A Phase I Study of Vandetanib in Combination with Vinorelbine/Cisplatin or Gemcitabine/Cisplatin as First-Line Treatment for Advanced Non-small Cell Lung Cancer

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Introduction: Vandetanib is a once-daily oral agent that selectively inhibits vascular endothelial growth factor receptor, epidermal growth factor receptor, and RET (REarranged during Transfection) signaling.

Methods: This Phase I study investigated the safety, tolerability, and pharmacokinetics of vandetanib when administered with either gemcitabine plus cisplatin (GC) or vinorelbine plus cisplatin (VC) in patients with previously untreated locally advanced or metastatic non-small cell lung cancer.

Results: Seventeen patients received vandetanib 100 mg/d plus VC ($n = 9$) or GC ($n = 8$). Three dose-limiting toxicities were reported in each treatment group: vandetanib + VC (pulmonary artery thrombosis and asymptomatic QTc prolongation [$n = 2$]); vandetanib + GC (peripheral ischemia [due to arterial occlusion], pulmonary embolism, and limb venous thrombosis). The protocol definition of a tolerable dose was not met, and no patients were recruited to receive vandetanib 300 mg plus VC or GC. There was no apparent pharmacokinetic interaction between vandetanib and vinorelbine or gemcitabine, but there was an approximate 30% increase in the exposure to cisplatin, which may be due to accumulation of total platinum and/or an interaction with vandetanib.

Conclusions: In this study, in patients with previously untreated advanced non-small cell lung cancer, vandetanib 100 mg/d in combination with either VC or GC was not tolerated.

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Vandetanib is a once-daily oral inhibitor of vascular endothelial growth factor receptor- and epidermal growth factor receptor-dependent signaling,[1] both of which are key pathways in non-small cell lung cancer (NSCLC). Vandetanib also inhibits RET (REarranged during Transfection) kinase activity, an important growth driver in certain types of thyroid cancer.[2] Phase III evaluation of vandetanib has demonstrated evidence of antitumor activity in patients with previously treated advanced NSCLC both as a monotherapy[3] and in combination with pemetrexed[4] or docetaxel.[5]

Both gemcitabine plus cisplatin (GC) and vinorelbine plus cisplatin (VC) are indicated for first-line treatment of patients with advanced NSCLC. The addition of anti-vascular endothelial growth factor therapy to platinum-based doublet chemotherapy has demonstrated a survival advantage in previously untreated patients with advanced NSCLC.[6] Because vandetanib targets vascular endothelial growth factor-dependent tumor angiogenesis, this background provided a reasonable rationale for preliminary evaluation of vandetanib in combination with GC or VC in the first-line setting. The primary objective of this phase I, multicenter, open-label study (6474IL0054) was to evaluate the safety, tolerability, and pharmacokinetics of vandetanib with GC or VC in patients with previously untreated advanced or metastatic NSCLC.

PATIENTS AND METHODS

Eligibility criteria included stage IIIB to IV NSCLC suitable for first-line therapy with GC or VC; World Health Organization performance status of 0 or 1; life expectancy ≥12 weeks; acceptable cardiac, hematopoietic, hepatic, and renal function; no prior chemotherapy or other systemic anticancer therapy; and no radiotherapy or major surgery within the 4 weeks preceding the start of study therapy. Patients with squamous histology were eligible, as were patients with pretreated clinically stable brain metastases.

In the first cohort, up to 10 patients in each treatment group were to receive continuous once-daily oral doses of

vandetanib 100 mg with up to six standard 21-day treatment cycles of GC (G: 1250 mg/m^2 intravenous [IV], days 1 and 8; C: 75 mg/m^2 IV, day 1) or VC (V: 25 mg/m^2 IV, days 1 and 8; C: 75 mg/m^2 IV, day 1). The decision to recruit patients into the GC or VC treatment groups was based on investigator preference and local prescribing policy. Following safety review of at least six evaluable patients, if a dose-limiting toxicity (DLT) that was considered to be possibly related to vandetanib was seen in more than two patients, enrollment into that cohort and dose escalation was halted. If less than two evaluable patients in the vandetanib 100 mg cohort experienced a vandetanib-related DLT, it was planned to enroll a second cohort of up to 10 patients in each treatment group to receive vandetanib 300 mg in combination with GC or VC. A patient was considered evaluable if they completed ≥6 weeks of treatment with vandetanib and chemotherapy or if a DLT was experienced within the first 6 weeks of treatment. There was no intrapatient dose escalation.

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3. A DLT was defined as any of the following (if considered to be possibly related to vandetanib or the combination of chemotherapy and vandetanib): grade 4 neutropenia or thrombocytopenia lasting more than 7 days; febrile neutropenia (temperature >38.5°C on at least two occasions in 24 hours, in association with grade 3 or 4 neutropenia); any other drug-related grade 3 or 4 nonhematological toxicity; QTc prolongation (a single QTc measurement ≥550 milliseconds; two consecutive QTc measurements ≥500 but <550 milliseconds; an increase of ≥100 milliseconds from baseline; or an increase of ≥60 milliseconds but <100 milliseconds from baseline QTc to a QTc value ≥480 milliseconds).

For PK assessments, blood samples were collected on the following days: vandetanib: days 2, 8, and 15 (cycle 1), days 1, 8, 15, and 21 (cycle 2), and days 1 and 2 (cycle 3); gemcitabine: day 1 (multiple samples up to 1.5 hours postinfusion) and day 2 of cycles 1 and 3; vinorelbine: day 1 (multiple samples up to 8 hours postinfusion) and day 2 of cycles 1 and 3; cisplatin: day 1 (multiple samples up to 8 hours postinfusion) and day 2 of cycles 1 and 3. Because vandetanib dosing did not commence until day 2, day 1 samples enabled collection of PK data from patients treated with chemotherapy alone. Samples taken on day 21 of cycle 2 allowed the determination of steady-state exposure to vandetanib alone. Sampling of gemcitabine, vinorelbine, cisplatin, and vandetanib at the start of cycle 3 allowed the PK data for each to be determined when administered in combination.

Plasma concentrations of vandetanib, gemcitabine (and its active metabolite difluorodeoxyuridine [dFdU]), and vinorelbine were analyzed by high-performance liquid chromatography with tandem mass spectrometry. Plasma concentrations of platinum (measured as equivalents of cisplatin) were determined using inductively coupled plasma-atomic emission spectrometry. All plasma concentration-time data were analyzed using noncompartmental methods. Tumor response, measured at baseline and approximately every 6 weeks thereafter, was assessed according to RECIST (Response Evaluation Criteria In Solid Tumors, version 1.0).

RESULTS

Patients

Seventeen patients received vandetanib 100 mg + GC (n = 8) or vandetanib 100 mg + VC (n = 9) (Table 1). The first patient entered the study on July 28, 2006, and the last patient visit was May 16, 2007. The demographic characteristics in this study were representative of a first-line, advanced NSCLC patient population; there were more females than males in the VC group, but this was not anticipated to affect the safety and tolerability results of the study.

Exposure

The mean duration of vandetanib treatment was 71 days (vandetanib + GC) and 95 days (vandetanib + VC). Three patients in the vandetanib + GC group and four patients in the vandetanib + VC group received more than or equal to four cycles of combined chemotherapy. Four patients discontinued all treatment during the first chemotherapy cycle: vandetanib + GC, peripheral ischemia due to arterial occlusion (n = 1); vandetanib + VC, pneumonia (n = 1), and a cisplatin-related AE (tinnitus, n = 1; nephrotoxicity, n = 1). Two patients in each treatment group experienced a vandetanib dose reduction/interruption: vandetanib + GC:pulmonary embolism (n = 1), interruption due to erythromycin treatment for an AE (n = 1); vandetanib + VC:asymptomatic QTc prolongation (n = 2). No patients were ongoing on vandetanib or chemotherapy at the end of the study.

Safety and Tolerability

The protocol definition of a tolerable dose was not achieved in vandetanib 100 mg + GC or VC groups. Therefore, no additional cohorts received vandetanib 300 mg with GC or VC. Six patients (three on GC and three on VC) experienced DLTs. In the vandetanib 100 mg + GC arm, one patient each experienced pulmonary embolism (asymptomatic; grade 4), limb venous thrombosis (grade 3), and peripheral ischemia (due to arterial occlusion; grade 2). In the

TABLE 1. Patient Characteristics

	Vandetanib 100 mg + GC (n = 8)	Vandetanib 100 mg + VC (n = 9)
Mean age, yr (range)	61 (40–72)	58 (46–65)
Male (n)	4	2
Female (n)	4	7
WHO performance status (n)		
0 (normal activity)	1	4
1 (restricted activity)	7	5
Stage of disease (n)		
IIIB	2	1
IV	6	8
No. of organs involved (n)		
1	1	1
2	4	2
≥3	3	6

GC, gemcitabine plus cisplatin; VC, vinorelbine plus cisplatin; WHO, World Health Organization.

vandetanib 100 mg + VC arm, one patient experienced a DLT of pulmonary artery thrombosis (grade 2), and two patients had asymptomatic QTc prolongation (grade 1 and grade 4, respectively). All DLTs were reported as serious AEs and resulted in permanent discontinuation of vandetanib except for the patient with reported grade 4 QTc prolongation, which was not reported as serious, resolved within 2 days, and was not accompanied by any other cardiac symptoms or electrocardiography findings.

The AEs observed in this study were generally consistent with the known safety profiles of vandetanib, GC, and VC. Commonly occurring AEs included constipation, nausea, and neutropenia (Table 2). Overall, nine patients had a grade 3 or 4 neutropenic AE: vandetanib + GC: neutropenia (grade 3, $n = 4$); vandetanib + VC: neutropenia (grade 3, $n = 2$), neutropenia and neutropenic sepsis (both grade 4, $n = 1$), neutropenic sepsis and febrile neutropenia (all grade 3, $n = 2$), and febrile neutropenia (grade 3, $n = 1$). Lower respiratory tract infection (grade 3, $n = 2$) was the only other grade 3 or 4 AE reported in more than one patient.

Pharmacokinetics

There was no apparent effect on the steady-state exposure to vandetanib 100 mg in the presence of either chemotherapy regimen (Table 3). Similarly, when steady-state exposure to vandetanib 100 mg had been attained, this had no apparent effect on the exposure to coadministered gemcitabine (and its metabolite, dFdU) or vinorelbine (Table 4). There was an approximately 30% increase in exposure to cisplatin in the presence of vandetanib (Table 4).

Efficacy

Eleven patients were evaluable for preliminary efficacy assessment (Table 5). One confirmed partial response was

TABLE 2. Adverse Events, Irrespective of Causality, Reported in ≥25% of Patients in Any Arm

	Vandetanib 100 mg + GC ($n = 8$)		Vandetanib 100 mg + VC ($n = 9$)	
MedDRA-Preferred Term	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Constipation	3	—	6	—
Nausea	5	—	4	—
Neutropenia	5	4 (G3)	4	2 (G3), 2 (G4)
Insomnia	2	—	5	1 (G3)
Anemia	—	—	6	1 (G3)
Dyspepsia	1		5	—
Fatigue	4	1 (G3)	2	—
Diarrhea	3	—	3	1 (G3)
Vomiting	3	—	3	—
Lethargy	—	—	4	—
Headache	3	1 (G3)	1	—
Lower respiratory tract infection	1	—	3	2 (G3)
Febrile neutropenia	—	—	3	3 (G3)
Urinary tract infection	2	—	1	1 (G3)
Dysgeusia	2	—	1	—
Dehydration	—	—	3	1 (G3)
Dyspnea	—	—	3	1 (G3)
Groin pain	—	—	3	—
Hypokalemia	—	—	3	1 (G3)
Rash	2	—	1	—
Dizziness	2	1 (G3)	—	—
Peripheral ischemia	2	—	—	—

GC, gemcitabine plus cisplatin; VC, vinorelbine plus cisplatin.

TABLE 3. Vandetanib Pharmacokinetic Data Alone and in Combination With Chemotherapy

	Vandetanib 100 mg + GC		Vandetanib 100 mg + VC	
	Vandetanib Alone	**Vandetanib + GC**	**Vandetanib Alone**	**Vandetanib + VC**
n	4	4	3	3
AUC_{ss} (ng · h/ml)*	9990 (23.2)	9144 (17.1)	8341 (12.0)	8386 (9.0)
$C_{ss,max}$ (ng/ml)*	418 (20.0)	451 (16.0)	440 (35.0)	378 (8.4)
t_{max} (h)†	8.0 (0,8.0)	9.0 (6.0,9.0)	7.0 (4.0,7.0)	8.0 (0,8.0)

*Values represent the geometric mean and coefficient of variation (CV%) in parentheses.

†Values represent the median value and the range in parentheses.

AUC_{ss}, area under plasma concentration-time curve during any dosing interval at steady state; $C_{ss,max}$, maximum steady-state drug concentration in plasma during dosing interval; GC, gemcitabine plus cisplatin; t_{max}, time to reach maximum concentration after drug administration; VC, vinorelbine plus cisplatin.

TABLE 4. Chemotherapy Pharmacokinetic Data Alone and in Combination with Vandetanib

Pharmacokinetic Analyte	n	**AUC (ng · h/ml)***	**$AUC_{(0-t)}$ (ng · h/ml)***	**C_{max} (ng/ml)***
Gemcitabine				
GC	4	10450 (20.0)	NA	17830 (13.8)
GC + vandetanib 100 mg	4	9847 (19.2)	NA	18850 (24.9)
dFdU (gemcitabine metabolite)				
GC	4	38260 (20.5)	NA	38850 (14.5)
GC + vandetanib 100 mg	4	39280 (20.1)	NA	36530 (19.3)
Vinorelbine				
VC	3	NA	269.6 (49.1)	165.0 (92.2)
VC + vandetanib 100 mg	3	NA	229.6 (47.3)	135.7 (43.7)
Cisplatin†				
VC or GC	5	NA	44650 (61.5)	3519 (13.8)
VC or GC + vandetanib 100 mg	5	NA	59240 (65.6)	5027 (18.1)

*Values represent the geometric mean and coefficient of variation (CV%) in parentheses.

†Only 2 patients were assessable for cisplatin PK in the vandetanib + GC group. The cisplatin data for both treatment groups were therefore combined.

AUC, area under the plasma concentration-time curve from zero to infinity; $AUC_{(0-t)}$, area under the plasma concentration-time curve from zero to the time of the last quantifiable concentration; C_{max}, maximum plasma drug concentration after single dose administration; dFdU, difluorodeoxyuridine; GC, gemcitabine plus cisplatin; VC, vinorelbine plus cisplatin.

TABLE 5. Tumor Assessment

Best Overall Response (RECIST)	Vandetanib 100 mg + GC (n = 8)	Vandetanib 100 mg + VC (n = 9)
Partial response	1	0
Stable disease ≥8 wk	3	1
Progressive disease	1	5
Not evaluable	3	3

GC, gemcitabine plus cisplatin; RECIST, Response Evaluation Criteria In Solid Tumors; VC, vinorelbine plus cisplatin.

observed (vandetanib 100 mg + GC). After two cycles of vandetanib + GC, a routine CT scan in this patient showed stable disease and pulmonary emboli. Vandetanib treatment was stopped, and the partial response was observed after continued GC treatment.

DISCUSSION

In this study, vandetanib 100 mg in combination with GC or VC was not tolerated as a first-line treatment for NSCLC. The DLTs observed in this study were predominantly thromboembolic events. Such events are commonly observed in patients with advanced cancer, and the underlying disease may have been a contributing factor. However, a causal relationship to cisplatin and/or vandetanib could not be excluded. Cisplatin is known to trigger platelet aggregation and/or enhance thromboxane formation by platelets,[7] and it is possible to hypothesize that an interaction with vandetanib on coagulation may have occurred. However, in vitro, vandetanib alone did not increase the coagulation index (ratio of endothelial cell surface tissue factor activity to tissue factor pathway inhibitor activity) and significantly inhibited the increased coagulation index resulting from treatment of endothelial cells with cisplatin and gemcitabine combined.[8] It is worth noting that patients receiving vandetanib 100 mg/d in combination with pemetrexed[9] or docetaxel[10] did not show an increase in thrombotic events during phase III evaluation of vandetanib in pretreated advanced NSCLC.

Based on the limited number of patients (n = 3–5) evaluable for PK, there did not appear to be any PK interaction between vandetanib and gemcitabine or vinorelbine when given in combination. The increase in exposure to cisplatin may be due to accumulation of total platinum in plasma, as has been observed previously with cisplatin monotherapy.[11] Another possibility is a potential interaction between cisplatin and vandetanib. Vandetanib has been shown to inhibit the organic cation transporter 2 (AstraZeneca study KMX083; data on file), which mediates cisplatin uptake in renal proximal tubules and is involved in cisplatin nephrotoxicity.[12] Inhibition of the organic cation transporter 2 by vandetanib may result in reduced proximal tubule uptake and, therefore, increased plasma levels of cisplatin. However, vandetanib did not seem to increase cisplatin-induced nephrotoxicity in this study (there was one AE of nephrotoxicity [Common Terminology Criteria for Adverse Events grade 1; vandetanib + GC arm]).

The use of vandetanib with cisplatin has also been investigated in patients with untreated, advanced head and neck cancer. In an ongoing phase I study, vandetanib 100 mg/d appears to be tolerable in combination with weekly cisplatin 30 mg/m^2 and radiotherapy.[13] An earlier phase II study in first-line NSCLC showed that vandetanib could be safely administered with paclitaxel and carboplatin.[14] Based on the results of this study, combining vandetanib with cisplatin plus gemcitabine or vinorelbine is not a feasible first-line regimen for NSCLC.

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REFERENCES

1. 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;62:4645–4655.
2. Carlomagno F, Vitagliano D, Guida T, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res* 2002;62:7284–7290.
3. Natale RB, Thongprasert S, Greco FA, et al. Vandetanib versus erlotinib in patients with advanced non-small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: a randomized, double-blind phase III trial (ZEST). *J Clin Oncol* 2009;27(15 Suppl):Abstract 8009.
4. de Boer R, Arrieta Ó, Gottfried M, et al. Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZEAL). *J Clin Oncol* 2009;27(15 Suppl):Abstract 8010.
5. Herbst RS, Sun Y, Korfee S, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZODIAC). *J Clin Oncol* 2009;27(18 Suppl):Abstract CRA8003.
6. 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;355:2542–2550.
7. Togna GI, Togna AR, Franconi M, et al. Cisplatin triggers platelet activation. *Thromb Res* 2000;99:503–509.
8. Ma L, Francia G, Viloria-Petit A, et al. In vitro procoagulant activity induced in endothelial cells by chemotherapy and antiangiogenic drug combinations: modulation by lower-dose chemotherapy. *Cancer Res* 2005;65:5365–5373.
9. de Boer R, Arrieta Ó, Gottfried M, et al. Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZEAL). Presented at the 2009 American Society of Clinical Oncology (ASCO), Orlando, FL May 29-June 2, 2009.
10. Herbst RS, Sun Y, Korfee S, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZODIAC). Presented at the 2009 American Society of Clinical Oncology (ASCO), Orlando, FL, May 29–June 2, 2009.
11. Gamelin E, Allain P, Maillart P, et al. Long-term pharmacokinetic behavior of platinum after cisplatin administration. *Cancer Chemother Pharmacol* 1995;37:97–102.
12. Ciarimboli G, Ludwig T, Lang D, et al. Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. *Am J Pathol* 2005;167:1477–1484.
13. Papadimitrakopoulou V, Frank SJ, Blumenschein GR, et al. Phase I evaluation of vandetanib with radiation therapy (RT) ± cisplatin in previously untreated advanced head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol* 2009;27(15 Suppl):Abstract 6016.
14. Heymach JV, Paz-Ares L, de Braud F, et al. Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol* 2008;26:5407–5415.