AstraZeneca

Clinical Study Protocol

Drug Substance	Vandetanib
Study Code	D4200L00012
Edition Number	1
Date	[redacted]

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™ , ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients.

ZELIG

Zactima in NSCLC **EL**derly patients **I**n combination with or versus **G**emcitabine

Sponsor:

AstraZeneca SpA - Palazzo Volta Via F. Sforza - 20080 BASIGLIO (MI)- Italy

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

Press F9 to update the title below

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™ , ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients

Co-ordinating Investigators / Study Principal Investigators

[redacted]

° Cattedra di Oncologia Medica

[redacted]

Study centre(s) and number of patients planned

This Phase II multi-centre study will be conducted in a minimum of 122 patients (61 per arm) chemonaïve aged ≥ 70 years with advanced non-small cell lung cancer (NSCLC). It is planned that approximately 20 centres in Italy will participate in the study and that each site will recruit approximately 6 patients.

Study period		Phase of development
Estimated date of first patient enrolled	[redacted]	II
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 vandetanib 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 vandetanib plus gemcitabine (Gemzar®) compared with gemcitabine plus placebo in chemonaïve (not including an adjuvant regimen) patients aged ≥ 70 years with advanced NSCLC.

The secondary objectives of the study are:

1. To evaluate the overall survival (OS) for vandetanib in combination with gemcitabine compared with gemcitabine plus placebo

2. To evaluate the proportion of patients alive at 1-year for vandetanib in combination with gemcitabine compared with gemcitabine plus placebo.

3. To evaluate 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 vandetanib in combination with gemcitabine compared with gemcitabine plus placebo

4. To study the tolerability and safety of vandetanib in combination with gemcitabine in chemonaïve (not including an adjuvant regimen) patients aged ≥ 70 years with locally advanced or metastatic NSCLC.

Study design

This is a parallel group, randomised, double-blind, placebo-controlled, multi-centre study design to assess whether the addition of vandetanib (100 mg) to gemcitabine (1200mg/m^2 given on day 1 and 8 of each 21 day cycle) in male and female chemonaïve patients aged ≥ 70 years with advanced NSCLC confers an advantage in terms of PFS.

Patients will be randomised in a 1:1 ratio to receive either vandetanib 100 mg plus gemcitabine or gemcitabine plus placebo. Patients will receive gemcitabine for up to a maximum of 6 cycles, after which period patients should continue on daily oral dosing with vandetanib/placebo alone until progression. Once a patient has met the study criteria for disease progression on vandetanib/gemcitabine or placebo/gemcitabine, randomised treatment

must be permanently discontinued. Investigators, remain at liberty to determine the most appropriate therapy for their patients after randomised treatment is discontinued.

Following discontinuation of study treatment (vandetanib/placebo and gemcitabine), 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. An interim analysis of safety data is planned after a cohort of 12 patients have been enrolled and completed the 1st cycle of trial therapy to confirm that the combination is tolerated.

Target patient population

Male or female patients aged 70 years or older with histologically or cytologically-confirmed advanced (stage IIIB with supraclavicular lymph node metastases or pleural effusion or stage IV) NSCLC chemonaïve and who have a performance status of 0 to 2 (WHO 1981).

Investigational product, dosage and mode of administration

Vandetanib (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 vandetanib/placebo will have their vandetanib/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 vandetanib/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 vandetanib/placebo must be withheld for more than 3 weeks for resolution of toxicity, the patient must be withdrawn from vandetanib/placebo treatment.

In the case of patients who discontinue vandetanib/placebo, but not gemcitabine therapy, because of toxicity attributed to vandetanib/placebo, these patients may continue to receive the scheduled treatment with gemcitabine (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 vandetanib or matching placebo described above, patients will receive gemcitabine 1200 mg/m^2 administered intravenously on days 1 and 8 of each 21 day cycle. Patients will receive up to but no more than 6 cycles of gemcitabine.

Patients who experience CTCAE grade 3 or 4 toxicity that is considered related to gemcitabine will have gemcitabine 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 gemcitabine, according to the dose reduction plan outlined in Section 3.2.3. If gemcitabine must be withheld for more than 3 weeks for resolution of toxicity, the patient will not restart gemcitabine treatment.

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

Duration of treatment

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

Patients will be randomised in a 1:1 ratio to receive either vandetanib 100 mg plus gemcitabine or gemcitabine plus placebo. Patients will receive gemcitabine for up to a maximum of 6 cycles, after which period patients should continue on daily oral dosing with vandetanib/placebo alone until progression. Once a patient has met the study criteria for disease progression on vandetanib/gemcitabine or placebo/gemcitabine, randomised treatment must be permanently discontinued. Investigators, remain at liberty to determine the most appropriate therapy for their patients after randomised treatment is discontinued.

Following discontinuation of study treatment (vandetanib/placebo and gemcitabine), patients will be followed up for survival, unless they withdraw consent.

Outcome variables

Efficacy

- Primary outcome variable:
  - Progression Free Survival (PFS)
- Secondary outcome variables:
  - Overall survival (OS)
  - Proportion of patients alive at 1-year
  - Overall Objective Response Rate (ORR), Disease Control rate (DCR) and Duration Of Response (DOR)

Safety

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

- Other measures of patient benefit

  – World Health Organisation Performance Status (WHO PS), Time to Deterioration of Performance Status.

Statistical methods

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

Assuming a median PFS of approximately 3 months for gemcitabine (Gridelli C et al 2003), a recruitment period of 12 months and minimum follow-up of 20 months, a minimum of 122 patients (61 per arm) will be enrolled in order to detect a 33.3% prolongation. When the sample size in each group is 61, an exponential maximum likelihood test of equality of survival curves with a 0.200 two-sided significance level will have 80% power to detect the difference between a vandetanib + gemcitabine exponential parameter, λ_1, of 0.1540 (median PFS of 4.5 months) and a Placebo + gemcitabine exponential parameter, λ_0, of 0.2310 (median PFS of 3 months), (a constant hazard ratio of 0.667); this assumes an accrual period of 12 months, a maximum follow-up time of 20 months, and no dropouts. For this comparison, 110 progression events are required (Machin D et al 1997).

PFS, overall survival (OS), DOR, and TDPS and will be analysed using a log-rank test. For PFS, OS, DOR 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 centre, tumour stage, number of organs involved, prior adjuvant chemotherapy, histology, smoking history, gender. 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.

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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 4.4.1.1)
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

Abbreviation or special term	Explanation
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism Pharmacokinetics
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
Co-ordinating Investigator	Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities.

Abbreviation or special term	Explanation
IRB	Institutional Review Board
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
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 4.4.1).
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

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 4.4.1.1).
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

1. INTRODUCTION

Investigators should be familiar with the vandetanib/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 J 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 D and Folkman J 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 SA and Achen MG 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 DW et al 1989). 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 G 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 N 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 K 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 G et al 1998). Interestingly, a correlation between VEGF expression and prognosis has been noted for several cancers (Maeda K 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 (Shou Y 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 KJ et al 1993; Millauer B et al 1994).

1.1.1 Vandetanib

1.1.1.1 Background

Vandetanib is an inhibitor of the tyrosine kinase domain of the VEGF receptor-2 (KDR or VEGFR-2). Vandetanib 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 F et al 2003; Wedge SR et al 2002). It has not been elucidated how much anti-tumour activity seen with vandetanib is through its activity against EGFR. Vandetanib 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 vandetanib according to RECIST (Therasse P 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 vandetanib 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 vandetanib, compared to those randomised to gefitinib (Natale RB et al 2005). Study 6474IL/0006 randomised patients to docetaxel in combination with placebo, vandetanib 100 mg, or vandetanib 300 mg. The results of this study demonstrated that vandetanib combined with docetaxel prolonged PFS in patients with NSCLC (Heymach JV et al 2007).

1.1.1.2 Summary of adverse events (AEs) in vandetanib studies

The most common AEs associated with vandetanib 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 vandetanib when administered in combination with standard 21-day treatment cycles of pemetrexed 500 mg/m^2, 24 patients with locally advanced or metastatic NSCLC were enrolled after failure of prior chemotherapy. An initial cohort of 10 patients received 100 mg vandetanib 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 vandetanib 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 vandetanib 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 100 mg vandetanib cohort were anorexia (80%), fatigue (60%), diarrhoea (40%) and in the 300 mg cohort diarrhoea (54%), fatigue (45%), dyspepsia (45%), nausea (36%).

In Study 6474IL/0003, patients with advanced 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 vandetanib 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 vandetanib 56.0 days and gefitinib 57.0 days. More patients discontinued therapy as a result of adverse events for those who received vandetanib (22.9%) compared to those who received gefitinib (10.6%).

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

Approximately 10% of patients who received vandetanib 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 vandetanib was 10 mmHg; the median increase in diastolic blood pressure was 6 mmHg.

An increased incidence of SAEs was noted in patients who received vandetanib 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 vandetanib. 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 vandetanib 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 vandetanib developed a haematologic event, as did 2 patients who received gefitinib. No patients who received vandetanib developed serious hepatotoxicity.

Regarding ECG findings, QTc prolongation was reported in 18 patients in Part A taking vandetanib and 7 patients in Part B taking vandetanib. 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 vandetanib or 300 mg of vandetanib. The median duration of therapy for each arm (docetaxel/placebo, docetaxel /vandetanib 100 mg, and docetaxel /vandetanib 300 mg) was 64 days, 127 days, and 61.5 days, respectively. More patients discontinued therapy as a result of AEs for those who received 300 mg vandetanib (31.8%) compared to those who received 100 mg (14.3%) or placebo (17.1%).

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

The most frequent AEs observed in this study were similar to those observed in prior studies for vandetanib 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 vandetanib arm compared with placebo, and for the 300 mg vandetanib arm compared with 100 mg vandetanib. The most common AEs and their frequencies as reported in the 300 mg vandetanib, 100 mg vandetanib 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 vandetanib-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 Gemcitabine (GEMZAR® , Eli Lilly and Company)

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis S-phase) and also blocking the progression of cells through the G1/S-phase boundary. gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate

(dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death. Apart from its favorable toxicity profile, gemcitabine has shown activity in many solid tumours, including Non-Small Cell Lung Cancer (NSCLC). Data from 2 randomized clinical studies (657 patients) support the use of Gemcitabine in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC. Gemcitabine plus cisplatin versus cisplatin: This study was conducted in Europe, the US, and Canada in 522 patients with inoperable Stage IIIA, IIIB, or IV NSCLC who had not received prior chemotherapy. Gemcitabine 1000 mg/m2 was administered on Days 1, 8, and 15 of a 28-day cycle with cisplatin 100 mg/m2 administered on Day 1 of each cycle. Single-agent cisplatin 100 mg/m2 was administered on Day 1 of each 28-day cycle. The primary endpoint was survival. The median survival time on the Gemcitabine plus cisplatin arm was 9.0 months compared to 7.6 months on the single-agent cisplatin arm (Log rank p=0.008, two-sided). Median time to disease progression was 5.2 months on the Gemcitabine plus cisplatin arm compared to 3.7 months on the cisplatin arm (Log rank p=0.009, two-sided). The objective response rate on the Gemcitabine plus cisplatin arm was 26% compared to 10% with cisplatin (Fisher's Exact p<0.0001, two-sided). No difference between treatment arms with regard to duration of response was observed. Gemcitabine plus cisplatin versus etoposide plus cisplatin: A second, multi-center, study in Stage IIIB or IV NSCLC randomized 135 patients to Gemcitabine 1250 mg/m2 on Days 1 and 8, and cisplatin 100 mg/m2 on Day 1 of a 21-day cycle or to etoposide 100 mg/m2 I.V. on Days 1, 2, and 3 and cisplatin 100 mg/m2 on Day 1 of a 21-day cycle. There was no significant difference in survival between the two treatment arms (Log rank p=0.18, two-sided). The median survival was 8.7 months for the Gemcitabine plus cisplatin arm versus 7.0 months for the etoposide plus cisplatin arm. Median time to disease progression for the Gemcitabine plus cisplatin arm was 5.0 months compared to 4.1 months on the etoposide plus cisplatin arm (Log rank p=0.015, two-sided). The objective response rate for the Gemcitabine plus cisplatin arm was 33% compared to 14% on the etoposide plus cisplatin arm (Fisher's Exact p=0.01, two-sided). Quality of Life (QOL): QOL was a secondary endpoint in both randomized studies. In the Gemcitabine plus cisplatin versus cisplatin study, QOL was measured using the FACT-L, which assessed physical, social, emotional and functional well-being, and lung cancer symptoms. In the study of Gemcitabine plus cisplatin versus etoposide plus cisplatin, QOL was measured using the EORTC QLQ-C30 and LC13, which assessed

physical and psychological functioning and symptoms related to both lung cancer and its treatment. In both studies no significant differences were observed in QOL between the Gemcitabine plus cisplatin arm and the comparator arm.

Gemcitabine is well tolerated and effective in elderly patients with advanced non-small cell lung cancer (NSCLC). Gemcitabine was compared with vinorelbine and with the combination vinorelbine plus gemcitabine in an open-label, randomized phase III trial in elderly patients with advanced NSCLC. Patients aged 70 years and older, enrolled between December 1997 and November 2000, were randomly assigned to receive intravenous vinorelbine (30 mg/m2 of body surface area), gemcitabine (1200 mg/m2), or vinorelbine (25 mg/m2) plus gemcitabine (1000 mg/m2). All treatments were delivered on days 1 and 8 every 3 weeks for a maximum of six cycles. The primary endpoint was survival. Survival curves were drawn using the Kaplan–Meier method and analysed by the Mantel–Haenszel test. Secondary endpoints were quality of life and toxicity. Of 698 patients available for intention-to-treat analysis, 233 were assigned to receive vinorelbine, 233 to gemcitabine, and 232 to vinorelbine plus gemcitabine. Compared with each single drug, the combination treatment did not improve survival. The hazard ratio of death for patients receiving the combination treatment was 1.17 (95% confidence interval [CI] = 0.95 to 1.44) that of patients receiving vinorelbine and 1.06 (95% CI = 0.86 to 1.29) that of patients receiving gemcitabine. Although quality of life was similar across the three treatment arms, the combination treatment was more toxic than the two drugs given singly. The combination of vinorelbine plus gemcitabine is not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC (Gridelli C et al 2003).

1.2 Rationale

Lung cancer is the most common form of cancer in most developed countries and is now the leading cause of cancer death in both men and women. Approximately 1.2 million new cases are diagnosed every year worldwide, with a mortality rate of 1.1 million (Parkin DM 2001). Approximately 80 to 85% of lung cancer subtypes are of non-small cell histology, including squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma (Ginsberg RJ et al 1997). Like other solid tumors, lung cancer may be considered to be a disease of elderly patients. Although the median age of patients with newly diagnosed non-small cell lung cancer (NSCLC) participating in clinical trials is 60 to 62 years, > 50% of diagnoses are made in patients aged > 65 years, and 30 to 40% are made in patients > 70 years old. The National Cancer Institute Surveillance Epidemiology End Results program reported that the age-adjusted incidence rate for NSCLC was 20.2 per 100,000 inhabitants > 65 years old; however, the age-adjusted incidence rate was 306.1 for those > 65 years old. In clinical trials, the definition of an elderly patient remains controversial. Epidemiologic literature2,6 uses an age of 65 years for the selection of elderly patients, but 70 years is commonly used in oncology trials. However, evidence shows an increased incidence of age-related changes in patients > 70 years old with increased risk of chemotherapy-induced toxicity, and this would therefore seem to be an appropriate cut-off,2,6 pending the availability of more reliable tools to define biological instead of chronological age. Despite the high incidence of NSCLC and its high mortality rate in elderly patients, the likelihood of receiving treatment of any type—in particular, chemotherapy— appears to decrease with increasing age. The decision to treat or

not to treat is frequently based on factors other than chronological age alone. Other important factors influencing the use of chemotherapy in the elderly include the presence of co-morbid diseases and performance status (PS). Age-related decreases in organ function, including reductions in renal, hepatic, and bone marrow function, have the potential to increase chemotherapy-related toxicity in the elderly; however, few guidelines are available with respect to the need for dose adjustments in this rapidly increasing patient population. Physician and patient concerns about age-related toxicity may, in part, provide an explanation for the low number of elderly participants in cancer trials. In an analysis of 495 phase II and III American Cooperative Group studies, it was found that patients with renal, hepatic, cardiac, or haematologic abnormalities were generally excluded, therefore potentially ruling out a large proportion of elderly patients (Rossi A, Gridelli C. 2006). Elderly patients also have approximately twice as many co-morbidities compared with the general population. This may have a considerable impact on their overall health and PS, which may further complicate chemotherapy or lead to less aggressive treatment for the elderly. Although co-morbidity influences treatment choice in NSCLC and is a predictor of outcome (in particular, survival), clinical trials seldom report co-morbid conditions or their severity, and a standardized way of assessing co-morbidity has not yet been defined. The number of elderly patients with NSCLC is likely to increase over the coming years; yet, data from chemotherapy trials designed specifically for elderly patients with NSCLC are lacking. Hutchins et al analyzed data from 164 Southwest Oncology Group (SWOG) trials and found that patients aged at least 65 years only comprised 39% of all participants in lung cancer trials (Hutchins LF et al 2000). Furthermore, until recently, patients aged > 80 years were usually excluded from chemotherapy trials. Studies of advanced NSCLC patients not limited by age have only recently been sufficiently large and appropriately designed to assess the place of chemotherapy. These studies have shown conclusively that patients with advanced NSCLC not only achieve a survival benefit from chemotherapy, but also often experience significant relief of cancer-related symptoms during treatment. A large meta-analysis demonstrated modest but significant survival advantages and no age related differences from the use of chemotherapy in patients with advanced NSCLC compared with supportive care alone. In addition, retrospective analyses of several individual clinical trials have shown that chemotherapy is just as effective in the elderly compared with their younger counterparts. It should be remembered that the elderly patients in these clinical trials represent only a select subset of the elderly population as a whole, in that they met the strict entry criteria mandated by the studies. However, these analyses suggest that, despite early pessimism, it now appears that chemotherapy should be considered for certain elderly patients (Gridelli C et al 2006, Gridelli C et al 2005, Gridelli C et al 2005).

Despite the optimization of chemotherapy regimens, treatment outcomes for advanced non-small cell lung cancer (NSCLC) are still considered to be disappointing. Thus, clinical research of new treatment strategies is warranted. Several targeted agents have been introduced into clinical trials in NSCLC, but to date, only a few of these new agents can offer hope of a substantial impact on the natural history of the disease (Gridelli C. 2007, Gridelli C. 2006, Gridelli C et al 2004, Rossi A, Gridelli C. 2006).

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 AB et al 2005) and in advanced colorectal cancer (CRC) when combined with Irinotecan/5 Fluorouracil/Leucovorin (Hurwitz H 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.

One of the main reasons for the failure of several clinical trials evaluating targeted therapy in lung cancer is the existence of multilevel cross-stimulation among the targets of the new biological agents along several pathways of signal transduction that lead to neoplastic events; blocking only one of these pathways allows others to act as salvage or escape mechanisms for cancer cells. Preclinical evidence of synergistic antitumor activity achievable by combining targeted agents that block multiple signaling pathways has recently emerged (Maione P et al 2006, Gridelli C et al 2006). The complexity of the signalling process in general further supports the need to interfere at different stages to avoid an escape mechanism for the cell. Whether the multitarget approach can be accomplished by using combinations of selective agents or specific agents that intrinsically target various targets is a matter of debate. Such a multitargeted strategy has recently been validated in a number of preclinical and clinical studies using receptor tyrosine kinase (RTK) inhibitors with broad target selectivity. 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 R et al 2005), suggesting that EGFR and VEGFR blockade may have significant activity in NSCLC even without chemotherapy. Very recently, erlotinib, at the dose of 150 mg/day, has been tested, as first-line treatment, prospectively in a phase II study in elderly patients aged more than 70 years with previously untreated advanced NSCLC to determine the MST, 1- and 2-year survival. The secondary end points included RR, TTP, toxicity and symptom improvement. Final results on 80 enrolled patients, are very interesting with encouraging activity (RR of 10%, SD of 41%), TTP (3.5 months), MST (10.9 months). The 1- and 2-year survival rates were 46% and 19%, respectively. The most common toxicities were acneiform rash (79%) and diarrhoea (69%). Four patients developed interstitial lung disease of grade $\geq$ 3, with one treatment-related death. The Author stated that erlotinib merits consideration for further investigation as a first-line therapeutic option in elderly patients (Jackman DM et al 2007).

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

Vandetanib is a novel and unique, orally available, small molecule tyrosine kinase inhibitor with potent anti-EGFR and anti-VEGFR activity. Vandetanib has been recently demonstrated active and well tolerated at daily doses of 100 to 300 mg alone and/or in combination with chemotherapy in advanced, pre-treated NSCLC.

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 vandetanib + 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) (Heymach JV et al 2007). 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 vandetanib + docetaxel compared to docetaxel alone. Furthermore, the 100 mg vandetanib + 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).

Single agent chemotherapy is considered a standard treatment for advanced non small cell lung cancer (NSCLC) elderly patients (Gridelli C et al 2003, Gridelli C. 2001). In advanced disease, single agent Gemcitabine proves to be active and well-tolerated. A phase III randomized trial showed that polychemotherapy with gemcitabine/vinorelbine does not improve any outcome as compared to single agent chemotherapy with vinorelbine or gemcitabine (Gridelli C et al 2003). In clinical practice, single agent chemotherapy should remain the standard treatment. The choice of the drug should be based on the toxicity profile of each drug and type of co-morbid conditions.

The major objective of this study is to evaluate the combination of vandetanib with gemcitabine in the first line setting in advanced NSCLC elderly patients (≥ 70 years of age), considering the low toxicity profile of both dugs that allows their evaluation in this patient population. In particular, we will evaluate in two parallel arms, the combination of vandetanib and gemcitabine versus vandetanib matching placebo and gemcitabine. This study will determine whether the addition of gemcitabine to vandetanib provides a significant prolongation of PFS when compared with gemcitabine in combination with placebo in chemonaïve elderly patients aged ≥ 70 years with advanced NSCLC.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to demonstrate an improvement in Progression free Survival (PFS) as assessed by RECIST criteria, for the combination of vandetanib plus gemcitabine (Gemzar®) compared with gemcitabine plus placebo in patients with locally advanced or metastatic NSCLC chemonaïve (not including an adjuvant regimen) elderly patients aged ≥ 70 years.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To evaluate the overall survival (OS) for vandetanib in combination with gemcitabine compared with gemcitabine plus placebo

2. To evaluate the proportion of patients alive at 1-year for vandetanib in combination with gemcitabine compared with gemcitabine plus placebo

3. To evaluate 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 vandetanib in combination with gemcitabine compared with gemcitabine plus placebo as assessed by RECIST criteria

4. To study the tolerability and safety of vandetanib in combination with gemcitabine 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

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, randomised, double-blind, placebo controlled, multi centre study designed to assess whether the addition of vandetanib (100 mg daily) to gemcitabine (1200mg/m^2 given on day 1 and 8 of each 21 day cycle) in chemonaïve patients aged ≥ 70 years with advanced NSCLC confers a statistically significant advantage in terms of PFS.

It is planned that approximately 10-15 centres in Italy will participate in the study and that each site will recruit about 10 patients per centre.

Patients will be randomised in a 1:1 ratio to receive either vandetanib 100 mg plus gemcitabine or gemcitabine plus placebo. Patients will receive gemcitabine for up to a maximum of 6 cycles, after which period patients should continue on daily oral dosing with vandetanib/placebo alone until progression. Once a patient has met the study criteria for disease progression on vandetanib/gemcitabine or placebo/gemcitabine, randomised treatment must be permanently discontinued. Investigators, remain at liberty to determine the most appropriate therapy for their patients after randomised treatment is discontinued.

Following discontinuation of study treatment (vandetanib/placebo and gemcitabine), 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.

Patients will be evaluated until discontinuation of vandetanib/placebo and gemcitabine or until objective progression is documented, which ever comes last, and will then be followed up for survival, unless they withdraw consent. Study assessments for patients who are on vandetanib/placebo and gemcitabine or gemcitabine alone (see Table 1).

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.

For patients who continue on vandetanib/placebo alone (before disease progression), see Table 2. For patients who have withdrawn from vandetanib/placebo and gemcitabine, see Table 3.

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 vandetanib/placebo will have their vandetanib/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 vandetanib 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 vandetanib/placebo. In the case of patients who discontinue vandetanib/placebo therapy because of toxicity attributed to vandetanib/placebo, these patients will continue to receive the scheduled treatment with gemcitabine (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 gemcitabine will have gemcitabine 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 gemcitabine, according to the dose reduction plan outlined in section 3.2.3. If gemcitabine must be withheld for more than 3 weeks for resolution of toxicity, the patient will not restart gemcitabine treatment. In the case of patients who discontinue combination therapy because of toxicity attributable to gemcitabine, patients may continue on vandetanib/placebo and will be followed for progression and survival.

Figure 1 Study flow chart

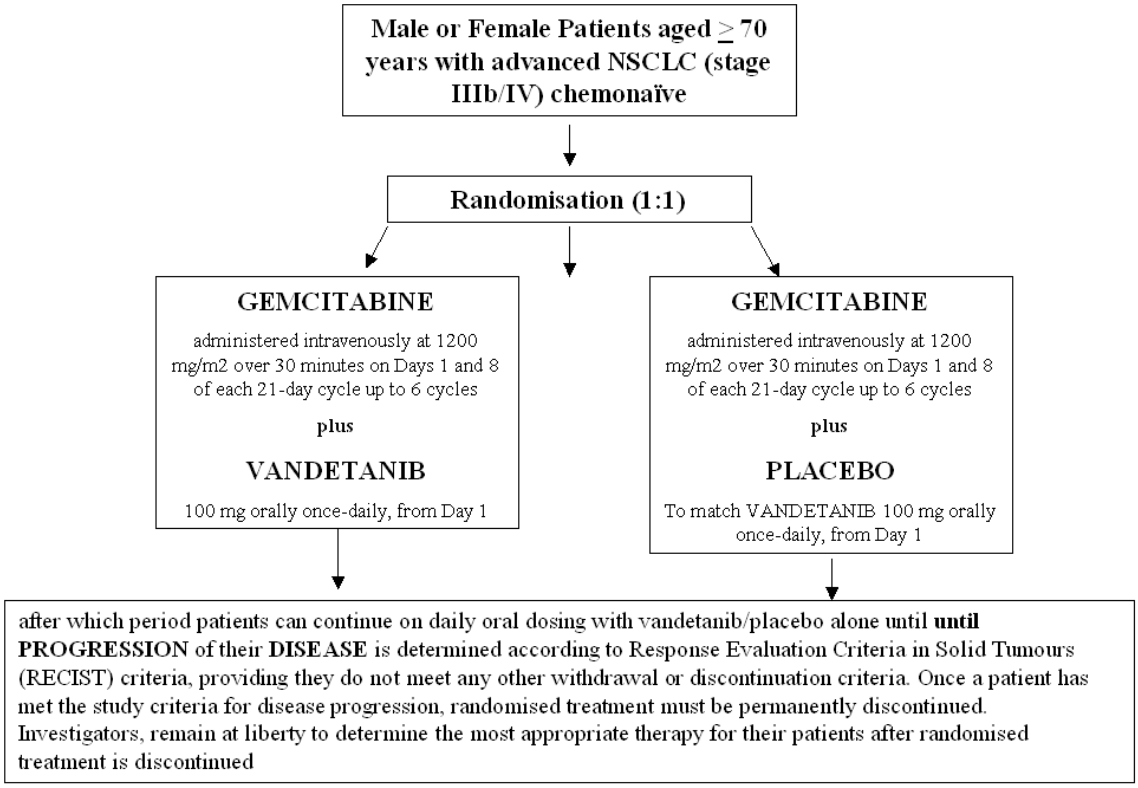


Table 1 Study plan: Screening to discontinuation of gemcitabine

Cycle	**Screen**		**1**			**2**			**3**			**4**			**5**			**6**		
Day (+/- 4 days)	-28to 0	-7 to 0	1	8	15	22/1	8	15	22/1	8	15	22/1	8	15	22/1	8	15	22/1	8	15
Visit	0		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week	0		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Informed consent	X																			
Medical history	X																			
Inclusion/exclusion criteria	X																			
Physical examinationa		X				X			X			X			X			X		
Vital signsb		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram		Xc	Xd	Xd		Xd				Xd					Xd					
Haematology/ clinical chemistrye		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X	X			X			X			X			X			X		
WHO Performance Status		X				X			X			X			X			X		
RECIST	Xf																			
Randomisation			X																	
Gemcitabine administration j			X	X		X	X		X	X		X	X		X	X		X	X	
vandetanib/placebo daily dosing g			◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Study treatment dispensing			Xg			X			X			X			X			X		

Cycle	Screen		1			2			3			4			5			6				
Tolerability/AE reporting	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

All assessments are to be performed before administration of vandetanib/placebo and gemcitabine, 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 ±4 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 gemcitabine and then at the start of each subsequent cycle. For patients who complete/discontinue gemcitabine and continue on vandetanib/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.

(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. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary 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 1, 2, 4, 8, 13 (weeks 1, 2, 4, 8, 13) and then every 3 months to and including discontinuation of vandetanib/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 3.2.3.3 for further details.

(e) 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 gemcitabine 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 or Sanaka 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 gemcitabine and continue on vandetanib/placebo, haematology and clinical chemistry will be performed every 3 weeks.

(f) RECIST is carried out at screening (within 4 weeks before the 1st dose) and every 6 weeks (+/- 4 days) thereafter. Scans performed for RECIST will be expected to cover the following: at screening cranial CT/MRI scans, chest CT/MRI scans and abdomen CT/MRI scans, including liver and adrenals (pelvic imaging is only required if clinically indicated) and bone scans. For patients with bone disease regular bone scans are not required, unless the patient becomes symptomatic. Follow up bone scans are not required unless new/worsening bone symptoms occur. 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 please refer to section 4.3.4.1

(g) Gemcitabine and vandetanib are both started on Day 1. vandetanib should be taken prior to gemcitabine infusion.

Table 2 Study plan: After Discontinuation of gemcitabine and ongoing vandetanib/placebo

Treatment Period	Every 3 Weeks	Every 6 Weeks	Every 3 Months
Physical examinationa	X		
Vital signsb	X		
Electrocardiogramc			X
Haematology/clinical chemistry	X		
Urinalysis	X		
WHO Performance Status	X		
RECISTd		X	
Study treatment dispensing	X		
Tolerability/AE reporting	X		
Concurrent medication	X		

All assessments are to be performed before administration of vandetanib/placebo and gemcitabine, 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 ±4 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 gemcitabine is discontinued within the first 12 weeks of treatment, ECGs must be performed at weeks 1, 2, 4, 8, 13 and then, every 3 months up to and including discontinuation.
(d) RECIST is carried out every 6 weeks (+/- 4 days) until progression. For patients with bone disease regular bone scans are not required, unless the patient becomes symptomatic. Follow up bone scans are not required unless new/worsening bone 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). For patients with cerebral metastases, regular cranial CT/MRI scans are not required, unless new/worsening symptoms occur.

Table 3 Study plan: Discontinuation of both vandetanib and gemcitabine

Cycle	Discontinuation	30-day f/up	60-day f/upa	Survival
Electrocardiogram	X			
Haematology/clinical chemistry	X			
Urinalysis	X			
Physical examinationb	X	X		
Vital Signs c	X	X		
WHO Performance Statusd	X	X		
RECISTe	X			
Survivalf				X
Subsequent anti-cancer therapyg	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 ±4 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) 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
(e) RECIST should be performed at the discontinuation visit. For patients with bone disease regular bone scans are not required, unless the patient becomes symptomatic. Follow up bone scans are not required unless new/worsening bone symptoms occurScans 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 cerebral metastases, regular cranial CT/MRI scans are not required, unless new/worsening symptoms occur..
(f) Assessments for survival should be made every 6 weeks. Survival information may be obtained via telephone contact.
(g) 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 II study will be appropriate to assess whether vandetanib plus gemcitabine confers a longer PFS benefit when compared with placebo plus gemcitabine in patients with advanced NSCLC. The population for this study will consist of chemonaïve patients aged ≥ 70 years and for whom gemcitabine is therefore an appropriate therapeutic option.

The dose level of vandetanib 100 mg has been chosen, as previous Phase I studies have demonstrated that chronic daily administration at this level is well tolerated.

The primary endpoint of PFS is a recognised appropriate efficacy end-point for phase II NSCLC studies. 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, to provide supportive data of the benefit of vandetanib.

The use of placebo control in this study will provide for a robust assessment of the benefit of vandetanib in combination with gemcitabine and is considered appropriate in this patient population because gemcitabine is the standard of care as a single-agent in the treatment of elderly 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 vandetanib treatment have already been discussed in Section 1.2. Patients in the active and placebo arms of the study will receive vandetanib/placebo in combination with gemcitabine and will be closely followed for disease progression. At this 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, vandetanib 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 vandetanib have experienced symptomatic arrhythmias or other events definitely related to QT prolongation. vandetanib 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 Vandetanib toxicity

In all cases where the dose of study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to study treatment, the investigator must contact and inform the AstraZeneca study physician.

For guidance on the management of QTc prolongation, see section 3.2.3.3.

For all other toxicities, the dose of study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 1 or better, and then study treatment may be restarted. Dose reduction/re-challenge for each toxicity criterion will be managed as discussed in the sections that follow.

Patients will be withdrawn from the study if toxicity does not resolve to ≤ CTCAE grade 1 within 3 weeks. If toxicity recurs during the study either at the same dose or reduced dose, the patient should be withdrawn from study treatment.

A guideline for vandetanib dose reduction is shown in the table below.

Table 4 Vandetanib dose reduction Guidelines

Original dose	Reduced dose	vandetanib dispensed for reduced dose	Tablets per daily dose
100 mg	100 mg every other day	100-mg vandetanib tablets	1 every other day

3.2.3.2 Gemcitabine toxicity

Gemcitabine Dose Modifications

Patients receiving gemcitabine should be monitored prior to each dose with a complete blood count (CBC), including differential and platelet count Dosage adjustments for hematological toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy. If marrow suppression is detected, gemcitabine dosage should be modified or suspended according to the following guidelines (see also the approved full Gemzar® prescribing information sheet).

Table 5 Gemcitabine Dosage Reduction Guidelines

Absolute granulocyte count (x 10 6 /L)		Platelet count (x 10 6 /L)	% of full dose
>/=1.000	and	>/=100.000	100
500-999	or	50.000-99.000	75
<500	or	<50.000	Hold

Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. gemcitabine should be administered with caution in patients with evidence of significant renal or hepatic impairment.

In general, for severe (Grade 3 or 4) non-hematological toxicity, except nausea/vomiting, therapy with gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician.

Dose adjustment for gemcitabine in combination with vandetanib / placebo for subsequent cycles is based upon observed toxicity. The dose of gemcitabine in subsequent cycles should be reduced to 800 mg/m^2 on Days 1 and 8 in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10^6/L for more than 5 days
- Absolute granulocyte count <100 x 10^6/L for more than 3 days
- Febrile neutropenia
- Platelets <25,000 x 10^6/L
- Cycle delay of more than one week due to toxicity

If any of the above toxicities recur after the initial dose reduction, for the subsequent cycle, gemcitabine should be given on Day 1 only at 800 mg/m2.

vandetanib and gemcitabine may have overlapping toxicities such as gastrointestinal (nausea and vomiting, and diarrhea), hepatic (elevations of one or both serum transaminases), cutaneous (skin rash, and pruritus), cardiovascular (myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension), metabolic (hypomagnesemia and hypokalemia), respiratory (dyspnea, interstitial lung disease), and renal (proteinuria and hematuria).

Please refer to the full Gemzar® prescribing information for additional important safety information

3.2.3.3 QTc prolongation

Patients will have ECGs performed to monitor QTc interval (using Bazett's correction) as outlined in the study plan. The screening QTc must be <480 msec. Up to 3 ECG 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) are excluded if QTc is ≥ 460 msec**. Baseline QTc will be determined by the average of 3 consecutive ECGs (within 5-10 minutes of one another) on Day 1.

For this study QTc prolongation is defined as:

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

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second 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 (≥ 460 msec for Appendix D Table 2 medications)

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

For a single QTc value of ≥550 msec or an increase of ≥100 msec from baseline, vandetanib must be withheld. ECGs and electrolytes should be followed 3 times a week until the QTc falls below 480 msec (460 msec for Appendix D Table 2 medications) or baseline, whichever is higher. vandetanib treatment may be resumed at a lower dose after the QTc recovers to <480 msec (≤ 460 msec for Appendix D Table 2 medications) or baseline.

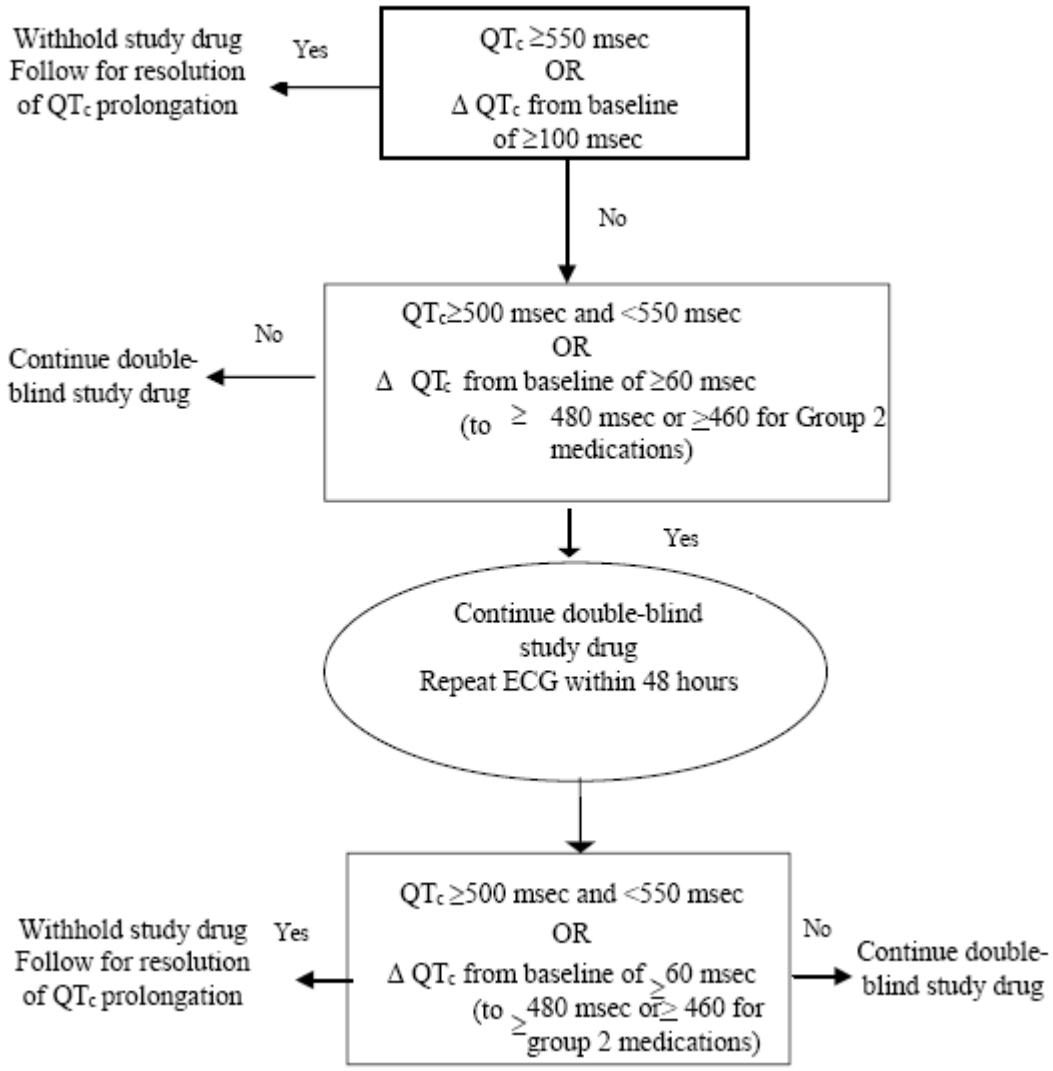
For a QTc interval ≥500 msec, but <550msec, or an increase of ≥60 msec but <100 msec from baseline QTc to a QTc value ≥480 msec (≥ 460 msec for Appendix D Table 2 medications), vandetanib may be continued, but a repeat ECG (in triplicate) must be obtained within 48 hours. If QTc prolongation is confirmed,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

Subjects who experience QTc prolongation may be given vandetanib at a reduced dose (see Section 3.4.2.3). If vandetanib is restarted after the QTc prolongation has resolved, ECGs should be performed as outlined in the study plan. If vandetanib must be withheld for >3 weeks to allow for QTc prolongation to recover to <480 msec (<460 msec for Appendix D Table 2 medications) or baseline, the subject will not be restarted on study medication. If QTc prolongation recurs after the dose reduction the subject must permanently discontinue vandetanib.

Management of Patients With QTc Prolongation

For a single QTc value of ≥ 550 msec or an increase of ≥ 100 msec from baseline, vandetanib must be withheld. ECGs and electrolytes should be followed 3 times a week until QTc falls below 480 msec (460 msec for Appendix D Table 2 medications) or baseline, whichever is higher. vandetanib treatment may be resumed at a lower dose after the QTc recovers to < 480 msec (<460 msec for Appendix D Table 2 medications) or baseline.

Figure 2 Management of patients with QTc prolongation



For a QTc interval ≥ 500 msec, but < 550 msec, or an increase of ≥ 60 msec but < 100 msec from baseline QTc to a QTc value ≥ 480 msec (≥ 460 msec for Appendix D Table 2 medications), vandetanib may be continued but a repeat ECG (in triplicate) must be obtained within 48 hours. If QTc prolongation is confirmed, vandetanib should be withheld. ECGs and electrolytes should be checked 3 times a week until QTc falls below 480 msec (460 msec for Appendix D Table 2 medications) or baseline, whichever is higher. vandetanib treatment may

be resumed at a lower dose, as outlined in section 3.4.2.3, after the QTc recovers to < 480 msec (<460 msec for Appendix D Table 2 medications) or baseline. If the patient does not meet the criteria for QTc prolongation at the repeat ECG, then the patient should continue treatment and resume the ECG schedule as outlined in the Study Plan.

If vandetanib is restarted after the QTc prolongation has resolved, ECGs should be performed 1, 2, 4, 8, 13 weeks and then every 3 months after treatment is restarted. If vandetanib must be withheld for >3 weeks to allow for QTc prolongation to recover to <480 msec (<460 msec for Appendix D Table 2 medications) or baseline, the patient will not be restarted on study medication. If QTc prolongation recurs after the dose reduction as detailed, the patient must permanently discontinue treatment with study medication.

For a single QTc value of ≥ 550 msec or an increase of ≥ 100 msec from baseline, vandetanib/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. vandetanib/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 (≥ 460 msec for Appendix D Table 2 medications), blinded vandetanib/placebo may be continued but the QTc must be re-evaluated within 48 hours with 3 consecutive ECGs. If QTc prolongation is confirmed, vandetanib/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. vandetanib/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 vandetanib/placebo is restarted after the QTc prolongation has resolved, it should be given at a reduced dose of vandetanib/placebo100 mg every other day and ECGs should be performed 1, 2, 4, 8, 13 weeks and then every 3 months after treatment is restarted. If vandetanib/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.

3.2.3.4 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, vandetanib/placebo and gemcitabine 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 vandetanib, 100 mg given every other day. Gemcitabine will be reduced to 75% of the original dose [i.e., 900 mg/m^2]). If grade 3 or 4 diarrhoea recurs after dose reduction, a further gemcitabine dose reduction may be undertaken at the discretion of the investigator, or the patient will permanently discontinue both vandetanib/placebo and gemcitabine.

If CTCAE grade 3 or 4 mucositis develops, all treatment must be withheld. vandetanib/placebo should be restarted as soon as the patient is able to swallow the tablets. Gemcitabine should be restarted upon resolution to CTCAE grade 1 and subsequently reduced by 50% to 600 mg/m^2. If CTCAE grade 3 toxicity recurs after dose reduction, a further gemcitabine 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.

3.2.3.5 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, vandetanib/placebo and gemcitabine should be withheld until recovery to grade 1 or baseline. The following actions should be instituted:
  - Gemcitabine should be reduced to 75% of the original dose [i.e., 900 mg/m^2])
  - vandetanib/placebo should be dose reduced from 100mg daily to 100mg every other day

If grade 3 or 4 cutaneous toxicity recurs after dose reduction, the patient will permanently discontinue vandetanib/placebo. A second dose reduction of gemcitabine (i.e. 50% of the

original dose, 600 mg/m^2) may be undertaken at the discretion of the investigator, or the patient will permanently discontinue both vandetanib/placebo and gemcitabine.

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

3.2.3.6 Other toxicity

If any other grade 3 or 4 toxicity that is not outlined in Sections 3.2.3.1to 3.2.3.5 develops and is attributable to either vandetanib/placebo or gemcitabine, vandetanib/placebo and gemcitabine should be withheld until the toxicity resolves to grade 1 or baseline. Upon recovery, patients may resume treatment at a permanently reduced dose; vandetanib 100 mg every other day and gemcitabine reduced. If vandetanib/placebo 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 gemcitabine dose reduction may be undertaken at the discretion of the investigator, or the patient will permanently discontinue both vandetanib/placebo and gemcitabine.

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, vandetanib/placebo must be discontinued and cannot be resumed until blood pressure is controlled to baseline level. Patients with CTCAE grade 4 hypertension should discontinue vandetanib/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 6 Summary of guidance on the management of toxicity for vandetanib/placebo and gemcitabine

Toxicity	Gemcitabine	vandetanib (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 vandetanib.
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.

Toxicity	Gemcitabine	vandetanib (100 mg/placebo)
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 gemcitabine or vandetanib/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.	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.
Grade 3 or 4 allergic reaction/hyper sensitivity that is clearly attributable to gemcitabine	Stop gemcitabine.	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 vandetanib
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 vandetanib
All other grade 3 or 4 toxicity related to gemcitabine and/or vandetanib/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.	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
2. Female or male aged 70 years or above
3. Histologic or cytologic confirmation of advanced NSCLC (stage IIIB with supraclavicular lymph node metastases or pleural effusion or stage IV) on entry into study
4. No prior anti-cancer therapies except in the adjuvant setting
5. WHO Performance status 0 - 2
6. One or more measurable lesions at least 10 mm in the longest diameter (LD) by spiral CT scan or 20 mm with conventional techniques according to RECIST criteria
7. Life expectancy of 12 weeks or longer

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 prior anti-cancer therapy except in the adjuvant setting
3. Prior treatment with gemcitabine
4. Prior treatment with VEGFR TKIs (previous treatment with bevacizumab [Avastin] in the adjuvant setting is permitted)
5. 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

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) (except for patients with known documented cases of Gilbert's syndrome)

11. Creatinine clearance <55 ml/min calculated by either Cockcroft –Gault, 24 hours urine collection, EDTA scan or other validated methods such as Sanaka Formula (see Appendix F).

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 vandetanib 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 $\geq$ 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

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).

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

24. Any concomitant medications that may cause QTc prolongation or induce Torsades de Pointes (see Appendix D for the lists of medications in Table 1 & Table 2) or induce CYP3A4 function (see Section 3.3.4)

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

26. 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

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

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

29. 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. 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)

2. 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 2 months after the last dose of vandetanib

3. 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 vandetanib

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

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

6. 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 gemcitabine

7. The study population is of subjects ≥ 70 years old, therefore is not expected that women of childbearing potential will be recruited in this study. Due to the experimental nature of vandetanib, female patients must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation.). Sexually active male patients must be surgically sterile or using an acceptable method of contraception during their participation in this study.

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.

3.3.5.3 Criteria for discontinuation

Patients may be discontinued from study treatment 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; investigational products should be returned by the patient. The discontinuation visit should take place as soon as possible after the last dose of vandetanib /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 by telephone contact with the patient, patient's family, or by contact with the patient's current physician. The date and details of the first and subsequent therapies for cancer after discontinuation of treatment will be collected.

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 vandetanib /placebo or chemotherapy must be reported to AstraZeneca and must be followed until resolution where possible.

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

3.4 Treatments

3.4.1 Identity of investigational product and gemcitabine

Descriptive information for gemcitabine can be found in Appendix H.

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

Table 7 Formulation of vandetanib

Tablet strength (mg)
vandetanib 100 mg tablet
Placebo to match vandetanib 100 mg tablet

AstraZeneca Pharmaceuticals Investigational Products will supply study medication. AstraZeneca Pharmaceuticals Investigational Products will pack vandetanib/placebo study treatment. vandetanib/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 Vandetanib or placebo regimen

Patients will be given single oral doses of 100 mg vandetanib or placebo daily. vandetanib 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 vandetanib or matching placebo. Patients will continue to receive study treatment until progression of their disease is determined according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, providing they do not meet any other withdrawal or discontinuation criteria. Once a patient has met the study criteria for disease progression on vandetanib / placebo / gemcitabine, randomised treatment must be permanently discontinued. Investigators, remain at liberty to determine the most appropriate therapy for their patients after randomised treatment is discontinued.

Patients enrolled in the study will be dispensed bottles of blinded vandetanib tablets; each bottle will contain vandetanib 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. vandetanib should be taken prior to the administration of gemcitabine but after the blood samples have been collected.

3.4.2.2 Gemcitabine

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

Gemcitabine will be administered at a dose 1200 mg/m^2 as an intravenous infusion on Day 1 and 8 of each 21-day cycle.

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

Patients will receive gemcitabine for up to a maximum of 6 cycles, as long as they do not meet a withdrawal criteria other than disease progression. Once a patient has met the study criteria for disease progression on vandetanib / placebo plus gemcitabine, randomised treatment must be permanently discontinued. Investigators, remain at liberty to determine the most appropriate therapy for their patients after randomised treatment is discontinued

After gemcitabine treatment is completed, patients can continue to receive blinded vandetanib/placebo as a monotherapy as long as the patients are benefiting from treatment, no other systemic anti-cancer therapy is added and no other withdrawal criteria is met.

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

3.4.2.3 Vandetanib dose reduction

Patients who have toxicity related to vandetanib/placebo may have their dose reduced (see section 3.2.3.1 to 3.2.3.5). Table 9 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 8 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

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 22:00 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

Labelling of the investigational product will be performed in accordance with current Good Manufacturing Practice. The labels used will be in accordance with current local regulations.

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.

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 randomization would be done strictly sequentially with blocks of randomization codes being sent to each center as needed.

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 vandetanib and gemcitabine or placebo and gemcitabine.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

Study treatment will be labelled with the patient randomisation number. The active and placebo tablets within each treatment arm will be identical in appearance, taste, and smell 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. 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 vandetanib and radiotherapy. Thus, the investigator may use his/her own discretion of whether to stop or continue vandetanib 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 4.3.4.1).

If the patient discontinues from vandetanib/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.

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

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

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

3.8 Treatment compliance

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

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

- Such deliveries are recorded

- Study treatments are handled and stored safely and properly

- Study treatments are only dispensed to study patients in accordance with the protocol

- Any unused products are returned for destruction in liaison with the AstraZeneca project team

- At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the Investigator or a pharmacist.

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

If the patient is not compliant after 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 9 shows the relationship between the objectives and outcome variables for this study.

Table 9 Objectives and outcome variables

Objective	Variable(s)
Primary	
To demonstrate an improvement in Progression Free Survival (PFS) for vandetanib plus gemcitabine combination compared with gemcitabine plus placebo in patients chemonaïve aged ≥ 70 years with advanced NSCLC	PFS, using RECIST criteria
Secondary	
To evaluate the overall survival for vandetanib in combination with gemcitabine compared with gemcitabine plus placebo	Overall survival
To evaluate the proportion of patients alive at 1-year after randomization for vandetanib in combination with gemcitabine compared with gemcitabine plus placebo	Proportion of patients alive at 1-year
To evaluate 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 vandetanib in combination with gemcitabine compared with gemcitabine plus placebo	Objective response rate (CR + PR), DCR (CR + PR + SD), and DOR as assessed using RECIST criteria
To investigate the TDPS during the period of treatment with investigational therapy	To investigate the TDPS during the period of treatment with investigational therapy
To study the safety and tolerability of vandetanib in combination with gemcitabine 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)

Abbreviations: AE = adverse event; CR = complete response; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; 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; WHO PS = World Health Organization Performance Status.

4.1 Primary variable

The primary outcome variable of this study is progression free survival 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 6.4.

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 4 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)
- Medical history, including all previous but now resolved significant medical conditions; additional data includes detailed smoking history, date of diagnosis, cytotoxic chemotherapy and other anti-cancer therapy history, tumour stage and number of organs involved, histologic type, prior radiation and radiation site, relevant surgical history, reason for withdrawal from prior therapy and most recent date of disease progression
- 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
- WHO PS

- Review of all concomitant medication & prior anti cancer therapy

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

4.3 Efficacy measurement and variables

4.3.1 Progression-free survival (PFS)

4.3.1.1 Methods of assessment

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

4.3.1.2 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.

4.3.2 Overall survival (OS)

4.3.2.1 Methods of assessment

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

4.3.2.2 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.

4.3.3 Proportion of patients alive at 1-year post randomization

Both the patients with known survival status at 1-year post randomization and patients lost to follow-up will be used to calculate the proportion of patients alive at 1-year post randomization.

4.3.3.1 Methods of assessment

The proportion of patients alive at 1-year post randomization is calculated from the date of randomisation to 1-year post randomization. The patients lost to follow-up will be considered in the group of patients who died.

4.3.4 Objective response, disease control and duration of response

4.3.4.1 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 within 28 days 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 gemcitabine}.

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.

4.3.4.2 Derivation or calculation of outcome variable

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

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

4.3.5.1 Methods of assessment

WHO PS is recorded according to the study plan (see Table 1, Table 2, and Table 3).

4.3.5.2 Derivation or calculation of variable

Baseline WHO PS is defined as the measurement recorded closest to, but not subsequent to, the first dose of vandetanib /Placebo or gemcitabine. 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.

4.4 Safety measurements and variables

The methods for collecting safety data are described below.

4.4.1 Adverse events

4.4.1.1 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 gemcitabine 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 require to hospitalise the patient or may require medical intervention to prevent one of the outcomes listed above.

Any event or hospitalisation 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.

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.

4.4.1.2 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 symptomatology

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

(b) Abnormal laboratory values/vital signs/ECGs

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

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

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

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 vandetanib or gemcitabine, **except those that are unequivocally due to disease progression**, an AE form and an SAE form should be completed, detailing the AE that resulted in the death (Please note that death is an outcome, not an event). The SAE must be reported to the study monitor within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

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

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

(g) Overdose

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

(h) Pregnancy

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

4.4.1.3 Reporting of serious adverse events

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

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

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

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

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

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

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

4.4.2 Laboratory safety measurements and variables

4.4.2.1 Methods of assessment

Routine haematology, clinical chemistry and urinalysis assessments will be conducted by the local laboratory at the participating institutions.

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, WBCa, APTTb, INRb
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.
(h) total, with manual or automated differentiation
(i) at screening only, unless patient is on anticoagulation therapy and requires additional evaluation

4.4.2.2 Derivation or calculation of outcome variables

Section 4.4 provides details on how AEs based on laboratory tests will be recorded and reported.

4.4.3 Vital signs, ECG and physical examination

4.4.3.1 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 to determine eligibility relating to QTc values.

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 (≥ 460 msec for Appendix D Table 2 medications)

For a QTc interval ≥ 500 msec, but <550 msec, or an increase of ≥ 60 msec but <100 msec from baseline QTc to a QTc value ≥ 480 msec (≥ 460 msec for Appendix D Table 2 medications), 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 3.2.3.3

It is recommended that a cardiologist at the site 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.

4.4.3.2 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), sinus rhythm (yes/no) and overall evaluation (normal/abnormal).

4.4.3.3 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.

4.4.3.4 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 4.4 for reporting of AEs. Conditions that are considered by the investigator to be unequivocally disease-related will not be recorded as AEs.

4.4.4 Other safety measurements and variables

Not applicable.

4.5 Volume of blood sampling and handling of biological samples

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]
Safety	Clinical chemistry	6[c]	12	72
	Haematology	4.5[c]	12	54
Total		10.5	24	126 mL

(j) Additional samples may be collected if required (e.g., for repeat safety assessments).
(k) These volumes are based on a patient completing 6 cycles of treatment and the discontinuation visit.
(l) 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.

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

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

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 9 for a description of the relationship between specific study objectives and outcome variables.

6.3 Description of analysis sets

Efficacy data from this study will be analyzed on an intention-to-treat (ITT) basis using randomised treatment.

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 vandetanib/gemcitabine.

6.4 Method of statistical analysis

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

For PFS, OS, DOR 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 adjuvant chemotherapy, histology, smoking history, gender. The conclusion will be based on the unadjusted analysis, which is considered as primary. If the unadjusted analysis and the adjusted analysis yield different results, the consequences of the covariate adjustment will be explored.

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

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

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

PFS, OS, DOR, andd 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 adjuvant chemotherapy, histology, smoking history, gender. The conclusion will be based on the unadjusted analysis, which is considered as primary. If the unadjusted analysis and the adjusted analysis yield different results, the consequences of the covariate adjustment will be explored. The results of the analyses will be presented in terms of odds ratios together with associated CIs and 2-sided p-values. The estimates of the differences in the response rates and the corresponding 2-sided 95% CIs will also be presented.

6.4.2 Proportion of patients alive 1-year post-randomisation

The proportion of patients alive 1-year post-randomisation will be summarized for each treatment group using appropriate summary statistics. In addition, multivariate statistics (i.e. logistic regression) will be produced to investigate the relationship between the proportion of patients alive 1-year post-randomisation and for tumour stage, number of organs involved, prior adjuvant chemotherapy, histology, smoking history, gender, ethnic origin.

6.4.3 WHO performance status

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

6.4.4 Safety and tolerability

Safety and tolerability data will be presented by treatment received. Appropriate summaries of these data will be presented. Safety and tolerability will be assessed in terms of AEs, laboratory data, ECG data, vital signs and weight, which will be collected for all 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.

6.5 Determination of sample size

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

Assuming a median PFS of approximately 3 months for gemcitabine (Gridelli C et al 2003), a recruitment period of 12 months and minimum follow-up of 20 months, a minimum of 122 patients (61 per arm) will be enrolled in order to detect a 33.3% prolongation. When the sample size in each group is 61, an exponential maximum likelihood test of equality of survival curves with a 0.200 two-sided significance level will have 80% power to detect the difference between a vandetanib + gemcitabine exponential parameter, λ_1, of 0.1540 (median PFS of 4.5 months) and a Placebo + gemcitabine exponential parameter, λ_0, of 0.2310 (median PFS of 3 months), (a constant hazard ratio of 0.667); this assumes an accrual period of 12 months, a maximum follow-up time of 20 months, and no dropouts. For this comparison, 110 progression events are required (Machin D et al 1997).

PFS, overall survival (OS), DOR, and TDPS and will be analysed using a log-rank test. For PFS, OS, DOR 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 centre, tumour stage, number of organs involved, prior adjuvant

chemotherapy, histology, smoking history, gender. 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.

6.6 Interim analyses

An interim analysis of safety data is planned after a cohort of 12 patients have been enrolled and completed the 1st cycle of trial therapy to confirm that the combination is tolerated. The study recruitment will be stopped for the analysis of safety data, and restarted depending upon the findings of the safety analysis.

6.7 Data monitoring board

This study will not use an external Independent Data and Safety Monitoring Board but the study team will review the safety data on an ongoing basis. Any safety issues will be promptly reported to the Principal Investigators.

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

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed

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

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

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

7.2 Audits and inspections

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

7.3 Training of staff

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

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

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

7.4 Changes to the protocol

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

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

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

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

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

7.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the 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:

- 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 vandetanib 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.

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.

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.

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.

8.3 Informed consent

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

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

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

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

8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and

disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

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

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

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

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

Role in the study	Name	Address & telephone number
Local Study Delivery Team Leader responsible for the protocol	[redacted]	[redacted]
Local Study Delivery Team Physician responsible for the protocol	[redacted]	[redacted]
AstraZeneca Drug Safety representative responsible for the protocol	[redacted]	[redacted]

Role in the study	Name	Address & telephone number
24-hour emergency cover		[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 4.4.1.**

9.3 Procedures in case of overdose

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

- Use of study 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.
- 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

The information on procedures in case of pregnancy is provided, even though it is not expected that pregnancy will occur in this patients population aged ≥ 70 years.

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, sexually active male patients must be surgically sterile or using an acceptable method of contraception during their participation in this study. See section 3.3.4 for more details.

In the event of pregnancy occurring while a patient is receiving vandetanib/gemcitabine, 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.

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Clinical Study Protocol: Appendix A	
Drug Substance	VANDETANIB
Study Code	D4200L00012
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Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™, ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients.

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

[redacted]

[redacted]

Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™ , ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients.

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[redacted]

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AstraZeneca Research and Development site representative [redacted]

[redacted]

[redacted]

Date
(Day Month Year)

SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR AND STUDY PRINCIPAL INVESTIGATOR

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™, ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients.

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.:

Signature: [redacted]

[redacted]

Date
(Day Month Year)

SIGNATURE OF NATIONAL CO-ORDINATING INVESTIGATOR AND STUDY PRINCIPAL INVESTIGATOR

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™, ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients.

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I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Centre No.:

Signature: [redacted]

Date
(Day Month Year)

SIGNATURE OF PRINCIPAL INVESTIGATOR

Phase II, Randomised, double-blind, two-arm, parallel study of Vandetanib (ZACTIMA™, ZD6474) plus Gemcitabine (Gemzar®) or Gemcitabine plus Placebo as first line treatment of advanced (stage IIIB or IV) Non Small Cell Lung Cancer (NSCLC) Elderly patients.

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Centre No.:

Signature:

_____ _____

Date
(Day Month Year)

Clinical Study Protocol: Appendix B

Drug Substance	VANDETANIB
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Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol: Appendix C	
Drug Substance	VANDETANIB
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Appendix C
WHO Performance Status

1. WHO PERFORMANCE STATUS

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

Table 1 WHO Performance Status

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

Clinical Study Protocol Appendix D	
Drug Substance	VANDETANIB
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Appendix D
Medications known to prolong QT

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

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

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

Concomitant use of these drugs (Table 1) is not allowed during the study or within 2 weeks of study entry (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment:

Table 1 Group 1 Drugs

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

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

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

If a patient is receiving one of the medications in this group (Table 2) prior to study entry, and it cannot be discontinued before study entry, then the screening QTc must be ≤ 460msec, and an additional ECG must be obtained 4-8 hours after the first dose of study medication. For patients who start on one of the drugs in this group while on the study, these drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the subject must be closely monitored, including regular checks of QTc and electrolytes (see Section 3.7.2 of the protocol).

Table 2 Group 2 Drugs

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

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Amoxapine	Tricyclic anti-depressant (depression)	
Azithromycin	Antibiotic (bacterial infection)	
Citalopram	Anti-depressant (depression)	
Clarithromycin	Antibiotic (bacterial infection)	TdP Cases in Literature
Clomipramine	Tricyclic antidepressant (depression)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Desipramine	Tricyclic anti-depressant (depression)	TdP Cases in Literature
Dolastron	Anti-nausea (nausea and vomiting)	
Doxepin	Anti-depressant (depression)	TdP Cases in Literature
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Fluconazole	Anti-fungal (fungal infection)	
Fluoxetine	Anti-depressant (depression)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron	Anti-nausea (nausea and vomiting)	
Imipramine	Anti-depressant (depression, pain, other)	TdP Cases in Literature
Indapamide	Diuretic (stimulates urine & salt loss)	TdP Cases in Literature, QT in animals
Isradipine	Anti-hypertensive (high blood pressure)	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lithium	Anti-mania (bipolar disorder)	
Mexilitine	Anti-arrhythmic (abnormal heart rhythm)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	

Drug – Generic Names	Drug Class (Clinical Usage)	Comments
Moxifloxacin	Antibiotic (bacterial infection)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nortriptyline	Tricyclic antidepressant (depression)	
Octreotide	Endocrine (acromegaly/carcinoid diarrhoea)	
Ofloxacin	Antibiotic (bacterial infection)	
Ondansetron	Anti-emetic (nausea and vomiting)	
Paroxetine	Anti-depressant (depression)	
Protriptyline	Tricyclic antidepressant (depression)	
Quetiapine	Anti-psychotic (schizophrenia)	
Risperidone	Anti-psychotic (schizophrenia)	
Roxithromycin	Antibiotic (bacterial infection)	
Salmeterol	Sympathomimetic (asthma, COPD)	
Sertraline	Antidepressant (depression)	Association not clear
Solifenacin	Muscarinic receptor antagonist (treatment of overactive bladder)	
Tacrolimus	Immune suppressant	TdP Cases in Literature
Tamoxifen	Anti-cancer (breast cancer)	
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Trimipramine	Tricyclic antidepressant (depression)	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

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Clinical Study Protocol Appendix E	
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Study Code	D4200L00012
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Appendix E
Response Evaluation Criteria in Solid Tumours (RECIST)

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LIST OF TABLES

1. DEFINITION OF MEASURABLE AND NON-MEASURABLE LESIONS

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

Table 1 Definition of Lesions

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

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

Bone lesions;

Leptomeningeal disease;

Ascites;

Pleural / pericardial effusion;

Inflammatory breast disease;

Lymphangitis cutis/pulmonis;

Abdominal masses that are not confirmed and followed by imaging techniques;

Cystic lesions.

Note: Previously irradiated lesions will not be considered measurable.

2. METHODS OF MEASUREMENT

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

2.1 Clinical lesions

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

2.2 Chest x-ray

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

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

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

In this study, it is recommended that examinations of the chest, abdomen and pelvis will be collected as part of the scheduled RECIST assessments.

2.4 Ultrasound

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

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

2.5 Endoscopy and laparoscopy

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

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

2.6 Tumour markers

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

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

2.7 Cytology and histology

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

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

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

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

3. TUMOUR RESPONSE EVALUATION

3.1 Assessment of overall tumour burden and measurable disease

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

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

3.1.1 Documentation of “target” and “non-target” lesions

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

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

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

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

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

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

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

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

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent" or "present with progression".

4. RESPONSE CRITERIA

4.1 Evaluation of target lesions

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

Table 2 Evaluation of Target Lesions

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

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

4.2 Evaluation of non-target lesions

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

Table 3 Evaluation of Non-Target Lesions

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

[a] Note: Appearance of new lesions only counts towards the overall visit response, not towards the response of target or non-target lesions. Tumour marker levels will not be taken into account for assessment of response in his study.

4.3 Evaluation of best overall response

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

Table 4 Evaluation of Best Overall Response

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

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to ensure "symptomatic deterioration" patients continue to have objective tumour assessments at withdrawal from trial and until progression is confirmed by imaging.

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

5. CONFIRMATORY MEASUREMENT

5.1 Confirmation

The main goal of confirmation of objective response is to minimize the risk of overestimation of the response rate. This aspect of response evaluation is particularly important in non-randomized trials where response is the primary endpoint. In this setting, to be assigned a status of PR or CR, changes in tumour measurements must be confirmed, preferably by repeat studies at the next scheduled RECIST assessment at every 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.

6. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

6.1 Chest X-ray (CXR)

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

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

6.2 CT

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

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

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

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

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

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

Intra-venous (IV) contrast agents should also be given, unless contra-indicated for medical reasons, such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. Although in clinical practice its use may add little, in the context of a clinical study where objective response rate based on measurable disease is the endpoint, unless an IV contrast agent is given, a significant number

of otherwise measurable lesions will not be measurable. In patients in whom the disease is apparently restricted to the periphery of the lungs, for example, the use of IV contrast agents appears unnecessary, but the aim of a clinical study is to ensure lesions are truly resolving, and there is no evidence of new disease at other sites scanned, eg, small metastases in the liver.

The method of administration of IV contrast agents is variable. Rather than try to institute rigid rules regarding methodology of administration of contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given such that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.

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

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

6.3 MRI

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

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

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

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

acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

7. REFERENCES

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

Clinical Study Protocol Appendix F	
Drug Substance	VANDETANIB
Study Code	D4200L00012
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix F
Cockcroft-Gault Formula and Sanaka Formula

1. MODIFIED COCKCROFT-GAULT FORMULA

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

US units:

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

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

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

SI units:

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

88.40 mg/dL = 1 µmol/L

The Cockroft Equation (Nephron 1976; 16:31) is adequate for most adult patients with normal muscle mass and serum creatinine (Scr) < 4.5 mg/dL

2. THE SANAKA EQUATION

For elderly pts (>60) with very low muscle mass and who do not have nephrotic syndrome or severe hepatic disease, the CLcr may be estimated by the Sanaka equation (Nephron 1996; 73:137-144):

CLcr (male) = ABW (19 Alb +32) / 100 Scr

CLcr female)= ABW (13 Alb +29) / 100 Scr

Where: Alb = plasma albumin level (g/dL); Scr = serum creatinine (mg/dL).

ABW = actual body weight in Kg

The metric version of the Sanaka equations:

CLcr (male) = ABW (2 Alb + 35) / 1.24 Scr

CLcr (female) = ABW (Alb + 22) / 0.87 Scr

Where: Alb = plasma albumin level (g/dL);

Scr = serum creatinine (µm/L).

ABW = actual body weight in Kg

Ideal Body Weight

Non-metric Version

IBW (male) = 50 + 2.3 (H - 60)

IBW (fem) = 45.5 + 2.3 (H - 60)

IBW= ideal body weight (Kg);

H = height in inches

The metric version

IBW (male) = 0.9 H - 88

IBW (fem) = 0.9 H - 92

H = height in centimeters.

Dosing Weight = DW = IBW + 0.4 (ABW - IBW). Where: ABW = actual body wt. in Kg

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Clinical Study Protocol Appendix G	
Drug Substance	VANDETANIB
Study Code	D4200L00012
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix G
New York Heart Association (NYHA) Cardiac Classification

1. NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system (Table 1 New York Heart Association Cardiac Classification) relates symptoms to everyday activities and the patient's quality of life.

Table 1 New York Heart Association Cardiac Classification

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

Clinical Study Protocol Appendix H	
Drug Substance	VANDETANIB
Study Code	D4200L00012
Appendix Edition Number	1
Appendix Date	[redacted]

Appendix H
Cover Gemcitabine (GEMZAR®) Label

RIASSUNTO DELLE CARATTERISTICHE DI PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

GEMZAR 200 mg, polvere per soluzione per infusione e per instillazione endovescicale
GEMZAR 1 g, polvere per soluzione per infusione e per instillazione endovescicale

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

	Flacone da 200 mg	Flacone da 1 g
Ogni flacone contiene:		
Principio attivo		
Gemcitabina cloridrato equivalente a gemcitabina	200 mg	1 g

Per gli eccipienti vedere 6.1

3. FORMA FARMACEUTICA

Polvere per soluzione per infusione e per instillazione endovescicale.

4. INFORMAZIONI CLINICHE

4.1 *Indicazioni terapeutiche*

GEMZAR è indicato nel trattamento di pazienti con carcinoma polmonare non a piccole cellule localmente avanzato o metastatico.
GEMZAR è indicato nel trattamento di pazienti con adenocarcinoma del pancreas localmente avanzato o metastatico. GEMZAR è indicato nei pazienti con carcinoma pancreatico refrattario alla terapia con 5-Fluorouracile. GEMZAR può apportare miglioramenti in termini di sopravvivenza, beneficio clinico significativo, od entrambi.
GEMZAR è indicato nel trattamento di pazienti con carcinoma della vescica.
GEMZAR, in combinazione con paclitaxel, è indicato nel trattamento di pazienti con carcinoma della mammella non resecabile localmente ricorrente o metastatico che hanno recidivato dopo chemioterapia adiuvante e/o neoadiuvante.
GEMZAR in combinazione con carboplatino è indicato nel trattamento di pazienti con carcinoma ricorrente dell'epitelio dell'ovaio che hanno recidivato almeno 6 mesi dopo terapia con platino.

4.2 *Posologia e modo di somministrazione*

GEMZAR può essere somministrato in regime di day-hospital.

Carcinoma del Polmone Non a Piccole Cellule
Pazienti adulti. La dose di gemcitabina generalmente consigliata è di 1.000 mg/m^2, da somministrare per via endovenosa in 30 minuti, una volta a settimana per 3 settimane consecutive (giorni 1-8-15), facendo poi seguire una settimana di riposo. Questo ciclo di 4 settimane può essere ripetuto.
La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco nel paziente.

Carcinoma del Pancreas
Pazienti adulti. La dose di gemcitabina generalmente consigliata è di 1.000 mg/m^2, da somministrare per via endovenosa in 30 minuti, una volta a settimana per 7 settimane consecutive facendo poi seguire una settimana di riposo. I cicli successivi dovranno consistere di somministrazioni una volta a settimana per 3 settimane consecutive, facendo poi seguire una settimana di riposo.
La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco nel paziente.

Carcinoma della Vescica

Pazienti adulti. La dose di gemcitabina generalmente consigliata è di 1.250 mg/m^2, da somministrare per via endovenosa in 30 minuti, nei giorni 1-8-15 di ciascun ciclo di 28 giorni. Questo ciclo di 4 settimane può essere ripetuto. La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco nel paziente.
Gemcitabina può essere somministrata in combinazione polichemioterapica con cisplatino. La dose di gemcitabina generalmente consigliata è di 1.000 mg/m^2, da somministrare per via endovenosa in 30 minuti, nei giorni 1-8-15 di ciascun ciclo di 28 giorni. La dose di cisplatino generalmente consigliata è di 70 mg/m^2, da somministrare il giorno seguente la somministrazione di gemcitabina oppure il giorno 2 di ciascun ciclo di 28 giorni. Questo ciclo di 4 settimane può essere ripetuto. La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco nel paziente. Uno studio clinico ha dimostrato una maggiore riduzione della funzionalità midollare quando il cisplatino era stato impiegato a dosi di 100 mg/m^2.
Uso endovescicale (vedi anche 5.1 "Proprietà farmacodinamiche"):
Pazienti adulti. Nel trattamento del carcinoma superficiale della vescica la dose raccomandata di gemcitabina da somministrare per via endovescicale è di 2000 mg diluiti in 100 ml o 50 ml di soluzione fisiologica (concentrazione pari a 20 o 40 mg/ml). La dose di farmaco deve essere somministrata per un tempo di instillazione pari a 60 minuti una volta a settimana per sei settimane consecutive. La concentrazione della soluzione non deve essere superiore a 40 mg/ml e riduzioni del dosaggio possono essere effettuate in base al grado di tossicità causata dal farmaco nel paziente.

Carcinoma della Mammella
Pazienti adulti. Gemcitabina in combinazione con paclitaxel è raccomandata somministrando paclitaxel (175 mg/m^2) per infusione endovenosa della durata di circa 3 ore il giorno 1, seguita da gemcitabina (1.250 mg/m^2) per infusione endovenosa della durata di 30 minuti nei giorni 1 e 8 di ciascun ciclo di 21 giorni. La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco nel paziente. I pazienti devono avere una conta assoluta dei granulociti di almeno 1.500/mm^3 prima di iniziare la somministrazione di gemcitabina associata a paclitaxel.

Carcinoma dell'Ovaio
Pazienti adulti. La dose di gemcitabina consigliata in combinazione con carboplatino è di 1.000 mg/m^2, da somministrare per infusione endovenosa in 30 minuti, nei giorni 1 e 8 di ciascun ciclo di 21 giorni. Il carboplatino verrà somministrato dopo la gemcitabina il giorno 1 in modo tale da raggiungere una AUC di 4,0 mg/ml per minuto. La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco sul paziente.

I pazienti in terapia con GEMZAR devono essere sottoposti prima di ogni somministrazione ad un controllo delle piastrine, dei leucociti e dei granulociti; se necessario, in caso di tossicità ematologica del paziente, il medico può ridurre o ritardare nel tempo la dose di gemcitabina da somministrare secondo il seguente schema:

GRANULOCITI		**PIASTRINE**	**DOSE DA SOMMINISTRARE**
>1.000/mm^3	**e**	**>100.000/mm^3**	**100% della dose**
500-1.000/mm^3	**o**	**50.000-100.000/mm^3**	**75% della dose**
<500/mm^3	**o**	**<50.000/mm^3**	**non somministrare**

Un esame obiettivo periodico del paziente e controlli della funzionalità epatica e renale devono essere effettuati per individuare una tossicità non ematologica. La riduzione del dosaggio nell'ambito di un ciclo o durante cicli successivi di terapia può essere effettuata in base al grado di tossicità causata dal farmaco sul paziente.
Le dosi devono essere sospese fino a quando, secondo il parere del medico, la tossicità non si è risolta.
Pazienti anziani. La gemcitabina è stata ben tollerata in pazienti sopra i 65 anni di età. Non c'è evidenza che nell'anziano siano necessari aggiustamenti della dose oltre a quelli già consigliati, sebbene la clearance e l'emivita di gemcitabina siano influenzate dall'età.

Compromissione renale e/o epatica. La gemcitabina dovrebbe essere usata con cautela e a dosaggi ridotti nei pazienti con insufficienza epatica e/o renale, in quanto le informazioni insufficienti provenienti da studi clinici non consentono di raccomandare una dose precisa per questa popolazione di pazienti.
Un'insufficienza renale di grado da lieve a moderato (filtrato glomerulare da 30 ml/min a 80 ml/min) non ha un effetto costante e significativo sulla cinetica di gemcitabina.

4.3 ***Controindicazioni***
Gemcitabina è controindicata nei pazienti che presentano ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti.
Gemcitabina è controindicata durante la gravidanza e l'allattamento (vedere 4.6).

4.4 ***Avvertenze speciali e opportune precauzioni d'impiego***
Il prolungamento del tempo di infusione ed un'aumentata frequenza di somministrazioni possono determinare un aumento della tossicità del farmaco.
GEMZAR può determinare riduzione della funzionalità midollare, come evidenziato dalla comparsa di leucopenia, piastrinopenia ed anemia. Comunque la riduzione della funzionalità midollare è di breve durata e generalmente non richiede riduzioni di dosaggio e solo raramente può comportare interruzione del trattamento.
E' necessario che la somministrazione del farmaco sia effettuata in centri specializzati, con personale e strutture adeguate poiché i pazienti in terapia con gemcitabina devono essere monitorizzati costantemente.
La terapia deve essere iniziata con cautela nei pazienti con funzionalità midollare compromessa.
Come per altri antitumorali, quando GEMZAR viene usato in combinazione o in sequenza con altri chemioterapici deve essere tenuta in considerazione la possibilità di una riduzione della funzionalità midollare cumulativa.
Nei pazienti in terapia con GEMZAR prima di ogni somministrazione devono essere effettuate la conta delle piastrine, dei leucociti e dei granulociti. In caso di riduzione della funzionalità midollare secondaria alla somministrazione del farmaco, dovrebbe essere valutata la possibilità di modificare o interrompere la terapia.
Gli elementi cellulari ematologici periferici possono continuare ad abbassarsi anche dopo interruzione della terapia.
La somministrazione di gemcitabina a pazienti con presenza di metastasi epatiche o con precedenti anamnestici di epatite, alcolismo, o cirrosi epatica può condurre ad una esacerbazione dell'insufficienza epatica di base.
Uso nei bambini
Sono stati eseguiti studi limitati di fase I e II con gemcitabina nei bambini in diversi tipi tumorali. Questi studi non hanno fornito dati sufficienti a determinare l'efficacia e la sicurezza del farmaco nei bambini.

4.5 ***Interazioni con altri medicinali e altre forme di interazione***
Radioterapia concomitante (effettuata contemporaneamente o separatamente entro un intervallo di tempo ≤ a 7 giorni): la tossicità associata con questa terapia combinata dipende da diversi fattori, inclusi dose e frequenza di somministrazione della gemcitabina, dose della radiazione, piano di trattamento radioterapico e tecnica applicata, tipo e volume di tessuto irradiato. Studi clinici e preclinici hanno dimostrato un'attività radiosensibilizzante della gemcitabina.
Nel corso di una sperimentazione clinica in cui GEMZAR è stato somministrato alla dose di 1.000 mg/m^2 per 6 settimane consecutive in concomitanza con una radioterapia toracica in pazienti con carcinoma polmonare non a piccole cellule, è stata osservata una tossicità significativa manifestatasi con gravi esofagiti e polmoniti potenzialmente a rischio di vita per i pazienti, particolarmente quelli trattati con radioterapia su campi estesi. I risultati di studi effettuati successivamente hanno suggerito che è realizzabile una somministrazione di gemcitabina a dosi inferiori in concomitanza con radioterapia in quanto presenta una tossicità prevedibile, come è risultato da uno studio di fase II su pazienti con carcinoma polmonare non a piccole cellule. Radioterapia al torace a dosi di 66Gy è stata somministrata in concomitanza con gemcitabina (600 mg/m^2, quattro volte) e cisplatino (80 mg/m^2, due volte) nel corso di 6 settimane. Svariati studi di fase I e II hanno dimostrato che è realizzabile una

somministrazione di gemcitabina in monoterapia a dosaggi fino a 300 mg/m^2/settimana in concomitanza con radioterapia nel trattamento del carcinoma polmonare non a piccole cellule e del carcinoma del pancreas. Il regime ottimale per una somministrazione sicura di GEMZAR in concomitanza con dosi radianti terapeutiche, non è stato ancora determinato in tutti i tipi tumorali.
Radioterapia non concomitante (effettuata separatamente in un periodo di tempo superiore ai 7 giorni): l'analisi dei dati non suggerisce alcun aggravamento della tossicità nel caso in cui la gemcitabina sia somministrata fino a 7 giorni prima o dopo l'effettuazione della radioterapia, ad eccezione del fenomeno di "recall" da radiazione. I dati indicano che la terapia con gemcitabina può essere iniziata dopo che gli effetti acuti della radioterapia si sono risolti o almeno dopo una settimana dalla sua effettuazione.

Lesioni da radiazione sono state osservate su tessuti bersaglio (es. esofagiti, coliti e polmoniti) in associazione con l'uso, sia concomitante che non, di gemcitabina.

4.6 ***Gravidanza e allattamento***
L'uso della gemcitabina è controindicato in gravidanza e durante l'allattamento per il potenziale danno per il feto o infante.
Nella specie umana non è stata accertata la sicurezza di questo farmaco in gravidanza.
Studi sperimentali condotti negli animali hanno evidenziato una tossicità sull'attività riproduttiva, difetti congeniti od altri effetti sullo sviluppo dell'embrione o del feto, sul corso della gestazione o sullo sviluppo peri- o post-natale.
La gemcitabina può causare danno fetale quando somministrata in donne in gravidanza ed ha dimostrato di possedere proprietà teratogeniche nei topi e nei conigli a dosaggi inferiori di 2 mg/m^2.
Nel caso in cui gemcitabina venga somministrata a pazienti in gravidanza o nel caso in cui la paziente rimanga incinta durante la terapia con gemcitabina, essa deve essere avvertita del potenziale danno per il feto.
Donne in età fertile dovrebbero essere sconsigliate di iniziare una gravidanza durante la terapia.
Non è noto se la gemcitabina od i suoi metaboliti sono escreti nel latte materno. Considerando che molti farmaci sono escreti nel latte materno ed i potenziali effetti collaterali gravi della gemcitabina nei lattanti, la madre deve esserne messa a conoscenza e deve essere valutato se sia più proficuo interrompere l'allattamento o sospendere la terapia, tenendo conto dell'importanza del farmaco per la madre e dei potenziali rischi per l'infante.

4.7 ***Effetti sulla capacità di guidare veicoli e sull'uso di macchinari***
L'uso di gemcitabina può causare sonnolenza di entità lieve o moderata. I pazienti dovrebbero pertanto essere avvertiti di usare cautela nella guida di autoveicoli o nell'operare con macchinari pericolosi, finché siano ragionevolmente sicuri che il trattamento farmacologico non interferisca sfavorevolmente su queste loro capacità.

4.8 ***Effetti indesiderati***
Sono stati osservati effetti indesiderati a carico dei seguenti apparati:
Ematopoietico: essendo la gemcitabina una sostanza con attività mielosoppressiva, a seguito della sua somministrazione possono verificarsi anemia, leucopenia e piastrinopenia. Inoltre, viene comunemente osservata neutropenia febbrile.
La riduzione della funzionalità midollare varia da lieve a moderata ed è più pronunciata per la conta dei granulociti.
Nei 2/3 dei pazienti che hanno presentato anemia solo il 7% aveva livelli di emoglobina inferiori a 8 g%. Nel 19% dei pazienti che avevano ricevuto trasfusioni, solo lo 0,2% di questi aveva interrotto la terapia a causa dell'anemia.
I leucociti risultano diminuiti nel 61% dei pazienti ma solo il 9% di questi aveva una conta leucocitaria inferiore a 2.000/mm^3 e solo lo 0,1% aveva dovuto interrompere la terapia per la leucopenia.
I granulociti risultano diminuiti nel 64% dei pazienti e quasi il 25% di essi presentava valori inferiori a 1.000/mm^3. La piastrinopenia è stata riscontrata nel 21% dei pazienti ma solo nel 5% di questi si avevano valori inferiori a 50.000/mm^3 e solo nello 0,4% dei pazienti con piastrinopenia fu interrotto il trattamento.

Una precedente terapia con agenti citotossici può determinare un aumento della frequenza e gravità della leucopenia, granulocitopenia e piastrinopenia. Non è dimostrata una tossicità ematologica cumulativa e l'anemia può essere trattata ricorrendo a trasfusioni.
In rari casi di piastrinopenia si è verificata anche emorragia, peraltro ritenuta correlata alla malattia del paziente. Sono stati comunemente riportati anche casi di piastrinosi (7,5%), che non hanno comunque richiesto l'interruzione del trattamento.
Apparato gastro-enterico: modificazioni delle transaminasi si presentano in circa i 2/3 dei pazienti, ma sono usualmente di lieve entità, transitorie e raramente comportano l'interruzione del trattamento.
Meno del 10% dei pazienti hanno avuto valori delle transaminasi superiori di 5 volte i valori normali e solo lo 0,5% dei pazienti ha interrotto il trattamento per alterazioni della funzionalità epatica. Aumenti della fosfatasi alcalina fino a valori 5 volte superiori quelli normali si sono verificati nel 6,6% dei pazienti ma potrebbero essere stati provocati da alterazioni a carico delle ossa. Valori di bilirubinemia 5 volte superiori quelli normali furono osservati nell'1,5% dei pazienti ma il 90% dei pazienti aveva valori di bilirubinemia normali.
La gemcitabina dovrebbe essere usata con cautela in pazienti con funzionalità epatica alterata.
La nausea, sia singolarmente che accompagnata da vomito, è stata osservata in circa 1/3 dei pazienti. Questo effetto indesiderato richiede una terapia in circa il 20% dei pazienti, è raramente dose-limitante ed è facilmente trattabile con gli antiemetici tradizionali. Solo lo 0,9% dei pazienti ha presentato vomito intrattabile e solo lo 0,9% dei pazienti ha interrotto il trattamento a causa della comparsa di nausea e vomito.
In alcuni pazienti (7%) è stata osservata diarrea di entità da lieve a moderata; solo raramente è stato necessario ricorrere alla terapia e comunque nessun paziente è stato costretto a sospendere il trattamento con gemcitabina a causa di questo effetto indesiderato.
E' stata inoltre osservata stomatite (7%).
Apparato renale: lieve proteinuria ed ematuria sono state riscontrate in circa la metà dei pazienti, ma raramente hanno raggiunto valori clinicamente significativi e non sono usualmente associate a variazioni della creatininemia o dell'uremia. La gemcitabina dovrebbe essere usata con cautela nei pazienti con funzionalità renale alterata.
Nei pazienti in trattamento con gemcitabina sono state raramente riportate segnalazioni cliniche compatibili con una sindrome uremica emolitica (H.U.S.). L'interruzione del trattamento costituisce la prima misura da adottare in presenza di segni sospetti di H.U.S.; il danno renale potrebbe non essere reversibile anche dopo l'interruzione del trattamento ed in tali casi dovrà essere preso in considerazione il ricorso alla dialisi.
Manifestazioni allergiche: circa il 25% dei pazienti ha presentato un eritema, associato a prurito nel 10% dei casi.
L'eritema è usualmente di lieve entità, non è dose-limitante e risponde alla terapia locale. Raramente sono state osservate desquamazione, vescicolazione ed ulcerazione. In rari casi (0,3%) la tossicità cutanea ha determinato sospensione del trattamento. La gemcitabina è generalmente ben tollerata durante l'infusione e sono stati osservati solo pochi casi di reazione nel sito di iniezione, ma nessun caso di necrosi tissutale nell'area circostante la sede di infusione.
In meno dell'1% dei pazienti è stato osservato broncospasmo dopo la somministrazione di gemcitabina; il broncospasmo è generalmente di lieve entità e transitorio, ma talora può richiedere trattamento per via parenterale.
La gemcitabina non deve essere somministrata a pazienti con accertata ipersensibilità al farmaco. Una reazione di tipo anafilattoide è stata osservata molto raramente.
Manifestazioni polmonari**:** circa il 10% dei pazienti, poche ore dopo la somministrazione di gemcitabina, ha presentato dispnea che, generalmente, è risultata essere di lieve entità, di breve durata, raramente dose-limitante e, di solito, è scomparsa senza effettuare alcuna terapia specifica. Non è nota l'etiopatogenesi di questo effetto e neppure è chiara la sua correlabilità con la gemcitabina.
Solo lo 0,6% dei pazienti ha interrotto il trattamento per la comparsa di dispnea e solo lo 0,1% di questi casi sono stati considerati correlati alla terapia.
Manifestazioni polmonari, talvolta gravi (come l'edema polmonare, la polmonite interstiziale, o la sindrome da distress respiratorio dell'adulto - ARDS), sono state riscontrate raramente durante terapia con gemcitabina. La causa di tali manifestazioni non è nota. Se si verificano tali manifestazioni, considerare la possibilità di interrompere il trattamento con gemcitabina. L'impiego tempestivo di misure di supporto adeguate può contribuire a migliorare il quadro clinico.

Manifestazioni a carico del sistema nervoso centrale: circa il 10% dei pazienti ha presentato sonnolenza di entità variabile e solo lo 0,1% di essi ha interrotto la terapia a causa di questo evento. Raramente sono state osservate anche astenia (con interruzione della terapia nell'1,4% dei pazienti) e parestesie (3,4%).
Sindrome simil-influenzale: una sindrome simil-influenzale è stata osservata in circa il 20% dei pazienti. Questa è risultata di lieve entità, di breve durata e, raramente, dose-limitante; solo nell'1,5% dei pazienti si è manifestata con una certa gravità.
Febbre, cefalea, mal di schiena, brividi, mialgia, astenia ed anoressia sono stati i sintomi più comunemente osservati. Altri sintomi possono essere: tosse, rinite, sensazione di malessere generale, sudorazione ed insonnia.
La febbre e l'astenia sono stati osservati anche come sintomi isolati. Il meccanismo di questa tossicità è sconosciuto; il paracetamolo, secondo il parere medico, può produrre un sollievo sintomatico.
Edema ed edema periferico: sono stati osservati in circa il 30% dei pazienti; in alcuni casi è stato osservato anche edema facciale.
L'edema e l'edema periferico, di entità da lieve a moderata, raramente dose-limitante, talvolta sono associati a dolore e sono generalmente reversibili dopo interruzione del trattamento con gemcitabina. L'etiopatogenesi di questa tossicità è sconosciuta e non risulta associata ad insufficienza cardiaca, epatica o renale.
Solo lo 0,7% dei pazienti ha interrotto il trattamento a causa della comparsa di edemi.
Sistema vascolare: sono stati osservati molto raramente segni clinici di vasculite periferica e gangrena.
Cute ed annessi: sono state osservate molto raramente reazioni cutanee gravi, comprendenti desquamazione ed eruzioni cutanee bollose.
Sistema epatobiliare: sono state osservate raramente alterazioni dei valori dei tests di funzionalità epatica comprendenti innalzamenti di aspartato aminotransferasi (AST), alanina aminotransferasi (ALT), gamma-glutamil transferasi (GGT), fosfatasi alcalina e dei livelli di bilirubina.
Lesione, avvelenamento e complicanze correlate alla procedura di somministrazione: sono stati osservati fenomeni di "recall" da radiazione.
Altri effetti indesiderati: minima perdita di capelli (13%), stitichezza (6%) e tossicità da radiazioni (vedi 4.5 "Interazioni con altri medicinali e altre forme di interazione").
Sono stati inoltre osservati pochi casi di ipotensione, di infarto del miocardio, di scompenso cardiaco e di aritmie, ma non c'è stata una chiara correlazione tra la somministrazione della gemcitabina ed una tossicità cardiaca.
Dopo somministrazione endovescicale sono stati osservati più frequentemente disuria, ematuria, urgenza di urinare e frequenza urinaria.

4.9 *Sovradosaggio*
Non esistono antidoti per il sovradosaggio di gemcitabina. Dosi uniche fino a 5.700 mg/m^2 sono state somministrate per infusione endovenosa in 30 minuti ogni 2 settimane con una tossicità clinicamente accettabile.
In caso di sospetto sovradosaggio, il paziente dovrebbe essere sottoposto ad appropriati esami ematologici e ricevere, se necessario, terapia di supporto.

5. PROPRIETA' FARMACOLOGICHE
5.1 *Proprietà farmacodinamiche*
Categoria terapeutica: Farmaci antineoplastici, Analoghi della pirimidina – ATC: L01BC05 - Gemcitabina
La gemcitabina viene metabolizzata a livello intracellulare dalla nucleoside-chinasi nei nucleosidi attivi difosfato e trifosfato.
L'attività citotossica della gemcitabina è dovuta all'inibizione della sintesi del DNA cellulare ad opera dei suoi due metaboliti attivi, la difluorodeossicitidindifosfato (dFdCDP) e la difluorodeossicitidintrifosfato (dFdCTP).
Inizialmente la dFdCDP inibisce la ribonucleotide reduttasi, che è l'unico enzima responsabile della catalizzazione delle reazioni producenti i trifosfati deossinucleosidici necessari per la sintesi del DNA. L'inibizione di questo enzima da parte della dFdCDP causa una riduzione della concentrazione dei deossinucleosidi in generale e, in particolare, della dCTP.

Secondariamente, la dFdCTP compete con la dCTP per l'incorporazione nel DNA. Similmente, una piccola quantità di gemcitabina può anche essere incorporata nel RNA. Di conseguenza, la riduzione nella concentrazione intracellulare della dCTP potenzia l'incorporazione della dFdCTP nel DNA (autopotenziamento).
La DNA e-polimerasi è essenzialmente incapace di rimuovere la gemcitabina e riparare le catene di DNA in replicazione. Dopo che la gemcitabina è stata incorporata nel DNA, un nucleotide supplementare viene aggiunto alle catene di DNA in replicazione. Dopo questa aggiunta, si verifica una completa inibizione dell'ulteriore sintesi del DNA (mascheramento della catena terminale). Dopo essere stata incorporata nel DNA, la gemcitabina appare indurre il programmato processo di morte cellulare conosciuto come apoptosi.
L'azione citotossica in vitro della gemcitabina dipende sia dalla concentrazione che dal tempo di esposizione. Presenta una specificità a seconda della fase del ciclo cellulare, uccidendo soprattutto quelle cellule che si trovano nella fase di sintesi del DNA (fase S) e bloccando, in particolari condizioni, il passaggio delle cellule dalla fase G1 alla fase S.

La gemcitabina mostra una significativa attività citotossica verso varie colture cellulari tumorali murine ed umane.

Una serie di studi di fase II ha dimostrato che la gemcitabina per via endovescicale è in grado di prolungare l'intervallo libero da recidive e di indurre risposte patologiche complete in pazienti con lesioni marker. L'uso di gemcitabina è indicato in pazienti affetti da carcinoma vescicale superficiale a basso-medio rischio recidivati dopo un trattamento endovescicale di prima linea (vedi 4.2 "Posologia e Modo di somministrazione").

5.2 ***Proprietà farmacocinetiche***
Dopo un'infusione di 30 minuti di una dose di 1.000 mg/m^2 di gemcitabina radiomarcata, il 92-98% della dose viene eliminato entro una settimana dalla somministrazione. Della quota eliminata, il 99% viene escreto per via urinaria ed è costituito dal metabolita inattivo uracilico 2'-deossi-2',2'-difluorouridina (dFdU), mentre meno dell'1% viene eliminato con le feci.
La gemcitabina si lega in modo trascurabile alle proteine plasmatiche e la sua distribuzione tissutale non è ampia.
La gemcitabina viene rapidamente metabolizzata in dFdU dalla citidina deaminasi presente nel fegato, nel rene, nel sangue ed in altri tessuti. Meno del 10% del farmaco viene eliminato per via urinaria in maniera immodificata. Il metabolita dFdU si distribuisce ampiamente nei tessuti e viene eliminato immodificato nelle urine. Non esistono studi condotti in pazienti con insufficienza renale od epatica.
L'eliminazione del metabolita dipende dall'escrezione renale; quindi, in caso di diminuita funzionalità renale dovrebbe determinarsi un accumulo di dFdU. Una alterazione della funzionalità epatica può ridurre la percentuale di formazione della dFdU, ma non influenzarne l'eliminazione.
A livello intracellulare la gemcitabina viene trasformata in metaboliti mono-, di- e trifosfati, che comunque non sono rilevabili nel plasma o nelle urine.
Ai dosaggi esaminati la farmacocinetica della gemcitabina è di tipo lineare.
I dati di farmacocinetica variano a seconda del sesso. Nelle donne i valori di clearance sono il 60-80% di quelli riscontrabili negli uomini e sono proporzionali alla superficie corporea. Quindi, a parità di dosaggio, i valori di clearance più bassi nelle donne possono dar luogo a concentrazioni plasmatiche più alte di quelle riscontrabili negli uomini. Anche nelle donne la clearance è rapida, rappresentando circa il 30% della portata cardiaca. La dose consigliata di 1.000 mg/m^2, nonostante i valori di clearance più bassi nelle donne, non dovrebbe comportare una riduzione del dosaggio di gemcitabina.
Al termine di un'infusione di 30 minuti di una singola dose di 1.000 mg/m^2 la gemcitabina produce un picco di concentrazione plasmatica di 10-40 mcg/ml; tali concentrazioni plasmatiche sono rappresentabili con una curva bifasica ed un'emivita terminale di 17 minuti.
Il volume medio di distribuzione del compartimento centrale è di 11 L/m^2 (variabile da 5 a 21 L/m^2), mentre il volume medio di distribuzione all'equilibrio (Vss) è di 17 L/m^2 (variabile da 9 a 30 L/m^2). La clearance sistemica media è di 90 L/h/m^2 (variabile da 40 a 130 L/h/m^2), mentre quella renale è di 2-7 L/h/m^2.
Con i tempi consigliati per la durata d'infusione, l'emivita varia da 32 a 94 minuti, a seconda dell'età e del sesso.

Dopo una singola dose di 1.000 mg/m^2/30 min. di gemcitabina il picco delle concentrazioni plasmatiche del metabolita dFdU varia da 28 a 52 mcg/ml ed è raggiunto 3-15 minuti dopo la fine dell'infusione. Tali concentrazioni plasmatiche sono rappresentabili con una curva trifasica e l'emivita media della fase terminale è di 65 ore (variabile da 33 a 84 ore).
Il volume medio di distribuzione del compartimento centrale del dFdU è di 18 L/m^2 (variabile da 11 a 22 L/m^2). Il volume medio di distribuzione all'equilibrio è di 150 L/m^2 (variabile da 96 a 228 L/m^2) e la clearance media del dFdU è di 2,5 L/h/m^2 (variabile da 1 a 4 L/h/m^2).
Dopo dosaggi settimanali ripetuti, non sono stati osservati fenomeni di accumulo per il metabolita dFdU.
Il metabolita attivo dFdCTP può essere isolato dalle cellule mononucleate del sangue periferico. E' stato così osservato che l'emivita della fase di eliminazione terminale di questo metabolita varia da 0,7 a 12 ore; le sue concentrazioni intracellulari aumentano in maniera direttamente proporzionale alla dose di gemcitabina per infusioni variabili da 35 a 350 mg/m^2/30 min. e producono valori di concentrazione all'equilibrio variabili da 0,4 a 5 mcg/ml.
A dosi capaci di produrre concentrazioni plasmatiche di gemcitabina superiori a 5 mcg/ml, i livelli intracellulari del metabolita dFdCTP non aumentano, suggerendo che la formazione del metabolita è saturabile nelle cellule mononucleate.
Le concentrazioni plasmatiche del metabolita ottenute dopo somministrazione di una dose di gemcitabina di 1.000 mg/m^2/30 min. risultano maggiori di 5 mcg/ml per almeno 30 minuti dopo la fine dell'infusione. Le concentrazioni plasmatiche di gemcitabina dovrebbero mantenersi superiori a 0,4 mcg/ml per un'altra ora.
In base agli studi effettuati, dopo somministrazione di gemcitabina per via endovescicale, l'assorbimento sistemico risulta essere minimo.

5.3 *Dati preclinici di sicurezza*
In una metodica eseguita *in vivo* la gemcitabina ha determinato danni citogenetici. La gemcitabina ha causato mutazione su cellule di linfoma murino (L5178Y) *in vitro*.
La gemcitabina causa nel topo maschio una ipospermatogenesi reversibile, dose- e posologia-dipendente. Sebbene gli studi sugli animali abbiano dimostrato un effetto sulla fertilità maschile, nessuna alterazione sulla fertilità femminile è stata osservata.
Non sono stati effettuati studi a lungo termine sugli animali per valutare il potenziale carcinogeno della gemcitabina.

6. INFORMAZIONI FARMACEUTICHE
6.1 *Elenco degli eccipienti*
Mannitolo (stabilizzante) e sodio acetato (tampone).

6.2 *Incompatibilità*
N.A.

6.3 *Periodo di validità*
3 anni se conservato a temperatura ambiente ed in confezionamento originale.

6.4 *Speciali precauzioni per la conservazione*
Dopo ricostituzione, il prodotto può essere conservato per 24 ore a temperatura ambiente.
Le soluzioni di gemcitabina ricostituite non devono essere conservate in frigorifero, poiché può verificarsi cristallizzazione.

6.5 *Natura e contenuto del contenitore*
Astuccio includente un flacone di vetro tipo I, contenente il prodotto sterile liofilizzato, tappato con tappo di adatto materiale elastomero e sigillato con ghiera di alluminio.

6.6 *Istruzioni per l'uso e la manipolazione*
Indipendentemente dalla via di somministrazione, la gemcitabina può essere ricostituita solo con soluzione di cloruro di sodio allo 0,9% (senza conservanti). Per le sue caratteristiche chimico-fisiche, si raccomanda che la concentrazione massima di gemcitabina dopo ricostituzione non superi il valore

di 40 mg/ml; concentrazioni superiori possono determinare un passaggio in soluzione incompleto, e devono perciò essere evitate.

a) Flacone da 200 mg

Per preparare la soluzione aggiungere alla polvere contenuta nel flacone almeno 5 ml di una soluzione di cloruro di sodio 0,9%. Agitare per favorire la dissoluzione.

b) Flacone da 1 g

Per preparare la soluzione aggiungere alla polvere contenuta nel flacone almeno 25 ml di una soluzione di cloruro di sodio 0,9%. Agitare per favorire la dissoluzione.

In caso di uso endovenoso, le soluzioni così preparate possono essere somministrate al paziente come tali, oppure ulteriormente diluite con soluzione di cloruro di sodio allo 0,9%.

In caso di uso endovescicale, le soluzioni così preparate devono essere ulteriormente diluite con soluzione di cloruro di sodio allo 0,9%.

Tutte le volte che la soluzione ed il contenitore lo consentono, prima di essere somministrati i farmaci per uso parenterale devono essere controllati nel loro aspetto per escludere la presenza di particelle o di un'alterazione del colore.

Devono essere tenute presenti le procedure per una manipolazione ed uno smaltimento appropriati dei farmaci anti-tumorali e su questo argomento esistono in letteratura numerose linee guida.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

Eli Lilly Italia S.p.A. - Sesto Fiorentino - FI

8. NUMERO DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

GEMZAR 200 mg polvere per soluzione per infusione e per instillazione endovescicale: A.I.C. 029452024

GEMZAR 1 g polvere per soluzione per infusione e per instillazione endovescicale: A.I.C. 029452012

9. DATA DI PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE

Prima autorizzazione:

GEMZAR 200 mg polvere per soluzione per infusione e per instillazione endovescicale: 22 Aprile 1996

GEMZAR 1 g polvere per soluzione per infusione e per instillazione endovescicale: 22 Aprile 1996

10. DATA DI REVISIONE DEL TESTO

Marzo 2007