Amended Clinical Study Protocol

Drug Substance ZD6474

Study Code D4200C00036

Edition Number [redacted]

A Phase III, Randomized, Double-blinded, Parallel Group, Multi-centre Study to Assess the Efficacy and Safety of ZD6474 (ZACTIMA™) in Combination with Pemetrexed (Alimta®) versus Pemetrexed alone in Patients with Locally-Advanced or Metastatic (stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) after Failure of 1st Line Anti-cancer Therapy

Sponsor: AstraZeneca [redacted]

AstraZeneca Research and Development site representative

[redacted] Date

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]		

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

[redacted]

PROTOCOL SYNOPSIS

A Phase III, Randomized, Double-blinded, Parallel Group, Multi-centre, Study to Assess the Efficacy and Safety of ZD6474 (ZACTIMA™) in Combination with Pemetrexed (Alimta®) versus Pemetrexed alone in Patients with Locally Advanced or Metastatic (stage IIIB or IV) Non-Small Cell Lung Cancer (NSCLC) after Failure of 1st Line Anti-cancer Therapy

Investigator

[redacted]

Study centre(s) and number of patients planned

This Phase III multi-centre study will be conducted in a minimum of 510 patients (255 per arm) with locally advanced or metastatic (IIIB-IV) non-small cell lung cancer (NSCLC) after failure of 1st line anti-cancer therapy. It is planned that approximately 100 centres in 20 countries will participate in the study and that each site will recruit approximately 5 patients.

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

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.

Objectives

The primary objective of this study is to demonstrate an improvement in progression-free survival (PFS) for the combination of ZD6474 plus pemetrexed (Alimta®) compared with pemetrexed plus placebo in patients with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy (not including an adjuvant regimen).

The secondary objectives of the study are:

1. To demonstrate an improvement in overall survival (OS) for ZD6474 in combination with pemetrexed compared with pemetrexed plus placebo

[redacted]

2. To demonstrate an improvement in the overall objective response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (DCR) (CR + PR + stable disease [SD] > 6 weeks) and duration of response (DOR) for ZD6474 in combination with pemetrexed compared with pemetrexed plus placebo

3. To demonstrate a beneficial effect on disease-related symptoms, in patients treated with ZD6474 in combination with pemetrexed, that is at least as good as that in patients treated with pemetrexed plus placebo based on the Lung Cancer Symptom Scale (LCSS)

4. To demonstrate an improvement in time to deterioration of disease-related symptoms (TDS) in patients treated with ZD6474 in combination with pemetrexed compared with patients treated with pemetrexed plus placebo based on the LCSS

5. To study the tolerability and safety of ZD6474 in combination with pemetrexed in patients with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy

6. To investigate the population pharmacokinetics (PK) of ZD6474 in this patient population and assess the PK-QTc relationship, PK-safety relationship, PK-efficacy relationship and PK-Pharmacodynamics (PD) relationship

The exploratory objectives of this study are the following:

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

2. To evaluate by single nucleotide polymorphism (SNP) genotyping using DNA extracted from a blood sample, the effects of genes involved in response to ZD6474 and drugs taken in combination with ZD6474 (i.e., pemetrexed)

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

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

5. To investigate the TDPS (time to deterioration in patient World Health Organization [WHO] Performance Status [PS]) during the period of treatment with investigational therapy)

[redacted]

6. To demonstrate a quality of life QoL for ZD6474 in combination with pemetrexed that is at least as good as that for patients treated with pemetrexed plus placebo based on the quality of life summation item of the LCSS.

Study design

This is a parallel group, international, randomised, double-blind, placebo-controlled, multi-centre study design to assess whether the addition of ZD6474 (100 mg) to pemetrexed (500mg/m^2 given on day 1 of each 21 day cycle) in patients with locally advanced or metastatic NSCLC who have received prior 1st line anti-cancer treatment confers an advantage in terms of PFS.

Patients will be randomised in a 1:1 ratio to receive either ZD6474 100 mg plus pemetrexed or pemetrexed plus placebo. Patients will receive pemetrexed for up to a maximum of 6 cycles, When pemetrexed treatment is discontinued, before or at the 6th cycle, patients should continue to receive daily oral dosing of blinded ZD6474/placebo as a monotherapy until progression, as long as no other discontinuation criteria is met. If another systemic anti-cancer treatment is started then study treatment should be stopped. Following discontinuation of study treatment (ZD6474/placebo and pemetrexed), patients will be followed up for survival, unless they withdraw consent. Disease progression is determined according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

Radiological evaluation using RECIST will be performed at baseline and every 6 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 treatment prior to objective disease progression they should continue to be assessed every 6 weeks, 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.

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 1st line anti-cancer therapy (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 (100 mg in tablet form) or matching placebo will be dosed orally, once daily, preferably at the same time each morning

Patients who experience Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 toxicity (see Section 3.2.3) that is considered related to ZD6474/placebo will have their

ZD6474/placebo treatment stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the patient may restart treatment with a reduced dose of ZD6474/placebo in a blinded manner. The dose may be reduced from 1 tablet a day to 1 tablet every other day. The study assessments should be continued as outlined in the study plan. If ZD6474/placebo must be withheld for more than 3 weeks for resolution of toxicity, the patient must be withdrawn from ZD6474/placebo treatment.

In the case of patients who discontinue ZD6474/placebo, but not pemetrexed therapy, because of toxicity attributed to ZD6474/placebo, these patients may continue to receive the scheduled treatment with pemetrexed (up to a maximum of 6 cycles) and will be followed for progression and survival unless they withdraw consent.

Comparator, dosage and mode of administration

In addition to ZD6474 or matching placebo described above, patients will receive pemetrexed 500 mg/m^2 administered intravenously over 10 minutes on Day 1 of each 21 day cycle. Patients will receive up to but no more than 6 cycles of pemetrexed.

Vitamin supplementation with daily oral low dose folic acid (approximately 400 µg) needs to start at least 5 days before the first dose of pemetrexed and must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive vitamin B12 at a dose of 1000 µg as an i.m. injection during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Premedication with dexamethasone (or equivalent) 4 mg twice daily, given the day before, the day of and the day after pemetrexed administration is also mandatory.

Patients who experience CTCAE grade 3 or 4 toxicity that is considered related to pemetrexed will have pemetrexed stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the patient may restart treatment with a reduced dose of pemetrexed, according to the dose reduction plan outlined in Section 3.2.3. If pemetrexed must be withheld for more than 3 weeks for resolution of toxicity, the patient will not restart pemetrexed treatment.

In the case of patients who discontinue pemetrexed because of toxicity attributable to pemetrexed, patients may continue on ZD6474/placebo and will be followed for progression and survival.

Duration of treatment

Pemetrexed will be administered according to a 21 day cycle and ZD6474/placebo will be administered once daily. The combination treatment will start from Day 1. Patients will receive pemetrexed for up to a maximum of 6 cycles, after which period patients can continue on daily oral dosing with ZD6474/placebo alone until progression.

When pemetrexed treatment is discontinued, before or at the 6th cycle, patients should continue to receive daily oral dosing of blinded ZD6474/placebo as a monotherapy until progression, as long as no other discontinuation criteria is met. If another systemic anti-

[redacted]

cancer treatment is started then study treatment should be stopped. Following discontinuation of study treatment (ZD6474/placebo and pemetrexed), patients will be followed up for survival, unless they withdraw consent.

Outcome variables

Efficacy

- Primary outcome variable:
  - PFS
- Secondary outcome variables:
  - Overall survival
  - ORR, DCR and DOR
  - Disease-related symptoms as measured by the LCSS
  - TDS as measured by the LCSS

Safety

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

Pharmacokinetic

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

Exploratory Outcome Variables

- Health economics
  - EQ5D questionnaire
- Other measures of patient benefit
  - TDPS
  - WHO PS

[redacted]

- Patient reported outcomes
  - QoL item from LCSS

Pharmacodynamic

- Plasma levels of vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor-2 (VEGFR-2) and basic fibroblast growth factor (bFGF)
- Plasma and serum levels of other biomarkers as surrogate markers of efficacy of ZD6474
- Expression levels of EGFR in archival tumour samples measured by Immunohistochemistry (IHC)
- Amplification of EGFR gene in archival tumour samples
- Amplification or expression status of other biomarkers in archival tumour samples
- EGFR mutational status and mutational status of other candidate genes, including the k-ras gene, in archival tumour tissue
- EGFR mutational status and mutational status of other candidate genes in circulating tumour DNA found in serum

Genetics

- Mutational status of candidate genes which may influence the disposition, efficacy, safety and tolerability of ZD6474 and drugs taken in combination with ZD6474 (i.e., pemetrexed)

Statistical methods

The primary comparison of interest is [pemetrexed + ZD6474 100 mg] and [pemetrexed + placebo] for progression-free survival (PFS).

There will be two co-primary analysis populations: the first will comprise all randomised patients; the second will comprise all randomised female patients. Accordingly, a nominal 2-sided significance level of 2.5% will be used for all analyses.

In order to detect a 35% prolongation (4-week prolongation) of overall PFS with 80% power at the 2-sided 2.44% significance level, a minimum of 425 progression events are required. Assuming a median PFS of 3 months for pemetrexed (Hanna et al 2004), a recruitment period of 12 months and minimum follow-up of 6 months, a minimum of 510 patients (255 per arm) will be enrolled.

PFS and overall survival (OS) will be analysed using a log-rank test. Objective response rate (ORR) and disease control rate (DCR) will be analyzed using logistic regression.

Safety and tolerability will be assessed in terms of AEs, laboratory data 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

TITLE PAGE 1
PROTOCOL SYNOPSIS 2
TABLE OF CONTENTS 9
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 15
1. INTRODUCTION 20
1.1 Background 20
1.1.1 ZD6474 21
1.1.1.1 Background 21
1.1.1.2 Summary of adverse events (AEs) in ZD6474 studies 22
1.1.2 Pemetrexed (ALIMTA®, Eli Lilly and Company) 24
1.2 Rationale 24
2. STUDY OBJECTIVES 26
2.1 Primary objective 26
2.2 Secondary objectives 26
2.3 Exploratory objectives 27
3. STUDY PLAN AND PROCEDURES 27
3.1 Overall study design and flow chart 27
3.2 Rationale and risk/benefit assessment 33
3.2.1 Rationale for study design, doses and control groups 33
3.2.2 Risk/benefit and ethical assessment 34
3.2.3 Toxicity management 35
3.2.3.1 Pemetrexed toxicity 35
3.2.3.2 QTc prolongation 36
3.2.3.3 Gastrointestinal toxicity 38
3.2.3.4 Cutaneous toxicity 38
3.2.3.5 Other toxicity 39
3.3 Selection of study population 41
3.3.1 Study selection record 41
3.3.2 Inclusion criteria 41
3.3.3 Exclusion criteria 42
3.3.4 Restrictions 44
3.3.5 Discontinuation of patients from treatment or assessment 45
3.3.5.1 Withdrawal from study 45
3.3.5.2 Procedures for withdrawal from study 45
3.3.5.3 Criteria for discontinuation 46

3.3.5.4 Procedures for discontinuation 46
3.3.5.5 Procedures for handling incorrectly enrolled patients 47
3.3.5.6 Procedures for discontinuation from biomarker and genetic aspects of the study 47

3.4 Treatments 48
3.4.1 Identity of investigational product and pemetrexed 48
3.4.2 Doses and treatment regimens 48
3.4.2.1 ZD6474 or placebo regimen 48
3.4.2.2 Pemetrexed 49
3.4.2.3 ZD6474 dose reduction 49
3.4.2.4 Missed or forgotten doses 50
3.4.3 Labelling 50
3.4.4 Storage 50
3.4.5 Accountability 50

3.5 Method of assigning patients to treatment groups 51

3.6 Blinding and procedures for unblinding the study 51
3.6.1 Methods for ensuring blinding 51
3.6.2 Methods for unblinding the study 51

3.7 Pre-study, concomitant and post-study treatment(s) 52
3.7.1 Other anti-cancer treatments 52
3.7.2 Other concomitant treatment 52

3.8 Treatment compliance 54

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES 54

4.1 Primary variable 56

4.2 Screening and demographic measurements 57

4.3 Patient-Reported Outcomes (PROs) 58
4.3.1 Lung Cancer Symptom Scale (LCSS) 58
4.3.1.1 Methods of assessment 58
4.3.1.2 Derivation or calculation of variable 58
4.3.2 Time to deterioration of disease related symptoms (TDS) 58
4.3.2.1 Methods of assessment 58
4.3.2.2 Derivation or calculation of outcome variable 58
4.3.3 Administration of PRO questionnaires 59
4.3.3.1 Instructions for scoring the LCSS 60

4.4 Health Economic measurements and variables 60
4.4.1 EQ5D 60
4.4.1.1 Methods of assessment 60
4.4.1.2 Derivation or calculation of variable 61

4.5 Pharmacokinetic measurements and variables 61
4.5.1 Collection of pharmacokinetic samples 61

4.5.2 Drug concentration measurements, and derivation or calculation of pharmacokinetic parameters 62
4.6 Efficacy and pharmacodynamic measurement and variables 62
4.6.1 Progression-free survival (PFS) 62
4.6.1.1 Methods of assessment 62
4.6.1.2 Derivation or calculation of outcome variable 63
4.6.2 Overall survival (OS) 63
4.6.2.1 Methods of assessment 63
4.6.2.2 Derivation or calculation of outcome variable 63
4.6.3 Objective response, disease control and duration of response 63
4.6.3.1 Methods of assessment 63
4.6.3.2 Derivation or calculation of outcome variable 65
4.6.4 Pharmacodynamic biomarker measurements and variables 65
4.6.4.1 Methods of assessment 65
4.6.4.2 Derivation or calculation of outcome variable 67
4.6.5 Time to deterioration in patient WHO Performance Status (TDPS) 67
4.6.5.1 Methods of assessment 67
4.6.5.2 Derivation or calculation of variable 67
4.7 Safety measurements and variables 67
4.7.1 Adverse events 67
4.7.1.1 Definitions 67
4.7.1.2 Recording of adverse events 69
4.7.1.3 Reporting of serious adverse events 71
4.7.2 Laboratory safety measurements and variables 72
4.7.2.1 Methods of assessment 72
4.7.2.2 Derivation or calculation of outcome variables 73
4.7.3 Vital signs, ECG and physical examination 73
4.7.3.1 Methods of assessment 73
4.7.3.2 12-lead ECG derivation or calculation of outcome variables 74
4.7.3.3 Vital signs and physical examinations - methods of assessment 74
4.7.3.4 Vital signs and physical examinations derivation or calculation of outcome variables 74
4.7.4 Other safety measurements and variables (not applicable) 74
4.8 Volume of blood sampling and handling of biological samples 74
4.8.1 Analysis of biological samples 75
4.8.1.1 Clinical chemistry samples 75
4.8.1.2 Pharmacokinetic samples 76
4.9 Genetic measurements and co-variables 76
5. DATA MANAGEMENT 76
5.1 Reporting of genotypic results 77
6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 77

6.1 Statistical evaluation – general aspects 77
6.2 Description of outcome variables in relation to objectives and hypotheses 77
6.3 Description of analysis sets 77
6.4 Method of statistical analysis 77
6.4.1 PFS, OS, TDS, TDPS and ORR 77
6.4.2 Symptoms and Quality of Life 78
6.4.3 WHO performance status 79
6.4.4 Safety and tolerability 79
6.4.5 Pharmacokinetics 79
6.4.6 Pharmacodynamics 80
6.4.7 Genetics 80
6.5 Determination of sample size 80
6.6 Interim analyses 81
6.7 Data monitoring board 81
7. STUDY MANAGEMENT 81
7.1 Monitoring 81
7.2 Audits and inspections 82
7.3 Training of staff 82
7.4 Changes to the protocol 83
7.5 Study agreements 83
7.6 Study timetable and end of study 83
8. ETHICS 84
8.1 Ethics review 84
8.2 Ethical conduct of the study 85
8.3 Informed consent 85
8.4 Patient data protection 85
9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY 86
9.1 AstraZeneca emergency contact procedure 86
9.2 Procedures in case of medical emergency 86
9.3 Procedures in case of overdose 86
9.4 Procedures in case of pregnancy 87
10. REFERENCES 87

[redacted]

LIST OF TABLES

PAGE

Table 1 Study plan: Screening to discontinuation of pemetrexed 30
Table 2 Study plan: After Discontinuation of pemetrexed and ongoing ZD6474/placebo 32
Table 3 Study plan: Discontinuation of both ZD6474 and pemetrexed 33
Table 4 Summary of guidance on the management of toxicity for ZD6474/placebo and pemetrexed 40
Table 5 Formulation numbers of ZD6474 48
Table 6 Dispensing for dose reduction 49
Table 7 Objectives and outcome variables 55
Table 8 PK endpoints related to each objective 61
Table 9 Classification of FISH status 66
Table 10 Laboratory safety variables 72
Table 11 Volume of blood to be drawn from each patient 75

LIST OF FIGURES

PAGE

Figure 1 Study flow chart 29
Figure 2 Management of patients with QTc prolongation 37

LIST OF APPENDICES

Appendix A Signatures (Not Applicable)
Appendix B Additional Safety Information
Appendix C WHO Performance Status
Appendix D Medications known to prolong QT
Appendix E Response Evaluation Criteria in Solid Tumours (RECIST)
Appendix F Lung Cancer Symptom Scale (LCSS)
Appendix G Cockcroft-Gault Formula
Appendix H EuroQol 5-Dimension (EQ5D) Questionnaire
Appendix I New York Heart Association (NYHA) Cardiac Classification

[redacted]

Appendix J Pharmacogenetics as Exploratory Objective

Appendix K ALIMTA® Label

Appendix L Handling and shipment of pharmacokinetic samples

LIST OF SUPPLEMENTS

CSP Supplement A Investigator and Study Administrative Structure

CSP Supplement B Local Study Delivery Team Contacts in the event of emergency, overdose or pregnancy

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
Assessment	An observation made on a variable involving a subjective judgement
AST	Aspartate aminotransferase
AZDD	AstraZeneca Drug Dictionary
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
$C_{ss, max}$	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)
CRC	Colorectal cancer
CRF	Case Report Form
CSA	Clinical Study Agreement
CSR	Clinical Study Report
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
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism Pharmacokinetics

[redacted]

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic Acid
DOR	Duration of response
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDTA	ethylenediaminetetraacetic acid
e.g.	For example
EGFR	Epidermal Growth Factor Receptor
EMEA	European Medicines Agency
EQ5D	EuroQoL 5 Dimension Instrument
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation
FFPE	Formalin fixed paraffin-embedded
GARFT	lycinamide ribonucleotide formyltransferase
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma glutamyl transpeptidase
GM-CSF	Granulocyte macrophage-colony stimulating factor
HDPE	High density polyethylene
HR	Hazard ratio
IB	Investigator's Brochure
IC_{50}	Inhibitory drug concentration, which causes a 50% reduction of a particular biological effect
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics 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

[redacted]

Abbreviation or special term	Explanation
ITT	Intention-to-treat
KDR	Kinase insert domain receptor
LBBB	Left bundle branch block
LCSS	Lung Cancer Symptom Scale
LD	Longest diameter
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LIMS	Laboratory Information Management System
LQTS	Long QT (the interval between Q and T on ECG) syndrome
LSDTP	Local Study Delivery Team Physician
Measurement	An observation made on a variable using a measurement device
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimetre of mercury
MRI	Magnetic Resonance Imaging
Msec	Millisecond
MTD	Maximum tolerated dose
NCI	National Cancer Institute
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.
PCRF	paper Case Report Form
PFS	Progression-free survival
PK	Pharmacokinetic

[redacted]

Abbreviation or special term	Explanation
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.
PS	Performance Status
PRO	Patient Reported Outcome
PVC	Premature ventricular contraction
QoL	Quality of Life
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
SAS	Statistical Analysis Software
SD	Stable disease (RECIST criteria)
SDT	Study Delivery Team
SDV	Source Data Verification
SNP	Single nucleotide polymorphism
SPF	Sun protection factor
SVC	Superior vena cava
TdP	Torsade de Pointes
TDPS	Time to deterioration in patient WHO PS
TDS	Time to deterioration of disease-related symptoms
TGA	Therapeutic Goods Association
TKI	Tyrosine kinase inhibitor
TS	Thymidylate synthase
TTD	Time to death
TTP	Time to progression
ULRR	Upper limit of reference range
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Abbreviation or special term	Explanation
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

[redacted]

1. INTRODUCTION

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

1.1 Background

Therapies that inhibit the growth of new blood vessels, so called angiogenesis inhibitors, offer considerable promise as anti-cancer agents. The link between angiogenesis and tumour progression and spread was first established some 35 years ago by Judah Folkman (Folkman 1971). Folkman noted that without new blood vessels, many tumours only grow to a few millimetres 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.

Vascular endothelial growth factor (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 VEGFR-1 (fms-like tyrosine kinase receptor [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 et al 2003), VEGFR-3 (fms-like tyrosine kinase receptor 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 tumour-associated blood

vessels. This resulted in inhibition of tumour growth and in tumour 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 nM, which was higher than that for VEGFR-2 (40nM) (Ciardiello et al 2003; Wedge et al 2002). It has not been elucidated how much anti-tumour activity seen with ZD6474 is 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 et al 2004 and Lynch 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.

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 (Therasse et al 2000).

Subsequently, 2 randomised Phase II studies (6474IL/0003 and 6474IL/0006) were performed in patients with NSCLC after failure of prior chemotherapy. 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 significant advantage in Overall Survival (OS), apart from a small numerical survival advantage observed in study 6474IL/0006 for the 100 mg ZD6474 + docetaxel arm compared to docetaxel alone (HR=0.91; CI=0.55-1.52; P=0.723). 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 D4200C00041, a phase I study with a primary objective to assess the safety and tolerability of once daily oral doses of ZD6474 when administered in combination with standard 21-day treatment cycles of pemetrexed 500 mg/m^2, 21 patients with locally advanced or metastatic NSCLC were entered into the study after failure of prior chemotherapy. An initial cohort of 10 patients received 100 mg ZD6474 in combination with pemetrexed. Once 6 evaluable patients (defined as C3/D2 completed or dose-limiting toxicity (DLT) experienced) were available, a Safety Monitoring Committee reviewed the safety data from all patients in the cohort. One DLT of prolonged QTc > 100 msec from baseline, but less than 500 msec, was identified in a patient with electrolyte instability, pericardial effusion, recurrent atrial fibrillation and other confounding factors. A second cohort of 11 patients received 300 mg ZD6474 in combination with pemetrexed. One DLT of Interstitial Lung Disease was reported in a female patient with a long smoking history. As per protocol, MTD was defined as the occurrence of less than 2 DLTs amongst 6 evaluable patients, therefore both dose levels of ZD6474 in combination with pemetrexed were considered tolerable. In the 100 mg cohort, 80% (n=8) of the patients continued study treatment beyond cycle 3, compared to only 45% (n=5) at 300 mg cohort. The most frequently reported AEs in the pemetrexed combination study were rash (10 [47.6%] patients), anorexia (10 [47.6%] patients), fatigue (10 [47.6%] patients) and diarrhoea (10 [47.6%] patients). The most commonly-experienced CTCAE grade 3 or 4 AEs were: increased GGT (19%), anorexia (14.3%), dyspnoea (14.3%), anaemia (9.5%), hyponatraemia (9.5%), febrile neutropenia (9.5%) and lymphopenia (9.5%). An increase in LFTs (CTCAE grade > 2) was observed in 12 (57.1%) patients, although only 4 patients had clinically-significant increases that were reported as AEs. The AEs consisted of GGT increase (CTCAE grade 3) in all 4 patients, accompanied by only mild transaminases increase (CTCAE grade 1 or 2) in 1 patient. The most frequently reported AEs in this study were consistent with those that have previously been reported for ZD6474 and pemetrexed.

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 one of two 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%).

[redacted]

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%).

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.

Regarding ECG findings, QTc prolongation 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, one 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, six occurred in the first 28 days and two in the following 28 days. The remaining four occurred sporadically, with the longest time to occurrence 323 days. There were three events of CTC grade 1 reversible dizziness in patients with a confirmed QTc prolongation occurring within the first 4 weeks; all three events also occurred within the first four 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 four 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, 127 days, and 61.5 days, respectively. More

[redacted]

patients discontinued therapy as a result of AEs for those who received 300 mg ZD6474 (31.8%) compared to those who received 100 mg (14.3%) or placebo (17.1%).

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 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 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%). Neutropenia were more frequent in ZD6474-containing arms, but this did not result in increased infection. Rash was observed in 15.9%, 16.7% and 9.8% of patients in the three arms, respectively.

1.1.2 Pemetrexed (ALIMTA®, Eli Lilly and Company)

Pemetrexed is a novel antifolate that exerts its antineoplastic activity by inhibiting multiple enzymes in the folate metabolism such as thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT).

Based predominantly on the favourable safety profile, pemetrexed is currently approved by Food & Drug Administration (FDA), European Medicines Agency (EMEA) and Therapeutic Goods Administration (TGA) in Australia as a second-line treatment of advanced NSCLC. The approval was based on the results of a phase III study, conducted by Hanna et al 2004, in which 571 patients with advanced NSCLC previously treated with chemotherapy were randomly assigned to pemetrexed or docetaxel. The median survival time for pemetrexed was 8.3 months versus 7.9 months for docetaxel (HR 0.99; 95% CI 0.82-1.2; noninferiority p=.266) and the median PFS was 2.9 months for each arm. Overall response rates were 9.1% and 8.8% (p= .105) for pemetrexed and docetaxel respectively. Pemetrexed caused less neutropenia, febrile neutropenia, neutropenic infections and need for granulocyte/macrophage colony stimulating factors as well as less severe alopecia. It is observed that severe haematologic toxicity occurs in patients with elevated baseline homocysteine concentration that can be reduced by folic acid and vitamin B12 supplementation.

A drug interaction between ibuprofen and pemetrexed has been observed. Daily ibuprofen doses of 400 mg qid reduce pemetrexed clearance by about 20% (and increase AUC by about 20%) in patients with normal renal function. Patients with mild to moderate renal insufficiency should avoid taking non steroidal anti-inflammatory drugs (NSAIDs) with short elimination half-lives at the time of pemetrexed administration.

1.2 Rationale

Lung cancer is the most common cancer in the world today with an estimated 1.2 million new cases and 1.1 million deaths worldwide in 2000 (Parkin 2001). Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer. The median survival for patients with stage IIIB or IV disease with current first-line chemotherapy regimens is approximately 7-10 months, the one-year survival rate is 35% (Ginsberg et al 1997) and

[redacted]

response rates range between 17-37%. Once patients experience treatment failure with initial therapy, response to further systemic treatment is approximately 10% (Hanna et al 2004). A further progress is anticipated from the novel therapeutic approach of combining existing chemotherapy with drugs that target specific signalling pathways of lung cancer progression.

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. Bevacizumab (Avastin™), an anti-VEGF recombinant humanized monoclonal antibody (rhuMAb), 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., Tarceva™) 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 reported on a Phase I/II study of Avastin and Tarceva in patients with NSCLC having shown an increased response rate and PFS (Herbst et al 2005), 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), the 100 mg ZD6474 + docetaxel treatment group demonstrated a reduction in the risk of disease progression over a given period of time by 36% compared to docetaxel alone (HR= 0.64, 95% CI: 0.39, 1.05, p= 0.074). This was statistically significant at the nominal significance level of 0.2 set for this Phase III study. This translates to an approximate 57% prolongation in PFS for 100 mg ZD6474 + docetaxel compared to docetaxel alone. Furthermore, the 100 mg ZD6474 + docetaxel arm demonstrated a small numerical advantage for time to death (TTD) compared to docetaxel alone but this difference was not statistically significant (HR=0.91; CI=0.55,1.52; p=0.723).

Pemetrexed as a single-agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. This study will determine whether the addition of pemetrexed to ZD6474 provides a significant prolongation of PFS when compared with pemetrexed in combination with placebo in patients who have failed a 1st line anti-cancer therapy.

Exploratory subgroup analyses of progression and survival data from previous Phase II studies in NSCLC have generated a hypothesis that the advantage for ZD6474 in combination with chemotherapy over chemotherapy alone may be most pronounced in female patients. In order to test this hypothesis, this study will incorporate two co-primary analysis populations.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to demonstrate an improvement in PFS as assessed by RECIST criteria, for the combination of ZD6474 plus pemetrexed (Alimta®) compared with pemetrexed plus placebo in patients with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy (not including an adjuvant regimen).

2.2 Secondary objectives

The secondary objectives of the study are:

1. To demonstrate an improvement in overall survival for ZD6474 in combination with pemetrexed compared with pemetrexed plus placebo

2. To demonstrate an improvement in the overall objective response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (DCR) (CR + PR + stable disease [SD] ≥ 6 weeks) and duration of response (DOR) for ZD6474 in combination with pemetrexed compared with pemetrexed plus placebo as assessed by RECIST criteria

3. To demonstrate a beneficial effect on disease-related symptoms, in patients treated with ZD6474 in combination with pemetrexed, that is at least as good as that in patients treated with pemetrexed plus placebo based on the Lung Cancer Symptom Scale (LCSS)

4. To demonstrate an improvement in time to deterioration of disease-related symptoms (TDS) in patients treated with ZD6474 in combination with pemetrexed compared with patients treated with pemetrexed plus placebo based on the LCSS

5. To study the tolerability and safety of ZD6474 in combination with pemetrexed in patients with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy by assessment of AEs, clinically significant laboratory or vital signs abnormalities and ECG changes

6. To investigate the population pharmacokinetics (PK) of ZD6474 in this patient population and assess the PK-QTc relationship, PK-safety relationship, PK-efficacy relationship and PK-PD relationship by evaluation of appropriate PK parameters

2.3 Exploratory objectives

The exploratory objectives of the study are:

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

2. To evaluate by single nucleotide polymorphism (SNP) genotyping using DNA extracted from a blood sample, the effects of genes involved in response to ZD6474 and drugs taken in combination with ZD6474 (i.e., pemetrexed)

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

4. To investigate patient health status index during the period of treatment with investigational therapy by assessment of the EQ5D

5. To investigate the TDPS during the period of treatment with investigational therapy

6. To demonstrate a quality of life QoL for ZD6474 in combination with pemetrexed that is at least as good as that for patients treated with pemetrexed plus placebo based on the quality of life summation item of the LCSS.

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, placebo controlled, multi centre study designed to assess whether the addition of ZD6474 (100 mg daily) to pemetrexed (500mg/m^2 given on day 1 of each 21 day cycle) in patients with locally advanced or metastatic NSCLC who have received prior 1st line anti-cancer treatment confers a statistically significant advantage in terms of PFS.

It is planned that approximately 100 centres in 20 countries will participate in the study and that each site will recruit about 5 patients per centre. In Europe it is estimated that 178 patients will be recruited, 30 in Germany, 25 in Spain, 25 in France, 10 in United Kingdom, 18 in Greece, 10 in Portugal, 25 in Italy, 15 in Belgium and 20 in Sweden.

Patients will be randomised in a 1:1 ratio to receive either ZD6474 100 mg plus pemetrexed or pemetrexed plus placebo. Patients will receive pemetrexed for up to 6 cycles. When pemetrexed treatment is discontinued, before or at the 6th cycle, patients should continue to

[redacted]

receive daily oral dosing of blinded ZD6474/placebo as a monotherapy until progression, as long as no other discontinuation criteria is met. If another systemic anti-cancer treatment is started then study treatment should be stopped. Following discontinuation of study treatment (ZD6474/placebo and pemetrexed), patients will be followed up for survival, unless they withdraw consent. Investigators remain at liberty to determine the most appropriate therapy for their patients after study treatment is discontinued, both pemetrexed and ZD6474/placebo must be discontinued before another therapy is added.

Patients will be evaluated until objective progression is documented, and will then be followed up for survival, unless they withdraw consent. Study assessments for patients who are on ZD6474/placebo and pemetrexed or pemetrexed alone see Table 1. For patients on ZD6474/placebo alone, see Table 2. For patients who have discontinued from ZD6474/placebo and pemetrexed, see Table 3. Disease progression is determined according to RECIST criteria.

Radiological evaluation using RECIST will be performed at baseline and every 6 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 treatment prior to objective disease progression they should continue to be assessed every 6 weeks, 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 3.2.3) that is considered related to ZD6474/placebo will have their ZD6474/placebo treatment stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the patient may restart treatment with a reduced dose of ZD6474 in a blinded manner, the dose may be reduced from 1 tablet per day to 1 tablet every other day. The study assessments should be continued as outlined in the study plan. If the patient has been off treatment for greater than 3 weeks due to toxicity, the patient must be withdrawn from ZD6474/placebo. In the case of patients who discontinue ZD6474/placebo therapy because of toxicity attributed to ZD6474/placebo, these patients will continue to receive the scheduled treatment with pemetrexed (up to a maximum of 6 cycles) and will be followed for progression and survival unless they withdraw consent.

Patients who experience CTCAE grade 3 or 4 toxicity that is considered related to pemetrexed will have pemetrexed stopped until resolution of the toxicity. When the toxicity has recovered to CTCAE grade 1 (or baseline), the patient may restart treatment with a reduced dose of pemetrexed, according to the dose reduction plan outlined in Section 3.2.3. If pemetrexed must be withheld for more than 3 weeks for resolution of toxicity, the patient will not restart pemetrexed treatment. In the case of patients who discontinue combination therapy because of toxicity attributable to pemetrexed, patients may continue on ZD6474/placebo and will be followed for progression and survival.

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

[redacted]

Figure 1 Study flow chart

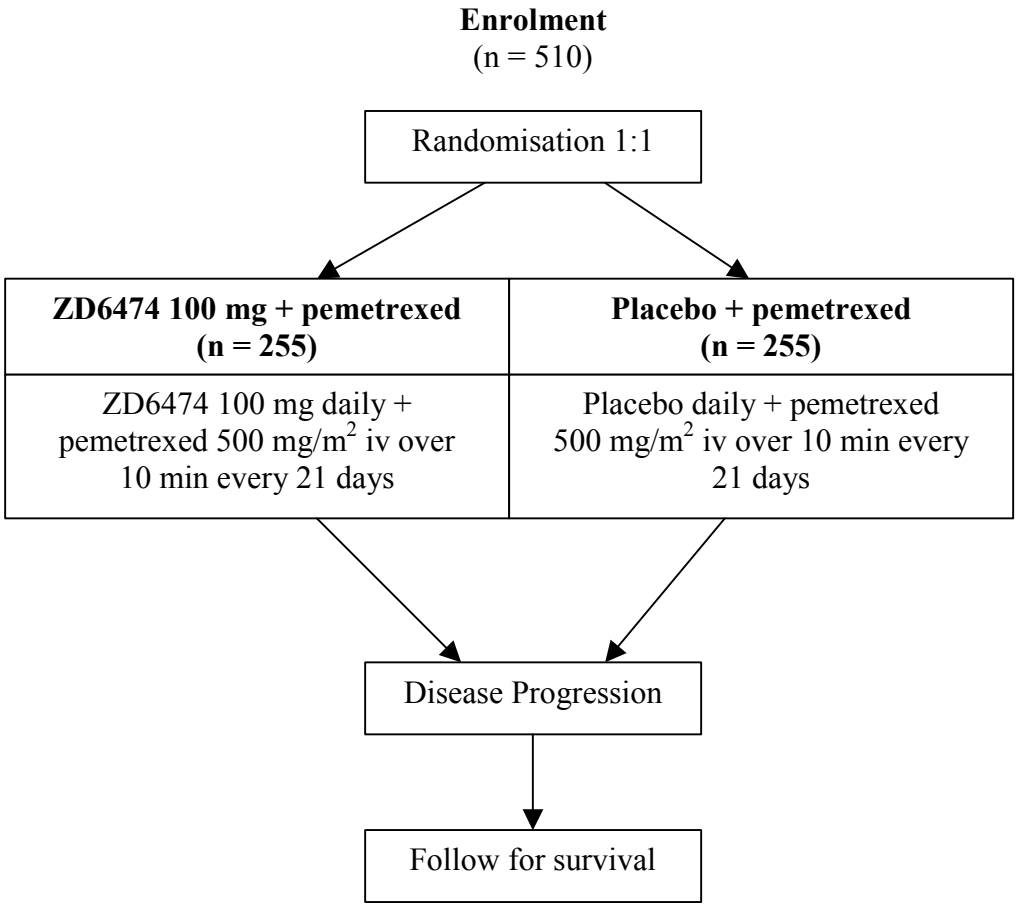


Table 1 Study plan: Screening to discontinuation of pemetrexed

Cycle	**Screen**		**1**			**2**			**3**	**4**	**5**	**6**
Day (+/- 3 days)	**-21 to 0**	**-7 to 0**	**1**	**8**	**15**	**22/1**	**8**	**15**	**22/1**	**22/1**	**22/1**	**22/1**
Visit	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**
Informed consent	X											
Medical history	X											
Inclusion/exclusion criteria	X											
Physical examination[a]		X				X			X	X	X	X
Vital signs[b]		X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram		X[c]	X[d]	X[d]		X[d]			X[d]		X[d]	
PK assessments[e]				X		X			X		X	
Haematology/ clinical chemistry[f]		X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X			X			X	X	X	X
Pregnancy test		X[g]										
WHO Performance Status		X				X			X	X	X	X
LCSS questionnaire[h]		X				X			X	X	X	X
EQ5D[h]		X				X			X	X	X	X
RECIST	X[i]								X[i]		X[i]	
Randomisation			X									
Pemetrexed administration[j]			X			X			X	X	X	X
ZD6474/placebo daily dosing[j]			◄	―	―	―	―	―	―	―	―	►
Study treatment dispensing			X[i]			X			X	X	X	X
Tolerability/AE reporting	X		X	X	X	X	X	X	X	X	X	X
Concurrent medication		X	X	X	X	X	X	X	X	X	X	X
Plasma biomarker blood sample[k]			X			X			X	X	X	X
Serum biomarker blood sample[l] (optional)			X									
Genetic blood sample (optional)			X[m]									
Archival samples (optional)			X[m]									

All assessments are to be performed before administration of ZD6474/placebo and pemetrexed, unless otherwise indicated. Assessments and treatment should be carried out as specified in the study plan. If the scheduled study day falls on a weekend or holiday, the visit/assessments may be delayed or advanced by ±3 days.

(a) Physical exam: Post screening, any clinically significant new findings or aggravated pre-existing conditions should be recorded as AEs.

(b) Vital signs including blood pressure, pulse, temperature and weight (and height at screening) will be performed weekly for the first 2 cycles of pemetrexed and then at the start of each subsequent cycle. For

[redacted]

patients who complete/discontinue pemetrexed and continue on ZD6474/placebo alone, weight will be measured every 3 weeks until discontinuation of study treatment and at the 30-day follow-up visit.

(c) 12-lead ECG must be performed at screening (within 7 days before the first dose). 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. If the patient is on one of the drugs listed in Appendix D, Table 2, that in the Investigator's opinion cannot be discontinued, the screening QTc must be < 460 msec for the patient to be eligible, and the patient will require additional ECG monitoring, refer to Section 3.7.2 for further guidance.

(d) On day 1, cycle 1, 12-lead ECGs are to be performed pre-infusion. Baseline QTc will be determined by the average of no less than 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 (performed 4-8 hours after the patient takes their oral medication) at Visits 3, 5, 8, 10 (weeks 2, 4, 7, 13) and then every 3 months to and including discontinuation of ZD6474/placebo. From visit 3 (week 2) onwards, one ECG is sufficient, however if QTc ≥ 500 msec but < 550 msec or there is an increase ≥ 60 msec but < 100 msec from baseline, then the QTc must be re-evaluated within 48 hours with 3 consecutive ECGs. If QTc prolongation occurs at one of the usual assessment times, or at any other time, please refer to Section 3.2.3.2 for further details.

(e) Blood samples for PK will be collected at Visits 3, 5, 8, 10 (weeks 2, 4, 7, 13).), 4-8 hours after oral intake of ZD6474/placebo which is also the time when ECGs will be performed. PK samples will be obtained from all patients. Plasma concentration of ZD6474 will be determined in all samples.

(f) Haematology and clinical chemistry will be performed once a week up to and including cycle 3, day 1 (week 7). After week 7, weekly haematology and clinical chemistry samples are optional, however these assessments must, at minimum, be performed every 3 weeks (i.e. weeks 10, 13, 16) until the end of pemetrexed treatment. Haematology, clinical chemistry and urinalysis need only be assessed at Day 1 if the screening assessments were taken more than 7 days before. At screening, patients with creatinine clearance < 55ml/min calculated by Cockroft-Gault are eligible for the study if creatinine clearance measurement by an alternative method (24h urine collection, EDTA scan or other validated method) meets the entry criterion. For patients who complete/discontinue pemetrexed and continue on ZD6474/placebo, haematology and clinical chemistry will be performed every 3 weeks.

(g) Premenopausal women of child bearing potential must have a negative pregnancy test within 7 days before first dose of study treatment.

(h) LCSS & EQ5D questionnaires are to be administered at screening (within 7 days before the 1st dose) and every 3 weeks thereafter. The LCSS & EQ5D questionnaires will be completed where the translation for the appropriate language is available. The LCSS & EQ5D questionnaires should be completed before the patient receives pemetrexed (even when delayed) and before given results of their tumour assessments.

(i) RECIST is carried out at screening (within 3 weeks before the 1st dose) and every 6 weeks (+/- 3 days) thereafter, until progression. If pemetrexed is delayed, RECIST should be assessed preceding the next administration of pemetrexed. Scans performed for RECIST will be expected to cover chest and abdomen, including liver and adrenals (pelvic imaging is only required if clinically indicated). For patients with bone disease regular bone scans are not required, unless the patient becomes symptomatic. Bone scans will be used in the assessment of disease progression only if worsening of existing lesions or appearance of new lesions is confirmed by CT/MRI or X-ray as per RECIST guidelines for non-measurable lesions. For patients with cerebral metastases, regular cranial CT/MRI scans are not required, unless new/worsening symptoms occur. For ad hoc additional scans performed for new/worsening symptoms (e.g., brain MRI) please refer to Section 4.6.3.1

(j) Pemetrexed and ZD6474 are both started on Day 1. Blood samples should be taken prior to pemetrexed infusion, (although this may not include the PK sample required at visits 3, 5, 8 and 10 which should be drawn 4-8 hours post ZD6474/placebo dosing.)

(k) Plasma biomarker blood samples should be taken prior to administration of pemetrexed (sample will be used to assess circulating protein biomarkers).

(l) Serum biomarker sample is optional, if consent is provided then sample should be taken prior to administration of pemetrexed (sample will be used to assess circulating protein biomarkers and also used to access the EGFR mutational status and mutational status of other candidate genes in circulating tumour DNA found in serum).

(m) Archival paraffin-embedded tumour sections and blood samples for genetic analysis should be collected from all consenting patients if available. If for any reason samples are not taken at visit 2, they may be taken at any visit until the last study visit.

[redacted]

Table 2 Study plan: After Discontinuation of pemetrexed and ongoing ZD6474/placebo

Treatment Period	Every 3 Weeks	Every 6 Weeks	Every 3 Months
Physical examination[a]	X		
Vital signs[b]	X		
Electrocardiogram[c]			X
Haematology/clinical chemistry	X		
Urinalysis	X		
WHO Performance Status	X		
LCSS questionnaire[d]	X		
EQ5D[d]	X		
RECIST[e]		X	
Study treatment dispensing	X		
Tolerability/AE reporting	X		
Concurrent medication	X		
Plasma biomarker blood sample	X		

All assessments are to be performed before administration of ZD6474/placebo and pemetrexed, unless otherwise indicated. Assessments and treatment should be carried out as specified in the study plan. If the scheduled study day falls on a weekend or holiday, the visit/assessments may be delayed or advanced by ±3 days.

(a) Physical exam: Post screening, any clinically significant new findings or aggravated pre-existing conditions should be recorded as AEs.
(b) Vital signs include blood pressure, pulse, temperature and weight. Weight must be obtained at discontinuation of study treatment and at the 30-day follow-up visit.
(c) When possible, ECGs should be performed at the same time throughout the study (performed after the patient takes their oral medication). If pemetrexed is discontinued within the first 12 weeks of treatment, ECGs must be performed at weeks 1, 2, 4, 7, 13 and then, every 3 months up to and including discontinuation.
(d) The LCSS & EQ5D questionnaires should be completed before the patient is given results of their tumour assessments.
(e) RECIST is carried out every 6 weeks (+/- 3 days), until progression. For patients with bone disease regular bone scans are not required, unless the patient becomes symptomatic. Bone scans will be used in the assessment of disease progression only if worsening of existing lesions or appearance of new lesions is confirmed by CT/MRI or X-ray as per RECIST guidelines for non-measurable lesions. For patients with cerebral metastases, regular cranial CT/MRI scans are not required, unless new/worsening symptoms occur. Scans performed for RECIST will be expected to cover chest and abdomen, including liver and adrenals (pelvic imaging is only required if clinically indicated).

[redacted]

Table 3 Study plan: Discontinuation of both ZD6474 and pemetrexed

Cycle	Discontinuation	30-day f/u	60-day f/ua	Survival
Electrocardiogram	X			
Haematology/clinical chemistry	X			
Urinalysis	X			
Physical examination[b]	X	X		
Vital Signs[c]	X	X		
LCSS questionnaire[d]	X	X		
EQ5D[d]	X	X		
WHO Performance Status[e]	X	X		
RECIST[f]	X			
Survival[g]				X
Plasma biomarker blood sample	X			
Subsequent anti-cancer therapy[h]	X	X	X	X
Adverse event review	X	X	X	
Concomitant medication	X	X	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, the visit/assessments may be delayed or advanced by ±3 days.

(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, pulse, temperature and weight. Weight must be obtained at discontinuation of study treatment and at the 30-day follow-up visit.
(d) The LCSS & EQ5D questionnaires should be completed before the patient is given results of their tumour assessments.
(e) WHO PS must be collected at discontinuation of study treatment, at the 30-day follow-up visit and until progression, unless the patient has withdrawn consent
(f) RECIST should be performed at the discontinuation visit, however a scan doesn't need to be carried out if one has already been done within the past 3 weeks and there is no sign of progression at the point of discontinuation. For patients who have not progressed at discontinuation, RECIST should still be assessed every 6 weeks.
(g) Assessments for survival should be made every 6 weeks. Survival information may be obtained via telephone contact.
(h) Details of the subsequent anti-cancer therapy after discontinuation of study treatment will be collected, unless the patient withdraws consent.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

A randomized, double blind, placebo controlled Phase III study will be appropriate to assess whether ZD6474 plus pemetrexed confers a longer PFS benefit when compared with placebo plus pemetrexed in patients with advanced NSCLC. The population for this study will consist

[redacted]

of patients who failed or cannot tolerate 1st-line anti-cancer therapy and for whom pemetrexed is therefore an appropriate therapeutic option.

The dose level of ZD6474 100 mg has been chosen, as previous Phase I studies have demonstrated that chronic daily administration at this level is well tolerated. Study D4200C00041 was a phase I study with a primary objective of safety and tolerability of once daily oral dosing of ZD6474 when administered in combination with standard 21-day treatment cycles of pemetrexed 500 mg/m2 in patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy. In this study, one DLT of prolonged QTc >100 msec from baseline, was identified in the first cohort of 10 patients receiving 100 mg ZD6474 in combination with pemetrexed. In the second cohort of 11 patients receiving 300 mg ZD6474 in combination with pemetrexed, again only one DLT of Interstitial Lung Disease was reported in a female patient with a long smoking history. As per protocol definition both dose levels of ZD6474 in combination with pemetrexed were considered tolerable. However, in the 100 mg cohort, 80% (n=8) of the patients continued study treatment beyond cycle 3, compared to only 45% (n=5) in the 300 mg cohort. The early withdrawals due to AEs or disease progression at 300 mg, the lack of confidence for better efficacy from other studies exploring ZD6474 300 mg in combination with chemotherapy and the current understanding that chemotherapy and EGFR TKIs given concurrently may have a negative interaction at least in a nonselected population, led to the decision to further explore ZD6474 100 mg dose level in combination with pemetrexed versus pemetrexed alone.

The primary endpoint of PFS in this study, rather than overall survival, is justified by the increasing prevalence of 3rd-line therapies that are available for patients who have disease progression after 2nd-line treatment. These subsequent therapies are likely to have regional variations in the standard of care and may result in imbalances in the subsequent therapy received by patients in the two treatment arms of the study. The survival outcomes for patients in the Phase II study 6474IL/0006 demonstrate the potential confounding nature of these subsequent therapies. This study will include overall survival as a secondary endpoint and all patients will be followed for survival. In addition, the study will include other measures of clinical benefit, including response rate, DCR, and measures of quality of life, to provide supportive data of the benefit of ZD6474.

The use of placebo control in this study will provide for a robust assessment of the benefit of ZD6474 in combination with pemetrexed and is considered appropriate in this patient population because pemetrexed is approved for use as a single-agent in the 2nd-line treatment of patients with NSCLC. By blinding patients and investigators, using a placebo control, 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

Potential benefits for locally advanced or metastatic NSCLC patients in terms of objective response and time to progression following ZD6474 treatment have already been discussed in Section 1.2. Patients in the active and placebo arms of the study will receive ZD6474/placebo in combination with pemetrexed and will be closely followed for disease progression. At this

[redacted]

point an alternative therapy may be considered. Potential risks in terms of safety have been reviewed in Section 1.1.1.2 of the study protocol. According to the emerging safety profile, ZD6474 produces repolarisation abnormalities in human myocardium consistent with change in T-wave morphology plus prolongation of the QT interval. To date, no patients treated with ZD6474 have experienced symptomatic arrhythmias or other events definitely related to QT prolongation. ZD6474 can also cause dose-related rash, diarrhoea and hypertension, all of which appear to be consistent with the pharmacologic activity of the drug and for which specific measures have been taken to ensure patient's safety.

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 4.

3.2.3 Toxicity management

3.2.3.1 Pemetrexed toxicity

In the event of the following toxicities, pemetrexed should be withheld and when the toxicity has resolved (to CTCAE grade 1 or baseline) pemetrexed may be administered at **75% of the previous dose**, unless the patient withdraws consent.

- CTCAE grade 4 neutropenia (nadir neutrophil count <0.5 x 109/L
- Any CTCAE grade 3 (except grade 3 transaminase elevation) or grade 4 non-hematologic toxicities except mucositis

In the event of the following toxicities, pemetrexed should be withheld and when the toxicity has resolved (to CTCAE grade 1 or baseline) pemetrexed may be administered at **50% of the previous dose**, unless the patient withdraws consent:

- CTCAE grade 4 thrombocytopenia (nadir platelet count <50 x 109/L regardless of nadir ANC).
- CTCAE grade 3 or 4 mucositis

All patients treated with pemetrexed must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment related hematologic and GI toxicities (Section 3.4.2.2).

Pemetrexed should be stopped for a grade 3 or 4 allergic reaction/hypersensitivity that is clearly related to pemetrexed. A re-challenge is permitted at the Investigator's discretion.

If toxicity recurs after the 1st dose reduction, a further dose reduction may be undertaken at the discretion of the investigator. Pemetrexed may be administered at **50% of the previous dose.**

[redacted]

For other toxicity, if pemetrexed must be withheld for more than 3 weeks for resolution of toxicity, or if CTCAE grade 3 or 4 toxicity listed above (except grade 3 transaminase elevations) recurs following the second dose reduction, the patient will not restart pemetrexed treatment.

For ZD6474/placebo dose changes in case of pemetrexed related cutaneous or GI toxicity, please refer to Table 4.

For hematological toxicity related to pemetrexed, there will be no ZD6474/placebo dose change, please refer to Table 4.

Patients should not be treated with subsequent cycles of chemotherapy until all of the following criteria are met:

- ANC $\geq 1.5 \times 10^9$/L
- Platelets $\geq 100 \times 10^9$/L
- Creatinine clearance ≥45 mL/min

3.2.3.2 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 a risk of QTc prolongation (see Appendix D, Table 2) will be excluded if QTc is ≥460 msec at screening. Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1.

The baseline QTc will be used in the determination of QTc prolongation. 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 being the mean of 3 consecutive ECGs):

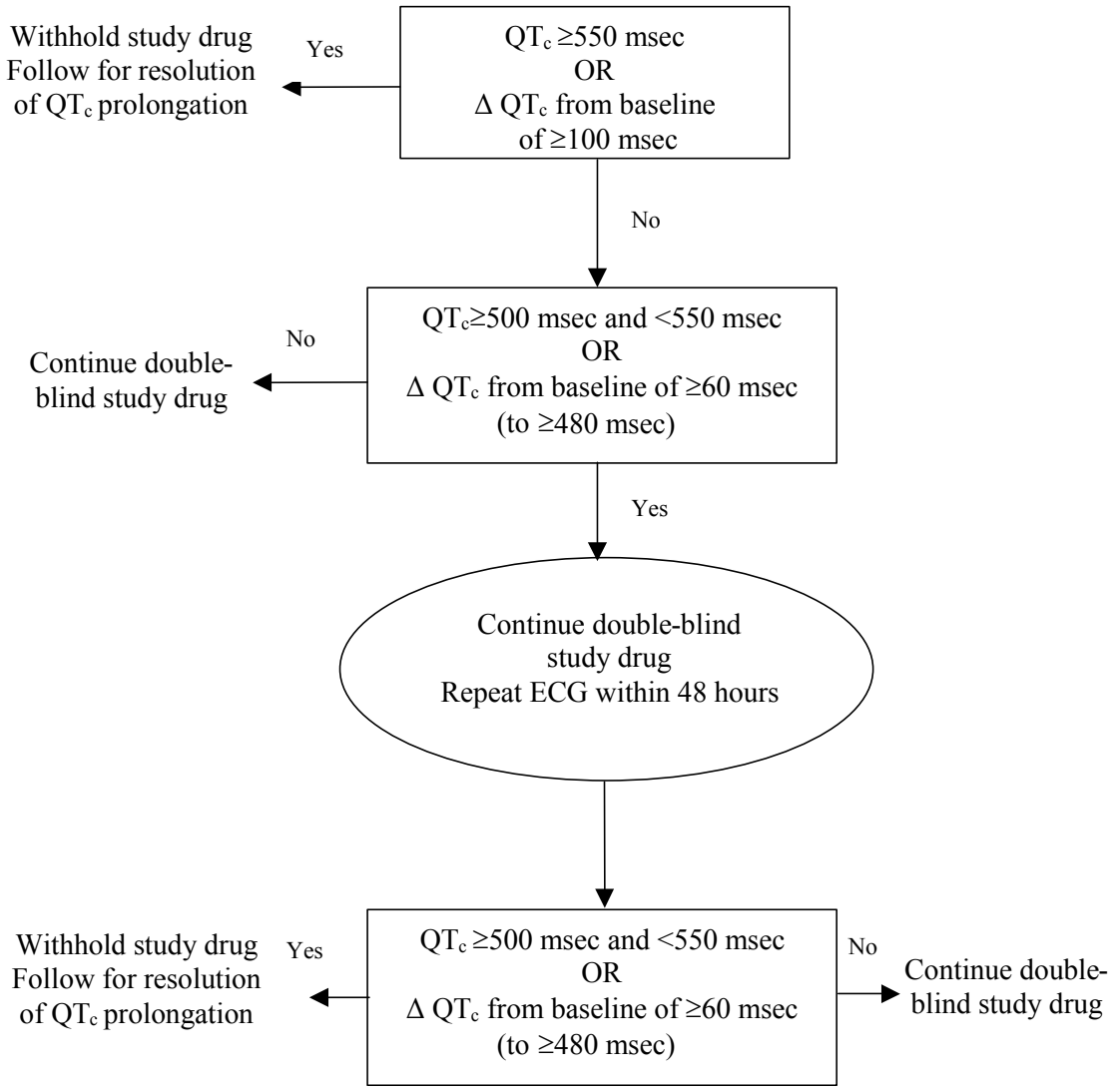
  - A QTc interval ≥500 msec, but <550 msec;

    OR

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

[redacted]

Figure 2 Management of patients with QTc prolongation



For a single QTc value of ≥550 msec or an increase of ≥100 msec from baseline, ZD6474/placebo 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/placebo treatment may be resumed at a lower dose after the QTc recovers to <480 msec or baseline.

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, blinded ZD6474/placebo may be continued but the QTc must be re-evaluated within 48 hours with 3 consecutive ECGs. If QTc prolongation is confirmed, ZD6474/placebo should be withheld. ECGs and electrolytes should be checked 3 times a week until QTc falls below 480 msec or baseline, whichever is higher. ZD6474/placebo treatment may be resumed at a lower dose after the QTc recovers to <480 msec 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 treatment and resume the ECG schedule as outlined in the Study Plan.

If ZD6474/placebo is restarted after the QTc prolongation has resolved, it should be given at a reduced dose of ZD6474/placebo100 mg every other day and ECGs should be performed 1, 2, 4, 7, 13 weeks and then every 3 months after treatment is restarted. If ZD6474/placebo must be withheld for >3 weeks to allow for QTc prolongation to recover <480 msec or baseline, the patient will not be restarted on study treatment. If QTc prolongation recurs after the dose reduction as detailed, the patient must permanently discontinue treatment with study treatment.

3.2.3.3 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 hypokalemia and severe hypomagnesemia as risk factors for QTc prolongation. No dose modifications will be made because of grade 1 or 2 diarrhoea. If grade 3 diarrhoea develops, ZD6474/placebo and pemetrexed should be withheld until diarrhoea resolves to grade 1 or below. Patients who are clinically unstable because of diarrhoea or other intercurrent medical illness must be admitted and evaluated using telemetry, until clinically stable. Upon recovery, treatment may resume at a permanently reduced dose of ZD6474, 100 mg given every other day. Pemetrexed will be reduced to 75% of the original dose [i.e., 375 mg/m^2]). If grade 3 or 4 diarrhoea recurs after dose reduction, a further pemetrexed dose reduction may be undertaken at the discretion of the investigator, or the patient will permanently discontinue both ZD6474/placebo and pemetrexed.

If CTCAE grade 3 or 4 mucositis develops, all treatment must be withheld. ZD6474/placebo should be restarted as soon as the patient is able to swallow the tablets. Pemetrexed should be restarted upon resolution to CTCAE grade 1 and subsequently reduced by 50% to 250 mg/m^2. If CTCAE grade 3 toxicity recurs after dose reduction, a further pemetrexed dose reduction may be undertaken at the discretion of the investigator, or the patient will permanently discontinue treatment. No attempt to make up missed doses will be undertaken.

3.2.3.4 Cutaneous toxicity

It is strongly recommended that all patients follow a program of sun protective measures while receiving study therapy and for 3-4 weeks after discontinuing study therapy. 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 (NCI CTCAE, Version 3).
- 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/placebo and pemetrexed should be withheld until recovery to grade 1 or baseline. The following actions should be instituted:
  - Pemetrexed should be reduced to 375 mg/m^2
  - ZD6474/placebo should be dose reduced from 100 mg daily to 100 mg every other day

If grade 3 or 4 cutaneous toxicity recurs after dose reduction, a further pemetrexed dose reduction at the discretion of the investigator, or the patient will permanently discontinue both ZD6474/placebo and pemetrexed.

If ZD6474/placebo or pemetrexed must be withheld for >3 weeks due to cutaneous toxicity, the patient will be discontinued.

3.2.3.5 Other toxicity

If any other grade 3 or 4 toxicity that is not outlined in Sections 3.2.3.1 to 3.2.3.4 develops and is attributable to either ZD6474/placebo or pemetrexed, ZD6474/placebo and pemetrexed should be withheld until the toxicity resolves to grade 1 or baseline. Upon recovery, patients may resume treatment at a permanently reduced dose; ZD6474 100 mg every other day and pemetrexed reduced to 375 mg/m^2. If ZD6474/placebo or pemetrexed must be withheld for more than 3 weeks for resolution of toxicity, the patient will not restart treatment. If grade 3 or 4 toxicity recurs after dose reduction, a further pemetrexed dose reduction may be undertaken at the discretion of the investigator, or the patient will permanently discontinue both ZD6474/placebo and pemetrexed.

Patients who develop CTCAE grade 3 hypertension may continue on therapy if blood pressure is controlled on antihypertensive medication. If blood pressure cannot be stabilized with increased antihypertensive medication, ZD6474/placebo must be discontinued and cannot be resumed until blood pressure is controlled to baseline level. Patients with CTCAE grade 4 hypertension should discontinue ZD6474/placebo and cannot resume therapy until blood pressure is controlled to baseline level. If study treatment must be interrupted for more than 3 weeks to allow for toxicity to resolve, the patient's participation in the study will be discontinued.

Table 4 Summary of guidance on the management of toxicity for ZD6474/placebo and pemetrexed

Toxicity	Pemetrexed	ZD6474 (100 mg/placebo)
QTc value ≥550 msec or prolonged ≥100 msec from baseline	No change	Withhold dose; if QTc recovers to <480 msec or baseline then permanently reduce dose to 100mg every other day. If QTc does not recover to <480 msec or baseline within 3 weeks, patient will permanently discontinue ZD6474.
QTc value ≥500 msec or prolonged ≥60 msec from baseline	No change	Continue dosing; repeat ECG (in triplicate) within 48 hours. If repeat ECG meets criteria, withhold dose; then if QTc recovers to <480 msec or baseline, reduce dose to 100 mg every other day. If QTc does not recover to <480 msec or baseline within 3 weeks, patient must permanently discontinue study treatment. Or, if the repeat ECG does not meet criteria, patient should continue study treatment.
Grade 4 neutropenia (platelets ≥ 50 x 10^9/L)	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 75% of previous dose	No change
Platelets <50 x 10^9/L	Withhold dose until platelets recover to >100 x 109/L, then permanently reduce dose to 50% of previous dose	No change
Grade 3 or 4 cutaneous attributable to either pemetrexed or ZD6474/placebo	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 75% of previous dose, a second dose reduction may be allowed. If dosing is interrupted for more than 3 weeks, patient will be discontinued.	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 100 mg every other day. If dosing is interrupted for more than 3 weeks, patient will be discontinued.

Table 4 Summary of guidance on the management of toxicity for ZD6474/placebo and pemetrexed

Toxicity	Pemetrexed	ZD6474 (100 mg/placebo)
Grade 3 or 4 allergic reaction/hyper sensitivity that is clearly attributable to pemetrexed	Stop pemetrexed. Pemetrexed can be re-challenged at the discretion of the Investigator.	No change
Grade 3 Hypertension	No change	Continue dosing if blood pressure is controlled with antihypertensive medication. If blood pressure cannot be controlled, withhold dose until blood pressure is controlled to baseline level. If dosing is interrupted for more than 3 weeks, patient will permanently discontinue ZD6474
Grade 4 Hypertension	No change	Withhold dose until blood pressure is controlled to baseline level. If dosing is interrupted for more than 3 weeks, patient will permanently discontinue ZD6474
All other grade 3 or 4 toxicity related to pemetrexed and/or ZD6474/placebo	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 75% of previous dose, a second dose reduction may be allowed. If dosing is interrupted for more than 3 weeks, patient will be discontinued.	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then permanently reduce dose to 100 mg every other day. If dosing is interrupted for more than 3 weeks, patient will be discontinued.

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 e.g., 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

[redacted]

2. Female or male aged 18 years or above

3. Histologic or cytologic confirmation of locally advanced or metastatic NSCLC (stage IIIB or IV) on entry into study

4. Failure of 1st line anti-cancer therapy (either radiological documentation of disease progression or due to toxicity) or subsequent relapse of disease following 1st line therapy

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. Previously irradiated lesions will not be considered measurable.

7. Life expectancy of 12 weeks or longer

8. Negative pregnancy test for women of childbearing potential only

For inclusion in this genetic research, patients must fulfil the following criterion:

1. Provision of informed consent for the genetic research

2. Provision of informed consent for tissue research

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. Patients have received 2nd-line or subsequent anti-cancer therapy

3. Prior treatment with pemetrexed

4. Prior treatment with VEGFR TKIs (previous treatment with bevacizumab [Avastin] is permitted)

5. Known or suspected brain metastases or spinal cord compression, unless treated at least 4 weeks before entry, and stable without steroid treatment for 10 days

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

[redacted]

7. The last dose of prior chemotherapy or other anti-cancer therapy is discontinued less than 3 weeks before the start of study therapy (6 weeks for nitrosoureas, mitomycin, and suramin)

8. Major surgery within 4 weeks before entry, or incompletely healed surgical incision

9. Neutrophils $<1.5 \times 10^9$/L or platelets $<100 \times 10^9$/L

10. Serum bilirubin >1.5 x the upper limit of reference range (ULRR)

11. Creatinine clearance <50 ml/min calculated by either Cockcroft –Gault, 24 hours urine collection, EDTA scan or other validated methods

12. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x ULRR in the absence of liver metastases, or > 5 x ULRR in the presence of liver metastases

13. Alkaline phosphatase (ALP) >2.5 x ULRR in the absence of liver metastases, or >5 x ULRR in the presence of liver metastases

14. Current active gastrointestinal disease that may affect the ability of the patient to absorb ZD6474 or tolerate diarrhoea

15. 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

16. Any unresolved toxicity greater than CTCAE Grade 2 from previous anti-cancer therapy

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

18. 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 asymptomatic sustained ventricular tachycardia. Atrial fibrillation, controlled on medication is not excluded

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

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

[redacted]

21. Presence of left bundle branch block (LBBB)

22. QTc with Bazett's correction unmeasurable or ≥ 480 msec on screening ECG (Note: If a patient has QTc interval ≥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 eligible if QTc is <460 msec.

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

24. Women who are pregnant or breast-feeding

25. Any concomitant medications that may cause QTc prolongation or induce Torsades de Pointes (see Appendix D for the lists of medications in Table 1 and Table 2) or induce CYP3A4 function (see Section 3.7.2). Drugs listed in Appendix D, Table 2, that in the investigator's opinion cannot be discontinued, are allowed, but only of the QTc is <460 msec

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

27. 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

28. Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment

29. Concomitant use of yellow fever vaccine or any live attenuated vaccines

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

3.3.4 Restrictions

1. Due to the experimental nature of ZD6474, female patients must be one year post-menopausal, surgically sterile, sexually abstinent or using an acceptable method of contraception defined as barrier methods in conjunction with spermicide, approved contraceptive implants, long-term injectable contraception or intrauterine hormonal devices for the duration of the study and for 2 months after the last dose of ZD6474/placebo to prevent pregnancy. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used. Male patients must be surgically sterile or using an acceptable method of contraception (defined as barrier methods of contraception in conjunction with spermicides)

during their participation in this study and for 2 month after last dose of ZD6474/Placebo.

2. The concomitant use of known CYP3A4 inducers (e.g., barbiturates, rifampicin, phenytoin, carbamazepine, troglitazone, St. John's Wort) must be avoided for the duration of the study (dexamethasone (or equivalent) may be given as a pre-medication for chemotherapy)

3. Concomitant use of drugs with a recognised risk of Torsades de Pointes (see Appendix D) should be avoided for the duration of the study and for 4 weeks after the last dose of ZD6474. Any drugs listed in Appendix D, Table 2, that in the Investigator's opinion cannot be discontinued, are allowed at entry provided the screening QTc <460 msec

4. Patients should follow a program of sun protective measures while receiving study treatment. Such measures should include application of sunblock, with a minimum sun protection factor (SPF) of 45, and adoption of clothing protection in full sun for the duration of the study and for 2 months after the last dose of ZD6474

5. Patients should not take any additional medication without the prior consent of the investigator

6. Concomitant use of any medication that may markedly affect renal function (e.g., vancomycin, amphotericin, pentamidine) should be avoided whilst patient is receiving pemetrexed, unless absolutely necessary

7. Patients should not take NSAIDS with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed

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

3.3.5 Discontinuation of patients from treatment or assessment

3.3.5.1 Withdrawal from study

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 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.

[redacted]

3.3.5.3 Criteria for discontinuation

Patients may be discontinued from study treatment (ZD6474/placebo and pemetrexed) and assessments at any time. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, 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
- Patient lost to follow-up
- Dose delay or interruption of more than 3 weeks due to toxicity
- Disease progression
- Any other anti-cancer treatment commenced

3.3.5.4 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up; diary cards, 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 /placebo or chemotherapy, whichever comes last.

If a patient discontinues study treatment prior to objective disease progression, then they should continue to be followed for objective disease progression as per the protocol schedule and then followed for survival.

Following objective disease progression, the patient should be followed up for survival (see Table 3) unless they withdraw consent. Survival status should be collected every 6 weeks by telephone contact with the patient, patient's family, or by contact with the patient's current physician. Investigators remain at liberty to determine the most appropriate therapy for their patients after study treatment is discontinued. The date and details of the first and subsequent therapies for cancer after discontinuation of study 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 /placebo or chemotherapy must be reported to AstraZeneca and must be followed until resolution where possible.

[redacted]

All patients who have any CTCAE grade 3 or 4 laboratory values at the time of discontinuation of study treatment 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.

3.3.5.5 Procedures for handling incorrectly 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.

3.3.5.6 Procedures for discontinuation from biomarker and genetic aspects of the study

Patients may withdraw consent from the biomarker research and/or the 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.

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for;

- The genetic research

and/or

- The biomarker research

It must be established whether the subject:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future or withdraws consent for the sample to be kept for genetic research in the future and wishes the blood sample to be destroyed

- Agrees to the serum and tumour samples (and any non-host DNA extracted from these samples) being kept for biomarker research or withdraws consent for the samples to be kept for biomarker research and wishes the paraffin-embedded tumor block to be returned to the hospital and the serum sample to be destroyed.

Destruction of the samples (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 or biomarker 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 tissue and serum samples taken for biomarker research, and/or the use of the blood sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample(s), which must be filed in the investigator study file.

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 pemetrexed

Descriptive information for pemetrexed can be found in Appendix K.

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

Table 5 Formulation numbers of ZD6474

Tablet strength (mg)	Formulation number
ZD6474 100 mg tablet	[redacted]
Placebo to match ZD6474 100 mg tablet	[redacted]

AstraZeneca Pharmaceuticals Investigational Products will pack ZD6474/placebo study treatment. ZD6474/placebo will be packed into white high-density polyethylene (HDPE) bottles with child resistant, tamper evident closures. Study treatment 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 placebo regimen

Patients will be given single oral doses of 100 mg ZD6474 or placebo daily. ZD6474 or placebo tablets must be taken whole and they must not be broken or crushed and dissolved. There are no food restrictions for the administration of ZD6474 or matching placebo. Patients can continue on daily oral dosing with ZD6474/placebo alone as long as they do not meet any withdrawal criteria.

Patients enrolled in the study will be dispensed bottles of blinded ZD6474 tablets; each bottle will contain ZD6474 100 mg or placebo tablets as determined by the randomisation scheme. Patients will take 1 tablet per day at the same time of day each morning.

3.4.2.2 Pemetrexed

Pemetrexed will be administered in 21-day cycles as follows:

Pemetrexed will be administered at a dose 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle. Vitamin supplementation with daily oral low-dose folic acid (approximately 400 μg) needs to start at least 5 days before the first dose of pemetrexed and must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

Patients must also receive vitamin B12 at a dose of 1000 μg as an i.m. injection during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Premedication with dexamethasone (or equivalent) 4 mg twice daily, given the day before, the day of and the day after pemetrexed administration is also mandatory.

Colony-stimulating factors (G-CSF, GM-CSF, etc.) should not be administered prophylactically in Cycle 1 and within 24 hours before pemetrexed administration. Concomitant use of erythropoietin will be permitted.

Patients will receive pemetrexed for up to a maximum of 6 cycles, as long as they do not meet any discontinuation criteria. When pemetrexed treatment is discontinued, before or at the 6th cycle, patients should continue to receive daily oral dosing of blinded ZD6474/placebo as a monotherapy until progression, as long as no other discontinuation criteria is met. If another systemic anti-cancer treatment is started then study treatment should be stopped.

If, in the opinion of the investigator, the patient cannot tolerate ZD6474/placebo in combination with pemetrexed, ZD6474/placebo will be discontinued. The patient may continue to receive pemetrexed alone, until they have received 6 cycles and should be followed according to the study plan, Table 1.

3.4.2.3 ZD6474 dose reduction

Patients who have toxicity related to ZD6474/placebo may have their dose reduced (see Section 3.2.3.1 to 3.2.3.5). Table 6 summarizes study treatment dispensing information in relation to toxicity management. Dose reductions will be performed in a blinded manner. Once a patient has been dose-reduced re-escalation to their initial dose will not be permitted.

Table 6 Dispensing for dose reduction

	Dose	Bottles dispensed	Tablet dispensed	Tablets per dose
Original dose	100 mg per day	1 per cycle	100 mg	1 daily
Reduced dose	100 mg every other day	1 every 2 cycles	100 mg	1 every other day

[redacted]

3.4.2.4 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 eCRF. The dose of study treatment may be repeated if vomiting occurs within 30 minutes of taking the study treatment.

3.4.3 Labelling

Each bottle of ZD6474 or placebo will have an investigational-use label permanently affixed to the outside and will be labelled in accordance with local regulations, stating that the drug is for clinical use only and should be kept out of reach of children. Information on the subject randomisation number, contents of the bottle, expiry date and batch number will be present on the label as well as a space for the date of dispensing to be added.

Instructions for use will be included. Each bottle will have a tear-off portion for putting into the patient records.

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 eCRFs 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 treatment 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, all unused drugs will be accounted for and destroyed locally at the study sites, if this capability exists. If this is not possible, investigational site personnel will return all unused drugs to the local AstraZeneca distribution site.

For US centres please return the medication to:

[redacted]

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. 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. 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 should follow the randomisation scheme provided by AstraZeneca and assign the next available randomisation number. The patient randomisation number will correspond to either ZD6474 and pemetrexed or placebo and pemetrexed.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

Study treatment will be labelled using a unique material identification number which is linked to the randomisation scheme. AstraZeneca 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 to which a patient has been randomised to, will be available to the investigator(s) or pharmacists at the study 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.

[redacted]

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.

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

3.7.1 Other anti-cancer treatments

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 subjected 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).

If the patient discontinues from ZD6474/placebo, the names and dates of up to three subsequent therapies for cancer after study treatment discontinuation, will be collected, unless the patient withdraws consent.

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.

Medications that are known to be potent inducers of CYP3A4 (e.g., rifampicin, phenytoin, carbamazepine, barbiturates, St. John's Wort) should be avoided during the study (dexamethasone (or equivalent) may be given as a pre-medication for chemotherapy).

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 treatment or during study. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

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, which in the investigator's opinion cannot be discontinued, the patient is eligible if the QTc is <460msec. In this case an additional ECG must be obtained 4-8 hours after the first dose of ZD6474/placebo. For patients who start on one of the drugs in this group while on 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 ECG 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

- Colony-stimulating factors (G-CSF, GM-CSF, etc) should not be administered prophylactically in Cycle 1 and within 24 hours before pemetrexed administration

- Interventional use of growth factors is allowed at the investigator's discretion. Concomitant use of erythropoietin will be permitted

- Vitamin supplementation with daily oral low-dose folic acid (approximately 400 μg) to be started at least 5 days before the first dose of pemetrexed and must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients must also receive vitamin B12 at a dose of 1000 μg as an i.m. injection during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Premedication with dexamethasone (or equivalent) 4 mg twice daily, given the day before, the day of and the day after pemetrexed administration is also mandatory. NSAIDS with short elimination half-lives must be restricted for a period of 2 days before, the day of, and 2 days following administration of pemetrexed

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.

[redacted]

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 counselling on the importance of taking study treatment as instructed, the investigator may withdraw the patient from study treatment.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

Table 7 shows the relationship between the objectives and outcome variables for this study.

Table 7 Objectives and outcome variables

Objective	Variable(s)
Primary	
To demonstrate an improvement in Progression Free Survival (PFS) for ZD6474 plus pemetrexed combination compared with pemetrexed plus placebo in patients with locally advanced or metastatic NSCLC after failure of 1st line therapy	PFS, using RECIST criteria
Secondary	
To demonstrate an improvement in overall survival for ZD6474 in combination with pemetrexed compared with pemetrexed plus placebo	Overall survival
To demonstrate an improvement in the overall objective response rate (ORR) (complete response [CR] + partial response [PR]), disease control rate (DCR) (CR + PR + stable disease [SD] $\geq$ 6 weeks) and duration of response (DOR) for ZD6474 in combination with pemetrexed compared with pemetrexed plus placebo	Objective response rate (CR + PR), DCR (CR + PR + SD), and DOR as assessed using RECIST criteria
To demonstrate a beneficial effect on disease-related symptoms, in patients treated with ZD6474 in combination with pemetrexed, that is at least as good as that in patients treated with pemetrexed plus placebo based on the LCSS	Based on the LCSS
To demonstrate an improvement in time to deterioration of disease-related symptoms (TDS) in patients treated with ZD6474 in combination with pemetrexed compared with patients treated with pemetrexed plus placebo based on the LCSS	Based on LCSS
To study the safety and tolerability of ZD6474 in combination with pemetrexed in patients with locally advanced or metastatic NSCLC after failure of 1st line anti-cancer therapy	Aes Vital signs Clinically significant laboratory abnormalities ECG abnormalities (including QTc)
To investigate the population PK of ZD6474 in this patient population and assess the PK-QTc relationship, PK-safety relationship, PK-efficacy relationship and PK-PD relationship	ZD6474 PK: AUC_{ss}, $C_{ss, max}$, CL/F, V_{ss}/F QTc Safety: Aes Efficacy: PFS, OS, ORR, DCR, DOR Individual predicted plasma concentrations

Table 7 Objectives and outcome variables

Objective	Variable(s)
Exploratory	
To investigate the correlation of epidermal growth factor receptor (EGFR) expression, EGFR gene amplification and mutation, and other related biomarker status with efficacy in archival tumour samples in those patients where such tumour material is available	EGFR mutation, Immunohistochemistry (IHC), FISH (EGFR gene copy number) K-ras mutational status
To evaluate by single nucleotide polymorphism (SNP) genotyping using DNA extracted from a blood sample, the effects of genes involved in response to ZD6474 and drugs taken in combination with ZD6474 (i.e., pemetrexed)	
To investigate in blood plasma and serum samples, the correlation of levels of circulating biomarkers with efficacy	VEGF VEGFR-2 Basic fibroblast growth factor (bFGF) EGFR mutation in tumour DNA from serum
To investigate patient health status index during the period of treatment with investigational therapy	EQ5D
To investigate the TDPS during the period of treatment with investigational therapy	WHO PS
To demonstrate a QoL for ZD6474 in combination with pemetrexed-treated patients that is at least as good as that for patients treated with pemetrexed plus placebo based on the quality of life summation item of the LCSS	LCSS

Abbreviations: AE = adverse event; AUCss = area under plasma concentration-time curve during any dosing interval at steady state; bFGF = basic fibroblast growth factor; CL/F = total body clearance of drug from plasma after an oral dose; Css, max = maximum steady state plasma concentration; CR = complete response; DCR = disease control rate; DNA = deoxyribonucleic Acid; DOR = duration of response; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; EQ5D= EuroQoL 5 Dimension Instrument; FISH = Fluorescence in situ hybridisation; ICH = Immunohistochemistry; LCSS = Lung Cancer Symptom Scale; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic ; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TDPS = Time to deterioration in patient WHO PS; TTD = time to death; VEGF = vascular endothelial growth factor; VEGFR-2 = vascular endothelial growth factor receptor-2; Vss/F = Volume of distribution (apparent) at a steady state after an oral dose; WHO PS = World Health Organization Performance Status.

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.

[redacted]

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 treatment 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 should planned to be within 3 weeks of the first dose of study medication, but assessments within a maximum of 4 weeks will still be acceptable).
- Medical history, including all available tumour characteristics
- Eligibility (inclusion/exclusion) criteria

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

- Physical examination, including measurement of height and weight
- Vital signs: resting blood pressure and pulse measurement, recording of body temperature
- 12-lead ECG
- Full haematology and clinical chemistry
- Urinalysis testing
- Urine pregnancy test in women of childbearing potential
- WHO PS
- LCSS questionnaire
- EQ5D
- Review of all concomitant medication & prior anti cancer therapy

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

[redacted]

4.3 Patient-Reported Outcomes (PROs)

The methods for collecting Patient Reported Outcomes (PRO) data are presented below.

4.3.1 Lung Cancer Symptom Scale (LCSS)

4.3.1.1 Methods of assessment

Disease symptom data will be assessed by use of the LCSS questionnaire (see Appendix F) as outlined in the study plan. The LCSS is comprised of a patient scale and an observer scale (for use by health care professionals). Each scale can be used either alone or together to measure changes in symptoms associated with lung cancer. In this study, only the patient scale will be utilized. The patient scale includes nine visual analogue scales and has a recall period of the past 24 hours. Six of the nine items address major symptoms of lung cancer (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain) while the remaining three visual analogue scales are summation items which assess total symptomatic distress, activity status and overall quality of life. LCSS has been validated with respect to its psychometric properties and sensitivity to clinical changes Hollen et al 1993, Hollen et al 1994a, Hollen et al 1994b, Hollen et al 1995.

4.3.1.2 Derivation or calculation of variable

The following scores will be derived from the LCSS questionnaire:

- Total score for the LCSS questionnaire (defined as an average of the aggregate score of all 9 items)
- Average Symptom Burden Index (defined as the average of the 6 symptom items)
- Single quality of life summative item

If responses to any of the 9 items is missing, then the total score for the LCSS will be treated as missing. If responses to only items 7, 8 or 9 are missing, then the Average Symptom Burden Index can be calculated, but the total score for the LCSS will be treated as missing.

4.3.2 Time to deterioration of disease related symptoms (TDS)

4.3.2.1 Methods of assessment

Symptoms of lung cancer will be assessed using the LCSS (see Appendix F).

4.3.2.2 Derivation or calculation of outcome variable

Baseline LCSS is defined as the LCSS questionnaire closest to, but not subsequent to, the first dose of ZD6474/placebo or pemetrexed with a non-missing LCSS score. At a given time point, deterioration in LCSS is defined as >= 10 mm change from baseline score Hollen and Gralla 2000.

TDS based on LCSS is defined as the interval from the date of randomisation to the first assessment of 'deterioration' which is confirmed at the next completed assessment.

[redacted]

If a deterioration of disease-related symptoms has not been observed at the time of analysis, time to deterioration LCSS will be censored as of the last non-missing LCSS assessment date.

4.3.3 Administration of PRO questionnaires

The LCSS questionnaire will be completed where the translation for the appropriate language is available.

LCSS should be given to patients at baseline and as detailed in the study plan, before assessments, prior to administration of pemetrexed and before imparting any news about the status of their disease. If pemetrexed is delayed, the LCSS questionnaire should be completed preceding the next administration of pemetrexed. The LCSS will be administered by the clinic staff in a face-to-face interview. The LCSS patient scale requires a second grade reading level and takes an average of 8 minutes to administer the first time (includes instruction time) and 3-5 minutes for subsequent administrations. A form will be completed by the clinic staff to detail if a questionnaire has been completed at each QoL visit, and if not, the reason will be recorded.

Each centre must allocate responsibility for the LCSS questionnaire 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 LCSS questionnaire, which will be collected using pCRF pages. 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 (Fallowfield et al 1987).

The instructions for completion of the LCSS questionnaire are:

- The patient must complete it in private in his or her own time. Help should not be given from relatives or clinical staff unless the patient is, for example, blind, illiterate, or too ill. If assistance is required, then the reason for assistance should be recorded. However, under no circumstances should help in interpreting the questions or in selecting responses be provided.
- The patient must complete it before any investigations or discussions about their disease with the clinic staff (including administration of pemetrexed treatment).
- Clinic staff who are administering the LCSS should remain with the patient to give instructions and answer any questions the patient might have.
- Questions must be asked in the following fixed order;

- An example question so patient understands how to complete the scale (for example a question about the weather)
- Appetite loss

[redacted]

- Fatigue
- Cough
- Shortness of breath
- Blood in sputum
- Pain
- Symptoms from lung cancer
- Normal activities
- Quality of life

Be sure that the patient understands that marks can be made on the end markers ("none" or "as much as it could be") of the visual analogue scale by extending the end mark. Many patients have a tendency to mark beside the line to mean "none" (0 mm) or "as much as it could be" (100 mm), which then is actually measured as 1-2 mm instead of zero.

4.3.3.1 Instructions for scoring the LCSS

1. If a patient cannot or refuses to complete an item or the full questionnaire, then record the reason for non-compliance (for example, too ill, could not understand questions, refused).

2. Measure each response with a ruler in millimetres starting from the left hand side of the scale. Be sure to measure from the exact point on the line of the left end marker. Round down to the nearest millimetre if between two millimetres.

3. Record the millimetres by each item as well as on a case report form in case of needing to recheck at a later date.

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

The EQ5D 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).

The EQ5D (The EuroQoL Group 1990) will be self-administered along with the LCSS. The EQ5D is a utility measure designed to provide an assessment of general health status of the

[redacted]

individual. This instrument is extensively validated and is available in several languages that facilitate its use in multinational studies.

The EQ5D questionnaire will be completed where the translation for the appropriate language is available.

4.4.1.2 Derivation or calculation of variable

The EQ5D descriptive system comprises 5 questions (see Appendix H) which generate possible health states which can be converted into a weighted health status index by applying scores from the appropriate available 'value sets'.

The responses on EQ5D will be used to derive a unique EuroQoL health state. For each EuroQoL health state there exists a corresponding valuation. This valuation will be used for health economic issues.

4.5 Pharmacokinetic measurements and variables

The table below shows the relationship between the PK endpoints and analysis of this study and the study objectives.

Table 8 PK endpoints related to each objective

Objective	Variable(s)
To investigate the population pharmacokinetics of ZD6474 in this patient population and assess the PK-QTc relationship, PK-safety relationship, PK-efficacy relationship and PK-PD relationship	ZD6474 PK: AUC_{ss}, $C_{ss,\ max}$, CL/F, V_{ss}/F QTc Safety: Aes Efficacy: PFS, OS, ORR, DCR, DOR Plasma level of biomarkers Individual predicted plasma concentrations

Abbreviations: AE = adverse event; PK = pharmacokinetic; AUC_{ss} = area under plasma concentration-time curve during any dosing interval at steady state; $C_{ss,\ max}$ = maximum steady state plasma concentration; CL/F = total body clearance of drug from plasma after an oral dose; V_{ss}/F = Volume of distribution (apparent) at a steady state after an oral dose, PFS = progression-free survival; OS = overall survival (defined as time to death), ORR = objective response rate; DCR = disease control rate, DOR = duration of response, QTc = QT interval corrected for heart rate by the Bazett's method (QT is the interval between Q and T on the ECG)

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 pharmacokinetic samples

Venous blood samples (6 mL) for the determination of ZD6474 concentrations in plasma will be taken 4-8 hours after oral intake of ZD6474 at visits 3, 5, 8, 10 (weeks 2, 4, 7 and 13). Each blood sample will be collected into a tube containing lithium heparin anticoagulant and mixed thoroughly. The blood samples will be centrifuged within 30 minutes of collection at 1000g for 10 minutes at room temperature to provide plasma for analysis. The plasma should be taken off immediately and stored in a plain tube at -20°C before transportation to the

[redacted]

central holding laboratory. The date and the time of collection will be recorded on the appropriate eCRF. For further details on collection, labelling, and shipping refer to appendix L and 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.

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 trials. Depending on the definition of the PK model parameter, estimates for all patients will be calculated using Bayesian based methodology. Parameters will include individual plasma drug clearance, estimated steady state area under the plasma concentration-time curve, estimated steady state maximum drug concentration, and volume 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.

4.6 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.

[redacted]

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 tumour assessment. This includes patients who are lost to follow-up or have withdrawn consent. For patients lost to follow-up without having progressed, death within a further 3 months will be considered an event, otherwise the patient will be censored for PFS at the time of their last tumour assessment date.

4.6.2 Overall survival (OS)

4.6.2.1 Methods of assessment

Patient'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 subjected 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 6 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 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 6 weeks, or as clinically indicated until progression is documented unless the patient withdraws consent.

After disease progression, patients should be followed up for survival every 6 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 scheduled imaging visit at 6 weeks and certainly not less than 3 weeks following the date when response was first measured {note: this is different from the minimum RECIST confirmation window of 4 weeks and is in line with 3 week cycles for pemetrexed}.

[redacted]

In the case of SD, follow-up measurements must have met the SD criteria at least once after the study entry at a minimum interval of 6 weeks from the date of first dose.

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 ≥6 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 and serum 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 treatment.

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 and serum samples

Plasma will be collected from venous blood (10 mL) as detailed in the study plan. Serum will be collected from venous blood (10 mL) from consenting patients only, as detailed in the study plan. Plasma protein levels of VEGF, bFGF and VEGFR-2 will be determined.

In consenting patients, serum samples will be used to investigate circulating protein biomarkers and EGFR mutation status and the mutation status of other genes in circulating tumour DNA. No DNA analysis of host genes will be performed.

If current assays become more sensitive, we will investigate other potential protein biomarkers associated with efficacy of ZD6474, including, in consenting patients EGFR mutation status and mutation status of other genes in circulating tumour DNA (see central laboratory manual for further details regarding sample collection, preparation and shipment).

Archival tumour samples

In patients where samples are available, archival, paraffin-embedded tumour samples should be collected for consenting patients for analysis of (i) EGFR expression, and related signal

[redacted]

transduction, proliferation and apoptosis markers, (ii) EGFR amplification, (iii) analysis of mutation status of the EGFR gene, and other candidate genes, 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 Fluorescence in situ hybridization (FISH) categories defined by Cappuzzo et al 2005. FISH has been used to measure the copy number of the EGFR gene in tumour samples from patients with NSCLC. 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).

Table 9 Classification of FISH status

	FISH 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

Patients will be asked to provide consent for AstraZeneca to collect and analyse 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 formalin fixed paraffin-embedded (FFPE) block presented on slides including 1 stained with haematoxylin and Eosin. Each section to be 5 micron thick.

or

3. 20 x recut sections from the tissue block presented in an eppendorf tubes. All unstained. Each section to be 5 micron thick.

[redacted]

See central laboratory manual for further details regarding sample collection, preparation and shipment.

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, Table 2 and Table 3).

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 /Placebo or pemetrexed. 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 pemetrexed 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 treatment – 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.

[redacted]

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 (CSR). 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 CSR.

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 treatment.

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

[redacted]

- 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 72 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 pemetrexed, **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.

[redacted]

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

[redacted]

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 treatment 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 laboratory parameters listed in Table 10 will be investigated. See Table 11 for total volume of blood samples to be collected.

Table 10 Laboratory safety variables

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

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransaminase; BUN = blood urea nitrogen; INR = international normalized ratio; LDH = lactate dehydrogenase; WBC = white blood cell count.
(a) total, with manual or automated differentiation
(b) at screening only, unless patient is on anticoagulation therapy and requires additional evaluation

[redacted]

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 Vital signs, ECG and physical examination

4.7.3.1 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 7 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.

Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1. The central ECG vendor will produce a report that is sent to the investigator providing an evaluation of the ECG results, from this report eligibility relating to QTc values will be determined.

When possible ECGs should be performed at the same time throughout the study, approximately 4-8 hours after the patient takes their study treatment at visit 3 (week 2), visit 5 (week 4), visit 8 (week 7), visit 10 (week 13) and every 3 months thereafter until discontinuation of study treatment. An additional ECG must be performed at the discontinuation visit.

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

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, the QTc must be re-evaluated within 48 hours with 3 consecutive ECGs (within 5-10 minutes of one another).

In the event of QTc prolongation, please see Section 3.2.3.2.

[redacted]

PK samples will be taken as close to or at the same time as the ECGs. Whenever possible the assessments should be carried out at the same time of day.

The investigator will perform an initial review of the ECG results. 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 11 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples [a]	Total volume (mL) [b]
Pharmacodynamic plasma biomarkers	VEGF, bFGF and VEGFR-2	10	7	70
Pharmacodynamic serum biomarkers (optional)	Circulating tumour DNA	10	1	10
Pharmacokinetic[c]	ZD6474	6	4	24
Safety	Clinical chemistry	6[d]	12	72
	Haematology	4.5[d]	12	54
Genetics (optional)	DNA storage	10	1	10
Total		26.5 – 46.5	37	240 mL

(a) Additional samples may be collected if required (e.g., for repeat safety assessments).
(b) These volumes are based on a patient completing 6 cycles of treatment and the discontinuation visit and patients consenting to the serum biomarker and genetic samples.
(c) PK sampling will be conducted on all patients, whilst patient is on combined therapy (i.e. ZD6474/placebo and pemetrexed)
(d) 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.

[redacted]

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 ZD6474 has been documented for 12 months in work done by AstraZeneca. Samples stored for longer than 12 months will not be analyzed. Refer to protocol Appendix L for details.

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.

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.

[redacted]

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 7 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 basis using randomized treatment. There will be two co-primary analysis populations:

1. all randomised patients;

2. all randomised female patients.

In addition, a per protocol analysis excluding significant protocol deviators will be carried out for the primary analysis of PFS and OS. This will be done for both co-primary analysis populations.

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/placebo.

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.

[redacted]

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 (except for the co-primary analysis population assessing female patients only), 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 97.5% 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 (except for the co-primary analysis population assessing female patients only), 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 97.5% CIs will also be presented.

6.4.2 Symptoms and Quality of Life

The focus of the statistical analysis of QoL assessments will be on the LCSS total scores. Other QoL scores (individual domain scores) will be summarized only. 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. For LCSS, 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

[redacted]

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. TDS will be analysed as described in Section 6.4.1.

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. TDS will be analysed as described in Section 6.4.1.

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 patients. 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 patient 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-patient 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 (Pharmacodynamic) 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 CSR.

[redacted]

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.

EGFR expression, amplification and mutation status from archival tumour tissue will also be listed and summarised by treatment. Results will be presented in terms of mean, median, sd, minimum, maximum and N.

EGFR mutational status in circulating DNA found in serum will be listed and summarised by treatment.

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

6.4.7 Genetics

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

6.5 Determination of sample size

The primary comparison of interest is (pemetrexed + ZD6474 100mg) and (pemetrexed + placebo) for PFS.

There will be two co-primary analysis populations: the first will comprise all randomised patients; the second will comprise all randomised female patients. Accordingly, a nominal 2-sided significance level of 2.5% 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 2.44% to allow for a single interim analysis.

In order to detect a 35% prolongation of overall PFS with 80% power at the 2-sided 2.44% significance level, a minimum of 425 progression events are required. Assuming a median PFS of 3 months for pemetrexed (Hanna et al 2004), a recruitment period of 12 months and minimum follow-up of 6 months, a minimum of 510 patients (255 per arm) will be enrolled. This equates to a 4-week improvement in median PFS time, i.e. a 4-month median PFS on pemetrexed plus ZD6474. If the addition of ZD6474 prolonged PFS by 25%, 510 patients would provide 53% power to detect a statistically significant difference, using a 2-sided 2.44% significance level.

It is assumed that the ratio of female:male patients in this study will be 1:1. In the all randomised female patients co-primary analysis population there will be 80% power to detect a 54% prolongation of progression. This equates to a 6.5 week improvement in the median time to progression in female patients; i.e. a 4.6 month median PFS on the pemetrexed plus ZD6474 arm.

[redacted]

The analysis of OS will be conducted at the time of analysis of the primary endpoint of PFS. Assuming a median OS of 8 months for pemetrexed alone (Hanna et al 2004) and a 35% prolongation of survival by the addition of ZD6474 to pemetrexed, it is estimated that 262 events (deaths) will have occurred at this time, in which case the power to detect the 35% prolongation of survival would be 57%. This equates to a 11-week improvement in the median OS; i.e. an 10.8-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 judgment, 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 213 PFS events have occurred in the overall population. If exactly 213 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 1979). The exact nominal significance level will be determined based on the exact number of events at the time of the interim analysis.

The statistician of the IDMC will perform the interim analysis and will present the results to other members of the IDMC. The IDMC will then make a recommendation that the study be stopped, amended or continue unchanged.

6.7 Data monitoring board

This study will use an external IDMC, which is composed of therapeutic area experts and statisticians, who are not employed by AstraZeneca, and do not have major conflicts of interest. This committee will review the results of the interim analysis. These results will not be revealed to any AstraZeneca personnel. The IDMC will make a recommendation whether the study should be continued or terminated. Once the IDMC has reached its recommendation, a report will be provided to AstraZeneca. This report will state only the IDMC's recommendation on whether the study should be continued or terminated (though if the study may continue subject to a protocol amendment, the details of the proposed amendment may also be included).

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 (CSA) 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

[redacted]

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 CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, 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:

[redacted]

- 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 Independent Ethics Committees (IECs) 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 Institutional Review Board (IRB) or IEC 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 IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

For US centres, the Principal Investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

For all countries except the US, AstraZeneca will provide IECs and Principal Investigators with safety updates/reports according to local requirements. For the US, each PI is responsible for submitting all safety updates/reports to the IRB for their study site.

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

[redacted]

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.

[redacted]

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 Team Leader responsible for the protocol at central R&D site	[redacted]	[redacted]
SDT Physician responsible for the protocol at central R&D site	[redacted]	[redacted]
	[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 1 day), symptomatic and supportive care should be given, and all details should be recorded.

- Use of study treatment 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.

[redacted]

- 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 treatment. 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/pemetrexed, 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

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

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.

[redacted]

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.

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.

Fallowfield et al 1987
Fallowfield LJ, Baum M, Magquire GP. Do psychological studies upset patients? J of the Royal Society of Medicine 1987;80:59.

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

Ferrara et al 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.

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.

Ginsberg et al 1997
Ginsberg RJ, Vokes EE and Raben A. Non-small-cell lung cancer-Cancer: Principles and Practice of Oncology. Fifth edition. Philadelphia PA; Lippincott-Raven, 1997:858-911.

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

Hanna et al 2004
Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with nonsmall-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597.

[redacted]

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.

Hollen et al 1993
Hollen PJ, Gralla RJ, Kris MG and Potanovich LM. Quality of life assessment in individuals with lung cancer: Testing the Lung Cancer Symptom Scale (LCSS). European Journal of Cancer 1993;29A:S51-S58.

Hollen et al 1994a
Hollen PJ, Gralla RJ, Kris MG, Cox C, Belani CP, Grunberg SM, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies: Psychometric assessment of the Lung Cancer Symptom Scale. Cancer, 1994;73:2087-2098.

Hollen et al 1994b
Hollen PJ, Gralla RJ, Kris MG and Cox C. Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Supportive Care in Cancer 1994;2:213-222.

Hollen et al 1995
Hollen PJ, Gralla RJ and Kris MG. An overview of the Lung Cancer Symptom Scale. In R.J. Gralla, & C.M. Moinpour (Eds.), Assessing quality of life in patients with lung cancer: A guide for clinicians 1995;57-63.

Hollen and Gralla 2000
Hollen PJ and Gralla RJ. Clinical vs statistical significance: Using the LCSS quality of life instrument and Karnofsky Performance Status (KPS) to approach the problem in patients with non-small cell lung cancer. Proc Am Soc Clin Oncol 2000(19);636a (Abstr #2510).

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.

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.

[redacted]

Lynch 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.

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):59-64.

O'Brien and Fleming 1979
S+ SEQTRIAL 2 User's Manual.

Paavonen et al 2000
Paavonen K, Puolakkainen P, Jussila L, Jahkola T, Alitalo K. Vascular endothelial growth factor receptor-3 in lymphangiogenesis in wound healing. Am J Pathol 2000;156:1499-1504.

Paez 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.

Parkin 2001
Parkin DM. Global cancer statistics in the year 2001. Lancet Oncol 2001;2:596.

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. ASCO Annual Meeting Proceedings 2005; Abstract No LBA4.

[redacted]

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.

[redacted]