A Randomized, Double-Blind, Phase IIa Dose-Finding Study of Vandetanib (ZD6474) in Japanese Patients With Non-Small Cell Lung Cancer

Katsuyuki Kiura, MD, PhD, Kazuhiko Nakagawa, MD, PhD,†*
Tetsu Shinkai, MD, PhD,‡ Kenji Eguchi, MD, PhD,§ Yuichiro Ohe, MD, PhD,‖
*Nobuyuki Yamamoto, MD, PhD,¶ Masahiro Tsuboi, MD, PhD,# Soichiro Yokota, MD, PhD,***
Takashi Seto, MD, PhD,†† Haiyi Jiang, MD,‡‡ Kazuto Nishio, MD, PhD,† Nagahiro Saijo, MD, PhD,§§
and Masahiro Fukuoka, MD, PhD†

Introduction: Vandetanib (ZACTIMA™) is a once-daily, oral anticancer drug that selectively inhibits vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) signaling. Vandetanib was evaluated as a monotherapy in a randomized, double-blind, dose-finding study in Japan.

Patients and Methods: Eligible patients with locally advanced or metastatic (stage IIIB/IV) or recurrent non-small cell lung cancer, previously treated with chemotherapy, were randomized to receive once-daily oral vandetanib 100, 200, or 300 mg (1:1:1). The primary objective was to determine the objective response rate for each vandetanib dose.

Results: Fifty-three patients received vandetanib (100 mg, $n = 17$; 200 mg, $n = 18$; 300 mg, $n = 18$). The objective response rate in each dose arm was 17.6% (3 of 17; 100 mg), 5.6% (1 of 18; 200 mg), and 16.7% (3 of 18; 300 mg). Common adverse events included rash, diarrhea, hypertension, and asymptomatic QTc prolongation. The adverse event profile was generally consistent with that reported previously for agents that inhibit the VEGFR or EGFR signaling pathways. Among the three responders evaluated for *EGFR* mutation, two had no mutation, and in one case, the *EGFR* mutation status could not be determined by direct DNA sequencing and amplification refractory mutation system assay of *EGFR* exons 19–21. Baseline plasma VEGF levels appeared to be lower in patients who experienced clinical benefit after vandetanib treatment.

Conclusion: In Japanese patients with advanced non-small cell lung cancer, vandetanib monotherapy (100–300 mg/d) demonstrated antitumor activity with an acceptable safety and tolerability profile.

Key Words: Non-small cell lung cancer, Vandetanib, EGFR, VEGFR.

(*J Thorac Oncol.* 2008;3: 386–393)

Non-small cell lung cancer (NSCLC) accounts for approximately 75% of lung cancers and is the leading cause of cancer-related death worldwide.[1] Despite the introduction of more effective chemotherapeutic agents, new approaches are required to further improve patient outcome and survival. A major focus of new anticancer research is the targeting of cell-signaling pathways that contribute to tumor growth and progression.

Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) are key drivers of tumor angiogenesis and cell proliferation, respectively, and both pathways have been validated as clinically relevant targets in NSCLC. The addition of bevacizumab, a humanized anti-VEGF-A monoclonal antibody, to paclitaxel and carboplatin has demonstrated clinical benefit in patients with NSCLC,[2] and the EGFR inhibitors gefitinib and erlotinib have demonstrated clinical activity as single agents in NSCLC.[3,4] Furthermore, EGFR is known to regulate the production of VEGF and other proangiogenic factors[5] and resistance to EGFR inhibition has been associated with increased expression of VEGF in a human tumor xenograft model of NSCLC.[6] Therefore, targeting the VEGFR and EGFR pathways may be more effective than inhibiting either pathway alone. This hypothesis is supported by the promising results from early clinical evaluation of erlotinib and bevacizumab in combination in patients with recurrent NSCLC.[7]

Vandetanib (ZACTIMA™) is a once-daily, orally available anticancer drug that inhibits VEGFR- and EGFR-dependent signaling,[8] as well as the RET (REarranged during

*Okayama Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital, Okayama, Japan; †Kinki University School of Medicine, Osaka, Japan; ‡Shikoku Cancer Center, Ehime, Japan; §Tokai University Hospital, Kanagawa, Japan; ‖National Cancer Center Hospital, Tokyo, Japan; ¶Shizuoka Cancer Center, Shizuoka, Japan; #Tokyo Medical University Hospital, Tokyo, Japan; **Toneyama National Hospital, Osaka, Japan; ††Kyushu Cancer Center, Fukuoka, Japan; ‡‡AstraZeneca KK, Osaka, Japan; and the §§National Cancer Center Hospital East, Chiba, Japan.

Disclosure: Haiyi Jiang is an employee of AstraZeneca. All other authors declare no conflict of interest.

Address for correspondence: Katsuyuki Kiura, MD, PhD, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital, 2-5-1Shikata-cho, Okayama 700-8558, Japan; E-mail: kkiura@md.okayama-u.ac.jp

Copyright © 2008 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/08/0304-0386

Transfection) receptor tyrosine kinase, which is an important growth driver in certain types of thyroid cancer.[9] Early clinical evaluation of vandetanib has demonstrated a promising efficacy and safety profile in a broad population of patients with advanced cancer. Phase I studies in advanced solid tumors conducted in the USA/Australia[10] and Japan[11] showed that once-daily doses of vandetanib (up to and including 300 mg) were generally well tolerated. In the Japanese study, objective tumor responses were observed in 4 of 9 patients with refractory NSCLC. Subsequent phase II studies in advanced NSCLC demonstrated antitumor activity both as a monotherapy and in combination with certain chemotherapy.[12–14] The positive outcome of these phase II trials led to the ongoing phase III evaluation of vandetanib in previously treated advanced NSCLC.

The primary objective of this randomized phase IIa study was to assess the objective response rate (ORR) to vandetanib (100, 200, or 300 mg/d) in Japanese patients with refractory NSCLC. The three doses investigated were selected based on the outcome of the Japanese phase I trial.[11]

PATIENTS AND METHODS

Patients

Patients with histologic or cytologic confirmation of locally advanced/metastatic (stage IIIB/IV) or recurrent NSCLC after failure of 1 or 2 platinum-based chemotherapy regimens were recruited from eight centers in Japan. The main eligibility criteria were age ≥20 years, a WHO performance status of 0 to 2, an estimated life expectancy ≥12 weeks, and completion of prior chemotherapy and/or radiotherapy at least 4 weeks before study entry (8 weeks for chest radiation and 6 weeks for mitomycin C). Patients with squamous cell histology were also eligible, and brain metastases were permitted if patients were asymptomatic and did not require corticosteroid treatment. Key exclusion criteria were a mixed small-cell and non-small cell histology, evidence of severe or uncontrolled systemic diseases, poorly controlled hypertension, a QTc interval ≥460 milliseconds by electrocardiogram during the screening period, and prior treatment with EGFR or VEGFR signaling inhibitors. All patients provided written informed consent. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, applicable guidelines on good clinical practice, local Institutional Review Board approval, and the AstraZeneca policy on Bioethics.

Study Design and Treatments

This was a randomized, double-blind, parallel-group, phase IIa dose-finding multicenter study to assess the efficacy and safety of vandetanib. A total of 53 patients were randomized (1:1:1) to receive once-daily oral vandetanib (100, 200, or 300 mg/d; Figure 1). Patients were stratified by histology (adenocarcinoma versus others), gender (male versus female), and smoking history (smoker versus nonsmoker). Treatment continued until a withdrawal or dose-interruption criterion was met. These criteria included progressive disease (PD), unacceptable toxicity, protocol noncompliance, or voluntary discontinuation by the patient.

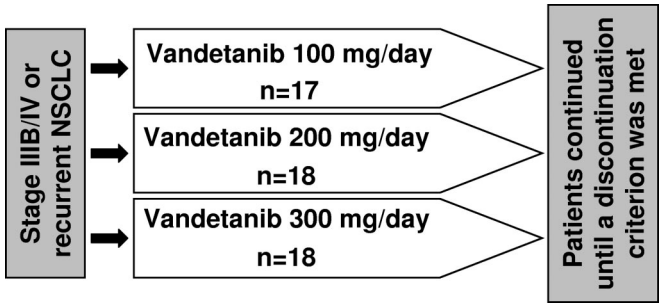

FIGURE 1. Study design.

Efficacy

The primary objective of the study was to determine ORR with vandetanib monotherapy, using the Response Evaluation Criteria in Solid Tumors (RECIST); assessments were performed at baseline and every 4 weeks for the first 24 weeks of treatment, and then every 8 weeks until withdrawal. A confirmed complete response or partial response (PR) was considered to be an objective tumor response. Investigator assessment of best overall tumor response was used for the primary analysis and these assessments were subsequently submitted to AstraZeneca for review by the response evaluation committee. Secondary efficacy endpoints included time to progression (TTP), duration of response (the time interval between the date of first documented objective tumor response until the date of PD or death), and disease control rate (DCR) for each dose of vandetanib. Time to progression was calculated from the date of randomization until the date of PD or death (in the absence of progression) and estimated using the Kaplan–Meier method. DCR was defined as confirmed complete response, PR, or stable disease (SD) ≥8 weeks.

Safety and Tolerability

Safety was assessed by monitoring for adverse events (AEs) and collecting laboratory data. All AEs were collected for up to 30 days after the last dose of vandetanib and were graded according to Common Terminology Criteria for Adverse Events (CTCAE, version 3). Unless otherwise clinically indicated, 12-lead electrocardiograms were performed twice at screening, weekly for the first 8 weeks of treatment, and then once every 4 weeks thereafter. Vandetanib treatment was interrupted following: a single QTc measurement ≥550 milliseconds; 2 consecutive QTc measurements ≥500 milliseconds but <550 milliseconds; an increase of ≥100 milliseconds from baseline; or an increase of ≥60 milliseconds from baseline QTc to a QTc value ≥460 milliseconds. Upon resolution of QTc prolongation, vandetanib treatment was recommenced at a reduced dose.

Pharmacokinetics

To investigate the pharmacokinetic (PK) profile of vandetanib, blood samples were collected on the same days as scheduled electrocardiogram measurements. Plasma concentrations of vandetanib were determined using reversed-phase liquid chromatography–mass spectrometry. The col-

Copyright © 2008 by the International Association for the Study of Lung Cancer

lected data were related to a nonlinear mixed effects model to estimate population PK using NONMEM V (v 1.1).

Tumor Biomarkers

An exploratory objective of this study was to investigate how variations in copy number or mutational status of the *EGFR* gene affect tumor response in advanced NSCLC patients receiving vandetanib treatment. Tumor biopsy samples were obtained from consenting patients, formalin-fixed, and embedded in paraffin. Gene copy number was investigated by fluorescence in situ hybridization using the LSI EGFR SpectrumOrange/CEP 7 SpectrumGreen probe (Vysis, Abbott Laboratories, IL) according to a previously published method.[15] Tumor samples had a high *EGFR* gene copy number if there was high gene polysomy (≥4 *EGFR* gene copies in ≥40% of tumor cells) or gene amplification (presence of tight *EGFR* gene clusters, an *EGFR* gene to chromosome 7 ratio of ≥2, or ≥15 copies of the *EGFR* gene per tumor cell in ≥10% of analyzed cells).

EGFR mutations were analyzed by DNA sequencing of exons 19–21, and additionally by using the amplification refractory mutation system (ARMS) assay to detect the exon 21 L858R point mutation and the most common exon 19 deletion (del G2235–A2249).[16]

Plasma Biomarkers

Plasma samples were collected from patients at baseline, day 29, and day 57, and stored at −70°C. The concentrations of the following angiogenic markers were determined by colorimetric Sandwich ELISA (R&D Systems, Minneapolis, USA): VEGF (Cat. #DVE00), the soluble angiopoietin receptor Tie-2 (Cat. #DTE200), and VEGFR-2 (Cat. #DVR200).

RESULTS

Patient Characteristics

Fifty-three patients were recruited from eight centers in Japan between December 27, 2004, and September 30, 2005. All were randomized on this study and received study drug. Patient characteristics and baseline demographics were generally similar in the three arms, and the patient populations were considered to be appropriate for the dose-finding objectives of this study (Table 1). At the time of data cut-off (23 January 2006), 11 patients were ongoing; PD was the most common reason for discontinuation ($n = 35$). Other reasons for discontinuation were AEs ($n = 6$) and withdrawal of consent ($n = 1$).

Efficacy

The overall ORR was 13.2% (95% CI: 5.5–25.3%) (7 of 53 patients), and all 7 responders were PRs (Table 2). According to vandetanib dose received, the ORRs were 17.6% (95% CI: 3.8–43.4%) (3 of 17 patients; 100 mg), 5.6% (95% CI: 0.1–27.3%) (1 of 18 patients; 200 mg), and 16.7% (95% CI:3.6–41.4%) (3 of 18 patients; 300 mg). In all cases, the response evaluation committee assessment of tumor responses was similar to the investigator assessments. The characteristics of those patients who achieved a PR are described in Table 3. Secondary efficacy assessments are presented in Table 2 and Figure 2.

Safety

Overall, the most common AEs were rash, diarrhea, hypertension, and QTc prolongation (Table 4). In general, no major differences were observed in the incidences of

TABLE 1. Patient Demographic and Baseline Characteristics (Full Analysis Set)

	Vandetanib 100 mg/d ($n = 17$)	Vandetanib 200 mg/d ($n = 18$)	Vandetanib 300 mg/d ($n = 18$)	Total ($n = 53$)
Median age, yr (range)	58 (30–78)	61 (43–77)	61 (44–77)	60 (30–78)
Male (%)	11 (64.7)	12 (66.7)	11 (61.1)	34 (64.2)
Female (%)	6 (35.3)	6 (33.3)	7 (38.9)	19 (35.8)
Smoking history[a]				
No (%)	5 (29.4)	8 (44.4)	7 (38.9)	20 (37.7)
Yes (%)	12 (70.6)	10 (55.6)	11 (61.1)	33 (62.3)
WHO performance status 0/1/2	5/12/0	7/11/0	6/12/0	18/35/0
Previous chemotherapy				
One regimen (%)	13 (76.5)	9 (50.0)	14 (77.8)	36 (67.9)
Two regimens (%)	4 (23.5)	9 (50.0)	4 (22.2)	17 (32.1)
Staging (%)				
IIIB	2 (11.8)	3 (16.7)	1 (5.6)	6 (11.3)
IV	14 (82.4)	12 (66.7)	15 (83.3)	41 (77.4)
Recurrent	1 (5.9)	3 (16.7)	2 (11.1)	6 (11.3)
Histology (%)				
Squamous	5 (29.4)	6 (33.3)	4 (22.2)	15 (28.3)
Adenocarcinoma	11 (64.7)	12 (66.7)	12 (66.7)	35 (66.0)
Other	1 (5.9)	0	2 (11.1)	3 (5.7)
Brain metastasis at study entry (%)	4 (23.5)	3 (16.7)	5 (27.8)	12 (23.6)

[a] No, patients who have smoked <100 cigarettes in their lifetime; Yes, patients who have smoked >100 cigarettes in their lifetime.

Copyright © 2008 by the International Association for the Study of Lung Cancer

TABLE 2. Efficacy Summary

	Vandetanib 100 mg/d (n = 17)	Vandetanib 200 mg/d (n = 18)	Vandetanib 300 mg/d (n = 18)
Primary efficacy assessment			
Best response (RECIST)			
Partial response, n (%)	3 (17.6)	1 (5.6)	3 (16.7)
Stable disease ≥8 wk, n (%)	5 (29.4)	6 (33.3)	8 (44.4)
Disease progression, n (%)	9 (52.9)	10 (55.6)	7 (38.9)
Not evaluable, n (%)	0	1 (5.6)	0
Secondary efficacy assessments			
Disease control ≥8 wk, n (%)	8 (47.1)	7 (38.9)	11 (61.1)
Duration of response (wk)			
Median (range)[ab]	na	na	15.9 (7.3–20.1)
Time to progression (wk)			
Median (range)[a]	8.3 (4.0–40.7)	12.3 (0–40.3)	12.3 (1.4–32.7)
No. of events	12	13	13

na, not applicable; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Median estimated using the Kaplan–Meier method.
[b] This parameter could not be estimated in the 100 and 200 mg/d arms owing to the lack of progressions by the date of data cut-off.

TABLE 3. Characteristics of Patients Who Were Partial Responders

Treatment (initial dose)	Gender	Age (yr)	Smoking History[a]	Histology	Previous Chemotherapy Regimens	Time to PR (d)	Duration of Response (d)
100 mg	Male	65	Yes	Adenocarcinoma	1	28	204[b]
100 mg	Female	72	No	Adenocarcinoma	1	78	141[b]
100 mg	Male	52	No	Adenocarcinoma	1	143	141[b]
200 mg	Female	69	No	Adenocarcinoma	1	26	140[b]
300 mg[c]	Male	69	Yes	Adenocarcinoma	2	31	51
300 mg	Female	68	No	Adenocarcinoma	1	28	81[b]
300 mg	Female	55	No	Adenocarcinoma	1	82	141

[a] No, patients who have smoked <100 cigarettes in their lifetime; Yes, patients who have smoked >100 cigarettes in their lifetime.
[b] Censored on the day of last tumor evaluation due to absence of disease progression (response ongoing at data cut-off).
[c] Patient started study treatment with 300 mg and the treatment was stopped 29 d after the start due to QTc prolongation. The patient re-started at a reduced dose level (200 mg) 35 d after the start.

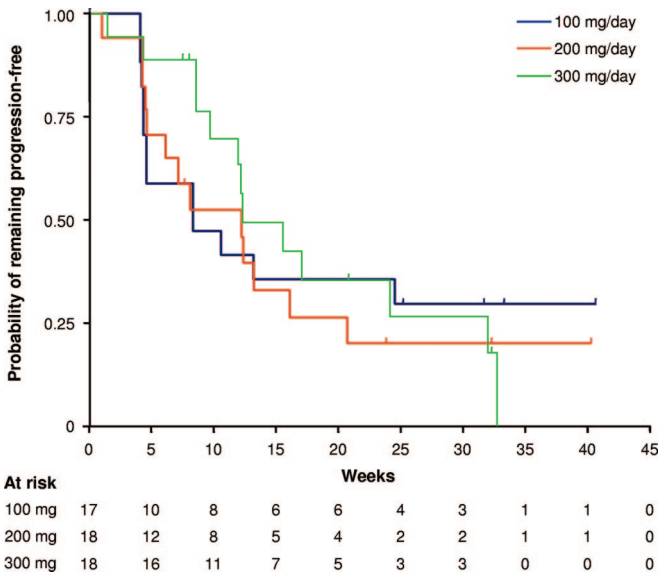

FIGURE 2. Kaplan–Meier curve for time to progression.

the common AEs across the three vandetanib arms, although the incidences of diarrhea, constipation, and abnormal hepatic function were numerically higher in the vandetanib 300 mg arm compared with the 100 or 200 mg arms. A dose-dependent increase in the incidence of CTC grade 3 and 4 events was observed; the incidence of these events in the 100, 200, and 300 mg dose arms were 29.4% (5 of 17 patients), 38.9% (7 of 18 patients), and 66.7% (12 of 18 patients), respectively. Of the 24 CTC grade 3 or 4 AEs considered by the investigator to be vandetanib-related, hypertension (100 mg, n = 4; 200 mg, n = 3; 300 mg, n = 3), and asymptomatic QTc prolongation (200 mg, n = 1; 300 mg, n = 1) were reported in more than one patient. Across the three dose levels, the AEs in this study were generally manageable with symptomatic treatment, dose interruption, or reduction.

Six patients discontinued vandetanib because of an AE considered by the investigator to be vandetanib-related: cryptogenic organizing pneumonia (COP), hepatic steatosis, and photosensitivity reaction (each n = 1, 200 mg arm); QTc prolon-

Copyright © 2008 by the International Association for the Study of Lung Cancer

TABLE 4. Number of Patients With Most Commonly Reported Adverse Events (Occurring in ≥10% Across all Treatment Groups), Regardless of Causality

MedDRA Preferred Term[a]	Vandetanib 100 mg/d (n = 17)	Vandetanib 200 mg/d (n = 18)	Vandetanib 300 mg/d (n = 18)	Total (n = 53)
Rash (%)	10 (59)	9 (50)	9 (50)	28 (53)
CTC grade 3/4	0/0	1/0	0/0	1/0
Diarrhea (%)	8 (47.1)	8 (44)	11 (61)	27 (51)
CTC grade 3/4	0/0	1/0	1/0	2/0
Hypertension (%)	8 (47)	10 (56)	7 (39)	25 (47)
CTC grade 3/4	4/0	3/0	3/0	10/0
ECG QTc prolonged (%)	4 (24)	9 (50)	8 (44)	21 (40)
CTC grade 3/4	0/0	1/0	1/0	2/0
Photosensitivity reaction (%)	2 (12)	5 (28)	5 (28)	12 (23)
CTC grade 3/4	0/0	0/0	0/0	0/0
Nasopharyngitis (%)	3 (18)	4 (22)	4 (22)	11 (21)
CTC grade 3/4	0/0	0/0	0/0	0/0
Dry skin (%)	2 (12)	4 (22)	5 (28)	11 (21)
CTC grade 3/4	0/0	0/0	0/0	0/0
Nausea (%)	3 (18)	3 (17)	4 (22)	10 (19)
CTC grade 3/4	0/0	0/0	0/0	0/0
Constipation (%)	2 (12)	1 (6)	6 (33)	9 (17)
CTC grade 3/4	0/0	0/0	0/0	0/0
Fatigue (%)	4 (24)	1 (6)	2 (11)	7 (13)
CTC grade 3/4	0/0	0/0	0/0	0/0
ECG QT prolonged (%)	1 (6)	2 (11)	4 (22)	7 (13)
CTC grade 3/4	0/0	0/0	0/0	0/0
Hepatic function abnormal (%)	1 (6)	1 (6)	4 (22)	6 (11)
CTC grade 3/4	0/0	0/0	1/0	1/0
Hematuria (%)	2 (12)	2 (12)	2 (12)	6 (11)
CTC grade 3/4	0/0	0/0	0/0	0/0

[a] MedDRA version 8.1.

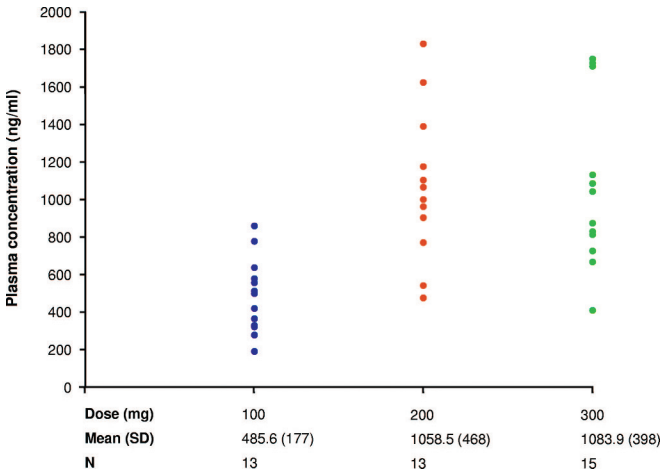

FIGURE 3. Observed maximum vandetanib plasma concentration at day 28. Patients who received dose reduction within the first 28 days were excluded.

gation, alanine aminotransferase increased, and erythema multiforme (each n = 1, 300 mg arm). Only COP was classed as a serious AE. Six patients had vandetanib dose reductions due to AEs (100 mg, n = 1; 200 mg, n = 1; 300 mg, n = 4).

Seven patients experienced eight respiratory-related events (COP, dyspnoea, interstitial lung disease [ILD], hypoxia, pneumonitis [all n = 1], and pneumonia [n = 3]). The incidence of these events in the three dose levels was 5.9% (1 of 17 patients; 100 mg), 11.1% (2 of 18 patients; 200 mg) and 22.2% (4 of 18 patients; 300 mg), respectively. Four of these events were considered to be related to vandetanib (COP, ILD, pneumonia [n = 2]). The ILD event was reported in a 64-year-old male patient in the 300 mg arm and resulted in patient death. This event was reported 8 days after vandetanib 300 mg was discontinued because of disease progression. No postmortem examination was performed and the investigator and a third-party physician considered the cause of death to be ILD.

All QTc prolongation was asymptomatic and manageable with dose interruption and/or reduction. The incidence of QTc prolongation was lower in the vandetanib 100 mg (24%) arm compared with the 200 mg (50%) and 300 mg (44%) arms. The mean change in QTc interval from baseline to week 3 (when maximum prolongation was observed) in the 100, 200, and 300 mg arms was +14 milliseconds (range, −25 to 29 milliseconds), +16.5 milliseconds (range, −36 to 49 milliseconds), and +27.6 milliseconds (range, 4 to 51 milliseconds), respectively. Protocol-defined QTc prolongation determined at the treatment site resulted in dose reduc-

Copyright © 2008 by the International Association for the Study of Lung Cancer

TABLE 5. Estimated Pharmacokinetic Parameters of Vandetanib[a]

	Clearance (L/h)	C_{max} (ng/ml)	Steady-state Exposure (ng/h/ml)	Half-life (d)	Accumulation Ratio
Median	10.2	1282	29,469	6.2	8.87
Minimum value	4.04	740	16,685	3.4	4.89
Maximum value	17.98	3018	74,257	13.8	19.85

[a] Simulated PK parameters if all patients ($n = 51$) were administered 300 mg vandetanib once a day for 56 d.

TABLE 6. Summary of Plasma Angiogenesis Biomarker Levels by Best Overall RECIST Response

Biomarker	Best Response (RECIST)	Median (range; *n*)		
		Baseline	Day 29	Day 57
VEGF (pg/ml)	PR	22.3 (0–264.2; $n = 6$)	73.2 (0–164.4; $n = 6$)	80.9 (28.7–183.7; $n = 6$)
	SD	37.0 (0–227.7; $n = 16$)	79.4 (38.5–281.6; $n = 16$)	97.4 (19.0–238.7; $n = 16$)
	PD	63.7 (0–897.7; $n = 21$)	121.0 (10.7–477.9; $n = 21$)	93.6 (63.9–343.2; $n = 5$)
	Total	51.5 (0–897.7; $n = 43$)	82.8 (0–477.9; $n = 43$)	95.5 (19.0–343.2; $n = 27$)
Tie-2 (ng/ml)	PR	23.5 (16.6–29.1; $n = 6$)	22.6 (19.8–38.8; $n = 6$)	23.3 (17.2–37.0; $n = 6$)
	SD	26.9 (6.0–33.6; $n = 16$)	27.4 (12.3–45.4; $n = 16$)	28.5 (23.3–52.4; $n = 16$)
	PD	28.5 (18.2–43.3; $n = 21$)	30.7 (18.0–56.3; $n = 21$)	30.2 (20.7–36.0; $n = 5$)
	Total	27.4 (6.0–43.3; $n = 43$)	29.2 (12.3–56.3; $n = 43$)	27.5 (17.2–52.4; $n = 27$)
VEGFR-2 (pg/ml)	PR	7406.5 (5564–9868; $n = 6$)	6418.5 (4878–8030; $n = 6$)	6001.5 (4846–7156; $n = 6$)
	SD	7577.5 (5622–8687; $n = 16$)	6819.5 (4666–8630; $n = 16$)	6450.5 (5024–8372; $n = 16$)
	PD	7861.0 (4981–11391; $n = 21$)	6910.0 (3763–11136; $n = 21$)	6710.0 (4131–8606; $n = 5$)
	Total	7721.0 (4981–11391; $n = 43$)	6881.0 (3763–11136; $n = 43$)	6563.0 (4131–8606; $n = 27$)

PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; Tie-2, soluble angiopoietin receptor; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2.

tion for five patients (300 mg, $n = 4$; 100 mg, $n = 1$); none of these QTc prolongation events met the protocol criteria for QTc prolongation by subsequent central review.

No significant abnormalities in any clinical laboratory variables were observed except for an increase of alanine aminotransferase (ALT increased) with CTC grade 3 in three patients in the vandetanib 300 mg arm.

Pharmacokinetic Results

The observed vandetanib plasma concentrations at day 28 for each evaluable patient are shown in Figure 3. These data were fitted to a one-compartment model to estimate population PK parameter values for the 300 mg arm, which were found to adequately characterize the observed plasma concentrations over time, and there was a good correlation between the individual predicted and observed data (data not shown). Estimates of the half-life ranged from 3.4 to 13.8 days, with a median population value of 6.2 days. The estimated time to PK steady state was approximately 1 month. Simulations from the PK characteristics of this patient population suggest a median steady-state exposure of approximately 29,500 ng/h/ml for a 300 mg dose administered once a day and an estimated median C_{max} of 1282 ng/ml (range, 740 to 3018 ng/ml). The estimated population PK parameters for the 300 mg arm are summarized in Table 5.

Tumor Biomarkers

Twenty-seven tumor samples were available for analysis and 12 of these were evaluable for determination of *EGFR* gene copy number by fluorescence in situ hybridization. Four of 12 evaluable patients had high *EGFR* gene copy number (best overall RECIST response of SD and PD, both $n = 2$) whereas the remaining eight patients did not (best overall RECIST response: PR, $n = 1$; SD, $n = 3$; and PD, $n = 4$). Nine of 27 samples were successfully sequenced for *EGFR* exons 19–21. In addition, 21 of 27 samples had successful ARMS analysis for L858R and the most common exon 19 deletion mutation (746–750). A confirmed mutation (exon 19 deletion [746–750]) was observed in a female nonsmoker from the 200 mg arm with adenocarcinoma and a high *EGFR* gene copy number (best RECIST response of PD). Of the remaining tumor samples, 21 had no *EGFR* mutation (by DNA sequencing or ARMS analysis), and in five cases, the *EGFR* mutation status could not be determined (not evaluable by either DNA sequencing or ARMS). Tumor samples were obtained from three patients who achieved a PR. Two of these tumor samples had no *EGFR* mutation and one had an unconfirmed result by direct DNA sequencing and ARMS assay of *EGFR* exons 19–21.

Blood Biomarkers

Median plasma levels of VEGF showed a trend to increase during the study period irrespective of clinical out-

Copyright © 2008 by the International Association for the Study of Lung Cancer

come. In contrast, plasma levels of VEGFR-2 showed a trend to decrease over the same period, whereas plasma Tie-2 levels did not seem to change (Table 6). Baseline plasma VEGF levels appeared to be lower in patients who experienced clinical benefit following vandetanib treatment: PR (median 22.3 pg/ml, $n = 6$) and SD (median 37.0 pg/ml, $n = 16$) versus PD (median 63.7 pg/ml, $n = 21$). Patients with a low (below median) baseline plasma VEGF level had a longer TTP (median, 24.1 week) than those with a high (above median) baseline VEGF level (median, 8.3 weeks) (Figure 4). No clear relationship was apparent between baseline levels of plasma Tie-2 and VEGFR-2 and tumor response.

DISCUSSION

The primary objective of this phase IIa study was to assess the ORR to three doses of vandetanib (100, 200, and 300 mg/d) in Japanese patients with advanced or recurrent NSCLC. These doses of vandetanib were selected based on the outcomes of a Japanese phase I study where it was observed that vandetanib was well tolerated up to a dose of 300 mg and objective tumor responses were observed in 4 of 9 patients with NSCLC at doses of either 200 or 300 mg.[11]

In this study, objective tumor responses were observed at all three doses of vandetanib. The ORR in the 100, 200, and 300 mg arms was 17.6% (3 of 17 patients), 5.6% (1 of 18 patients), and 16.7% (3 of 18 patients), respectively. The DCR and TTP were similar across the three dose arms. It was noted that 50% (9 of 18) of the patients in the 200 mg arm had failed two previous chemotherapy regimens, compared with 23.5% (4 of 17 patients) and 22.2% (4 of 18 patients) in the 100 and 300 mg arms, respectively. It is possible that these differences contributed to the lower ORR observed in the 200 mg arm, although the number of patients in each dose arm was too small to allow any definitive conclusions to be made.

Vandetanib was well tolerated at 100, 200, and 300 mg dose levels in this study. Overall, AEs were generally mild and manageable with symptomatic treatment, dose interruption or reduction. In addition, the AE profile was consistent with that determined during phase I evaluation in patients with advanced solid tumors[10,11] and phase II monotherapy data in NSCLC.[12] Furthermore, the AE profile was also consistent with that reported previously for agents that inhibit the VEGFR[17,18] or EGFR[4,19] signaling pathways. In general, no apparent dose dependence was noted in the incidence of the common AEs in this study except for asymptomatic QTc prolongation (24%, 56%, and 44% for the 100, 200, and 300 mg dose arms, respectively), an event that was manageable by dose interruption/reduction.

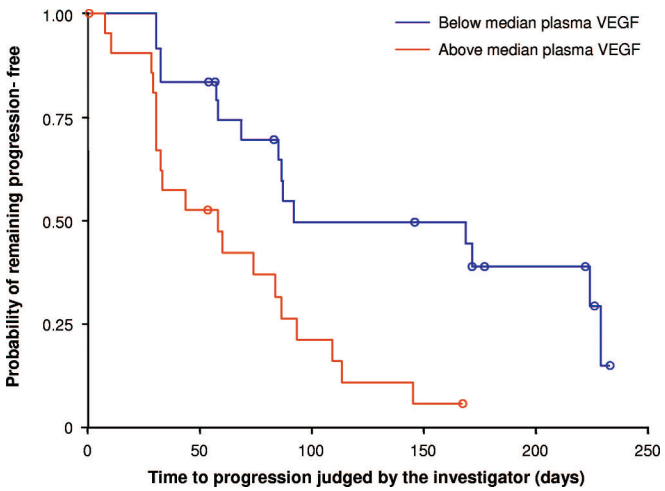

FIGURE 4. Kaplan–Meier curve of low (below median) versus high (above median) baseline plasma VEGF and time to progression.

A notable feature of this study, and the phase II program for vandetanib in NSCLC, is that patients with squamous cell histology or stable brain metastases were permitted to enter the trials. Both of these factors have been associated with an increased risk of bleeding, including severe life-threatening hemoptysis in NSCLC patients with squamous histology in a randomized phase II study of bevacizumab with carboplatin and paclitaxel.[20] These events have also been reported with other inhibitors of VEGF/VEGFR signaling, such as sunitinib and sorafenib.[17,18] Importantly, no CNS hemorrhage AEs or hemoptysis attributable to vandetanib were reported in this study.

The PK profile in this NSCLC patient population was consistent with that seen previously during Phase I evaluation in Japanese and USA/Australian patients with a range of solid tumors.[10,11]

In patients with NSCLC, specific *EGFR* mutations are associated with increased sensitivity to EGFR tyrosine kinase inhibitors,[21,22] and a better survival outcome with gefitinib has been shown to correlate with high *EGFR* gene copy number.[23] In this study, an exploratory analysis of tumor samples for amplification of *EGFR* gene copy number and somatic mutations of the *EGFR* gene revealed no clear relationship between *EGFR* mutation or gene amplification status and clinical outcome in patients receiving vandetanib. The *EGFR* mutation frequency of 4% (1 of 27 patients) is lower than that previously reported,[24,25] and further studies are needed to evaluate *EGFR* mutation status as a possible predictive marker for vandetanib therapy in advanced NSCLC.

In addition to *EGFR* mutation/amplification status, plasma profiling of cytokines and angiogenic factors may be a feasible approach for identifying blood-based prognostic and activity markers for therapies in NSCLC. Preliminary analysis of plasma concentrations of the angiogenesis markers VEGF and VEGFR-2 in the present study revealed that patients with PR or SD were more likely to have low baseline levels of VEGF than those with PD. It has been shown previously that low pretreatment levels of circulating VEGF correlated with a good response to gefitinib treatment in patients with NSCLC.[26] The significance of the relationship between these biomarkers and clinical outcome requires further investigation.

In conclusion, vandetanib monotherapy (100–300 mg/d) demonstrated antitumor activity with an acceptable safety and tolerability profile in Japanese patients with advanced NSCLC. Based only on this study, there is no com-

Copyright © 2008 by the International Association for the Study of Lung Cancer

pelling evidence to identify the optimal dose of vandetanib monotherapy in this population of patients; further investigation of vandetanib doses in the range 100 to 300 mg is warranted in Japanese patients with advanced NSCLC. Other randomized phase II studies of vandetanib in advanced NSCLC have demonstrated improvements in progression-free survival with vandetanib 300 mg as a monotherapy versus gefitinib[12] and with the combination of vandetanib 100 mg and docetaxel.[14] Phase III evaluation of vandetanib in a broad population of patients, both as monotherapy at 300 mg (versus placebo in patients previously treated with anti-EGFR therapy [ZEPHYR]; versus erlotinib [ZEST]) and at 100 mg in combination with docetaxel (ZODIAC) or pemetrexed (ZEAL), has been initiated in global trials.

ACKNOWLEDGMENTS

This study, including editorial assistance provided by Chris Watson of Mudskipper Bioscience, was supported financially by AstraZeneca. ZACTIMA is a trademark of the AstraZeneca group of companies.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355: 2542–50.
3. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;21:2237–46.
4. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–32.
5. Ciardiello F, Troiani T, Bianco R, et al. Interaction between the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF) pathways: a rational approach for multi-target anticancer therapy. *Ann Oncol* 2006;17:vii109–vii114.
6. Viloria-Petit A, Crombet T, Jothy S, et al. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. *Cancer Res* 2001;61: 5090–101.
7. Herbst RS, Johnson DH, Mininberg E, et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. *J Clin Oncol* 2005;23:2544–55.
8. Wedge SR, Ogilvie DJ, Dukes M, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res* 2002;62:4645–55.
9. Ichihara M, Murakumo Y, Takahashi M. RET and neuroendocrine tumors. *Cancer Lett* 2004;204:197–211.
10. Holden SN, Eckhardt SG, Basser R, et al. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGFReceptor signaling, in patients with solid, malignant tumors. *Ann Oncol* 2005;16:1391–7.
11. Tamura T, Minami H, Yamada Y, et al. A Phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. *J Thorac Oncol* 2006;1:1002–9.
12. Natale RB, Bodkin D, Govindan R, et al. ZD6474 versus gefitinib in patients with advanced NSCLC: Final results from a two-part, double-blind, randomized Phase II trial. *Proc Am Soc Clin Oncol* 2006;abst 7000.
13. Heymach J, Paz-Ares L, de Braud F, et al. Randomized phase II study of vandetanib (VAN) alone or in combination with carboplatin and paclitaxel (CP) as first-line treatment for advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2007;25(Suppl 18):abst 7544.
14. Heymach JV, Johnson BE, Prager D, et al. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. *J Clin Oncol* 2007;25:4270–7.
15. Cappuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst* 2005;97:643–55.
16. Horiike A, Kimura H, Nishio K, et al. Detection of epidermal growth factor receptor mutation in transbronchial needle aspirates of non-small cell lung cancer. *Chest* 2007;131:1628–34.
17. Gatzemeier U, Blumenschein G, Fosella F, et al. Phase II trial of single-agent sorafenib in patients with advanced non-small cell lung carcinoma. *Proc Am Soc Clin Oncol* 2006;24:abst 7002.
18. Socinski MA, Novello S, Sanchez JM, et al. Efficacy and safety of sunitinib in previously treated, advanced non-small cell lung cancer (NSCLC): Preliminary results of a multicenter phase II trial. *Proc Am Soc Clin Oncol* 2006;24:abst 7001.
19. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366: 1527–37.
20. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184–91.
21. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–39.
22. Pao W, Miller V, Zakowski M, et al. EGFReceptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* 2004;101:13306–11.
23. Hirsch F, Varella-Garcia M, Cappuzzo F, et al. Combination of EGFR gene copy number and protein expression predicts outcome for advanced non-small-cell lung cancer patients treated with gefitinib. *Ann Oncol* 2007;18:752–60.
24. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304: 1497–500.
25. Janne PA, Engelman JA, Johnson BE. Epidermal growth factor receptor mutations in non-small-cell lung cancer: implications for treatment and tumor biology. *J Clin Oncol* 2005;23:3227–34.
26. Yoshimoto A, Kasahara K, Nishio M, et al. Changes in angiogenic growth factor levels after gefitinib treatment in non-small cell lung cancer. *Jpn J Clin Oncol* 2005;35:233–8.

Copyright © 2008 by the International Association for the Study of Lung Cancer