AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib (ZD6474)
Study Code	D4200C00044
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A Phase III, International, Randomised, Double-Blind, Parallel-Group, Multi-Centre Study to Assess the Efficacy of Vandetanib (ZACTIMA™, ZD6474) Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in Patients With Locally Advanced or Metastatic (Stage IIIB-IV) Non-Small Cell Lung Cancer (NSCLC) after Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI)

Study dates: First patient enrolled: 8 November 2006
Last patient enrolled: 9 October 2008
Data cut-off date: 19 October 2009

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

The study involved 174 sites in 22 countries.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To demonstrate an improvement in overall survival (OS) for vandetanib plus best supportive care (BSC) compared with placebo plus BSC in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior therapy with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)	OS	Efficacy
Secondary	**Secondary**	
To demonstrate an improvement in progression-free survival (PFS) for vandetanib plus BSC compared with placebo plus BSC	PFS	Efficacy
To demonstrate an improvement in the objective response rate (ORR), disease control rate (DCR) and duration of response (DOR) for vandetanib plus BSC compared with placebo plus BSC using Response Evaluation Criteria in Solid Tumors (RECIST)	ORR = complete response (CR) + partial response (PR) DCR = CR + PR + stable disease (SD) ≥8 weeks DOR	Efficacy
To study the safety and tolerability of vandetanib plus BSC compared with placebo plus BSC	Adverse events (AEs), laboratory data, vital signs and electrocardiogram (ECG) changes	Safety
To demonstrate beneficial effects in time to deterioration of disease-related symptoms (TDS) assessed by the combined score of lung cancer subscale (LCS) plus pain and fatigue for vandetanib plus BSC compared with placebo plus BSC	TDS (assessed by combined score of LCS plus pain and fatigue)	Patient reported outcome

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

Study design

This was a parallel group, international, randomised, double-blind, placebo-controlled, multi-center study design to assess whether vandetanib (300 mg daily) plus BSC conferred an advantage in terms of OS compared with placebo plus BSC in patients with locally advanced or metastatic NSCLC who had received prior therapy with an EGFR TKI.

Target subject 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) and

failure of prior therapy with an EGFR TKI in patients who had received at least 1 but no more than 2 prior chemotherapy regimens. Patients were to have 1 or more measurable lesions, WHO Performance status 0 to 2 and life expectancy of ≥12 weeks.

Based on the median time to death after failure with EGFR TKI therapy (ie, time from progression until death) of 4.5 months for the erlotinib arm in the BR21 study and 4.9 months for the gefitinib 250 mg arm in the IDEAL study, a median OS of approximately 5 months was assumed for this study for the placebo arm. In order to detect a 33% prolongation in OS with ≥90% power at the 2-sided 4.8% significance level (adjusted from 5% to account for a single interim analysis), a minimum of 690 deaths were required. In total 930 patients were to be randomized in a 2:1 ratio to receive either vandetanib 300 mg or placebo.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of investigational product and study treatment

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Vandetanib 100 mg	1 or 2 x 100 mg[a] tablet, once daily, oral	AstraZeneca	F013025	33306K05, 40707B06, 41941I06, 41957I06, 41960D06, 42349H06
Vandetanib 300 mg	1 x 300 mg tablet, once daily, oral	AstraZeneca	F013383	33307H05, 40764I06, 43742B06, 43768I06, 43814C06
Placebo to match vandetanib 100 mg	1 or 2 x 100 mg[a] tablet, once daily, oral	AstraZeneca	F013044	32640E05
Placebo to match vandetanib 300 mg [b]	1 x 300 mg tablet, once daily, oral	AstraZeneca	F013385	33662F05, 43086I06, 51137F07

[a] For dose reduction purposes (ie, patients who had toxicity related to vandetanib/placebo). For patients who required dose reduction to 200 mg, 2 x 100 mg tablets were to be taken.

[b] As the results of a potential packaging error relating to batch F013385 (placebo to match vandetanib 300 mg), it is possible that a small number of patients might have received a small number of vandetanib 100 mg tablets in place of the intended placebo. However, all potentially affected bottles of tablets were recalled for the current study and no 'rogue' tablets were found. AstraZeneca believe that the potential impact on patient safety or the efficacy results of the current study are minimal.

Duration of treatment

Patients could receive blinded vandetanib/placebo until objective disease progression, as long as in the Investigator's opinion they were benefiting from treatment and they did not meet any other withdrawal criteria.

Statistical methods

The primary analysis was for OS, comparing vandetanib 300 mg and placebo. For both OS and PFS the nominal (5%) significance level was adjusted to account for a single interim analysis, resulting in a final significance level of 4.8% for both OS and PFS. PFS, OS and TDS were analyzed using a log-rank test. ORR and DCR were analyzed using logistic regression. DOR was summarized only. The primary analysis population for efficacy was the Full Analysis Set of all randomized patients.

Safety and tolerability were assessed based on AEs, laboratory data, ECG data, vital signs and weight. The Safety Analysis Set included all randomized patients who received at least 1 dose of randomized treatment; safety data were summarized by treatment received.

Subject population

A total of 924 patients were randomized (617 in the vandetanib arm and 307 in the placebo arm) and are included in the Full Analysis Set; 922 patients received randomized treatment (616 in the vandetanib arm and 306 in the placebo arm). Three patients randomized to receive placebo received at least one dose of vandetanib; these 3 patients are included in the vandetanib arm in the Safety Analysis Set (619 in vandetanib arm and 303 in placebo arm). Only a small proportion of patients were ongoing on randomized treatment at data cut-off (2.3% in the vandetanib arm and 0.3% in the placebo arm).

The 2 treatment arms were well balanced at baseline with respect to demographic and baseline characteristics. Patients were representative of an advanced NSCLC population who had received two or three prior therapies.

Summary of efficacy results

There was no statistically significant difference in clinical efficacy between vandetanib and placebo in terms of OS (primary endpoint) (Table S3). In terms of secondary endpoints, there was a statistically significant improvement for vandetanib over placebo for PFS, ORR and DCR, but no statistically significant difference for TDS.

Table S3 Summary of key efficacy findings (Full Analysis Set)

Endpoint **Randomized treatment**	**Endpoint data**		**Treatment effect (vandetanib versus placebo)**		
Overall survival (OS)	**N**	**Median OS**	**HR[a]**	**95.2% CI**	**2-sided p-value**
Vandetanib 300 mg	617	8.5 months	0.95	0.81, 1.11	0.5273
Placebo	307	7.8 months			
Progression-free survival (PFS)	**N**	**Median PFS**	**HR[a]**	**95.2% CI**	**P-value**
Vandetanib 300 mg	617	1.9 months	0.63	0.54, 0.74	<0.0001
Placebo	307	1.8 months			

Table S3 Summary of key efficacy findings (Full Analysis Set)

Endpoint Randomized treatment	Endpoint data		Treatment effect (vandetanib versus placebo)		
Objective response rate (ORR)[b]	**N**	**Response rate**	**OR[c]**	**95% CI**	**P-value**
Vandetanib 300 mg	617	2.6%	4.06	1.15, 25.78	0.0276
Placebo	307	0.7%			
Disease control rate (DCR)	**N**	**Response rate**	**OR[c]**	**95% CI**	**P-value**
Vandetanib 300 mg	617	30.6%	2.38	1.69, 3.42	<0.0001
Placebo	307	15.6%			
Time to deterioration of disease-related symptoms (TDS)	**N**	**Median TDS**	**HR[a]**	**95% CI**	**P-value**
Vandetanib 300 mg	617	6.1 weeks	0.98	(0.82, 1.16)	0.7991
Placebo	307	7.1 weeks			

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 Objective response rate = complete response + partial response.
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; CI = confidence interval.

Summary of pharmacodynamic results

The results of pharmacodynamic analyses on levels of VEGF, VEGFR-2, bFGF and other exploratory biomarkers in plasma samples collected post-baseline (ie, during the treatment period) will be reported separately.

Summary of pharmacogenetic results

Baseline blood samples were collected from consenting patients and stored at site for possible future DNA extraction. Samples were collected from 523 patients; these may be used for future evaluation, by single nucleotide polymorphism, of the effects of genes involved in response to vandetanib. These analyses will be reported at a later date, if and when data become available.

Summary of safety results

A larger proportion of patients in the vandetanib arm than the placebo arm experienced AEs (592 [95.6%] patients versus 268 [88.4%] patients), AEs of CTCAE grade 3 or higher (296 [47.8%] patients versus 106 [35.0%] patients), SAEs (160 [25.8%] patients versus 63 [20.8%] patients), or AEs leading to discontinuation of study treatment (75 [12.1%] patients versus 16 [5.3%] patients). The proportion of patients with a fatal SAE was similar in both treatment arms (24 [3.9%] patients on vandetanib versus 12 [4.0%] patients on placebo).

AEs reported more frequently (>5% difference) in the vandetanib arm than the placebo arm were diarrhea (287 [46.4%] patients versus 34 [11.2%] patients), rash (262 [42.3%] patients versus 33 [10.9%] patients), hypertension (164 [26.5%] patients versus 9 [3.0%] patients), nausea (139 [22.5%] patients versus 52 [17.2%] patients), pruritus (70 [11.3%] patients versus 16 [5.3%] patients), proteinuria (56 [9.0%] patients versus 10 [3.3%] patients), dry skin (50 [8.1%] patients versus 8 [2.6%] patients) and electrocardiogram QT prolonged (37 [6.0%] patients versus 1 [0.3%] patient). The only AE reported more frequently (>5% difference) in the placebo arm than the vandetanib arm was constipation (63 [20.8%] patients versus 89 [14.4%] patients).

The following common AEs were seen at a similar rate between treatment arms (vandetanib versus placebo, respectively): vomiting (84 [13.6%] patients versus 38 [12.5%] patients), fatigue (110 [17.8%] patients versus 51 [16.8%] patients), asthenia (67 [10.8%] patients versus 31 [10.2%] patients), cough (109 [17.6%] patients versus 55 [18.2%] patients), dyspnea (107 [17.3%] patients versus 57 [18.8%] patients), decreased appetite (144 [23.3%] patients versus 64 [21.1%] patients) and dizziness (69 [11.1%] patients versus 27 [8.9%] patients).

The most common AEs resulting in patients discontinuing investigational product (vandetanib versus placebo, respectively) were rash (11 [1.8%] patients versus 0%), pneumonia (5 [0.8%] patients versus 2 [0.7%] patients), fatigue or asthenia (5 [0.8%] patients versus 0%), dyspnea (4 [0.6%] patients versus 2 [0.7%] patients), diarrhea (4 [0.6%] patients versus 0%), erythema multiforme (3 [0.5%] patients versus 0%) and hemoptysis (3 [0.5%] patients versus 0%). All other AEs leading to discontinuation of investigational product were reported in no more than 2 patients in either treatment arm.

The most common SAEs (>1%) observed in patients who received vandetanib or placebo (respectively) were pneumonia (21 [3.4%] patients versus 6 [2.0%] patients), dyspnea (12 [1.9%] patients versus 5 [1.7%] patients), pleural effusion (5 [0.8%] patients versus 5 [1.7%] patients), pulmonary embolism (3 [0.5%] patients versus 5 [1.7%] patients), diarrhea (8 [1.3%] patients versus 0%) and hypertension (7 [1.1%] patients versus 0%).

Most of the MedDRA terms for those SAEs that proved fatal were reported by only 1 or 2 patients in either of the treatment arms. The exceptions for patients who received vandetanib or placebo (respectively) were pneumonia (3 [0.5%] patients versus 3 [1.0%] patients) and death (3 [0.5%] patients versus 0%).

Certain pre-specified groups of AEs were identified as being of interest, based on pharmacologic class or previous studies with vandetanib. The pre-defined groupings were: rash, diarrhea, nausea/vomiting, embolic and thrombotic events (venous), hemorrhages, interstitial lung disease (ILD) and similar events, ischemic cerebrovascular conditions, ischemic heart disease, seizures and QTc-related events.

Grouped events of rash (340 [54.9%] versus 56 [18.5%] patients), diarrhea (287 [46.4%] versus 35 [11.6%] patients) and nausea/vomiting (178 [28.8%] versus 67 [22.1%] patients) were reported at higher incidence in the vandetanib arm compared with placebo. There was no increase in the incidence of thromboembolic events (11 [1.8%] versus 10 [3.3%] patients),

ILD or similar events (7 [1.1%] versus 2 [0.7%] patients), ischemic cerebrovascular conditions (7 [1.1%] versus 5 [1.7%] patients) or ischemic heart disease (7 [1.1%] versus 3 [1.0%] patients) in the vandetanib arm compared with placebo.

The proportion of patients with the grouped event of seizures was small, but this grouped event was reported at a higher frequency in the vandetanib arm than the placebo arm (10 [1.6%] versus 2 [0.7%] patients). Most of the patients with seizures had pre-existing brain metastases or developed brain metastases during the study.

There was a larger proportion of patients with hemorrhagic events in the vandetanib arm than the placebo arm (72 [11.6%] versus 27 [8.9%] patients). This was in part due to the increased frequency of epistaxis (18 [2.9%] versus 2 [0.7%] patients). Similar proportions of patients in the vandetanib and placebo arms reported hemoptysis (26 [4.2%] versus 14 [4.6%] patients) or any type of pulmonary hemorrhage[1] (31 [5.0%] versus 16 [5.3%] patients).

The incidence of QTc-related events as a grouped term was reported by 40 (6.5%) patients in the vandetanib arm and 3 (1.0%) patients in the placebo arm and the AE of prolonged electrocardiogram QT was reported for 37 (6.0%) patients in the vandetanib arm and 1 (0.3%) patient in the placebo arm. Protocol-defined QTc prolongation was reported by 40 (6.5%) patients in the vandetanib arm during randomized treatment, but none of the patients who experienced confirmed QTc interval increases were symptomatic. No patient in this study had an AE of torsade de pointes.

Proteinuria was reported as an AE by 56 (9.0%) patients in the vandetanib arm and 10 (3.3%) patients in the placebo arm. Most AEs of proteinuria were CTCAE grade 1 or 2 with CTCAE grade 3 proteinuria reported in only 5 (0.8%) patients receiving vandetanib. There were no cases of CTCAE grade 4 proteinuria (nephrotic syndrome) reported in this study. There were 2 (0.3%) patients in the vandetanib arm with an SAE of renal failure or acute renal failure; one of the cases was associated with diarrhea and vomiting and the other with bilateral renal metastases and renal impairment on admission. Urinalysis data showed that a higher percentage of patients developed new onset proteinuria in the vandetanib arm versus placebo arm (426 [68.8%] patients versus 84 [27.7%] patients), or new onset hematuria (141 [22.8%] patients versus 32 [10.6%] patients).

Median hemoglobin levels were higher in vandetanib-treated patients. However, increases in hemoglobin did not result in an increased incidence of thomboembolic events.

Elevations of alanine aminotransferase (ALT) >3x upper limit of normal (ULN), >5x ULN and >8x ULN in the vandetanib and placebo arms, respectively, were reported for 27 (4.4%) patients versus 3 (1.0%) patients, 6 (1.0%) patients versus 1 (0.3%) patient, and 2 (0.3%) patients versus 0%. One patient in each treatment arm had a combined elevation of ALT >3x ULN and bilirubin >2x ULN whilst on study treatment, suggesting hepatic injury and

[1] This includes the preferred terms of 'hemoptysis', 'pulmonary hemorrhage', 'bronchial hemorrhage' and 'respiratory tract hemorrhage'.

cholestasis. The patient in the vandetanib arm had pre-existing liver metastases and rapidly progressive disease. No patient discontinued vandetanib due to AEs relating to elevated liver function tests.

A larger proportion of patients in the vandetanib arm than the placebo arm had an elevated amylase value of CTCAE grade 1-4 during treatment (143 [23.8%] patients versus 46 [15.5%] patients) or an elevated lipase value of CTCAE grade 1-4 during treatment (141 [24.0%] patients versus 33 [11.3%] patients), mostly of CTCAE grade 1 or 2. One patient in the vandetanib arm who had an amylase elevation of CTCAE grade 4 had an SAE of pancreatitis reported; investigational product was permanently discontinued due to this SAE. One patient in the vandetanib arm who had a lipase elevation of CTCAE grade 3 had this abnormality reported as an SAE; investigational product was interrupted for 9 days and the SAE completely resolved.