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A phase I study of zibotentan (ZD4054) in patients with metastatic, castrate-resistant prostate cancer

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Abstract

Purpose—To assess the maximum well-tolerated dose (MWTd), dose limiting toxicity (DLT), antitumor activity, pharmacokinetics and pharmacodynamics of ZD4054, a novel specific endothelin-A (ET_A) receptor antagonist, in patients with metastatic prostate cancer.

Experimental Design—Patients with metastatic, castrate-resistant prostate cancer (CRPC) were treated with escalating doses of oral ZD4054 (10 – 200 mg) once daily. The initial cohort received 28 daily doses (Period 1). Patients who had evidence of clinical benefit and who had not met any of the criteria for withdrawal were allowed to receive ZD4054 at their current dose level until they no longer derived clinical benefit (Period 2). Pharmacokinetics of ZD4054 and changes in PSA and bone markers were also assessed.

Results—Sixteen patients were evaluable for the safety and single dose PK analyses. Eleven patients completed Period 1, and nine patients proceeded to Period 2. DLTs were encountered at 22.5 mg; one patient had grade3 dyspnea and peripheral edema and a second patient had grade3 headache and intraventricular hemorrhage. Enrolment was expanded at the 15 mg dose level to further determine the safety and tolerability of ZD4054. No DLTs were seen at 15 mg, and the most frequent adverse events were headache, peripheral edema, fatigue, nasal congestion and nausea.

Conclusions—The MWTd for ZD4054 was 15 mg orally daily. The predominant adverse events observed were consistent with those reported for this class of drugs, and prolonged stable disease was noted in some patients. Phase III studies with ZD4054 in men with metastatic CRPC are ongoing.

INTRODUCTION

Prostate cancer is the most common solid tumor diagnosed in men in the United States. In 2008, an estimated 186,320 new cases will be diagnosed and 28,660 men will die from prostate cancer (1). Bone metastases are common in advanced prostate cancer and are associated with significant morbidity, including pain. Androgen deprivation therapy is the mainstay of treatment for advanced prostate cancer, but virtually all men with metastatic disease will eventually develop CRPC. Patients with CRPC have a poor prognosis with a median survival of approximately 18 months (2). While chemotherapy with docetaxel plus

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prednisone has been shown to prolong median overall survival, the median improvement is only 2 – 2.5 months (3–5). Clearly, new agents are needed for the treatment of CRPC to delay disease progression and improve quality of life.

Endothelins (ETs) and their receptors play an important role in cell growth and survival and have been implicated in tumor development and progression. The ETs constitute a family of three closely related 21-amino acid peptides, ET-1, -2, and -3, that are expressed by a variety of mammalian cells and exert paracrine and autocrine effects through the ET receptors, ET_A and ET_B, to modulate normal physiologic functions such as vasomotor tone, cell proliferation, tissue differentiation and hormone production (6–10). Accumulating evidence suggests that the tumorigenic effects of ET-1 are mediated by binding to ET_A. Overexpression of ET_A has been reported in several human cancer cell lines and tumor types, including prostate, ovary, cervix, breast, colon, lung, kidney cancers as well as in bone metastases (10), and activation of ET_A is involved in the regulation of mitogenesis, apoptosis, angiogenesis, metastasis and bone remodeling in tumors. The role of ET_A in these neoplastic processes has made it an attractive therapeutic target for novel anti-cancer agents.

A growing body of evidence suggests that the ET-1/ET_A axis is involved in the pathophysiology of prostate cancer. ET-1 is produced by epithelial cells in the normal prostate, and seminal fluid has the highest concentrations of ET-1 in the body (11). Elevated ET-1 concentrations (12) and increased ET_A expression have both been demonstrated in prostate cancer (13,14). In addition, an evaluation of circulating ET-1 showed that men with CRPC had plasma ET-1 levels that were two times higher than those found in men with organ-confined disease or in men without prostate cancer (15). Increases in ET-1 levels may result from decreased protease cleavage, and loss of neutral endopeptidase 24.11, a cell-surface enzyme involved in deactivation of ET-1, has been linked to the progression of prostate cancer cells to an androgen independent state (16). In cancer cell lines, exogenous ET-1 has been shown to induce proliferation, and the mitogenic effect was enhanced by the addition of other growth factors, suggesting that ET-1 may act synergistically with other growth factors to promote the progression of prostate cancer (12). The effects of ET-1 were inhibited by a selective ET_A antagonist, but not by an ET_B antagonist (12).

Studies have shown that ET-1 and ETs may be involved in mediating nociceptive effects and in osteoblastic activity in prostate cancer. Studies have shown that ET-1 stimulates mitogenesis in osteoblasts (15,17) and decreases osteoclast-mediated bone resorption and osteoclast motility (18). ET-1 levels are elevated in men with prostate cancer who have osteoblastic metastases, and cell culture and xenograft studies have shown that ET-1 produced by prostate tumors resulted in increased osteoblastic activity and inhibited osteoclast function (20,17,19). This effect was diminished by an ET_A-selective antagonist (17). Clinical testing of an orally bioavailable, selective ET_A receptor antagonist, atrasentan (ABT-627, Abbott Laboratories), has demonstrated benefit in PSA progression, markers of bone turnover, and pain in men with prostate cancer, but has not demonstrated significant improvement in survival or time to cancer progression (20,21).

ZD4054 is a nonpeptide, orally bioavailable, specific inhibitor of the ET_A receptor. In mouse erythroleukemic cells, it shows high affinity for ET_A without measurable affinity for ET_B (22). In a randomized, placebo-controlled trial with healthy male volunteers, administration of a single oral dose of ZD4054 resulted in reduction of the vasoconstrictive effects of ET-1 on the brachial artery (22). This effect was mediated by the specific inhibition of ET_A, and no effect was seen on ET_B signaling.

Based on results from the dose finding study performed in healthy volunteers and the proposed mechanism of action in prostate cancer, we conducted a multicenter phase IIa dose escalation study of ZD4054 in men with metastatic, castrate-refractory prostate cancer.

PATIENTS AND METHODS

Patient Selection

Eligible patients had histologically- or cytologically-confirmed metastatic adenocarcinoma of the prostate and evidence of disease progression (defined radiographical progression on bone or CT scan or increasing PSA confirmed on two consecutive measurements, with a minimum PSA value ≥ 5 ng/mL). All patients had to have evidence of castrate-resistant disease as evident by a serum testosterone level of ≤ 50 ng/dL. Patients who were on an LHRH agonist or an anti-androgen were required to continue them for the duration of the study. Patients who discontinued anti-androgen therapy were required to wait at least six weeks prior to enrollment to exclude an anti-androgen withdrawal response. Other entry criteria included: age ≥ 18 ; World Health Organization (WHO) performance status of 0–1; adequate hepatic function (total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN) and alanine aminotransferase and aspartate aminotransferase $\geq 3 \times$ the institutional ULN); adequate renal function as defined by a calculated (Cockcroft-Gault formula) creatinine clearance ≥ 60 ml/min; and a life expectancy of at least 3 months. Exclusion criteria included the following: > 2 prior systemic therapies; ≤ 4 weeks since prior chemotherapy or radiation therapy; initiation of a bisphosphonate within 4 weeks; epilepsy or other seizure disorder; concurrent therapy with a significant CYP3A4 inhibitor; evidence of prolonged QTc interval; and any serious concomitant medical conditions that would place the patient at excessive or unacceptable risk of toxicity. Written informed consent was obtained from all patients, and the study protocol was approved by the Institutional Review Boards of the participating institutions.

Study Design

This was a multi-center, open-label, non-randomized phase IIa dose escalation study to determine the safety and tolerability of ZD4054 given orally in men with metastatic CRPC to determine the MWTd. Secondary endpoints were effects on PSA levels, effect on biomarkers of bone turnover and analysis of pharmacokinetics. The initial cohort received 28 daily doses (Period 1). Patients who had evidence of clinical benefit during the first 28 days were continued until there was a DLT or evidence of disease progression (Period 2).

Treatment Plan

ZD4054 tablets were supplied by AstraZeneca (Cheshire, UK) and were administered orally once daily. The starting dose of ZD4054 in the first cohort (Period 1) was 10 mg PO daily, and dose escalation proceeded in a stepwise fashion (15, 22.5, 32.5 and 50 mg) in cohorts of three patients, with an initial planned maximum of 200 mg daily. The initial cohort received 28 doses over 29 days (no dose was given on day 2 to allow PK determination). For dose-escalation to occur, three assessable patients had to complete at least seven doses of ZD4054 at the 10 mg or 15 mg dose levels during days 1 through 8 without DLT or 14 doses of ZD4054 > 15 mg during days 1 through 15 without DLT. However, determination of MWTd was based on safety analysis through the entire 29-day period for all patients. Dose escalation occurred in the standard 3 by 3 fashion. The MWTd was defined as the dose level below that at which > 1 out of 3 or ≥ 2 out of 6 evaluable patients experienced DLTs. No intra-patient dose escalation was permitted, and dose reduction for patients who experienced a DLT was not allowed for the determination of the MWTd.

DLT was evaluated by National Cancer Institute Common Toxicity Criteria 2.0 and defined as a toxicity that was at least possibly related to ZD4054 including: $\geq$ grade 3 headache with onset within 24 hours of receiving ZD4054 despite maximum supportive care; $\geq$ grade 2 rhinitis leading to withdrawal from protocol; and any other $\geq$ grade 3 toxicity deemed related to treatment.

Since headache and rhinitis have been observed with other ET_A -receptor antagonists, patients were proactively monitored for these symptoms. Any patient reporting a headache was instructed to take acetaminophen 1 g immediately at onset, to be repeated every 4 hours (maximum 4 g per 24 hour period) until resolution of the headache. If the headache persisted or worsened despite the administration of full-dose acetaminophen, treatment was left to the discretion of the treating physician. Patients with ongoing headaches were given an ongoing supply of analgesics and instructed to document any doses taken and the time of resolution of the headache. Patients experiencing rhinitis were treated with over-the-counter decongestants or antihistamines as needed.

All patients were scheduled to receive at least the initial course of 28 oral doses over 29 days (Period 1). Patients who had evidence of clinical benefit and who had not met any of the criteria for withdrawal were allowed to receive ZD4054 at their current dose level until they no longer derived clinical benefit, experienced a DLT that did not resolve to CTC grade ≤ 1 or met other withdrawal criterion. No intra-patient dose escalation was permitted, and dose reduction was only permitted for patients who experienced a DLT after consultation with AstraZeneca and the principal investigators. Each additional cycle was considered to be 28 days in length. All study-related procedures were performed during the extension period at the specific times outlined below.

Pretreatment and Follow-up Studies

After baseline assessments including a complete medical history, physical examination, laboratory studies (CBC, PTT, INR, chem7, PSA and urinalysis) and a 12-lead electrocardiogram (EKG) were performed, the complete blood counts and serum chemistries were repeated weekly for the first month, and then at the beginning of each new course (every 4 weeks) of therapy. Vital signs, performance status, PSA, bone markers, urinalysis, 12-lead EKG and toxicity were also assessed weekly for the first month, and then at the beginning of each additional course of therapy thereafter. Routine laboratories included: complete blood count, electrolytes, BUN and creatinine. Bone markers included: bone alkaline phosphatase (ALP), procollagen type I N propeptide (PINP), C-terminal telopeptide of type I collagen (CTX) and type I collagen-cross-linked N telopeptide (NTx). A baseline bone scan was also performed within 12 weeks prior to enrollment if applicable.

Pharmacokinetic Evaluation

Blood samples were collected after obtaining written informed consent. Patient blood samples were collected in heparin-containing tubes and centrifuged. Plasma samples were transferred into individually-labeled cryovials, stored at -20°C and transported to AstraZeneca for analysis. A maximum of 21 blood samples were obtained for each patient during treatment Period 1. The plasma concentration-time profile was characterized during the first 48 hours following the administration of the day 1 dose on the following schedule: pre infusion, 1, 2, 3, 4, 6, 12, 18, 24, 30, 36 and 48 hours. Trough samples were collected before the next administration of ZD4054 on days 8 and 15, and on final evaluation if possible. Steady-state plasma concentration-time profiles were obtained on day 29 from blood samples collected immediately before ZD4054 administration, and at 1, 2, 3, 4, 6 and 24 hours after the day 29 dose.

ZD4054 plasma concentrations were determined for all patients using high-performance liquid chromatography with tandem mass-spectrometric (HPLC-MS-MS) detection by York Bioanalytical Solutions Ltd, Upper Poppleton, York, UK. Non-compartmental methods were used by AstraZeneca for the evaluation of plasma concentration-time data following the single dose administration of ZD4054 and on day 29 of the multiple dose phase. The maximum observed plasma concentration ($C_{\max}$) and the time of $C_{\max}$ ($t_{\max}$) were determined by inspection of the plasma concentration-time curve. The terminal rate constant (λ_z) was estimated by linear regression of the terminal portion of the log-transformed concentration-time data where there were sufficient data to determine the terminal phase (i.e., when the terminal phase could be followed for at least 3 half-lives). The terminal half-life was calculated as $0.693/\lambda_z$. The area under the plasma concentration-time curve from zero to the last measurable time-point, $AUC_{(0-t)}$ was calculated using the linear up-log down trapezoidal rule, and was extrapolated to infinity using λ_z to obtain AUC. The area under the plasma concentration-time curve from zero to 24 hours post-dose, $AUC_{(0-24)}$, was calculated using the linear up-log down trapezoidal rule. The apparent clearance (CL/F) was determined from the ratio of dose/AUC and the apparent volume of distribution at steady state (V_{ss}/F) was calculated as mean residence (MRT) $\times$ CL/F.

Accumulation ratio (R_{ac}) was calculated as the ratio of the $AUC_{(0-24)}$ on day 29 and $AUC_{(0-24)}$ at single dose. The ratio of day 29 $AUC_{(0-24)}$ and the single dose AUC was used for the evaluation of any temporal change (T_c) in the pharmacokinetics of ZD4054.

RESULTS

Patient characteristics

Between June 2003 and October 2005, 16 patients were enrolled in this study at two participating sites. Baseline characteristics of these patients are summarized in Table 1. The median age was 65 years (range 49–81 years), and all patients had a performance status of 0–1. Of the 16 patients enrolled in this study, 11 patients completed Period 1, and 9 patients completed Period 2. Of the five patients who discontinued therapy during Period 1, two stopped at the 15 mg dose level (one due to progressive disease and one due to toxicity) and 3 stopped at the 22.5 mg dose level (one for an erroneously reported QTc prolongation and two due to toxicity). All 16 patients were included in the safety analysis and the single-dose PK analysis. Eleven patients were included in the multiple dose PK analysis.

Dose-escalation and toxicity

Sixteen patients were evaluable for the safety and single dose PK analyses. The common treatment-related toxicities by dose are summarized in Table 2. The starting dose was 10 mg. No DLTs were observed in the first three patients, and subsequent doses were escalated according to Table 2. No DLTs were observed in the first 3 patients treated with 15 mg, and three patients were then enrolled at the dose level receiving 22.5 mg. Two patients at the 22.5 mg dose level experienced DLTs (grade 3 peripheral edema and grade 3 intraventricular hemorrhage). Consequently, an additional 7 patients were enrolled at the level receiving 15 mg for further safety analysis.

The main toxicity associated with ZD4054 in this study was headache, which occurred in 2 (66.7%), 9 (90%) and 3 (100%) patients in the 10, 15 and 22.5 mg dose cohorts, respectively (Table 2). The majority of the headaches were grade 1 and 2, with the exception of one patient who experienced a grade 3 headache at the 22.5 mg dose level. Other common toxicities included peripheral edema (10 patients), fatigue (7 patients), arthralgia (5 patients), rhinitis, nausea and sinus congestion (4 patients each). Most of these toxicities were grade 1 and 2, with the exception of one patient who experienced grade 3 pleural

effusion and dyspnea in the 15 mg cohort, one patient who experienced grade 3 peripheral edema requiring discontinuation of therapy at the 22.5 mg cohort, and one patient who experienced grade 3 headache and intraventricular hemorrhage at 22.5 mg. Grade 1 or 2 vomiting was reported in 3 patients. There were no treatment-related deaths on study, but one patient died due to progressive disease after withdrawal from the study.

Efficacy

Although not a primary endpoint of this trial, patients underwent disease assessment following every cycle of therapy. While no objective antitumor responses were seen, 9 patients (3 receiving 10 mg and 6 receiving 15 mg) tolerated therapy and had evidence of clinical benefit with stable PSA levels or imaging during Period 1. Of the 6 patients treated during Period 2, there was no evidence of PSA response; however, a transient decrease in the rise in PSA levels was observed in patients who continued on treatment (data not shown).

ZD4054 pharmacokinetics

Single dose PK studies of ZD4054 were conducted in all 16 patients, and multiple-dose PK analysis was performed in 11 patients. Assessment of C_{max} , AUC and $AUC_{(0-t)}$ values following single and multiple dose administration of ZD4054 revealed that exposure increased proportionately with dose. The single dose PK data showed that the apparent clearance and volume of distribution were low, and the mean terminal half-life was between 7.0 hr and 9.2 hr at all three dose levels. Minimal accumulation of ZD4054 was observed with repeat dosing, steady state concentrations were achieved by at least day 8 of treatment (five days of daily administration), and no temporal change in the PK of ZD4054 was seen after repeated dosing.

Pharmacodynamic analysis

Assessment of bone markers (bone ALP, PINP, CTx and NTx) showed considerable intra- and inter-patient variability, and there were no significant trends in the data for any of the pharmacodynamic endpoints.

DISCUSSION

The use of ET receptor antagonists in prostate cancer is scientifically compelling as ET receptor antagonists can provide both direct antitumor effects, as well as impact the tumor environment, by inhibiting osteoblast proliferation, bone remodeling, and release of growth factors that may aid the spread of tumor within the osseous metastasis. Prior studies with atrasentan (ABT-627, Abbott Laboratories), another ET receptor antagonist currently in clinical development, showed an improvement in pain and a trend towards improvement in time to progression (versus placebo) (20,21), and ongoing trials with this agent are being conducted.

ZD4054 is a specific ET_A receptor antagonist, unlike atrasentan, which has some ET_B receptor affinity. By inhibiting only the ET_A receptor, the beneficial effects of ET_B on apoptosis and antinociceptive effects should be preserved. This phase IIa dose escalation study of the specific ET_A -receptor antagonist, ZD4054, in men with metastatic CRPC, showed that continuous oral administration was well-tolerated at 10 mg and 15 mg daily. The MWTd was defined at 15 mg daily. Toxicities were consistent with those previously reported for this class of drugs, and were predominantly grade 1–2 headache, peripheral edema, and nasal congestion. No PSA responses were observed. Prolonged stable disease was seen in some patients, with one patient in the 15 mg cohort maintaining a stable PSA for 20 months.

A multi-center phase II, randomized, double blind, placebo-controlled trial with ZD4054 has since been performed (23,24). A total of 312 asymptomatic or mildly symptomatic patients with CRPC and bone metastasis were randomized into one of three treatment arms: 15mg ZD4054 once daily; 10mg ZD4054 once daily or placebo. The primary end point was progression free survival (PFS) using a composite endpoint, with the secondary endpoint being overall survival (OS). While there was not a statistically significant difference in PFS between the ZD4054 and placebo arms, preliminary survival data suggested an improvement in OS. These results suggest that ZD4054 may be providing clinical efficacy in prostate cancer.

Phase III studies are currently being performed to evaluate the efficacy of ZD4054. Given the favorable side effect profile of ZD4054, this agent may also provide additional efficacy in combination therapy with other anticancer agents. A combination study with docetaxel forms part of the Phase III program, and it will be of interest to learn if there are any additive or synergistic effects of ZD4054 in terms of improved efficacy or symptom management when it is administered with chemotherapy.

In addition to prostate cancer, early studies showed that ETs and their receptors are expressed in several cell lines and tumor types (25) and may play a role in several other cancers, including ovary (26), cervix (27,28), breast (29), melanocytes (30), kidney (31), lung, colon, central nervous system, and in Kaposi's sarcoma (32). While the clinical activity of the ET-1/ET receptor axis has been studied primarily in prostate cancer, preclinical work is ongoing to determine whether ET_A receptor antagonists may be used in the treatment of ovarian cancer. Future studies will be aimed at evaluating ZD4054 in other tumors.

In summary, this study was designed to determine the MWTd of oral ZD4054 in patients with CRPC. Oral administration of ZD4054 given continuously daily was well-tolerated, with the MWTd determined to be 15 mg daily. ZD4054 has a favorable pharmacokinetic profile for continuous daily dosing. Phase III trials evaluating ZD4054 in patients with CRPC, with rising PSA and no evidence of radiographical metastasis, as well as those with asymptomatic metastatic CRPC are currently underway to assess whether ZD4054 can delay progression of clinical and radiographical metastasis. Likewise, a Phase III trial assessing docetaxel with or without ZD4054 is being undertaken in chemotherapy-naïve patients.

TRANSLATIONAL RELEVANCE

This first-in-human study reports on the safety and tolerability of a novel, specific endothelin-A receptor antagonist, ZD4054, in men with metastatic castrate-resistant prostate cancer. Survival in advanced prostate cancer is poor despite standard therapies, and new regimens are needed to enhance the efficacy of treatments for patients with hormone-refractory disease. The maximum-well tolerated dose was established in this study, and subsequent clinical trials evaluating the efficacy of ZD4054 are being conducted based on these results. Likewise, a Phase III trial assessing docetaxel with or without ZD4054 is being undertaken in chemotherapy-naïve patients.

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Table 1

Patient Characteristics

	<i>n</i>
Total	16
Median age, year (range)	65 (49–81)
Gender	
Male	16
Race	
Caucasian	15
Black	1
Patients completed	11
Patients discontinued	5

Table 2

Tolerability profile **

Description	ZD4054 Dose (mg)			
	10 (n=3)	15 (n=10)	22.5 (n=3)	All (n=16)
Dyspnea		1	1	2
Peripheral edema			1	1
Headache			1	1
Pleural effusion		1		1
IVH			1	1
Cataract	1			1

** Includes all grade 3 and 4 non-hematologic toxicity at least possibly related to treatment.

Abbreviations: IVH, Intraventricular hemorrhage