A Phase I Dose-Escalation Study of ZD6474 in Japanese Patients with Solid, Malignant Tumors

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Introduction: ZD6474 (vandetanib) is an orally available inhibitor of vascular endothelial growth factor receptor, epidermal growth factor receptor, and RET receptor tyrosine kinase activity. This study assessed the safety and tolerability of escalating doses of ZD6474 in Japanese patients with solid, malignant tumors.

Methods: Adult patients with solid tumors refractory to standard therapy received a once-daily oral dose of ZD6474 (100–400 mg) in 28-day cycles, until disease progression or unacceptable toxicity was observed.

Results: Eighteen patients were treated at doses of 100 mg ($n = 3$), 200 mg ($n = 6$), 300 mg ($n = 6$), and 400 mg ($n = 3$). Dose-limiting toxicities at the completion of cycle 2 were hypertension ($n = 3$), diarrhea ($n = 1$), headache ($n = 1$), toxic skin eruption ($n = 1$), and alanine aminotransferase increase ($n = 1$). A dose of 400 mg/day was considered to exceed the maximum tolerated dose (MTD). Toxicities were manageable with dose interruption and/or reduction. Objective tumor response was observed in four of nine patients with non-small cell lung cancer (NSCLC) at doses of either 200 or 300 mg. Terminal half-life was about 90–115 hours. Plasma trough concentrations achieved steady-state conditions after approximately 1 month of daily dosing.

Conclusions: It was concluded that a dose of 400 mg/day was considered to exceed the MTD, and doses for phase II study were thought to be not more than 300 mg/day. The objective response observed in some NSCLC patients is encouraging for further studies in this tumor type.

Key Words: Phase I study, ZD6474, Vandetanib, Non-small cell lung cancer

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Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis and plays an essential role in the formation and maintenance of the vasculature by activating protease expression, endothelial cell proliferation and migration, and capillary vessel formation.[1–4] Enhanced secretion of VEGF from tumor tissue induces vascular permeability and results in the development of a network of highly permeable, immature vessels that are characteristic of pathological angiogenesis.[5] Although VEGF binds to VEGFR-1 (Flt-1) and VEGFR-2 (KDR or Flk-1) on vascular endothelial cells, activation of VEGFR-2 alone is sufficient to stimulate VEGF-mediated angiogenesis.[6] Pathological angiogenesis is necessary for the progression of solid, malignant tumors,[7] and inhibition of VEGF-dependent signaling has been identified as a key antiangiogenic strategy.[8,9] The clinical value of inhibiting VEGF signaling in colon cancer,[10] non-small cell lung cancer (NSCLC),[11] and breast cancer[12] has been confirmed with bevacizumab, an anti-VEGF antibody.

Epidermal growth factor receptor (EGFR)-dependent signaling is an important pathway contributing to the growth and metastasis of tumor cells, and aberrant EGFR tyrosine kinase activity has been reported in a number of human tumors.[13,14] One consequence of upregulated EGFR tyrosine kinase activity is increased expression of proangiogenic factors, including VEGF,[15,16] which may lead to possible paracrine and autocrine stimulation of angiogenesis.

ZD6474 (vandetanib; ZACTIMA) is a novel inhibitor of VEGFR, EGFR, and RET tyrosine kinase activity.[17–20] As such, ZD6474 has the potential to inhibit two key pathways in tumor growth: VEGF-dependent tumor angiogenesis, and EGFR- and RET-dependent tumor cell proliferation and survival. Indeed, preclinical evaluation of ZD6474 has demonstrated potent inhibition of VEGF-dependent signaling and angiogenesis in vivo, as well as dose-dependent inhibition of tumor growth, including profound regression in established PC-3 prostate tumors. More recently, the results of a phase I study of ZD6474 conducted in the United States and Australia showed that once-daily continuous oral dosing was generally well tolerated in patients with advanced tumors.[21]

We report the results of a phase I, open-label, nonrandomized, multicenter clinical study of ZD6474 in Japanese patients with advanced solid tumors. The primary objective

of the study was to assess the safety and tolerability of escalating oral doses of ZD6474, with the aim of establishing the maximum tolerated dose (MTD) and the recommended doses for further phase II study assessment. Additional objectives included evaluation of antitumor activity and assessment of single- and multiple-dose pharmacokinetics.

PATIENTS AND METHODS

Patients

Adult patients between 20 and 74 years of age with solid, malignant tumors refractory to standard therapies, or for which no appropriate therapy exists, were eligible for inclusion. Patients were required to have a life expectancy ≥3 months and a World Health Organization performance status of 0 or 1. The main exclusion criteria were significant cardiac, hematopoietic, hepatic or renal dysfunction; severe complications (including active double cancers); any gastrointestinal disease that would affect drug bioavailability; poorly controlled hypertension; CNS tumors and metastases; systemic anticancer therapy or radiotherapy within the previous 4 weeks; unresolved adverse effects from prior anticancer therapy or radiotherapy; and incomplete recovery from prior surgery. All patients provided written informed consent. The trial was approved by the ethics committee of institutional review board and was conducted in accordance with the Declaration of Helsinki and guidelines for good clinical practice.

Study Design

This was an open-label, nonrandomized, multicenter dose-escalation study. Patients received a single oral dose of ZD6474 (100, 200, 300, or 400 mg), which was followed by a 7-day observation period (cycle 0; Figure 1). On day 8, patients started a once-daily ZD6474 dosing regimen at the same dose as they had received in cycle 0 for a total of 28 days (cycle 1). Further 28-day treatment cycles were repeated at the same dose. A dose-limiting toxicity (DLT) was defined as any toxicity of at least grade 3 according to common toxicity criteria (CTC version 2.0) that was related to ZD6474 treatment, or grade 2 diarrhea daily for >7 days or grade 3 diarrhea despite maximum antidiarrheal support; ≥grade 2 skin toxicity for >7 days that affected the patient's subjective well-being and required cessation of treatment, despite supportive care; and QT or corrected QT (QTc) prolongation ≥490 msec, or a rise of ≥60 msec from baseline QT or QTc to ≥460 msec. QTc values were obtained using Bazett's[22] method of correction.

The initial dose of ZD6474 was set at 100 mg/day, based on the minimum toxic effect dose in rats as well as safety data from U.S./Australian phase I study. Dose escalation was performed when a minimum of three patients per dose level had completed cycle 1 (28 days) without experiencing a DLT. The MTD was defined as the dose of drug at which 33.3% of patients experienced a DLT during cycle 1 that was not controlled with symptomatic therapy. Once the MTD was established, three or more additional patients were enrolled at the two highest dose levels below the MTD. This was to further characterize the safety, tolerability, and biological activity of ZD6474.

Assessment of Safety and Tolerability

The primary objective was to assess the safety and tolerability of escalating oral doses of ZD6474. After full physical examination at enrollment, adverse events (AEs) were recorded at each scheduled study visit.

Electrocardiograms (ECGs) were recorded at the screening visit, on days 1 (baseline) and 2 of cycle 0, and three times per week up to day 21 of cycle 1. If no prolongation of QT or QTc occurred, ECGs were performed weekly up to day 14 of cycle 2, every 2 weeks until the end of cycle 3 and monthly during subsequent cycles; and 29 days after the last dose. Vital signs (blood pressure, pulse rate, and body temperature) were measured before and 2, 4, 6, 8, and 10 hours after the drug administration on day 1, and then every 24 hours until day 7 of cycle 0; every 24 hours until day 15 of cycle 1; weekly thereafter until the end of cycle 2; once every 2 weeks during subsequent cycles; and at withdrawal.

Blood chemistry and hematological assessments were performed at the screening visit; predose of cycle 0; predose and on days 8, 15, 22, and 29 of cycles 1 and 2; every 2 weeks (days 15 and 29) during subsequent cycles; at withdrawal; and on days 15 and 29 after the last dose. Electrolytes were measured weekly for patients who experienced diarrhea or vomiting. Urinalysis was performed at the screening visit; on day 2 of cycle 0; on days 15 and 29 of cycle 1; on day 29 during subsequent cycles; at withdrawal; and on days 15 and 29 after the last dose.

Pharmacokinetic Assessment

The pharmacokinetic profile of ZD6474 was assessed after both single and multiple dosing. During cycle 0, blood

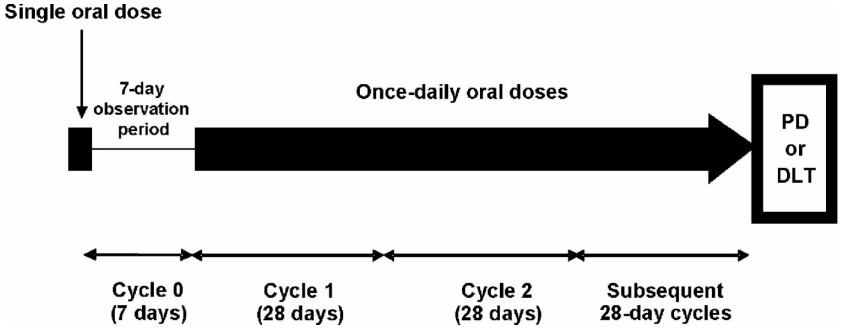

FIGURE 1. Study design. PD, progressive disease; DLT, dose-limiting toxicity.

