AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	ZD6474 (ZACTIMA™)
Study Code	D4200C00068
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An Open-Label, Two-Stage, Phase II Study to Evaluate the Efficacy and Tolerability of ZD6474 in Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Carcinoma

Study centre(s)

This study was conducted at 9 study sites in Australia, Canada, Italy, Netherlands, Romania, Spain, Switzerland, and the United States.

Publications

None at the time of the writing of this report.

Study dates		Phase of development
First patient enrolled	29 August 2006	Therapeutic exploratory (II)
Last patient completed	31 January 2008	

Objectives

The primary objective of this study was to determine the objective response rate in patients treated with vandetanib 100 mg monotherapy.

The secondary objectives of the study were as follows:

1. To determine the safety and tolerability of vandetanib treatment in this patient population

2. To determine progression-free survival (PFS) of hereditary medullary thyroid cancer (MTC) in patients following vandetanib 100 mg therapy

3. To determine the disease control rate (DCR), duration of objective response (DOR) and duration of disease control with vandetanib

4. To assess the change in performance status (PS) from baseline of patients given vandetanib using World Heath Organization (WHO) PS

5. To determine whether treatment with vandetanib results in a decrease of stool frequency in patients with symptomatic diarrhoea associated with hereditary MTC ("symptomatic response")

6. To assess of the effect of vandetanib 100 mg dose on CTN and CEA levels

7. To characterize the population pharmacokinetics of vandetanib in patients with hereditary MTC

8. To characterize the pharmacokinetic-pharmacodynamic relationship between vandetanib exposure and changes in QTc prolongation, adverse events (AE), response, PFS, and changes in CTN and CEA levels

The exploratory objectives were as follows:

1. To determine if the baseline plasma level of CTN and/or CEA has prognostic significance for patients with MTC, and whether levels of CTN and CEA increase or decrease in response to the administration of vandetanib

2. To investigate the effects of vandetanib on quality of life (QOL) by using the Functional Assessment of Cancer Therapy General Scale (FACT-G)

3. To evaluate the effects of vandetanib on the activity of the REarranged during Transfection (RET) oncoprotein, epidermal growth factor receptor (EGFR), vascular endothelial growth factor-2 (VEGFR-2) signalling pathway in tumor tissue

4. Confirm germline RET mutation is present in tumor tissue.

5. To evaluate the effects of vandetanib on circulating protein biomarkers of angiogenesis, tumor burden or urine biomarkers.

Study design

This was an international phase II, multicenter, open-label study to establish the effect of once daily oral doses of vandetanib 100 mg in approximately 15 patients with locally advanced or metastatic hereditary MTC for whom no standard of therapeutic option was available.

Target patient population and sample size

Patients with locally advanced or metastatic hereditary MTC for whom no standard therapeutic option was available

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

Vandetanib 100-mg (batch # 33306K05, 40766C06, 41415A06, and 33307H05) and 300-mg tablets (batch # 40766C06 and 33307H05) administered orally once daily, preferably at the same time each morning.

Duration of treatment

Patients remained on the vandetanib 100-mg dose until objective disease progression. Upon disease progression, all patients that the investigator believed may have been obtaining benefit from vandetanib 100-mg therapy were permitted to receive post-progression vandetanib 300-mg treatment. Patients remained in the study as long as the investigator felt that they were obtaining benefit from treatment, objective disease progression occurred at this dose, or another discontinuation criterion was met. Patients who did not enter post-progression vandetanib 300-mg treatment were discontinued from 100-mg treatment, and entered directly into follow up.

Criteria for evaluation (main variables)

- **Primary outcome variable:**

  Objective response rate

- **Secondary outcome variables:**

1. Incidence and type of AEs, clinically significant laboratory abnormalities, electrocardiographic changes, and vital signs
2. DCR, DOR, and duration of disease control
3. PFS
4. PS over time (based on WHO criteria)
5. Decrease in symptomatic diarrhea
6. Serum CTN and CEA levels
7. Population pharmacokinetic estimates

8. Relationship between pharmacokinetic and pharmacodynamic variables for vandetanib exposure and measurements of QTc, and changes in serum CTN and CEA levels

– **Exploratory outcome variables**

1. Baseline CTN and CEA levels

2. FACT-G score

3. EGFR, phospho-EGFR, vascular endothelial growth factor (VEGF), VEGFR-2, phospho-VEGFR-2, RET, phospho-RET, mitogen-activated protein kinase (MAPK), phospho-MAPK, Src homology 2 domain containing (SHC), phospho-SHC, Phospholipase C gamma (PLCγ), Phosphorylated Phospho-Lipase C gamma, (pPLCγ), CTN ribonucleic (RNA)

4. RET gene mutation in tumors

5. Serum protein expression profile

6. Plasma VEGF, VEGFR2, and basic fibroblast growth factor (bFGF)

7. Urine catecholamine, metanephrine, and normetanephrine

Statistical methods

For each patient, baseline tumour burden prior to drug administration was assessed using the sum X_{sum} = sum{ $X_0,\ldots,X_k$} of tumour LD measurements obtained prior to study drug initiation. To examine the post-drug tumour measurements (denoted by $Y_0, \ldots, Y_k$), Y_{sum} at any given time point was compared with the baseline (X_{sum}), such that the relative change from baseline was calculated:

$$100*(X_{sum} - Y_{sum})/ X_{sum}.$$

The primary objective of this study was to determine the objective response rate in patients treated with vandetanib 100 mg monotherapy.

Fifteen evaluable patients (defined as patients receiving at least 1 dose of vandetanib) were to be recruited and followed for 3 months. Vandetanib 100 mg treatment was considered to have activity if 1 or more of the 15 patients experienced a confirmed objective, biochemical, or symptomatic CR or PR. Patients with stable disease continued in the study as long as the investigator judged that the patient was gaining benefit from this treatment.

The sample size of 15 patients was selected on the basis that if no responses were seen in 15 patients, the probability that the true objective response rate was 20% or greater was less than 0.05.

Efficacy data for this study were summarized and analyzed on an intention-to-treat basis. The efficacy analysis population (full analysis set) consisted of all patients who received at least 1 dose of vandetanib.

The safety analysis population (safety analysis set) comprised all patients who received at least 1 dose of study treatment. Safety and tolerability were assessed in terms of AEs, laboratory data, vital sign data, and ECG changes, which were collected for all patients.

Patient population

Demographic and baseline characteristics are displayed in Table S1.

Table S1 Demographic and baseline characteristics (full analysis set)

Demographic or baseline characteristic		Vandetanib 100 mg[a] (N=19)	
Sex (n and % of patients)	Male	13	(68.4)
	Female	6	(31.6)
Age (years)	Mean (standard deviation)	44.7	(14.1)
	Range	22 to 79	
Age category (n and % of patients)	≥18 to <65	17	(89.5)
	≥65 to <75	1	(5.3)
	≥75	1	(5.3)
Race (n and % of patients)	Caucasian	18	(94.7)
	Other	1	(5.3)
Ethnic group (n and % of patients)	Not applicable	17	(89.5)
	Native Hawaiian/Pacific islander	1	(5.3)
	Other	1	(5.3)
Baseline characteristics			
Disease stage	IVA	1	(5.3)
	IVC	18	(94.7)
Time since diagnosis (years)[b]	Mean (standard deviation)	13	(10)
	Range	5 to 33	
Locally advanced disease sites	Total	9	(47.4)
	Lymph nodes	7	(36.8)
	Neck	1	(5.3)
	Other sites	1	(5.3)

Table S1 Demographic and baseline characteristics (full analysis set)

Demographic or baseline characteristic		Vandetanib 100 mg[a] (N=19)	
Metastatic disease sites	Total	18	(94.7)
	Adrenal	1	(5.3)
	Bone and locomotor	8	(42.1)
	Gastrointestinal	1	(5.3)
	Hepatic (including gall bladder)	16	(84.1)
	Lymph nodes	8	(42.1)
	Neck	4	(21.1)
	Respiratory	8	(42.1)
	Other metastatic sites	1	(5.3)
Previous therapies for MTC	Anticancer therapy	6	(31.6)
	Radiotherapy[c]	4	(21.0)
	Chemotherapy[d]	2	(10.5)
Associated findings			
Family history of MTC	Yes	14	(73.7)
	No	3	(15.8)
	Unknown	2	(10.5)
Associated endocrinopathies	MEN 2a	17	(89.5)
	FMTC	1	(5.3)
	MEN 2b	1	(5.3)
RET mutation status	Unknown[e]	2	(10.5)
	Yes	17	(89.5)
Point location	- 618	2	(10.5)
	- 620	2	(10.5)
	- 634	9	(47.4)
	- 768	1	(5.3)
	- 918	1	(5.3)
	- Other (380 codon)	1	(5.3)
	- Other (608)	1	(5.3)
WHO performance status at entry	(0) Normal activity	16	(84.2)
	(1) Restricted activity	1	(5.3)

Table S1 Demographic and baseline characteristics (full analysis set)

Demographic or baseline characteristic		Vandetanib 100 mg[a] (N=19)	
	(2) In bed ≤50% of the time	2	(10.5)
	(3) In bed >50% of the time	0	
	(4) 100% bedridden	0	

[a] Initial treatment received.
[b] Time since diagnosis was from diagnosis to first dose date N=11.
[c] Includes one patient (E2901003) who received palliative radiotherapy.
[d] These are patients who received 4 cycles of chemotherapy.
[e] When RET mutation status was unavailable, a diagnosis of HMTC was based on family history.
FMTC Familial medullary thyroid carcinoma; MEN Multiple Endocrine Neoplasia; n Number; N Number of patients in treatment group; NR Not recorded; RET REarranged during Transfection (proto-oncogene); WHO World Health Organization.

Efficacy and pharmacokinetic results

Primary variable

Results for objective response are presented in Table S 2. The objective response rate was 15.8% (95% confidence interval [CI] of 3.4, 39.6)

Table S 2 Objective response with vandetanib 100 mg (full analysis set)

Objective response	Response, thyroid cancer	Vandetanib 100 mg (N=19)	
		n	(%)
Response	CR	0	
	PR	3	(15.8)
	Total	3	(15.8)
Non-response	SD > 8 weeks	12	(63.2)
	Progression	3	(15.8)
	Not evaluable	1	(5.3)
	Total	16	(84.2)

CR Complete response, PR Partial response, SD stable disease.

Results for secondary variables were as follows:

- **PFS:** The estimated median PFS could not be calculated for patients who received vandetanib 100 mg because of insufficient follow-up.

- **DCR, DOR, and duration of disease control:** The DCR was 68.4% (95% CI of 43.4, 87.4) (13/19 patients), with a median duration of disease control of 256 days. The median duration of response from the onset of response was 168 days, and the median duration of response from first dose was 252 days..

- **Performance status over time (based on WHO criteria):** Overall, no marked improvement in PS was evident in patients treated with vandetanib 100 mg.

- **Symptomatic diarrhea:** There were no symptomatic responses.

- **CTN and CEA:** A total of 15.8% of patients (3/19 patients) experienced a reduction in CTN of at least 50% that was sustained for at least 4 weeks. A total of 5.3 % of patients (1/19 patients) experienced a reduction in CEA of at least 50% from baseline that was sustained for at least 4 weeks.

- **Pharmacokinetics:** The mean (± SE) estimated clearance from patients was 13.0 ± 1.00 $L.h^{-1}$, with the volume of distribution at 3850 L, giving an estimated half-life of approximately 9 days. Steady state was estimated to have been achieved by Day 28 for the majority of patients.

- **Pharmacokinetic-pharmacodynamic relationship:** QTc was found to change in a non-linear manner with the predicted plasma concentrations, such that a maximum change of 20 to 30 ms was reached within 1 month of dosing.

  Although data were limited there was no clear evidence of increasing QTc with increasing plasma concentration, and values appeared to remain constant at 20 to 30 ms up for average steady-state concentrations of up to 400 to 500 $ng.mL^{-1}$ for the 100 mg dosing level.

  Baseline QTc was recorded at 418 ms, and there was high residual variability ± 13.2 ms. There was no apparent increase in mean QTc after 28 days of dosing.

  No correlation could be identified with either serum CTN or CEA and predicted plasma concentrations..

- **Patient reported outcomes/QOL**: Overall, patients in the study showed a marginal reduction in the overall FACT-G scores from baseline; however, no conclusions could be drawn due to the small sample size of the study.

Safety results

A summary of patients who had an AE in any category is displayed in Table S 3.

Table S 3 Number (%) of patients who had an adverse event in any category (safety analysis set)

Category of adverse event	Number (%) of patients who had an AE in each category[a]
	Vandetanib 100 mg (N=19)
Any AE	18 (94.7)
Any SAE (including events leading to death)	4 (21.1)
SAE leading to death	1 (5.3)
AE leading to discontinuation of vandetanib treatment	3 (15.8)
Drug-related AE	17 (89.5)
CTCAE grade 3 or higher AEs	6 (31.6)
OAE	2 (10.5)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; OAE Other significant adverse event; SAE Serious adverse event.

Common AEs that occurred with vandetanib 100 mg treatment are grouped by preferred term in Table S4.

Table S4 Most commonly reported AEs, group by preferred term and sorted by decreasing order of frequency

	Vandetanib 100 mg (N=19)	
Preferred term	**n**	**(%)**
Diarrhoea	9	(47.4)
Fatigue	8	(42.1)
Rash	5	(26.3)
Constipation	4	(21.1)
Photosensitivity reaction	3	(15.8)
Nausea	3	(15.8)
Back pain	3	(15.8)
Anorexia	3	(15.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; OAE Other significant adverse event; SAE Serious adverse event.

AEs of CTCAE grade 3 and higher that occurred with vandetanib 100 mg treatment included SAEs of aspiration pneumonia that led to death, phaeochromocytoma and diabetes insipidus, and an AE of muscular weakness that led to discontinuation of vandetanib 100 mg treatment.

Overall, the changes in clinical laboratory values were mild with all but 1 change to CTCAE grade 1 or 2. One patient who had undergone a bilateral adrenalectomy prior to study entry developed grade 3 hyponatremia that was observed on the final assessment prior to data cutoff.

With respect to vital signs changes, elevated pulse was observed in 5 (26.3%) patients; changes from baseline >20 bpm occurred in 4 (21.1%) patients. Elevated diastolic blood pressure (>95 mm Hg) was observed in 7 (36.8%) patients; changes from baseline >15 mm Hg were observed in 12 (63.2%) patients. Elevated systolic blood pressure (>160 mm Hg) was observed in 2 (10.5%) patients.

QTc prolongation was observed in 1 patient during vandetanib 100 mg treatment. The QTc prolongation was successfully managed through interruption and reduction of the patient's vandetanib dose.