AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD6474
Study Code	D4200C00062
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An Open-Label, Phase I Study to Assess the Maximum Tolerated Dose of ZD6474 (ZACTIMA™) Given Concomitantly with Radiation Therapy or Concomitantly with Weekly Cisplatin Chemotherapy and Radiation Therapy in Patients with Previously Untreated, Unresected, Stage III−IV Head and Neck Squamous Cell Carcinoma

Study dates: First patient enrolled: 28 December 2006
Last patient enrolled: 8 September 2009

Phase of development: Clinical pharmacology (I)

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

Study centers

A total of 3 centers from the United States of America (USA) enrolled patients into this study.

Publications

Papadimitrakopoulou V, Heymach J, Frank SJ, Myers J, Lin H, Tran HT, et al. Updated clinical and biomarker results from a phase I study of vandetanib with radiation therapy (RT) with or without cisplatin in locally advanced head and neck squamous cell carcinoma (HNSCC). American Society of Clinical Oncology (ASCO) 47th Annual Meeting; 2011 Jun 3-7; Chicago, Illinois. J Clin Oncol 2011;29(15 Suppl 1): Abstract 5510.

Papadimitrakopoulou V, Frank SJ, Blumenschein GR, Chen C, Kane M, Cohen EE, et al. Phase I evaluation of vandetanib with RT ± cisplatin in previously untreated advanced head and neck squamous cell carcinoma (HNSCC). American Society of Clinical Oncology (ASCO) 45th Annual Meeting; 2009 May 29-Jun 2; Orlando, Florida. J Clin Oncol 2009;27(15 Suppl 1): Abstract 6016.

Objectives and criteria for evaluation

The primary and secondary objectives reported in the CSR are summarised in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	Safety
To determine the safety profile, tolerability and MTD of vandetanib in combination with RT and vandetanib in combination with RT+cisplatin chemotherapy in patients with previously untreated, unresected, Stage III-IV HNSCC.	AEs, PEs, vital signs, laboratory data, ECGs.	
Secondary	**Secondary**	Efficacy
To define the ORR, DCR and LRCR per RECIST criteria.	ORR, DCR, LRCR by RECIST.	
To assess rate of LRR and distant disease recurrence at 2 years.	LRR ± distant disease at 2 years.	Efficacy
To assess PFS and duration of loco-regional control.	PFS and duration of loco regional control.	Efficacy
To investigate whether there was any change in the steady-state exposure to vandetanib due to RT or RT + cisplatin, or the method of administration.	Vandetanib: Cmax, tmax, AUC (0-24).	PK

AE: Adverse event; AUC(0-24): Area under the plasma concentration-time curve from zero to 24 hours post dose; AUC(0-t): Area under the plasma concentration-time curve from zero to time t; Cmax: Maximum concentration; CEC: Circulating endothelial cell; DCR: Disease control rate; ECG: Electrocardiogram; EGFR: Epidermal growth factor receptor; HIF: Hypoxia inducible factor; HNSCC: Head and neck squamous cell carcinoma; LRCR: loco-regional control rate; LRR: Loco-regional recurrence; MTD: Maximum tolerated dose; ORR: Objective tumor response rate; PD: Pharmacodynamic; PE: Physical examination; PFS: Progression-free survival; PK: Pharmacokinetic; RECIST: Response Evaluation Criteria in Solid Tumors; RT: Radiation therapy; tmax: Time to maximum plasma concentration; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.
Note: The Exploratory objectives and outcome variables are reported in the CSR.

Study design

This was a Phase I, multi-centre, open-label, non-comparative, dose-escalation study of up to 3 doses of vandetanib in combination with RT (Treatment Regimen 1) and up to 3 doses of vandetanib in combination with cisplatin+RT (Treatment Regimen 2) in patients with previously untreated, unresected head and neck squamous cell carcinoma (HNSCC) to determine a maximum tolerated dose (MTD) for each treatment regimen.

Target subject population and sample size

The patient population included male and female patients aged ≥18 years with histologically or cytologically confirmed previously untreated, unresected Stage III–IV HNSCC. The patient should have presented with Stage III–IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx that had not been previously treated or resected, with no proven hematogenous metastatic disease; a World Health Organization performance status of 0 to 1; one or more measurable lesions at least 10 mm in the longest diameter by spiral computerized tomography scan or 20 mm with conventional techniques; and a life expectancy of ≥12 weeks.

It was planned to enroll approximately 48 evaluable patients during an approximately 24-month period.

Patients were assigned to 1 of 2 treatment regimens based on their disease stage. Patients with a disease stage of T1N2a, T1N2b, T1N2c or T2N2a were eligible for either regimen and assignment to a treatment regimen was at the investigator's discretion. Patients who were at an eligible stage of disease for Treatment Regimen 2, but were not candidates for chemotherapy, could be assigned to Treatment Regimen 1 at the investigator's discretion. Within each treatment regimen, there was a cohort of patients receiving a specified dose. The starting vandetanib dose in each treatment regimen was 100 mg. The planned doses to be explored in the study were 100 mg, 200 mg, and 300 mg.

A minimum of 6 patients were to be enrolled in each cohort for each regimen (6 potential cohorts in total). One cohort expansion (to a total of 12 patients) was to occur in each regimen at MTD, once the MTD was identified.

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

The details of investigational product are provided in Table S2.

Table S2 Details of investigational product and any other study treatments

Investigational product or other treatment	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number
Vandetanib	100 mg white film-coated tablet, once daily orally	AstraZeneca	2000096135, 2000104275
Vandetanib	300 mg white film-coated tablet, once daily orally	AstraZeneca	2000113362

Duration of treatment

As determined by the dosing cohort, the patient took 1x100 mg tablet (100 mg dose), 2x100 mg tablet (200 mg dose) or 1x300 mg tablet (300 mg dose) daily at the same time of day each morning until they completed the 2-week monotherapy phase plus the 6-week or 7-week concomitant treatment period, or until they met a criteria for discontinuation, whichever came first. For those patients assigned to Treatment Regimen 2, vandetanib was taken prior to the administration of cisplatin due to the timings of the required electrocardiogram (ECG) and pharmacokinetic (PK) samples.

Cisplatin was provided from commercial suppliers and was supplied by the investigator's pharmacy. Cisplatin (30 mg/m^2 intravenous) was administered weekly to patients in Treatment Regimen 2 for 7 weeks.

For RT, the assignment of radiation treatment depended on the treatment regimen. Patients were treated with intensity-modulated radiation therapy (IMRT). It was expected, however, that a few patients on Treatment Regimen 2 may have required treatment with non-IMRT. Non-IMRT may have been required for patients in whom very little normal tissues could be spared with IMRT, very advanced tumors where the boundaries of the target volumes were unclear, or patients who were not able to tolerate the treatment position for a sufficient duration for IMRT.

Patients who received Treatment Regimen 1 were all treated with IMRT. The gross tumor and lymph node metastasis including non-palpable lymph nodes suspicious for metastasis according to radiologic criteria received 30 fractions (5/week for 6 weeks) of 2.2 Gy/fraction, total 66 Gy (accelerated fractionation).

Patients who received Treatment Regimen 2 could be treated with IMRT or non-IMRT. The gross tumor and lymph node metastasis including non-palpable lymph nodes suspicious for metastasis according to radiologic criteria received 35 fractions (5/week for 7 weeks) of 2 Gy/fraction, total 70 Gy.

Statistical methods

Safety and tolerability were the primary endpoints. The primary objective of the study was to determine the MTD and overall safety profile of orally administered escalating doses of vandetanib in combination with RT and in combination with RT and cisplatin chemotherapy.

The MTD was to be determined for each treatment regimen. The estimate of MTD was defined as the dose level below the unacceptable dose level where at least 2 of 6 (33%) of the patients experienced dose-limiting toxicity. Safety data was not formally analyzed. Descriptive statistics were used to summarize the safety data. Safety was assessed through summaries of the frequency and severity of adverse events (AE), changes in laboratory test results, changes in vital signs and ECGs.

Analyses of the secondary variables were descriptive in nature. No formal statistical comparisons between the treatment regimens were made. Efficacy data, including derived variables, was listed by patient alongside the treatment regimen and cohort.

The objective tumor response rate, disease control rate, loco-regional control rate (LRCR), 2-year loco-regional recurrence (LRR), 2-year recurrence rate, median progression-free survival (PFS), median duration of loco-regional control for each treatment regimen and cohort was presented with associated 95% confidence intervals (CIs). The 95% CIs were calculated using Wilson's score interval method. In addition, for median PFS and median duration of loco-regional control, Kaplan Meier plots were presented split by treatment regimen and cohort.

PK parameters for vandetanib and cisplatin (measured as total platinum) were determined by non-compartmental methods using winnonlin version 5.2. Vandetanib maximum concentration ($C_{max\ ss}$) and time to maximum plasma concentration (t_{max}) were determined by visual examination and area under the plasma concentration-time curve from zero to 24 hours post dose ($AUC_{0-24)}$ was determined by the trapezoidal rule. Cisplatin C_{max} was determined by visual examination and AUC_{0-24} was determined by the trapezoidal rule. Where pre-dose concentrations were not available, the 24-hour concentration was used as the pre-dose value in order to determine the AUC_{0-24}.

Analysis of pharmacodynamic (PD) biomarker data was exploratory in nature. Appropriate summaries of these levels were produced to investigate the level of correlation with vandetanib dosing. Only baseline data was listed and summarized for the human papilloma virus (HPV) biomarker data by treatment regimen and cohort.

Subject population

Please note: Vandetanib+RT regimen (vandetanib 100 mg+RT and vandetanib 200 mg+RT) is referred to as Treatment Regimen 1 and vandetanib+cisplatin+RT regimen (vandetanib 100 mg+cisplatin+RT and vandetanib 200 mg+cisplatin+RT) is referred to as Treatment Regimen 2 to maintain consistency with clinical study protocol (CSP).

Patient disposition is summarized in Table S3. The first patient was enrolled on 28 December 2006, the last patient was enrolled on 8 September 2009 and the last patient completed the study on 1 December 2011. A total of 38 patients from 3 centers were enrolled into the study. Of these, 33 patients received treatment and 5 patients did not receive treatment. The reasons for not receiving treatment were: incorrect enrolment/screening failure (4 patients) and voluntary discontinuation by patient (1 patient).

A total of 6 (18.2%) patients prematurely discontinued vandetanib, 2 (6.1%) patients discontinued cisplatin and 1 (3.0%) patient discontinued RT prior to completing the full course of treatment. The main reason for discontinuation was AEs (5 [15.2%], 2 [6.1%] and 1 [3.0%] patients discontinued vandetanib, cisplatin and RT, respectively). At the time of data cut-off (02 December 2011), 12 (36.4%) patients had withdrawn from the study prior to completion. Overall, 21 (63.6%) patients had completed the 2 year follow-up in the study.

The mean age of patients was 55 years (range: 43 to 72 years) with the majority of the population from the ≥18 to <65 years age group (27 [81.8%] patients). The patient population comprised more males (28 [84.8%]) and Caucasian patients (32 [97%]). All patients received concomitant medications during the study; the most commonly used being natural opium alkaloids. Overall, 7 patients were reported with protocol deviations for the use of disallowed concomitant medication.

Although the study was not randomized, demographic characteristics, baseline disease characteristics, and medical histories were similar across the treatment regimens with the exception of TNM (Tumor; Node; Metastasis) staging which differed between treatment regimens because of the criteria used by treating physicians to select treatment. The study population was representative of the intended target population.

Table S3 Summary of patient disposition

	Number (%) of patients				
	-Vandetanib + Cisplatin + RT-		**-Vandetanib + RT-**		
	100mg (N=15)	**200mg (N=6)**	**100mg (N=6)**	**200mg (N=6)**	**Total (N=33)**
Patients enrolled[a]					38
Patients who received treatment	15 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Patients who did not receive treatment					5
Incorrect enrollment					4
Voluntary discontinuation by subject					1
Patients who completed 2 year follow-up	6 (40.0)	3 (50.0)	6 (100.0)	6 (100.0)	21 (63.6)
Patients who received Vandetanib	15 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Patients who discontinued Vandetanib	2 (13.3)	3 (50.0)	0 (0.0)	1 (16.7)	6 (18.2)
Adverse event	1 (6.7)	3 (50.0)	0 (0.0)	1 (16.7)	5 (15.2)
Voluntary discontinuation by subject	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Patients who received cisplatin	13 (86.7)	5 (83.3)	0 (0.0)	0 (0.0)	18 (54.5)
Patients who discontinued cisplatin	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	2 (6.1)
Adverse event	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	2 (6.1)
Patients who received radiotherapy	13 (86.7)	5 (83.3)	6 (100.0)	6 (100.0)	30 (90.9)
Patients who discontinued radiotherapy	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.0)
Adverse event	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.0)

Table S3 Summary of patient disposition

	Number (%) of patients				
	-Vandetanib + Cisplatin + RT-		-Vandetanib + RT-		
	100mg (N=15)	200mg (N=6)	100mg (N=6)	200mg (N=6)	Total (N=33)
Patients who withdrew from study	9 (60.0)	3 (50.0)	0 (0.0)	0 (0.0)	12 (36.4)
Death	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.0)
Safety reasons	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.0)
Subject lost to follow-up	1 (6.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (6.1)
Voluntary discontinuation by subject	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)
Other	6 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (18.2)

[a] Informed consent received.
RT Radiotherapy.
Incorrect enrollment refers to screening failures.
'Other' reasons: Recurrence/progression of disease.
Patients (E0001003, E0001018) on the Vandetanib+ Cisplatin + RT 100mg regimen, and 1 patient (E0001012) in the Vandetanib+ Cisplatin + RT 200mg regimen, withdrew from treatment before receiving Cisplatin or Radiotherapy.
Data derived from Table 11.1.1.

Summary of efficacy results

The majority of patients had responded and had disease control and loco-regional control in all groups. The majority of patients did not have LRR or recurrence at 2 years in all groups (0% in all groups with the exception of the vandetanib 100 mg+cisplatin+RT group where the LRR rate and recurrence rate were 30.8%). Only patients with a loco-regional best objective response of CR were included for LRR and only patients with an overall best objective response of CR were included for recurrence rate.

All responders had showed complete response (CR) with an exception of 1 patient in the vandetanib 200 mg+RT group who had a partial response (PR). Across each of the groups, patients' tumors generally responded extremely well to each treatment regimen. There were only 4 patients (2 patients each in vandetanib+cisplatin+RT 100 mg and 200 mg groups, respectively) who did not respond and 3 of these patients did not have any follow-up response evaluation criteria in solid tumors (RECIST) assessments.

The study had 3 patients with HPV-ve disease status and all 3 patients had progression or recurrence of disease. Of the 24 HPV+ve patients, 2 patients had recurrence or progression of disease.

Median PFS and median duration of loco-regional control were not reached in any of the groups.

Summary of PK results

Mean plasma concentrations of vandetanib were higher for the 200 mg vandetanib group than the 100 mg group following repeat dosing (Day 15 and 50). Vandetanib concentrations were higher at Week 8 than Week 3 due to increased exposure between Day 15 and Day 50 for the 100 mg and 200 mg doses in combination with RT or cisplatin+RT. This is consistent with the long half-life of vandetanib (10-20 days) resulting in accumulation between Weeks 3 and 8 and with dose-related increases in exposure seen within this dose range in previous studies.

Cisplatin exposure was determined on Day 15 and Day 50. There was no evidence of a difference in cisplatin exposure (C_{max} or AUC_{0-24}) between background therapy of vandetanib 100 mg or 200 mg. In combination with vandetanib 100 mg and 200 mg, cisplatin exposure was higher on Day 50 after repeat dosing than on Day 15. This suggests that there was some accumulation of cisplatin on multiple dosing and the exposure determined in this study was consistent with exposures achieved in other studies at equivalent doses.

Summary of safety results

Table S4 summarizes the number of patients who experienced at least 1 AE. All patients from both Treatment Regimen 1 and Treatment Regimen 2 received vandetanib orally. The median total duration of exposure to vandetanib were close to the expected duration in each regimen (8 weeks for Treatment Regimen 1 and 9 weeks for Treatment Regimen 2). The median number of weeks of cisplatin was also close to the expected 7 weeks in the vandetanib 100 mg and 200 mg groups. Most patients in all treatment groups had at least 1 AE; 6 (100%) patients each in the vandetanib 100 mg+RT, vandetanib 200 mg+RT, and vandetanib 200 mg+cisplatin+RT group and 14 (93.3%) patients in vandetanib 100 mg+cisplatin+RT group.

More than 50% of the patients in each treatment group experienced constipation (27 [81.8%] patients), dry mouth (25 [75.8%]), nausea (25 [75.8%]), dysphagia (24 [72.7%]), diarrhea (23 [69.7%]), oral pain (21 [63.6%]), fatigue (28 [84.8%]), radiation skin injury (29 [87.9%]), oropharyngeal pain (26 [78.8%]), weight decreased (26 [78.8%]) and dysgeusia (22 [66.7%]). Some of these AEs are known to be caused by vandetanib (constipation, nausea, diarrhea, dysgeusia, weight decreased, dry mouth and dysphagia); however, they may also be attributable to the effects of RT or cisplatin or to the symptoms of head and neck cancer or to a combination of these medications.

Most patients in all treatment groups experienced at least 1 event of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher. The most common events of Grade 3 or higher were related to mouth and included stomatitis (11 [33.3%] patients), dysphagia (10 [30.3%]), oropharyngeal pain (8 [24.2%]), and mucosal inflammation (9 [27.3%]), all of which occurred in >20% of patients. These events tended to occur in all treatment arms, probably reflecting both tumor effects and effects of radiation therapy.

In total, 4 patients experienced dose level toxicities (DLTs). In Treatment Regimen 1, no patient experienced a DLT in the vandetanib 100 mg+RT group while 1 patient experienced

DLT in the vandetanib 200 mg+RT group. Therefore, both the 100 mg and 200 mg dose levels of vandetanib were tolerated as per the definition outlined in the protocol. However, due to slow enrollment, the 300 mg group was not explored and the MTD could not be determined for Treatment Regimen 1. In Treatment Regimen 2, vandetanib 100 mg was well tolerated with no DLTs and was determined to be the MTD because 3 patients from the vandetanib 200 mg+cisplatin+RT group experienced DLTs.

There was 1 death reported in the study in vandetanib 200 mg+cisplatin+RT group. A total of 7 patients experienced serious adverse events (SAEs); 1 (16.7%) patient in vandetanib 200 mg+RT group, 3 (20.0%) patients in vandetanib 100 mg+cisplatin+RT group, and 3 (50.0%) patients in vandetanib 200 mg+cisplatin+RT group. Overall, the only SAE experienced by >10% patients was diarrhea; 1 (16.7%) patient in vandetanib 200 mg+RT group and 3 (50.0%) patients in vandetanib 200 mg+cisplatin+RT group. Five (15.2%) patients had AEs leading to discontinuation of vandetanib and the most common AEs leading to discontinuation of vandetanib were diarrhea (2 [6.1%] patients) and blood creatinine increase (2 [6.1%] patients). There were no patients who experienced AEs leading to discontinuation of cisplatin or RT. There were no patients with an AE where the action taken was recorded as dose reduction of vandetanib because it is only possible to record 1 action taken, so the action taken recorded was dose interruption for these patients. There was 1 (16.7%) patient each on the vandetanib 100 mg+RT group and vandetanib 200 mg+cisplatin+RT group who experienced AEs leading to dose interruption of vandetanib.

Laboratory values of CTCAE Grade 3 were observed as follows: Alanine aminotransferase was seen in 1 (16.7%) patient in vandetanib 200 mg+RT group; hyponatremia was seen in 2 (13.3%) and 2 (33.3%) patients in the vandetanib+cisplatin+RT 100 mg and 200 mg groups, respectively, and hypokalemia was seen in 1 (6.7%) patient in the vandetanib 100 mg+cisplatin+RT group. Overall, no patients met the protocol-defined criteria for QT prolongation and no patient had a QT interval corrected for heart rate by Bazett's method (QTc) of ≥500 msec.

Table S4 Summary of number (%) of patients who had at least 1 AE

	-Number (%) of patients-				
	-Vandetanib + Cisplatin + RT-		-Vandetanib +RT-		
AE category	**100mg (N=15)**	**200mg (N=6)**	**100mg (N=6)**	**200mg (N=6)**	**Total (N=33)**
Any AE	14 (93.3)	6 (100.0)	6 (100.0)	6 (100.0)	32 (97.0)
SAEs with outcome of death	0	1 (16.7)	0	0	1 (3.0)
Any SAE (including events with outcome = death)	3 (20.0)	3 (50.0)	0	1 (16.7)	7 (21.2)
Any AE of CTCAE grade 3 or higher	12 (80.0)	5 (83.3)	6 (100.0)	6 (100.0)	29 (87.9)
AEs causally related to Vandetanib	14 (93.3)	6 (100.0)	6 (100.0)	6 (100.0)	32 (97.0)

Table S4 Summary of number (%) of patients who had at least 1 AE

	-Number (%) of patients-				
	-Vandetanib + Cisplatin + RT-		-Vandetanib +RT-		
AE category	**100mg (N=15)**	**200mg (N=6)**	**100mg (N=6)**	**200mg (N=6)**	**Total (N=33)**
AEs leading to discontinuation of Vandetanib	1 (6.7)	3 (50.0)	0	1 (16.7)	5 (15.2)
AEs leading to discontinuation of cisplatin	0	2 (33.3)	0	0	2 (6.1)
AEs leading to discontinuation of RT	0	2 (33.3)	0	0	2 (6.1)
AEs leading to dose reductions of Vandetanib	0	0	0	0	0
AEs leading to dose interruptions of Vandetanib	0	1 (16.7)	1 (16.7)	0	2 (6.1)

Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than one category are counted once in each of those categories.
Patients (E0001003, E0001018) on the Vandetanib+ Cisplatin + RT 100mg regimen, and 1 patient (E0001012) in the Vandetanib+ Cisplatin + RT 200mg regimen, withdrew from treatment before receiving Cisplatin or Radiotherapy.
RT Radiotherapy.
Data derived from Table 11.3.2.1.1.