AstraZeneca

Clinical Study Report Synopsis

Drug	Vandetanib (ZD6474)
Study	D4200C00032
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A Phase III, Randomized, Double-Blinded, Multi-Center Study to Assess the Efficacy and Safety of Docetaxel (TAXOTERE™) in Combination with Vandetanib (ZACTIMA™, ZD6474) versus Docetaxel (TAXOTERE™) in combination with Placebo in Patients With Locally Advanced or Metastatic (Stage IIIb – IV) Non-small Cell Lung Cancer (NSCLC) after Failure of 1st Line Anti-Cancer Therapy

Study dates:

First patient enrolled: 8 May 2006
Last patient enrolled: 14 March 2008
Data cut-off date: 22 August 2008

Phase of development:

Therapeutic confirmatory (III)

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

International Co-ordinating Investigator

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Study centers and number of patients planned

This Phase III multi-center study was to be conducted in a minimum of 1380 patients (690 patients per treatment arm) with locally-advanced or metastatic (IIIB-IV) non-small cell lung cancer (NSCLC), after failure of 1st line anti-cancer therapy. The study involved 198 centers in 25 countries.

Study period

The first patient was enrolled on 8 May 2006, and the last patient was enrolled on 14 March 2008. The data cut-off date was 22 August 2008.

Publications

None at the time of writing this report.

Objectives

Primary objective:

The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) for the combination of vandetanib plus docetaxel (TAXOTERE®, Sanofi-Aventis) compared with docetaxel plus placebo in patients with locally-advanced or metastatic non-small cell lung cancer (NSCLC) after failure of 1st-line anti-cancer therapy.

Secondary objectives

The secondary objectives of the study were:

1. To demonstrate an improvement in overall survival (OS) for vandetanib in combination with docetaxel compared with docetaxel 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 docetaxel compared with docetaxel plus placebo as assessed by Response Evaluation Criteria in Solid Tumors (RECIST).

3. To demonstrate a beneficial effect on disease-related symptoms, in patients treated with vandetanib in combination with docetaxel, that is at least as good as that in patients treated with docetaxel plus placebo based on the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) lung cancer subscale (LCS).

4. To demonstrate a quality of life (QoL) for ZACTIMA in combination with docetaxel-treated subjects that is at least as good as that for subjects treated with docetaxel plus placebo by assessment of the FACT-L and the trial outcome index (TOI)

5. To demonstrate an improvement in time to deterioration of disease-related symptoms (TDS) based on the FACT-L LCS for vandetanib in combination with docetaxel compared with docetaxel plus placebo.

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

7. To investigate the population pharmacokinetics (PK) of ZACTIMA in this patient population and assess the PK-QTc relationship, PK-safety relationship and PK-efficacy relationship.

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

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, randomized, double-blind, placebo-controlled, multi center study, designed to assess whether the addition of vandetanib (administered as 100 mg once daily tablet) to docetaxel (75 mg/m^2 [60 mg/m^2 Japan only]) administered intravenously (IV) over at least 1 hour on Day 1 of each 21-day cycle) in patients with locally advanced or metastatic NSCLC who had received prior 1st-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 docetaxel or with a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) (previous treatment with bevacizumab [AVASTIN®, Genetech] was permitted). Patients were to have WHO Performance status 0-1, and 1 or more measurable lesions.

In order to detect a 25% prolongation of overall PFS with >90% power at the 2-sided 2.44% significance level, a minimum of 1176 progression events were required. Assuming a median PFS of 3 months for docetaxel, a recruitment period of 19 months and minimum follow-up of 3 months, a minimum of 1380 patients (690 per arm) were to be randomized.

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

SI Details of investigational product and study treatments

Investigational product	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
Docetaxel	75 mg/m^2 IV[b] infusion, every 21 days	Sanofi-Aventis Bridgewater NJ, US	NDC 0075-8001-80	n/a

Vandetanib and placebo were supplied as white film-coated tablets. Descriptive information for docetaxel can be found in the Amended CSP Appendix K (see Appendix 12.1.1).

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

[b] 60 mg/m^2 IV for Japan only

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). Docetaxel was administered at a dose 75 mg/m^2 (60 mg/m^2 for Japan only) as an intravenous infusion over at least a 1-hour period on Day 1 of each 21-day cycle, up to a maximum of 6 cycles. After 6 cycles of docetaxel, 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 (primary and secondary outcome variables)

The primary efficacy variable for this study was PFS. Secondary efficacy variables included OS, ORR, DCR, DOR, HRQL (assessed using the FACT-L TOI), disease-related symptoms and TDS (both assessed using the lung cancer subscale [LCS] of the FACT-L instrument).

Pharmacokinetics (secondary outcome variables)

Secondary outcome variables: Vandetanib PK - AUC_{ss}, C_{ss}, C_{max}, CL/F, V_{ss}/F; safety - AEs, QTc; efficacy - PFS, OS, ORR, DCR, DOR; plasma level of biomarkers; individual predicted plasma concentrations. In addition, plasma levels of the N-desmethyl and N-oxide metabolites of vandetanib, and their relationship to plasma levels of vandetanib were also analyzed.

Safety (secondary outcome variable)

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 docetaxel compared with placebo plus pemetrexed, for PFS. There were to be 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 2.48%, respectively, after adjustment for an interim analysis. PFS, OS and TDS were analyzed using a log-rank test. ORR and DCR were to be analyzed using logistic regression.

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

Subject population

A total of 1391 patients (including cohorts of patients from Japan [n=143] and China [n=230]) were randomized to treatment (694 in the vandetanib arm and 697 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 S 2 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 + docetaxel	694	17.3 weeks	0.79	0.70, 0.90	<0.0001
Placebo + docetaxel	697	14.0 weeks			
Overall survival	**N**	**Median survival**	**HR[a]**	**97.52% CI**	**P-value**
Vandetanib 100 mg + docetaxel	694	10.6 months	0.91	0.78, 1.07	0.1962
Placebo + docetaxel	697	10.0 months			
Objective response rate[b]	**N**	**Response rate**	**OR[c]**	**97.5% CI**	**P-value**
Vandetanib 100 mg + docetaxel	694	17.3%	1.84	1.29, 2.64	0.0001
Placebo + docetaxel	697	10.2%			

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.

The study demonstrated a significant improvement in PFS for vandetanib in combination with docetaxel compared with docetaxel plus placebo for the overall population (Table S2) Median PFS was 17.3 weeks with vandetanib versus 14.0 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, suggest that the PFS benefits observed are fairly consistent across subgroups. There was no evidence of a significant qualitative interaction for either Japan or China and the rest of the world in this study, therefore all analyses were performed based on the overall population, which included both countries.

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

There was a significant advantage in the vandetanib arm versus the placebo arm for ORR (Table S2).

The other secondary endpoints (DCR, DOR and the patient reported outcome 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 (plasma biomarkers), and EGFR and KRAS mutation (tumor biomarkers) 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 of the effects of genes involved in response to vandetanib and docetaxel. 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 docetaxel (median number of docetaxel cycles was 4.0 in each arm and the median dose intensity for docetaxel was more than 98% in each arm). Most patients reported at least 1 AE (97.1% vs 97.2% for the vandetanib and placebo arms, respectively). Compared with placebo a greater proportion of patients discontinued randomized treatment due to AEs (22.2% vs 11.0%), had reductions or interruptions of randomized treatment (22.8% vs 14.1%), had a serious AE (SAE: 38.2% vs 33.3%) or had a fatal SAE (6.1% vs 5.5%).

The following common AEs (incidence >10%) were increased (>5%) in the vandetanib arm relative to placebo: rash (42.2% vs 24.2%), diarrhoea (41.9% vs 32.6%), neutropenia (32.1% vs 26.7%). In addition, hypertension was notably higher in the vandetanib arm (6.0% vs 1.7%).

The following common AEs were seen at a similar rate between treatment arms (vandetanib vs placebo, respectively): constipation (17.1% vs 20.3%), stomatitis (11.9% vs 11.6%), fatigue (30.3% vs 31.2%), pyrexia, (19.6% vs 17.2%), asthenia (15.5% vs 13.5%), cough (18.9% vs 19.0%), dyspnea (17.3% vs 20.6%) alopecia (33.4% vs 34.8%), leukopenia (18.4% vs 15.7%), anorexia (29.0% vs 29.7%), myalgia (13.1% vs 11.3%), insomnia (13.5% vs 10.6%).

The following common AEs were seen less frequently (<5%) in the vandetanib arm compared with the placebo arm (vandetanib vs placebo, respectively): nausea (23.1% vs 31.9%), and vomiting (15.5% vs 20.7%). In addition anemia was seen notably less frequently in the vandetanib arm (10.3% vs 14.9%).

The most common AEs resulting in discontinuation from vandetanib or placebo (respectively) were: rash (4.4% vs 0.4%), interstitial lung disease (ILD) (1.5% vs 0.4%), photosensitivity reaction (1.0% vs 0%), dyspnea (1.0% vs 0.6%) and pneumonia (1.0% vs 0.9%).

The most common SAEs observed in patients who received vandetanib or placebo (respectively) were: pneumonia (4.8% vs 3.8%), febrile neutropenia (6.7% vs 5.5%), neutropenia (2.3% vs 2.6%), dyspnea (3.2% vs 3.0%), rash (2.2% vs 0.1%), and diarrhea (2.0% vs 1.6%).

Most of the MedDRA terms for those SAEs that proved fatal were reported for only 1 or 2 patients in either of the treatment arms. The exceptions for patients who received vandetanib or placebo (respectively) were: respiratory failure (0.6% vs 0.9%), dyspnea (0.6% vs 0.1%),

ILD (0.4% vs 0%), pneumonia (0.7% vs 0.9%), sepsis (0.4% vs 0.4%), cardiac arrest (0.1% vs 0.4%), renal failure (0.3% vs 0.1%).

Other adverse events included QTc prolongation which, according to the protocol-definition, was seen in 13 (1.9%) patients in the vandetanib arm compared with none in the placebo arm. Two of these led to discontinuation of therapy. There were 17 cases of ILD on vandetanib (12 in Japan and 5 outside Japan) and 6 on placebo (5 in Japan and 1 outside Japan); 3 were fatal. Two cases of severe skin reactions (1 case of Stevens-Johnson syndrome and 1 case of toxic skin eruption), both in the vandetanib arm, were fatal. There was one case suggestive of reversible posterior leukoencephalopathy syndrome [RPLS] observed in the vandetanib arm. Hemoptysis was seen less frequently in the vandetanib arm than the placebo arm (5.8% vs 7.2%) for all patients. Some important grouped terms were reported by fewer patients on vandetanib vs placebo, respectively: ischaemic heart disease (3 vs 10 patients) and venous thromboembolic events (14 vs 27 patients). The grouped event of ischemic cerebrovascular conditions was reported by more patients in the vandetanib arm compared with placebo (4 vs 2 patients).

Hemoglobin concentrations were higher in the vandetanib arm whereas neutrophils and platelet counts were decreased. New reports of proteinurea were seen in 53.2% of patients receiving vandetanib compared with 25.9% in the placebo arm. New reports of hematuria were seen in 9.5% of patients receiving vandetanib compared with 7.0 in the placebo arm. There was a trend for increased median serum creatinine over time in the vandetanib arm compared with the placebo arm, but there were no CTCAE Grade 3 or 4 AEs related to creatinine concentration findings. There were 13 patients in the vandetanib arm with ALT elevated 3 times ULN compared with 7 in the placebo arm.