Clinical Study Report Synopsis

Drug Substance	Vandetanib
Study Code	D4200C00008
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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 dates: First subject enrolled: 12 November 2004
Last subject last visit: 22 February 2008

Phase of development: Therapeutic exploratory (II)

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

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Study centre(s)

Thirty-five patients were recruited at 7 centers (6 centers in the US and 1 center in France). Of these, 30 patients received initial treatment with ZD6474 300 mg.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary objective of this study was to assess the objective response of ZD6474 (300 mg) given as monotherapy in patients with locally advanced or metastatic hereditary MTC.

Secondary objectives of the study were:

1. To determine the response in basal levels of serum CTN after treatment with ZD6474 ("biochemical response");

2. To determine whether treatment with ZD6474 results in a decrease of stool frequency and an improvement in stool consistency in patients with symptomatic diarrhea associated with MTC ("symptomatic response");

3. To determine the time to progression (TTP, also referred to as progression-free survival [PFS]) of MTC in patients following ZD6474 therapy;

4. To determine the disease control rate, duration of objective response, and duration of disease control with ZD6474;

5. To assess the change in performance status (PS) from baseline of patients given ZD6474 using World Heath Organization (WHO) PS;

6. To characterize the population PK of ZD6474 in patients with MTC;

7. To characterize the pharmacokinetic-pharmacodynamic (PK-PD) relationship between ZD6474 exposure and changes in QTc prolongation, adverse events (AEs), response, TTP, and changes in CTN and carcinoembryonic antigen (CEA) levels;

8. To determine the safety and tolerability of ZD6474 treatment in this patient population.

The exploratory objectives of this study were:

1. To characterize functional activity of tumor using 2-[F-18] fluor-2-deoxy-D-glucose positron emission tomography (FDG-PET);

2. To determine in selected patients with a biochemical complete response (CR), the change in basal serum CTN levels following a calcium-pentagastrin stimulation test;

3. To determine if the baseline plasma level of CEA has prognostic significance for patients with MTC, and whether it increases or decreases in response to the administration of ZD6474;

4. To evaluate the effects of ZD6474 in tumor tissue on DNA microarray patterns;

5. To investigate the effects of ZD6474 on quality of life (QOL) and disease-related diarrhea by using the Functional Assessment of Chronic Illness Therapy – Diarrhea (FACIT-D);

6. To explore patient-reported changes in the use of anti-diarrheal medications as related to the FACIT-D; and

7. To evaluate the effects of ZD6474 on the activity of RET, EGFR, and VEGFR signaling pathways in tumor tissue.

Study design

This was a 2-stage, phase II study to determine the efficacy and tolerability of treatment with ZD6474 (300 mg daily) in patients with locally advanced or metastatic hereditary MTC.

Target subject population and sample size

Patients with measurable, locally advanced or metastatic hereditary MTC.

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

ZD6474 300 mg administered orally once daily, preferably at the same time each morning: batch numbers BN2000061166, BN2000061096, BN2000081595, BN2000086221, BN2000087944, BN2000092906, BN2000095865, BN2000106347, BN2000108164, BN2000109893, BN2000113399, BN2000113401, BN2000113403, BN2000061093, BN2000086223, BN2000093266, BN2000095867, BN2000099354, BN2000100422, BN2000103909, BN2000106599, BN2000084699, BN2000084736, BN2000096331, BN2000084708, BN2000096338.

Duration of treatment

Patients who demonstrated a response or stable disease (SD) remained in the study as long as they were benefiting from treatment (ie, an objective, biochemical, or symptomatic CR, partial response [PR] or SD), there was no evidence of tumor progression, and they met no other withdrawal criteria. Amendment 006 allowed for patients demonstrating progression by Response Evaluation Criteria in Solid Tumors (RECIST) criteria to continue on trial and receive study medication if the investigator, with approval from AstraZeneca, believed the patients were deriving clinical benefit from ZD6474 therapy. To facilitate study conduct, study evaluations were arranged into assessment periods. For the purposes of this study, an assessment period was 28 days (prior to protocol Amendment 007) and 12 weeks in duration (following approval of Amendment 007). Patients were required to complete all assessments

as were previously required for the every 28 day visits after approval of Amendment 007. Following Amendment 008, patients who had not met any criteria for withdrawal at the time of last subject/last visit (ie, at the time of data cutoff) would only be required to have specified safety assessments performed at the every 12 week visits. In order for AstraZeneca to continue to supply study drug, all patients had to return for visits every 12 weeks on an outpatient basis for completion of the required safety assessments until the patient terminated from the study.

Criteria for evaluation (main variables)

Efficacy

- **Primary outcome variable:**
  − Objective measurable tumor response: The complete eradication of MTC tumor burden, as determined by radiographic disappearance of all tumors, following administration of ZD6474 denoted an objective CR. Objective PR was defined by RECIST criteria.

- **Secondary outcome variables:**
  − Biochemical response: The reduction of elevated basal serum CTN levels to normal following the administration of ZD6474 denoted a biochemical CR. The reduction of elevated serum CTN levels by 50% or more following administration of ZD6474 denoted a biochemical PR;

  − Symptomatic response: The reduction of frequency and improvement in consistency of stool to normal levels (no more than 2 solid stools daily without concomitant anti-diarrheal medication) following administration of ZD6474 denoted a symptomatic CR. An improvement in stool consistency to mostly semisolid and decrease in stool frequency to 50% or greater (with or without concomitant anti-diarrheal medication) of baseline value following administration of ZD6474 was defined as a symptomatic PR;

  − TTP (referred to as progression-free survival [PFS]): the time from the date of first dose of study medication until the date of objective progression or death;

  − Disease control rate (defined as CR + PR + SD ≥24 weeks), duration of disease control and duration of objective response;

  − PS assessed monthly (prior to Amendment 007) and then every 12 weeks (following approval of Amendment 007) using the World Health Organization (WHO) criteria.

- **Safety outcome variables (secondary):**
  − Incidence, type, and grade of AEs as determined by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3, clinically significant laboratory abnormalities, and electrocardiogram (ECG) abnormalities.

- **Pharmacokinetics-Pharmacodynamics (PK-PD)**
  − Total body clearance of drug at steady state (CLss/f) and volume of distribution at steady state (Vss/f) of ZD6474 following administration of multiple oral doses, with associated inter-patient variabilities. Individual empirical Bayesian-derived maximum concentration (Cmax), area under the curve at steady state (AUCss), and minimum concentration (Cmin) values;

  − Probability of QTc prolongation and the concentration of ZD6474 associated with risk. Probability of AEs, response, TTP, changes in CTN and CEA levels, and determination of whether AUCss, Cmax, or Cmin was the most significant predictor of these events or changes.

- **Exploratory outcome variables:**
  − Functional activity of tumor using FDG-PET;

  − The change in basal CTN levels following a calcium-pentagastrin stimulation test in patients with a biochemical CR;

  − The relationship of the baseline level of CEA to response and the effects of ZD6474;

  − DNA microarray patterns;

  − QOL and disease-related diarrhea using the FACIT-D questionnaire;

  − Patient-reported changes in the use of anti-diarrheal medications as related to the FACIT-D;

  − Activity of the RET, EGFR and VEGFR signaling pathways in tumor tissue.

Statistical methods

The primary objective of this study was to assess the efficacy (CR and PR) of ZD6474 (300 mg) given as monotherapy in patients with hereditary MTC. A 2-stage study was employed to investigate the efficacy of treatment at the 300-mg dose level as defined by tumor shrinkage confirmed by radiological criteria. For each patient, baseline tumor burden prior to drug administration was assessed using the sum Xsum = sum{X0,…,Xk} of tumor longest diameter (LD) measurements obtained prior to study drug initiation. To examine the postdrug tumor measurements (denoted by Y0,…,Yk)), Ysum at any given timepoint was compared with the baseline (Xsum), such that the relative change from baseline was calculated: 100*(Xsum – Ysum)/ Xsum. The primary objective of the study was to evaluate the success rate as previously discussed, as defined by the number of patients demonstrating an objective tumor response (CR or PR) to therapy.

For stage 1 of this trial, the first 15 evaluable patients (defined as patients receiving at least 1 dose of ZD6474) were followed up for 3 months. ZD6474 treatment was considered to be

promising if 1 or more of the 15 patients experienced a confirmed objective, biochemical, or symptomatic CR or PR. If there were no patients demonstrating response, the trial would not open the second stage. Patients with SD could continue on study drug as long as investigator judged the patient was gaining benefit from this treatment.

If stage 1 of this trial was successful, an additional 15 evaluable patients were recruited, to give a minimum total of 30 evaluable patients. At the end of the trial, a successful efficacy outcome would be considered an objective tumor response rate of ≥20% of patients. Assuming a null hypothesis of an objective tumor response rate of <20%, and an alternative hypothesis of an objective tumor response rate (CR and PR patients) of ≥20%, with 30 evaluable patients and using a one-sided hypothesis test with a significance level of 5%, there would be ≥80% power to reject the null hypothesis in favor of the alternative hypothesis if the true objective tumor response rate was ≥40%.

Efficacy data for this study were summarized and analyzed on an intention-to-treat (ITT) basis. The efficacy analysis population consisted of all patients who received at least 1 dose of ZD6474.

The safety population 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. Appropriate summaries of these data were presented.

Subject population

Thirty-five patients were recruited at 7 centers (6 centers in the US and 1 center in France). Of these, 30 patients received initial treatment with ZD6474 300 mg. Thirteen patients were discontinued from ZD6474 therapy for the following reasons: patient not willing to continue treatment (n=2), AEs (n=7), and disease progression (n=4). Of these, 11 patients terminated the study (no further post discontinuation assessments were performed), and the investigator decided to withdraw study treatment from 2 patients, ie they completed the study. Seventeen patients were ongoing treatment at the time of data cutoff on 22 February 2008. (The cutoff date was determined based on when the patients in the trial had had at least 18 months of treatment.)

At the time of data cutoff on 22 February 2008, 13 patients had discontinued from ZD6474 therapy for the following reasons: patient not willing to continue treatment (n=2), AEs (n=7), and disease progression (n=4). Of these, 2 patients completed the study and 11 patients terminated the study (no further post discontinuation assessments were performed) due to death (n=2), patient lost to follow-up (n=2), and patient not willing to continue treatment (n=7). Seventeen patients were ongoing treatment at the time of data cutoff (22 February 2008).

There were more females than males (21 and 9, respectively), and the majority of patients were Caucasian. The mean age for this study population was 48.7 years (range, 20 to 77 years), with the majority of patients younger than 65 years. All but 1 patient had metastatic

disease at the time of trial entry. In this study, the majority of patients had Multiple Endocrine Neoplasia Type 2a (MEN2a), which is representative of the general MTC population. All 30 patients (100%) had previously undergone disease-related surgery; 36.7% had received radiotherapy, and 26.7% had received other cancer therapy. The WHO PS score at study entry was 0 (normal activity) for 50.0% of the patients, 1 (restricted activity) for 46.7%, and 2 (in bed ≤50% of the time) for 3.3% (1 patient). Protocol deviations were primarily associated with failure to adhere to scheduled assessments.

Summary of efficacy results and pharmacokinetic results

The primary objective of this study was to assess the objective response of ZD6474 (300 mg) given as monotherapy in patients with locally advanced or metastatic hereditary MTC. The primary method for determining objective response was based on the site-reviewed computed tomography (CT)/magnetic resonance imaging (MRI) scans using RECIST criteria. All CT/MRI scans were also reviewed by a centrally appointed vendor, using modified RECIST criteria, following approval of Amendment 005. The central review data were intended to supplement the primary, site-reviewed method of assessment of response.

Secondary efficacy endpoints included PFS (including death by any cause within 3 months of the last tumor assessment), disease control rate, duration of objective response and disease control, biochemical response (CTN), symptomatic response (stool consistency and frequency), and PS (WHO). Exploratory analyses of biochemical response (CEA), quality of life (FACIT-D), and patient-reported changes in the use of anti-diarrheal medication were also examined.

At the time of data cutoff (22 February 2008), 20% (6/30) of patients in the ITT population who received ZD6474 300 mg had an objective response (CR + PR, based on site-read assessment). A further 53% (16/30) of patients experienced SD ≥24 weeks, and 20% (6/30) of patients experienced SD ≥8 and <24 weeks.

Progression status at the time of data cutoff showed 8 (26.7%) patients with RECIST progression, 20 (66.7%) with no progression and alive at the time of analysis, and 2 (6.7%) patients who died >3 months after last RECIST. The median PFS was 27.9 months (849 days).

The median duration of objective response from first response until progression or death was 10.2 months (311 days), and from first dose until progression or death was 18.5 months (562 days). The median duration of disease control from first dose until progression or death from any cause was 18.5 months (564 days). Disease control (≥24 weeks) was observed in 22 (77.3%) patients.

Based upon the central-read data, an objective response was observed in 16.7% (5/30) of patients. A total of 9 (30.0%) patients showed RECIST progression at the time of data cutoff and the median PFS was 34.7 months (1057 days). The median duration of objective response from first response until progression or death was 16.4 months (500 days), and from first dose until progression or death was 19.3 months (587 days). The median duration of disease control

from first dose until progression or death from any cause was 18.3 months (556 days). Disease control (≥24 weeks) was observed in 20 (66.7%) patients.

A biochemical CTN response was observed in 80% (24/30) of patients. A biochemical CEA response was observed in 53% (16/30) of patients. Substantial decreases in CTN and CEA were observed in the majority of patients. Of the 6 patients demonstrating objective response, the largest CTN decreases ranged from 73% to 99% and the largest CEA decreases ranged from 21% to 91%.

For patients with abnormal stools at baseline, no symptomatic response was observed. Because SD lasting for at least 24 weeks was used in the definition of disease control (in addition to confirmed objective response), WHO PS at 24 weeks was evaluated. Fourteen (46.7%) patients had no change compared to baseline, and 2 patients (6.7%) had a shift from WHO PS of 1 at baseline to zero at Week 24. Four patients (13.3%) showed a worsening in PS at the 24-week visit.

Patients were enrolled sequentially into the study and were observed for varying amounts of time. Therefore, a 1-year follow-up period from date of first dose of ZD6474 was used to assess the FACIT-D due to declining number of patients who had follow-up beyond 365 days to provide meaningful interpretation. Over the 1-year follow-up period, patients in the study exhibited a trend towards diminished HRQL specific to diarrhea and clinically significant worsening of diarrhea symptoms. However, no firm conclusions can be drawn due to the open-label study design and the exploratory nature of the analysis.

The PK-PD relationships between ZD6474 exposure and AEs, objective response, PFS, changes in QTc interval, and changes in CTN and CEA levels were explored. The results showed no correlation between mean ZD6474 plasma concentration and AEs, best objective response, or PFS. Non-linear PK-PD relationships were seen between ZD6474 plasma concentration and increased QTc interval, decreased CTN levels, and decreased CEA levels.

Summary of safety results

All 30 patients received initial treatment with ZD6474 300 mg and were therefore included in the analysis of safety. Twenty-four (80.0%) patients had either dose reduction or dose interruption during the study. Twenty-one (70%) patients had dose reductions due to AEs; 10 patients had dose reductions without interrupting administration of ZD6474, and 11 patients had a temporary interruption of ZD6474 administration and then had subsequent dose reduction. The median time to first dose reduction was 149 days (95% confidence interval [CI] 82.0, 257.0).

Table S1 Number (%) of patients who had an adverse event in any category (safety analysis set)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]	
	ZD6474 300 mg/day[b] (N=30)	
Any adverse events	30	(100.0)
Serious adverse events	11	(36.7)
Serious adverse events leading to death	2	(6.7)
Serious adverse events not leading to death	10	(33.3)
Discontinuations of study treatment due to adverse events	7	(23.3)
Drug-related[c] adverse events	30	(100.0)
CTCAE grade 3 or 4 adverse events	24	(80.0)
CTCAE grade 3 or 4 drug-related[c] adverse events	19	(63.3)
Other significant adverse event	17	(56.7)

[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.
[b] Initial treatment received.
[c] In the opinion of the investigator.
CTCAE Common Terminology Criteria for Adverse Events; N Number of patients in treatment group.
As of data cutoff on 22 February 2008.

Overall, the highest incidence of AEs (by system organ class) was observed in general disorders and administration site conditions; gastrointestinal disorders; skin and subcutaneous tissue disorders; and nervous system disorders. The most common AEs by preferred term were diarrhea (70.0%), rash (66.7%), fatigue (63.3%), and nausea (63.3%). Five groups of AEs were prespecified by event type; the incidences of AEs for each group were: rash (83.3%), diarrhea (70.0%), nausea/vomiting (66.7%), QTc-related events (26.7%), and dizziness/seizures (26.7%).

Most AEs were CTCAE grade 1 or 2; the most common grade 3 AEs included ECG QT prolonged (20.0%), diarrhea (10.0%), nausea (10.0%), and hypertension (10.0%). There were 2 grade 4 AEs (azotemia and muscle weakness). For AEs grouped by event type, grade 3 AEs included ECG QT prolonged (20.0%), rash (13.3%), nausea/vomiting (13.3%), and diarrhea (10.0%). All of these events were managed with dose interruptions/reductions.

A total of 2 patients had died at the time of data cutoff; both deaths occurred for reasons other than progression of thyroid cancer (colon cancer and cardiac failure). Neither of these serious AEs (SAEs) was considered by the investigator to be related to ZD6474. The SAEs with outcomes other than death occurred in 10 (33.3%) patients and included events relating to the

gastrointestinal disorders (hemorrhagic diarrhea, hemorrhagic intestinal diverticulitis, dysphagia, gastrointestinal obstruction, nausea, acute pancreatitis, and vomiting); infections and infestations (empyema, gastroenteritis, pneumonia, and sinusitis); investigations (ECG QT prolonged); nervous system disorders (convulsion and cranial neuropathy); and renal and urinary disorders (azotemia). All of these SAEs were grade 2 or 3 with the exception of one grade 4 azotemia. Except for the 2 patients with an SAE leading to death, SAEs in all other patients were resolved at the time of data cutoff. No specific SAE occurred in more than 1 patient, and most (9 of 17 SAEs) were not considered by the investigator to be related to ZD6474.

The AEs resulting in discontinuation of ZD6474 occurred in 7 (23.3%) patients. These included cardiac failure, colon cancer, hemorrhagic diarrhea, gastrointestinal obstruction, nausea, increased blood creatinine, increased blood urea nitrogen (BUN), QTc prolongation, and acne.

Other significant AEs (OAEs) included headache (46.7%) and dizziness (26.7%). All of these events were CTCAE grade 1 or 2, with the exception of one incidence of headache (grade 3). Only 1 incidence of headache resulted in dose interruption, and most OAEs were resolved at the time of data cutoff.

There were few hematological or clinical chemistry abnormalities noted during the study. One patient was reported to have an AE of grade 4 azotemia (verbatim term, hypercalcemia uremia); however, all BUN and creatinine values for this patient were within normal limits throughout the study. Electrolyte imbalances were managed with electrolyte replacement.

Patients treated with ZD6474 tended to have increases in systolic/diastolic blood pressure. Additionally, the AE incidence of hypertension was approximately 33%; however, the hypertension was CTCAE grade 1 or 2 in the majority (7 of 10) of patients. No definitive trends in weight gain/loss were observed.

Overall, 8 (27%) patients had QTc prolongation. Two patients had QTc prolongation based on the original QTc prolongation criteria (Amendment 005 changed the criteria from an increase of ≥60 msec over baseline to an absolute value ≥460 msec, to ≥60 msec over baseline to an absolute value ≥480 msec). All QTc prolongations were clinically asymptomatic and were resolved at the time of data cutoff. All QTc prolongations were managed with the protocol-defined regimen for handling QTc prolongation.

Overall, no new or unexpected physical findings were observed.