AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib (ZD6474)
Study Code	D4200C00036
Edition Number	1
Date	18 May 2009

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

Study dates: First patient enrolled: 09 January 2007
Last patient enrolled: 29 February 2008
Data cut-off date: 05 September 2008

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers and number of patients planned

This Phase III multi-center study was to be conducted in a minimum of 510 patients (255 per arm) with locally advanced or metastatic (Stage IIIB-IV) non-small cell lung cancer (NSCLC), after failure of first-line anti-cancer therapy. The study involved 118 centers in 21 countries.

Study period

The first patient was enrolled on 09 January 2007, and the last patient was enrolled on 29 February 2008. The data cut-off date was 05 September 2008.

Publications

None at the time of writing this report.

Primary objective:

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

Secondary objectives:

The secondary objectives of the study were:

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

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

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

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

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

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

Exploratory objectives were also undertaken and are presented in the main body of the Clinical Study Report (CSR).

Study design

This was a parallel-group, international, randomized, double-blind, placebo-controlled, multi-center study, designed to assess whether the addition of vandetanib (administered as 100 mg once daily tablet) to pemetrexed (500 mg/m^2 administered intravenously [iv] over 10 minutes on Day 1 of each 21-day cycle) in patients with locally advanced or metastatic NSCLC who had received prior first-line anti-cancer treatment, conferred a statistically significant advantage in terms of PFS.

Target patient population and sample size

The target population was male and female patients aged ≥18 years with histologic or cytologic confirmation of locally advanced or metastatic NSCLC (Stage IIIB or IV), having failed first-line anti-cancer therapy or with subsequent relapse of disease following first-line therapy. Patients were not to have received prior treatment with pemetrexed or with a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) (previous treatment with bevacizumab [AVASTIN®] was permitted). Patients were to have WHO Performance status 0 to 2, and 1 or more measurable lesions.

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

Investigational product and study treatment: dosage, mode of administration and batch numbers

Table S1 Details of investigational product and study treatments

Investigational product/ Study treatments	Dosage strength and form, route of administration, dosing schedule	Manufacturer	Formulation number	Batch numbers[a]
Vandetanib	100-mg tablet, oral, daily	AstraZeneca Macclesfield, UK and AstraZeneca iPR, Canovanas, Puerto Rico	F013025	42484B06, 40707B06, 33306K05, 43542A06, 41412J06, 41959C06, 41939K06, 42173B06
Placebo	Placebo to match vandetanib 100-mg tablet, oral, daily	AstraZeneca Macclesfield, UK	F013044	33640I05, 32640E05, 43063D06, 33640I05, 43065I06
Pemetrexed	500 mg/m^2 iv infusion, every 21 days	Eli Lilly and Company, US	NDC 0002-7623-01	n/a

[a] Batch numbers are not required for non-investigational products; the pemetrexed was sourced locally by the study centers.

Duration of treatment

Patients received single oral doses of 100 mg vandetanib or placebo daily, and could continue on daily oral dosing with vandetanib/placebo alone as long as they did not meet any withdrawal criteria (including progression). Pemetrexed was to be administered at a dose of 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle, up to a maximum of 6 cycles. After 6 cycles of pemetrexed, patients continued on vandetanib/placebo monotherapy until progression, as long as they did not meet any discontinuation criteria.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Efficacy

The primary efficacy variable for this study was PFS. Secondary outcome variables included OS, ORR, DCR, DOR, disease-related symptoms and TDS (both assessed by the LCSS total score and average symptom burden index [ASBI] score from the LCSS instrument).

Pharmacokinetics

Secondary outcome variables: Vandetanib PK - AUC_{ss}, C_{ss}, C_{max}, CL/F, V_{ss}/F; safety – adverse events (AEs), QTc; efficacy - PFS, OS, ORR, DCR, DOR; plasma level of biomarkers; individual predicted plasma concentrations.

Criteria for evaluation - safety (main variables)

Secondary outcome variables: Incidence and type of AEs, clinically significant laboratory or vital sign abnormalities, and electrocardiogram (ECG) changes

Statistical methods

The primary comparison of interest was vandetanib 100 mg plus pemetrexed compared with placebo plus pemetrexed, for PFS. There were 2 co-primary analysis populations: all randomized patients, and all randomized female patients. Accordingly, a nominal 2-sided significance level of 2.5% was used for all analyses, except for PFS and OS where the significance levels were 2.42% and 2.46%, respectively, after adjustment for an interim analysis. PFS, OS and TDS were analyzed using a log-rank test. ORR and DCR were analyzed using logistic regression.

Safety and tolerability were assessed in terms of AEs, laboratory data, and ECG changes which were to be collected for all patients. AEs were listed individually by patient and summarized by treatment group.

Subject population

A total of 534 patients were randomized to treatment (256 to the vandetanib arm and 278 to the placebo arm). Only a small number of patients were still ongoing on randomized treatment at data cut-off (30 [11.7%] in the vandetanib arm versus 23 [8.3%] in the placebo arm). Overall, the demographic and baseline characteristics were well balanced between treatment arms, and were consistent with those expected in patients with advanced NSCLC.

Summary of efficacy results

The key efficacy results of the study are presented in Table S2.

Table S2 Summary of the key efficacy findings (Full analysis set)

Endpoint **Randomized treatment**	**Endpoint Data**		**Treatment effect (vandetanib vs placebo)**		
Progression-free survival	**N**	**Median PFS**	**HR[a]**	**97.58% CI**	**p-value**
Vandetanib 100 mg + pemetrexed	256	17.6 weeks	0.86	0.69, 1.06	0.1075
Placebo + pemetrexed	278	11.9 weeks			
Overall survival	**N**	**Median survival**	**HR[a]**	**97.54% CI**	**p-value**
Vandetanib 100 mg + pemetrexed	256	10.5 months	0.86	0.65, 1.13	0.2190
Placebo + pemetrexed	278	9.2 months			
Objective response rate[b]	**N**	**Response rate**	**OR[c]**	**97.5% CI**	**p-value**
Vandetanib 100 mg + pemetrexed	256	19.1%	2.75	1.49, 5.08	0.0002
Placebo + pemetrexed	278	7.9%			

a HR= Hazard Ratio. A value <1 favours vandetanib. The analysis was performed using a log rank test with treatment as the only factor.
b Overall response rate = complete + partial responses
c OR=Odds Ratio. A value >1 favours vandetanib. The analysis was performed using a logistic regression model with treatment as the only factor.

N, Number of patients included in the analysis; PFS, progression-free survival; CI, confidence interval.

There was a trend for improved PFS for patients in the overall population in the vandetanib plus pemetrexed arm, compared with the placebo plus pemetrexed arm that was not statistically significant (Table S2). Median PFS was 17.6 weeks with vandetanib versus 11.9 weeks with placebo. The results of the sensitivity analyses were supportive of the primary analysis results for PFS in the overall population.

There was no evidence of a differential advantage for the co-primary analysis population of female patients for any efficacy endpoint. Visual inspection, and the lack of significance of the global interaction test, suggests that the PFS benefits observed are fairly consistent across subgroups, with the possible exception of squamous cell carcinoma; data suggest that adding vandetanib to pemetrexed may not benefit patients with squamous cell carcinoma.

There was a trend for improved OS for patients in the vandetanib plus pemetrexed arm, compared with the placebo plus pemetrexed arm that was not statistically significant (Table S2).

The study demonstrated an improvement in ORR for vandetanib in combination with pemetrexed compared with pemetrexed plus placebo that was statistically significant for the overall population (Table S2).

The other secondary endpoints (DCR, DOR and the patient-reported outcome [PRO] analyses) were supportive of the key efficacy findings.

The clinical relevance of progression status in this study was supported by the observation that better RECIST responses appeared to be associated with better PRO outcomes in this study.

Summary of pharmacokinetic results

The PK data from this study were used in a combined PK analysis with data from another Phase III study with a similar design and patient population, and same vandetanib dose.

There appeared to be no differences in the PK of vandetanib between males and females, or between racial groups.

Summary of pharmacodynamic results

The results of PD analyses on plasma samples of VEGF, VEGFR-2, bFGF, and EGFR mutation in tumor DNA from serum, will be presented in separate reports.

Summary of pharmacokinetic/pharmacodynamic relationships

There was an increase in QTc values with increasing plasma concentration. No clear relationship could be demonstrated between exposure and AEs or efficacy. At the time of writing the CSR, only baseline biomarker data was available for VEGF, VEGFR-2 and bFGF, so PK-PD analysis of these biomarkers was not possible.

Summary of pharmacogenetic results

Baseline blood samples were collected from consenting patients. DNA was extracted and stored for possible future evaluation, by single nucleotide polymorphism (SNP), of the effects of genes involved in response to vandetanib and pemetrexed. These analyses will be reported at a later date, if and when data becomes available.

Summary of safety results

Administration of vandetanib did not compromise the ability to administer full doses of pemetrexed (median number of cycles was 5.0 in the vandetanib arm compared with 4.0 in the placebo arm). The median pemetrexed dose intensity was 99% in both arms. Most patients reported at least one AE (96.2% vs 96.7% for the vandetanib and placebo arms, respectively). Compared with placebo a greater proportion of patients discontinued from randomized therapy due to AEs (15.8% vs 11.4%), had dose reductions or interruptions of randomized therapy (20.0% vs 19.8%), had a serious AE (SAE) (32.3% vs 34.4%) or had a fatal SAE (5.4% vs 4.4%).

The following common AEs (>10% in either treatment arm) were increased (>5% difference) in the vandetanib arm relative to placebo: rash (38.1% vs 26.4%), diarrhea (26.2% vs 18.3%) and hypertension (11.5% and 2.9%).

The following common AEs were seen at a similar rate between treatment arms (vandetanib vs placebo, respectively): constipation (20.0% vs 19.8%), pruritus (10.8% vs 14.7%), cough (25.0% vs 21.6%), back pain (10.0% vs 11.0%), anorexia (21.5% vs 23.8%), headache (10.8% vs 14.3%) insomnia (13.1% vs 9.9%), neutropenia (8.8% vs 11.4%).

The following common AEs were seen less frequently (<5%) in the vandetanib arm compared with the placebo arm (vandetanib vs placebo, respectively): fatigue (38.5% vs 45.4%), nausea (28.8% vs 37.4%), vomiting (15.4% vs 22.3%), anemia (8.1% vs 22.0%), pyrexia (11.5% vs 17.2%), and asthenia (10.8% vs 16.5%).

The most common AEs (>1%) resulting in patients discontinuing vandetanib or placebo (respectively) were: rash (2.7% vs 0%), thrombocytopenia (1.2% vs 0.4%), pneumonia (0.8% vs 1.5%) and vomiting (0% vs 1.1%).

The most common SAEs (>2%) observed in patients who received vandetanib or placebo (respectively) were: dyspnea (3.1% vs 3.7%), pulmonary embolism (1.2% vs 2.2%), pneumonia (2.7% vs 3.7%), vomiting (1.2% vs 2.2%), pyrexia (2.7% vs 1.1%), fatigue (0.4% vs 2.2%), and anemia (0.8% vs 2.6%).

Most of the MedDRA terms for those SAEs that proved fatal were reported by only one or 2 patients in either of the treatment arms. The exceptions for patients who received vandetanib or placebo (respectively) were: respiratory failure (1.2% vs 0%), and pneumonia (1.2% vs 0.7%).

There was no increase in hemorrhagic events, venous thromboembolic events, or ischemic cardiac events in patients treated with vandetanib compared with placebo. Hemoptysis, as an event expected in patients with advanced NSCLC, was reported in 14 (5.4%) and 19 (7.0%) patients in the vandetanib vs placebo arms respectively. Patients with squamous cell histology had a higher incidence of hemoptysis in both treatment arms compared with patients with non-squamous histology, though this was numerically lower on the vandetanib arm compared with the placebo arm. Arterial thromboembolic events were reported in very few patients in the study. The incidence of ischemic cerebrovascular conditions was higher on the vandetanib arm (4 patients vs 0 patients on the placebo arm); one of the cases was fatal, secondary to thrombocytopenia. One patient in each arm was reported to have developed interstitial lung disease (ILD); neither of the ILD cases was fatal. The incidence of QTc prolongation was less than 1% in this study, and none of the patients who experienced confirmed QTc interval increases were symptomatic. Protocol-defined QTc prolongation was experienced in only one patient (vandetanib arm).

Proteinuria was reported as an AE in 8 (3.1%) versus 3 (1.1%) patients in the vandetanib vs placebo arms. No cases of nephrotic syndrome were reported in this study. Urinalysis data showed that a higher percentage of patients developed proteinuria in the vandetanib vs placebo arm (55.0% vs 28.9%); however, there was no increase in the incidence of renal AEs on the vandetanib arm. Median hemoglobin levels were higher in vandetanib-treated patients. A greater number of patients treated with vandetanib had elevations of ALT (14.6% vs 8.4% in the vandetanib vs placebo arms); however, this did not appear to be clinically significant.