 4.5.2 for a summary of the methodology to be used in the PK analysis.

The individual plasma concentration will be listed by centre, patient, sample date and sample time.

Clinical Pharmacology (AstraZeneca R&D, UK) will use these individual plasma concentrations to perform a population PK analysis. This analysis will generate population mean estimates of CL/F and Vss/F, together with their associated inter-subject variability estimates. The model will also generate individual predicted values of CL/F and individual predicted plasma concentrations. These will be used in the PK-PD analysis looking at the relationship between efficacy (PFS, OS and ORR), and AEs, including the prolongation of QTc, and PD biomarkers for ZD6474.

Full details of the analysis and methodology used will be presented in a population PK-PD (Pharmaco-Dynamic) analysis plan prepared prior to the start of the analysis, and the results of these analyses will be presented in a separate PK-PD analysis report which will be issued as an appendix to the main Clinical Study Report (CSR).

6.4.6 Pharmacodynamics

Plasma VEGF, VEGFR-2 and bFGF data will be listed and summarised by treatment group. Changes from baseline will also be listed and summarised by treatment group. Results will be presented in terms of mean, median, sd, minimum, maximum and N.

Expression and amplification levels of EGFR from archival tumour tissue will also be listed and summarised by treatment group as well as changes from baseline. Results will be presented in terms of mean, median, sd, minimum, maximum and N.

6.4.7 Genetics

EGFR mutational status will be listed and summarised by treatment group.

Mutational status of other candidate genes in archival tumour samples will also be listed and summarised by treatment group.

Mutational status of other target genes and genotyping data on absorption, metabolism and excretion (ADME) genes will be listed and summarised.

Mutational status of EGFR and other candidate genes in circulating cell-free tumour DNA found in plasma will be reported separately as an addendum to the main study report.

6.5 Determination of sample size

There will be one primary analysis population comprising all patients. A nominal 2-sided significance level of 5% will be used for all analyses, except for the primary endpoint of PFS

and the secondary endpoint overall survival where the nominal significance level will be adjusted to approximately 4.88% to allow for a single interim analysis.

In order to detect a 25% prolongation of overall Progression-Free Survival (PFS) with >90% power at the 2-sided 4.88% significance level, a minimum of 1110 progression events are required. Assuming median PFS of 2.2 months for Erlotinib, a non-linear recruitment period of 15 months and minimum follow-up of 7 months, a minimum of 1150 patients will be randomised. This equates to a 2-week improvement in the median TTP; i.e. a 2.75-month median PFS on the ZD6474 arm. The estimate of median PFS for Erlotinib has been taken from a randomised, placebo-controlled, phase III Erlotinib study (Shepherd et al 2005).

The analysis of overall survival (OS) will be conducted at the time of analysis of the primary endpoint of PFS. Assuming median OS of 6.7 months for Erlotinib (Shepherd et al 2005), it is estimated that 769 events (deaths) will have occurred at this time, in which case the power to detect a 25% prolongation of survival would be 87%. This equates to a 7-week improvement in the median OS; i.e. an 8.375-month median OS on the ZD6474 arm.

6.6 Interim analyses

The IDMC will review the safety data every three months and could recommend terminating the study at any stage if, in the committee's judgement, the relationship between potential benefits and risks to patients were to become unacceptable.

A single interim analysis to assess superiority of the PFS and overall survival endpoints will be performed when **approximately** 555 PFS events have occurred in the overall population. If exactly 555 events overall are reported at the time of the interim analysis, the nominal significance levels for these tests will be 0.14% (O'Brien and Fleming TR 1979, S+SEQTRIAL 2 User's Manual). The exact nominal significance level will be determined based on the exact number of events at the time of the interim analysis.

6.7 Data monitoring board

This study will use an external IDMC, comprising of at least 3 individuals who are not employed by AstraZeneca, and do not have major conflicts of interest. The remit and function of the IDMC is specified in Supplement A.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study site to:

- Determine the adequacy of the facilities

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study)

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (e.g., clinic charts).

- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research.

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

7.2 Audits and inspections

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

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to

the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first patient is entered into the study, the investigational staff will be trained to use the WBDC system by AstraZeneca personnel or delegates.

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic research with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the Co-ordinating Investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to or approved by each Ethics Committee, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s) who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

7.6 Study timetable and end of study

Before a patient's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Approval of the study by the Ethics Committee
- Approval of the study, if applicable, by the regulatory authority.

The approximate date of enrolment of the first patient is expected in [redacted] and the approximate date when the last patient is expected to have completed the study is [redacted] AstraZeneca will notify the Investigator when recruitment is completed.

The end of study will be declared once a program has been established for remaining patients still receiving ZD6474 study treatment after the final analysis of this trial has occurred.

8. ETHICS

8.1 Ethics review

AstraZeneca will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

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

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in Appendix J.

8.3 Informed consent

The principal investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by randomisation code / study code / initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Local Study Delivery Team Physician (LSDTP). If the LSDTP is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address & telephone number
Study Delivery Leader responsible for the protocol at central R&D site	[redacted]	[redacted]
SDT Physician's responsible for the protocol at central R&D site	[redacted]	[redacted]
24-hour emergency cover	[redacted]	[redacted]

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

9.3 Procedures in case of overdose

There is currently no known antidote to ZD6474. In the event of an overdose (> 1 dose within 24 hours), symptomatic and supportive care should be given, and all details should be recorded.

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the eCRFs as an AE of 'Overdose' unless there are associated symptoms or signs.
- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs.
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. In addition, the overdose should be reported on the separate AZ "Clinical Study Overdose Report Form."

- An overdose without associated symptoms should not be recorded as an AE in the eCRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.4 Procedures in case of pregnancy

No data are available on pregnant or lactating women for either treatments. Women of childbearing potential must be advised to avoid pregnancy during the study and must be using an acceptable method of contraception, see section 3.3.4 for more details.

In the event of pregnancy occurring while a patient is receiving ZD6474/Erlotinib, the study drug should be discontinued and AstraZeneca should be contacted for advice.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to AstraZeneca on the pregnancy outcomes report form.

10. REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.

Beal and Sheiner 1988-1998
Beal SL, and Sheiner LB (1988-1998). NONMEM Users Guides. Part I-VIII. NONMEM Project Group C255, University of California at San Francisco.

Bergman et al 1994
Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30A:635-42.

Bottomley et al 2003
Bottomley A, Efficace F, Thomas R, Vanvoorden V, Ahmedzai SH. Health-Related Quality of Lfe in Non-Small-Cell Lung Cancer : Methodologic Issues in Randomised Controlled Trials. J Clin Oncol. 2003;21(15):2982-92.

Cappuzzo et al 2005
Cappuzzo F, Hirsch F, Rossi E, Bartolini S, Ceresoli G, Bemis L, et al. Epidermal Growth Factor Receptor Gene and Protein and Gefitinib Sensitivity in Non–Small-Cell Lung Cancer**.** J. Natl. Cancer Inst 2005;97(9):643-655.

Ciardiello et al 2003
Ciardiello F, Caputo R, Damiano V, Caputo R, Troiani T, Vitagliano D, et al. Antitumour effects of ZD6474, a small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitor, with additional activity against EGFR tyrosine kinase. Clin Cancer Res 2003;9(4):1546-56.

Cull et al 2002
Cull A, Sprangers M, Bjordal K, Aaronson N, West K, Bottomley A. Guidelines for translating EORTC Questionnaires. Brussels : Quality of Life Study Group Publications. EORTC Publication;2002.

Douillard 2007
Douillard JY, Kim E, Hirsh V, Mok T, Socinski M, Gervais R, et al. Gefitinib (IRESSA) versus docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer pre-treated with platinum-based chemotherapy: a randomized, open label phase III study (INTEREST). J Thorac Oncol 2007;2(8):S305-S306.

Dvorak et al 1995
Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol 1995;146:1029-1039.

Earle 2004
Earle C. Outcomes Research in Lung Cancer. J Natl Cancer Inst Monographs 2004:56-77.

Fayers et al 2001
Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3rd edition. Brussels, EORTC Publication, 2001.

Fayers and Machin 2000
Fayers PM, Machin D. Quality of Life: Assessment, Analysis and Interpretation. John Wiley & Sons, Chichester (2000) ISBN: 0-471-96861-7.

Ferrara 1999
Ferrara N. Molecular and biological properties of vascular endothelial growth factor. J Mol Med 1999;77:527-543.

Ferrara and Gerber 2003
Ferrara N, Gerber H P, LeCouter J. The biology of VEGF and its receptors. Nature Medicine 2003;9(6):669-676.

Folkman 1971
Folkman J. Tumour angiogenesis: therapeutic implications. N Engl J Med 1971;285:1182-1186.

Garratt et al 2002
Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. "Quality of life measurement: bibliographic study of patient assessed health outcome measures" BMJ 2002;324(7351):1417–1417.

Gasparini et al 1997
Gasparini G, Toi M, Gion M, Verderio P, Dittadi R, Hanatani M, ET AL. Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma. J Natl Cancer Inst 1997;89:139-147.

Hanahan and Folkman 1996
Hanahan D and Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumourigenesis. Cell 1996;86:353-364.

Herbst et al 2005
Herbst R, Johnson DH, Mininberg E, Carbone DP, Henderson T, Kim ES, et al. A Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/EGFR tyrosine kinase inhibitor Erlotinib for patients with recurrent non-small-cell lung cancer. Journal of Clinical Oncology 2005;23:2544-2555.

Hurwitz et al 2004
Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350(23):2335-42.

Kim et al 1993
Kim KJ, Li B, Winer J, Armanini M, Gillet N, Phillips HS, et al. Inhibition of vascular endothelial growth factor induced angiogenesis suppresses tumour growth in vivo. Nature 1993;62:841-844.

Kosmidis 1996
Kosmidis P. Quality of life as a new end point. Chest 1996;109:S110-S112 (Suppl 5).

Leung et al 1989
Leung DW, Cachianes G, Kuang WJ, Goeddel DV and Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306-1309.

Maeda et al 1996
Maeda K, Chung Y-S, Ogawa Y, Takatsuka S, Kang SM, Ogawa M, et al. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. Cancer 1996;77:858-863.

Millauer et al 1994
Millauer B, Shawver LK, Plate KH and Risau W. Glioblastoma growth inhibited in vivo by a dominant negative Flk-1 mutant. Nature 1994;367:576-579.

Neufeld et al 1999
Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999;13(1):9-22.

Niklinska et al 2001
Niklinska W, Burzykowski T, Chyczewski L and Niklinski J. Expression of vascular endothelial growth factor (VEGF) in non-small cell lung cancer (NSCLC): association with p53 gene mutation and prognosis. Lung Cancer 2001;34(Suppl 2):S59-64.

O'Brien and Fleming TR 1979
O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-556.

Osoba et al 1998
Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-144.

Paavonen et al 2000
Paavonen, K, Puolakkainen P, Jussila L, Jahkola T and Alitalo K. Vascular Endothelial Growth Factor Receptor-3 in Lymphangiogenesis in Wound Healing. American Journal of Pathology 2000;156(5):1499-1504.

Roche Products Limited 2005
Roche Products Limited, Summary of Product Characteristics (SmPC) updated Friday 23rd September 2005

S+SEQTRIAL 2 User's Manual
S+SEQTRIAL 2 User's Manual , Insightful Corporation, Seattle, WA, 2002.

Sandler et al 2005
Sandler AB, Gray R, Brahmer J, Dowlati A, Schiller JH, Perry MC, et al. Randomised phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) trial - E4599. Abstract No. LBA4. 2005 ASCO Annual Meeting Proceedings.

Sarna et al 2002
Sarna L, Padilla G, Holmes C, Tashkin D,Brecht ML, Evangelista L. Quality of life of long-term survivors of non-small cell lung cancer. J Clin Oncol 2002;20:2920-2929.

Shepherd et al 2005
Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Huat Tan E, Hirsh V, Thongprasert S, et al. Erlotinib in Previously Treated Non-Small-Cell Lung Cancer. N Engl J Med 2005;353:123-32.

Shou et al 2001
Shou Y, Hirano T, Gong Y, Kato Y, Yoshida K, Ohira T, et al. Influence of angiogenetic factors and matrix metalloproteinases upon tumour progression in non-small-cell lung cancer. British Journal of Cancer 2001;85(11):1706-12.

Siemeister et al 1998
Siemeister G, Martiny-Baron G and Marmé D. The pivotal role of VEGF in tumour angiogenesis: Molecular facts and therapeutic opportunities. Cancer Metastasis Rev 1998;17:241-248.

Stacker and Achen 1999
Stacker SA and Achen MG. The vascular endothelial growth factor family: Signaling for vascular development. Growth Factors 1999;17:1-11.

The EuroQoL Group 1990
The EuroQoL Group. EuroQoL – a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

Therasse et al 2000
Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumours. Journal of the National Cancer Institute 2000;92(3):205-216.

Wedge et al 2002
Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumour growth following oral administration. Cancer Res 2002;62(16):4645-55.

Young et al 2002
Young T, de Haes H, Fayers P, Brandberg E, Vanvoorden V, Bottomley A. Guidelines for assessing quality of life in clinical trials. 2nd ed. Brussels : EORTC Quality of Life Study Group Publications; 2002. ISBN 2-930064-27-7.

Clinical Study Protocol: Appendix B

Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

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

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

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

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol: Appendix C

Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix C
WHO Performance Status

1. WHO PERFORMANCE STATUS

The table below (Table 1) details the WHO Performance Status to measure how well a subject is able to perform ordinary tasks and carry out activities of daily living.

Table 1 WHO Performance Status

	Score
Fully active, able to carry out all usual activities without restrictions and without the aid of analgesia.	0
Restricted in strenuous activity, but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains subjects who are fully active, as in grade 0, but only with the aid of analgesics.	1
Ambulatory and capable of all self-care, but unable to work. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled, unable to carry out any self-care and confined totally to bed or chair.	4

AstraZeneca

Clinical Study Protocol: Appendix D	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix D
Medications Known to Prolong QT

1. MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES (TDP)

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsade de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP.

1.1 Group 1 - Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

Concomitant use of these drugs is not allowed during the study or within 2 weeks of study entry (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment:

Table 1 Group 1 Drugs

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Albuterol (by parenteral administration)	Bronchodilator (asthma)	Inhaled Albuterol at normal doses acceptable
Amiodarone	Anti-arrhythmic (heart rhythm)	F>M, TdP Cases in Literature
Arsenic trioxide	Anti-cancer (leukaemia)	TdP Cases in Literature
Bepridil	Anti-anginal (heart pain)	F>M
Chlorpromazine	Anti-psychotic/antiemetic (schizophrenia/nausea)	TdP Cases in Literature
Chloroquine	Anti-malaria (malaria infection)	
Cisapride	GI stimulant (stimulates GI motility)	Open Prescription Restricted F>M
Disopyramide	Anti-arrhythmic (heart rhythm)	F>M
Dofetilide	Anti-arrhythmic (heart rhythm)	
Domperidone	Anti-nausea (nausea)	
Droperidol	Sedative/hypnotic (anaesthesia adjunct)	TdP Cases in Literature
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F>M
Halofantrine	Anti-malarial (malaria infection)	F>M
Haloperidol	Anti-psychotic (schizophrenia, agitation)	
Ibutilide	Anti-arrhythmic (heart rhythm)	F>M

Table 1 Group 1 Drugs

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Levomethadyl	Opiate agonist (narcotic dependence)	
Mesoridazine	Anti-psychotic (schizophrenia)	
Methadone	Opiate agonist (pain control/ narcotic dependence)	F>M
Pentamidine	Anti-infective (pneumocystis pneumonia)	F>M
Pimozide	Anti-psychotic (Tourette's tics)	F>M, TdP Cases in Literature
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F>M
Salbutamol (by parenteral administration)	Bronchodilator (asthma)	Inhaled salbutamol at normal doses acceptable
Sotalol	Anti-arrhythmic (heart rhythm)	F>M
Sparfloxacin	Antibiotic (bacterial infection)	
Thioridazine	Anti-psychotic (schizophrenia)	

1.2 Group 2 - Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes

If a patient is receiving one of the medications in this group prior to study entry, and it cannot be discontinued before study entry, then the screening QTc must be ≤460 msec, and an additional ECG must be obtained 4 – 8 hours after the first dose of study medication. For patients who start one of the drugs in this group while on the study, these drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes (see Section 3.7.2 of the protocol).

Table 2 Group 2 Drugs

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Alfuzocin	Alpha 1-blocker (Benign prostatic hyperplasia)	
Amantadine	Dopaminergic/Anti-viral/Anti-infective (Parkinson's disease)	

Table 2 Group 2 Drugs

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Amitriptyline	Tricyclic anti-depressant (depression)	
Amoxapine	Tricyclic anti-depressant (depression)	
Azithromycin	Antibiotic (bacterial infection)	
Citalopram	Anti-depressant (depression)	
Clarithromycin	Antibiotic (bacterial infection)	TdP Cases in Literature
Clomipramine	Tricyclic antidepressant (depression)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Desipramine	Tricyclic anti-depressant (depression)	TdP Cases in Literature
Dolastron	Anti-nausea (nausea and vomiting)	When this 5-HT anti-emetic is administered as a single recommended dose, no additional monitoring of the ECG or electrolytes is required
Doxepin	Anti-depressant (depression)	TdP Cases in Literature
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Fluconazole	Anti-fungal (fungal infection)	
Fluoxetine	Anti-depressant (depression)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron	Anti-nausea (nausea and vomiting)	When this 5-HT anti-emetic is administered as a single recommended dose, no additional monitoring of the ECG or electrolytes is required
Imipramine	Anti-depressant (depression, pain, other)	TdP Cases in Literature
Indapamide	Diuretic (stimulates urine & salt loss)	TdP Cases in Literature, QT in animals

Table 2 Group 2 Drugs

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Isradipine	Anti-hypertensive (high blood pressure)	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lithium	Anti-mania (bipolar disorder)	
Mexilitine	Anti-arrhythmic (abnormal heart rhythm)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	
Moxifloxacin	Antibiotic (bacterial infection)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nortriptyline	Tricyclic antidepressant (depression)	
Octreotide	Endocrine (acromegaly/carcinoid diarrhoea)	
Ofloxacin	Antibiotic (bacterial infection)	
Ondansetron	Anti-emetic (nausea and vomiting)	When this 5-HT anti-emetic is administered as a single recommended dose, no additional monitoring of the ECG or electrolytes is required
Paroxetine	Anti-depressant (depression)	
Protriptyline	Tricyclic antidepressant (depression)	
Quetiapine	Anti-psychotic (schizophrenia)	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	
Salmeterol	Sympathomimetic (asthma, COPD)	
Sertraline	Antidepressant (depression)	Association not clear
Solifenacin	Muscarinic receptor antagonist (treatment of overactive bladder)	
Tacrolimus	Immune suppressant	TdP Cases in Literature
Tamoxifen	Anti-cancer (breast cancer)	

Table 2 Group 2 Drugs

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Trimipramine	Tricyclic antidepressant (depression)	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

AstraZeneca

Clinical Study Protocol: Appendix E	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix E
Response Evaluation Criteria in Solid Tumors (RECIST)

1. DEFINITION OF MEASURABLE AND NON-MEASURABLE LESIONS

Measurable and non-measurable lesions are defined in Table 1 below.

Table 1 Definition of Lesions

Lesion	Definition
Measurable	Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral computed tomography (CT) scan
Non-measurable	All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions

Lesions that are considered as truly non-measurable include the following:

- Bone lesions;
- Leptomeningeal disease;
- Ascites;
- Pleural / pericardial effusion;
- Inflammatory breast disease;
- Lymphangitis cutis/pulmonis;
- Abdominal masses that are not confirmed and followed by imaging techniques;
- Cystic lesions.

Note: Previously irradiated lesions will not be considered measurable.

2. METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

2.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

2.2 Chest x-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, computed tomography (CT) is preferable.

2.3 Computer Tomography (CT) and Magnetic Resonance Imaging (MRI)

CT and MRI might be 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 the chest, abdomen and pelvis. Head and neck and extremities usually require specific protocols.

In this study, it is recommended that examinations of the chest and abdomen will be collected as part of the scheduled Response Evaluation Criteria in Solid Tumors (RECIST) assessments. Pelvis will be included if clinically indicated.

2.4 Ultrasound

Ultrasound (US) should not be used to measure tumor lesions for objective response evaluation. It is however a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

As ultrasound is not appropriate for assessing objective response, it will not be used as part of the RECIST assessment in this study.

2.5 Endoscopy and laparoscopy

The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilization of such techniques for objective tumour response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

As these methods have not been validated for assessing objective response, they will not be used as part of the RECIST assessment in this study.

2.6 Tumor markers

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

Tumor markers are not measured in this study and will not contribute to the response assessment.

2.7 Cytology and histology

These techniques can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (eg, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

Cytology and histology are not relevant to confirmation of residual benign tumors in lung cancer and will not be used in this context in this study.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

In the absence of negative cytology findings for pleural effusion that worsens or appears, this will be considered to be disease progression due to new lesions or progression of non-target lesions.

3. TUMOUR RESPONSE EVALUATION

3.1 Assessment of overall tumor burden and measurable disease

To assess objective response, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included where measurable disease is defined by the presence of at least one measurable lesion.

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.1 Documentation of "target" and "non-target" lesions

All measurable lesions up to a maximum of 10 lesions representative of all involved organs (maximum of 5 lesions per organ) 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) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as

reference to further characterize the objective tumor response of the measurable dimension of the disease.

The LD will be measured and recorded for all target lesions identified at baseline at follow-up assessments and the sum LD calculated.

If a lesion splits into two or more parts, then the sum of the LDs of those parts is recorded.

If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and zero recorded for the other lesion.

If a lesion becomes to small to measure, then the size below which measurement cannot be accurately obtained should be substituted for the LD and used in the sum LD.

If a lesion cannot be measured accurately due to progression, then the maximum measurable LD should be used in the sum LD and response assessment.

If a lesion has become non measurable or evaluable for some other reason and it is not possible to assign an estimate of the longest diameter then this lesion should be excluded from response assessment.

All other lesions (or sites of disease) 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 "present with progression".

4. RESPONSE CRITERIA

4.1 Evaluation of target lesions

The definitions for the evaluation of target lesions are provided in Table 2 below.

Table 2 Evaluation of Target Lesions

Evaluation[a]	Definition
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started

a. Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

4.2 Evaluation of non-target lesions

The definitions used to determine the objective tumor response of non-target lesions are provided in Table 3 below.

Table 3 Evaluation of Non-Target Lesions

Evaluation[a]	Definition
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Non-Complete Response (non-CR/Non-Progression [non-PD])	Persistence of one or more non-target lesion or/and maintenance of tumor marker level above the normal limits
Progression (PD)	Unequivocal progression of existing non-target lesions

a. Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions.

4.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For this study, the sponsor will derive visit and overall response. Best overall response will be derived as part of the study analysis by AstraZeneca. In general, the patient's best response assignment will depend on the achievement of both measurement (Table 4) and confirmation criteria.

Table 4 Evaluation of Best Overall Response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

Note: 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 ensure "symptomatic deterioration" patients continue to have objective tumor assessments at withdrawal from trial and until progression is confirmed by imaging.

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

5. CONFIRMATORY MEASUREMENT

5.1 Confirmation

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. This aspect of response evaluation is particularly important in non-randomized trials where response is the primary endpoint. In this setting, to be assigned a status of PR or CR, changes in tumor measurements must be confirmed, by repeat studies at the next scheduled RECIST assessment at 8 weeks and certainly not less than 4 weeks following the date when response was first measured.

6. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies and as such these protocols for CT and MRI scanning may differ from those employed in clinical practice at various institutions. The use of standardized protocols allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

6.1 Chest X-ray

Not only should the film be performed in full inspiration in the posterior-anterior (PA) projection, but also the film to tube distance should remain constant between examinations. However patients in trials with advanced disease may not be well enough to fulfill these criteria and such situations should be reported together with the measurements.

Lesions bordering the thoracic wall are not suitable for measurements by chest X-ray, since a slight change in position of the patients can cause considerable differences in the plane in which the lesion is projected and may appear to cause a change which is not real. These lesions should be followed by CT or MRI. Similarly, lesions bordering or involving the mediastinum should be documented on CT or MRI.

6.2 CT

CT scans of the thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest. As a rule of thumb, the minimum size of the lesion should be no less than double the slice thickness. Lesions smaller than this are patient to significant "partial volume" effects and such a lesion may appear to have "responded" or "progressed" on subsequent examinations, when in fact they remain the same size. This minimum lesion size for a given slice thickness at baseline ensures that any lesion appearing smaller on subsequent examinations will truly be decreasing in size.

The type of CT scanner is important regarding the slice thickness and minimum sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be10mm, provided the images are reconstructed contiguously at 5mm intervals. For conventional CT scanners, the minimum sized lesion should be 20 mm using a contiguous slice thickness of 10 mm.

The fundamental difference between spiral and conventional CT is that conventional CT acquires the information only for that particular slice thickness scanned, which is then expressed as a two dimensional representation of that thickness or volume as a gray scale image. The next slice thickness needs to be scanned before it can be imaged and so on. Spiral CT acquires the data for the whole volume imaged, typically the whole of the thorax or upper abdomen in a single breath hold of about 20-30 seconds. To view the images, a suitable reconstruction algorithm is selected, by the machine, so the data are appropriately imaged. As suggested above, for spiral CT, 5 mm re-constructions can be made thereby allowing a minimum sized lesion of 10 mm.

Spiral CT is now the "standard" in most hospitals involved in cancer management in US, Europe and Japan, so the comments related to spiral CT are pertinent. However, some institutions involved in clinical trials will have conventional CT, but the number of these scanners will decline as they are replaced by spiral CT.

Other body parts, where CT scans are of different slice thickness, (such as the neck, which are typically of 5 mm thickness) or in the young pediatric population, where the slice thickness may be different, the minimum sized lesion allowable will be different. However, it should be double the slice thickness. The slice thickness and the minimum sized lesion should be specified in the study protocol.

In patients in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses. This is almost universally undertaken routinely.

Intra-venous (IV) contrast agents should also be given, unless contra-indicated for medical reasons, such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. Although in clinical practice its use may add little, in the context of a clinical study where objective response rate based on measurable disease is the endpoint, unless an IV contrast agent is given, a significant number of otherwise measurable lesions will not be measurable. In patients in whom the disease is apparently restricted to the periphery of the lungs, for example, the use of IV contrast agents appears unnecessary, but the aim of a clinical study is to ensure lesions are truly resolving, and there is no evidence of new disease at other sites scanned, eg, small metastases in the liver.

The method of administration of IV contrast agents is variable. Rather than try to institute rigid rules regarding methodology of administration of contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent

should be given such that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.

All images from each examination should be included and not "selected" images of the apparent lesion. This is to ensure that if a review is undertaken, the reviewer can satisfy him/herself that no other abnormalities co-exist. All window settings should be included, particularly in the thorax where lung and soft tissue windows should be considered.

When measuring lesions, lesions should be measured on the same window setting on each examination. It is not acceptable to measure a lesion on lung windows on one examination, then on soft tissue settings on the next. In the lung, it does not really matter whether lung or soft tissue windows are used for intra-parenchymal lesions, provided a thorough assessment of nodal and parenchymal disease has been undertaken and the target lesions are measured as appropriate using the same window settings for repeated examinations throughout the study.

6.3 MRI

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Some of the factors involved include the magnet strength (high field magnets require shorter scan times, typically 2-5 minutes), the coil design and patient co-operation. Wherever possible, the same scanner should be used. For instance, the images provided by a 1.5T scanner will differ from those using a 0.5T scanner. Although, a comparison can be made, it is not ideal.

Moreover many patients with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is at this point in time the imaging modality of choice.

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is therefore, not acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

7. REFERENCES

Therasse P et al 2000
Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. Journal of the National Cancer Institute 2000;92(3):205-216.

Clinical Study Protocol: Appendix F	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix F
EORTC QLQ-C30 plus QLQ-LC13 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire plus Lung Cancer Module)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Clinical Study Protocol: Appendix G	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix G
Cockcroft-Gault Formula

1. MODIFIED COCKCROFT-GAULT FORMULA

Creatinine Clearance should be calculated for this study using the modified Cockcroft-Gault formula.

US units:

Modified Cockcroft-Gault formula is calculated by the following formula:

([140 – age{yrs}] x [actual weight{kg}]) / (72 x serum creatinine[mg/dL])

- Multiply by another factor of 0.85 if female
- Intended for ages 18-110, serum creatinine 0.6-7 mg/dL

SI units:

([140 – age{yrs}] x [actual weight{kg}]) / ([72 x serum creatinine{μmol/L}] x [0.0113])

AstraZeneca

Clinical Study Protocol: Appendix H	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix H
EuroQoL 5-Dimension (EQ5D) Questionnaire

EQ - 5D

(ENGLISH VERSION FOR THE UK)

(validated for use in Eire)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

AstraZeneca

Clinical Study Protocol: Appendix I	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix I
New York Health Association (NYHA) Cardiac Classification

1. NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system (Table 1) relates symptoms to everyday activities and the patient's quality of life.

Table 1 New York Heart Association Cardiac Classification

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

AstraZeneca

Clinical Study Protocol: Appendix J	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	2
Appendix Date	[redacted]

Appendix J
Pharmacogenetics as Exploratory Objective

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS FOR PHARMACOGENETICS

The following abbreviations and special terms are used in this appendix to the clinical study protocol.

Abbreviation or special term	Explanation
ADME	Absorption, distribution, metabolism and excretion
°C	Degrees Celsius
CGG	Clinical genotyping group
CRF	Case report form
CSR	Clinical study report
DGG	Development genetics group
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetra-acetic acid
EGFR	Epidermal growth factor receptor
FFPE	Formalin fixed paraffin embedded
IC	Inhibitory concentration
ICH	International conference on harmonization
IEC	Independent ethics committee
IRB	Institutional review board
LIMS	Laboratory information management system
mL	Milliliter
nM	Nanomolar
PD	Pharmacodynamic
PK	Pharmacokinetic
SNP	Single nucleotide polymorphism
UK	United Kingdom
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1. PHARMACOGENETICS SYNOPSIS

The pharmacogenetic research described in this appendix will be submitted for regulatory approval, where applicable and ethical approval and implemented with the Clinical Study Protocol. All sections of the clinical study protocol apply to the pharmacogenetics research described in this appendix. This appendix details additional procedures and considerations for inclusion of patients in the pharmacogenetics component of the study.

1.1 Study center(s) and number of patients planned for genetic sampling

The pharmacogenetics part of the study will be conducted in as many countries and centers as possible that are participating in the main study.

1.2 Objectives

To collect archival formalin fixed paraffin embedded (FFPE) tumour tissue for DNA extraction and banking for future testing by evaluation of EGFR mutational status and mutational status of other candidate genes.

To collect a blood sample for DNA extraction and storage for future testing by evaluation of single nucleotide polymorphisms (SNPs) by genotyping of genes involved in the response to ZD6474.

1.3 Study design

It is proposed to collect optional blood and tissue samples pre-dose for retrospective genetic analysis. Provision of a blood and tissue sample for genetic analysis will be optional for all patients entering the study and will involve a separate consent procedure. A patient's acceptance of this procedure will not be a requirement for his or her participation in the main study.

1.4 Target population

All consenting participants in all countries participating in the pharmacogenetics part of this study.

1.5 Statistical methods

The number of patients who will agree to participate in the pharmacogenetic component of the study is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

2. BACKGROUND TO PHARMACOGENETICS

AstraZeneca plans to include investigations into genetic variations and their effect on drug response as part of the drug development program for all projects where it is considered to be appropriate. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilized to bring better drugs to the market.

ZD6474 is an inhibitor of the vascular endothelial growth factor (VEGF) tyrosine kinase receptor-2 (KDR, or VEGFR-2). It is expected that this molecule may be beneficial in a broad range of human malignancies, and perhaps other diseases, that are dependent upon VEGF-mediated angiogenesis. ZD6474 also inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase, though at an inhibitory concentration (IC50) of 500 nanomolar (nM), which was higher than that for VEGFR-2 (40 nM). It has not been elucidated how much anti-tumour activity is seen with ZD6474 through its activity against EGFR. If its activity is EGFR mediated, then EGFR mutational analysis of tissue could explain response. Recently, in two separate publications Paez JG et al 2004 and Lynch TJ et al 2004, published data in which tumour characteristics that predict for sensitivity to IRESSA™ have been identified. Pre-treatment tumour tissue from patients who had responded to IRESSA therapy was evaluated. Somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) were observed in tumours from eight of nine in one series, and similar mutations were observed in tumours in five of five in the other. No mutations were found in the tissue of patients who had progressive disease as their best response to IRESSA therapy, and mutations were not found in the normal lung tissue of patients whose tumours expressed the mutations.

It is planned to collect tumour samples to establish the mutational status of EGFR gene and to relate this to clinical data derived from a number of studies for ZD6474 , therefore a systematic collection of deoxyribonucleic acid (DNA) for pharmacogenetic analysis (derived from tumour samples taken from consenting study patients) will be performed.

Additionally, patients will be invited to provide a blood sample for DNA storage. This may be used to study polymorphisms in the genes that can affect the absorption, distribution, metabolism and elimination of ZD6474 and response to ZD6474 .

This analysis will not have any bearing on susceptibility of the patient or their family members to any diseases or conditions.

2.1 Rationale for pharmacogenetics

AstraZeneca intends to apply pharmacogenetics to the ZD6474 clinical development program to explore how genetic variations may affect the clinical parameters associated with ZD6474 .

The benefits of being able to explore associations between EGFR mutational status and clinical outcomes within the ZD6474 program include explaining sensitivity to ZD6474 .

It would also be logical to ensure that consent obtained would allow analysis of other genes involved in oncogenic pathways or genes downstream of EGFR.

For the blood sample, AstraZeneca encourages the banking of DNA samples from its clinical trial populations. New scientific data may emerge that may require genotyping to explain response to ZD6474

3. PHARMACOGENETIC OBJECTIVES

3.1 Tumour

To collect plasma and archival paraffin embedded tumour tissue for DNA extraction and banking for future testing by evaluation of EGFR mutational status and mutational status of other candidate genes.

Other genes that may be investigated include kdr, Src, Ras, raf, other Erb family genes.

In addition to the above named genes, which are believed may influence therapeutic response to ZD6474 , it is likely that additional information on other genes important for this drug and for the response to ZD6474 in lung cancer for which the drug is being developed will become available in the future. It is therefore important to retain the possibility of investigating additional genes in the context of ZD6474

3.2 Blood

To collect a blood sample for DNA extraction and storage for future testing by evaluation of mutational status of target genes and genotyping data on ADME genes.

4. PHARMACOGENETICS PLAN AND PROCEDURES

4.1 Pharmacogenetics plan

This appendix to the Clinical Study Protocol has been patiented to peer review according to AstraZeneca standard procedures.

The patient will be asked to participate in this pharmacogenetic component. If the patient agrees to participate, archival tumour samples will be collected from sites on patients who allow consent for their samples to be used for pharmacogenetic analysis. Additionally, 10mL EDTA blood sample will be collected on day 1 of the study prior to the 1st dose of study medication.

4.2 Selection of pharmacogenetics population

4.2.1 Study selection record

All patients at centers in countries participating in the pharmacogenetics part of this study will be asked to participate in the genetic research. Participation in this genetic component of the

clinical study is voluntary and if a patient declines to participate in the genetic research component of the study there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in the main body of the clinical study protocol.

4.2.2 Inclusion criteria

For inclusion in the genetic component to the study, patients must fulfill all of the inclusion criteria described in the main body of the study protocol and:

1. Provision of informed consent for genetic research and tissue sampling

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

4.2.3 Exclusion criteria

There are no exclusion criteria for the genetic component to the study.

4.2.4 Discontinuation of patients from the genetic component of the study

4.2.4.1 Criteria for discontinuation

Specific reasons for discontinuing a patient from the genetic component of the study are:

Withdrawal of consent to the genetics aspects of the study. Patients may withdraw from the genetic research component of the study at any time, independent of any decision concerning participation in other aspects of the clinical study described in the main body of the Clinical Study Protocol. Voluntary discontinuation will not prejudice further treatment.

4.2.4.2 Procedures for discontinuation

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future.
- Withdraws consent for the sample to be kept for genetic research in the future and wishes the blood sample to be destroyed and any FFPE tumour block received returned to the hospital. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

5. GENETIC MEASUREMENTS AND CO-VARIABLES

5.1 Summary of genetics objectives and analysis

The purpose of the pharmacogenetic component of the study is to generate data for use in retrospective analyses. Analyses from the tumour DNA will explore EGFR mutational status as it relates to clinical outcome variables. The results of the pharmacogenetic analyses will not form part of the clinical study report for this study. The results may be pooled with pharmacogenetic data from other studies on ZD6474 to generate hypotheses to be tested in future studies.

5.2 Collection of samples for genetic research

5.2.1 Tumour

Patients will be asked to provide consent for AstraZeneca to collect and analyze samples(s) of their archival tumour material.

We will ask the person responsible for sending the sample to provide one of the following depending on which format is more convenient.

1. Formalin-fixed, paraffin-embedded blocks.

   or

2. 20 x recut sections from the FFPE block presented on slides including 1 stained with haematoxylin and Eosin. Each section to be 5 micron thick.

Samples will be labeled with the protocol study number, center number, enrolment code (E-code), sample ID and the date of sample preparation. No personal identifiers (patient name) will be placed on the tube or accompanying documentation, except for date of birth, which is required on the accompanying documentation to ensure unequivocal identification of the correct sample, in the case of an enrolment code typographical error. A record of the date of the patient consent to the genetic research, the date the archival samples were obtained, and the sample site (primary or metastatic, and if metastatic, which site) will be recorded. A copy of the record should accompany the shipment and a duplicate retained at site for monitoring.

Samples of tumour material may be kept for up to 15 years after the main study is completed. Tumour samples can also be returned back to the hospital at the end of the study if required.

5.2.2 Collection of blood samples for genetic research

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample (10 mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labeled with the protocol study number, center number, enrolment code and/or randomization number and date of sample collection. No personal identifiers (patient name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the eCRF.

Genotype is a stable parameter; therefore if for any reason the blood sample is not drawn at Day 1, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

5.2.3 Sample processing and shipping

Blood samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within one month of collection (and referenced as blood samples) and must remain frozen at all times.

Where possible, blood samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that blood samples arrive within working hours. A requisition sheet, detailing the protocol study number, center number, enrolment code and/or randomization number and date of blood sample collection, should accompany the shipment.

5.2.4 Storage and coding of DNA samples

The processes adopted for the coding and storage of blood and tumour samples for genetic analysis are important to maintain patient confidentiality.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will be used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The blood samples and data for genetic analysis in this study will be coded. Each blood sample will be labeled with the study number and patient number. Only the investigator will be able to link the blood sample to the individual patient. The sample and data will not be labeled with a personal identifier. The link between the patient enrolment/randomization code and the DNA number will be maintained.

This link file and any corresponding genetic data will be stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca, Alderley Park, UK. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent. Access to the link file will require written authorization from the Clinical Development Team Leader.

DNA and blood samples from this genetic research will be destroyed 15 years after the main study is completed.

5.2.5 Summary of genetic assessments and analysis

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to ZD6474 and/or susceptibility to or prognosis of NSCLC under investigation in this protocol. The results of the genetic research will not form part of the clinical study report for this study. The results may be pooled with genetic data from other studies on ZD6474 to generate hypotheses to be tested in future studies.

For consenting patients, blood samples will be collected, and DNA extracted and stored for future testing of mutational status of genes that are either targets for ZD6474 , or which may modify the effectiveness of the agent.

5.2.6 Derivation or calculation of genetic parameters

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

6. DATA MANAGEMENT OF GENETICS COMPONENTS

Only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database.

The genotypic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

6.1 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician

or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the pharmacogenetic component of this study is unknown. It is therefore not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

8. STUDY MANAGEMENT

8.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study site to:

- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study).

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- Perform source verification of the genetic consent of participating patients and ensure that the investigational team is adhering to the specific requirements of this genetic research.

8.2 Training of staff

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic research with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

8.3 Changes to the protocol

Any changes to the pharmacogenetic research will comply with the principles described in Section 7.4 of the main body of the protocol.

8.4 Study agreements

The principal investigator at each center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail. Specific reference to the genetic requirements will be included in the study agreement(s).

9. ETHICS

9.1 Ethics review

In addition to documenting Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval of the clinical study, where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the IRB or IEC. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

9.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in section 4.2.4 of this Appendix.

9.3 Informed consent

The genetic research is optional and the patient may participate in the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the Tumour Biopsy consent form and Genetic research consent Form (either or both as appropriate). Copies of all 3 signed and dated consent forms must be given to the patient and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the genetic aspect of the study at any time.

9.4 Patient data protection

Reference to participation in this genetic research should not be recorded into the patients' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient, however, it must be recognized that there are exceptional circumstances where individuals may see both genetic data and a patient's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

10. REFERENCES

Lynch TJ et al 2004
Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350(21):2129-39.

Paez JG et al 2004
Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304(5676):1497-500.

Clinical Study Protocol: Appendix K	
Drug Substance	ZD6474
Study Code	D4200C00057
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix K
Tarceva® Label

1. ERLOTINIB (TARCEVA®, ROCHE PRODUCTS LIMITED)

Investigative sites should be familiar with the dosing recommendations and safety profile of Erlotinib (Tarceva®). Information on the Erlotinib label, including updates to label changes, can be obtained from ROCHE via their mailing address or the Tarceva® websites.

ROCHE Products mailing address and Tarceva® website address:

USA:	Other (for none USA):
OSI Pharmaceuticals Suite 110 58 South Service Road Melville, NY 11747	F. Hoffmann-La Roche Ltd Pharmaceuticals Division Grenzacherstrasse 124 CH-4070 Basel Switzerland
Web Site: http://www.tarceva.com	Website: http://www.tarceva.net