AstraZeneca

Clinical Study Report Addendum (Final Analysis) Synopsis

Drug Substance	ZD4054
Study Code	D4320C00020
Edition Number	1
Date	2 June 2009

A Phase I Study of ZD4054 in Combination with Docetaxel in 2 Parts, an Open-Label, Non-Randomised, Dose-Finding Part and a Double-Blind, Placebo-Controlled, Randomised Dose Expansion Part, in Patients with Metastatic Hormone-Refractory Prostate Cancer (data cut-off 10 December 2008)

Study dates:	First patient enrolled: March 2006 Last patient completed: ongoing at data cut-off
Phase of development:	Clinical pharmacology (I)

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

Summary of relevant information

This is an addendum to the Clinical Study Report (CSR) synopsis for study D4320C00020 dated 25 July 2008, which reported the *primary* analysis results (data cut-off 5 March 2008). No dose-limiting toxicities (DLTs) were observed during Cycle 1 of treatment with ZD4054 10 mg or 15 mg, both in combination with docetaxel; hence MTD for ZD4054 was established at 15 mg (primary variable), which was the dose administered in Part B. No further Part A data has since been generated - please refer to the CSR for presentation and discussion of Part A results, as reported at the *primary* analysis.

Part B *final* analysis results (data cut-off 10 December 2008) are reported in this CSR addendum, and supersede the Part B *primary* analysis results provided in the CSR dated 25 July 2008 (data cut-off 5 March 2008). Any Part A information included here is provided for completeness.

Study centre(s)

This study was a multi-centre study conducted in the United Kingdom (2 study centres), Germany (2 study centres) and in the USA (3 study centres).

Publications

None at the time of writing this report.

Objectives and variables

Part A only: The primary objective of this study was to identify a maximum tolerated dose (MTD) of ZD4054 in combination with docetaxel by evaluation of the incidence of dose limiting toxicities (DLTs) (from adverse events (AEs), laboratory tests, physical examination and vital signs) during Cycle 1 of treatment with ZD4054 and docetaxel.

The secondary objectives of this study were:

To evaluate the safety and tolerability profile of ZD4054 when administered in combination with docetaxel by assessment of AEs, laboratory tests, physical examination and vital signs.

The exploratory objectives of this study were to investigate the effect of ZD4054 in combination with docetaxel on: Objective response rate and Prostate specific antigen (PSA) response rate; the rate of rise of PSA; the appearance of bone lesions on bone scans; bone-related biomarkers; and pain. Additionally, an optional pharmacogenetic sample was to be collected from consenting patients and stored for further investigation – these results will be reported separately to this CSR addendum.

Study design

This was a two-part, multi-centre study designed to establish a MTD of ZD4054 in combination with docetaxel, and to explore its safety, tolerability, PK profiles and clinical efficacy in patients with metastatic hormone refractory prostate cancer. Part A followed an

open-label, dose-finding design to establish the MTD of ZD4054 when administered in combination with docetaxel. Part B followed a double-blind, randomised design to assess ZD4054 versus placebo, both in combination with docetaxel (randomised 2:1, respectively), administered for up to 10 cycles (and more than 10 cycles at the discretion of the Investigator), as long as there was no evidence of disease progression and they met no other withdrawal criteria.

Target patient population and sample size

Male patients, surgically castrated or continuously medically castrated with LHRH analogue, with histological or cytological confirmation of prostate cancer; evidence of metastatic disease on CT scan, MRI, or bone scan (no positron-emission tomography or Prostacint); evidence of progressive disease after most recent therapy including hormonal therapy (as defined by disease progression by CT/MRI; bone scan progression: appearance of 1 or more new lesions since last bone scan on bone scan attributable to prostate cancer; or rising PSA over the course of at least 1 month despite antiandrogen withdrawal); World Health Organization (WHO) performance status 0 to 2; and life expectancy of 12 weeks or longer.

Patients were to be enrolled until there were up to 12 evaluable patients in Part A, and 30 evaluable patients in Part B.

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

ZD4054 2.5 mg, 10 mg and 15 mg tablets for once-daily oral administration (batch numbers: 33563H05, 30165J05, 51051J07, 30166G05, 50910B07). In Part A, the starting dose of ZD4054 was 10 mg - escalated to 15 mg or reduced to 5 mg in order to establish the MTD. In Part B, the ZD4054 dose used was the MTD identified in Part A (ie, 15 mg, see below).

Matching placebo for once-daily oral administration (Part B only) (batch numbers: 94316K02 43614B06).

Docetaxel 75 mg/m^2 administered via a 1-hour intravenous infusion (Day 1 of each cycle).

Pre-medications: dexamethasone 8 mg po administered 12 h, 3 h, and 1 h pre-docetaxel infusion; and prednisone/prednisolone 5 mg po bid (Days 1 – 21).

Duration of treatment

Part A: ZD4054 alone was administered in a run-in period of 1 week (Days -6 to 0, Cycle 1). From Day 1 Cycle 1, ZD4054 and docetaxel were administered concurrently. Only during Cycle 1, ZD4054 was stopped on Day 15, and administration resumed on Day 2 Cycle 2, when patients continued daily dosing of ZD4054 in combination with docetaxel.

Part B: ZD4054/placebo and docetaxel were administered concurrently from Day 1 Cycle 1.

Up to 10 cycles of treatment (and more than 10 cycles at the discretion of the Investigator) were to be administered, as long as there was no evidence of disease progression and they met no other withdrawal criteria. Each cycle of treatment lasted 21 days.

Statistical methods

The primary analysis was performed following an *initial* data cut-off 3 months after the last patient entered the study (ie, 5 March 2008). Full details are provided in the CSR. The *final* analysis (data cut-off 10 December 2008) was declared once all patients had been given the opportunity to receive a minimum of 10 cycles of combination therapy. Subsequent to this *final* analysis, no new data will be collected on the clinical study database. For patients continuing on open-label study treatment beyond final data cut-off, data collection will be limited to SAEs only, which will be captured on the patient safety database and reported as appropriate.

Part B: 3 main populations were defined: the intention to treat population (ITT; full analysis set) comprising all randomised patients; the safety population comprising all randomised patients who had received at least one dose of study treatment; and the Per Protocol population (PP) comprising all randomised patients who had received treatment, had valid post-baseline assessment data, and who did not violate the recruitment criteria or deviate from the protocol procedures. The PP analysis set was not used to assess the PSA response endpoint in the *final* analysis. In addition, the following populations were also defined: the objective response population comprising only those patients with measurable malignant soft tissue disease at baseline and had received treatment; the bone population comprising only those patients who had bone lesions present at baseline and had received treatment; and the patient-reported outcomes population (PRO) comprising only those patients who had valid brief pain inventory (BPI) data at baseline and had received treatment.

Patient population (Part B - *final* analysis; data cut-off 10 December 2008)

Patient disposition, key demographic data, and number of patients in each population analysed are summarised in Table S1 below. Overall the treatment groups were comparable with regards to demographic and key baseline characteristics, and the patient population was considered to be adequately representative of the target patient population for ZD4054.

Table S1 Patient population and disposition (Part B)

	Number (%) of patients	
	ZD4054	**Placebo**
	N = 20	**N = 11**
Demographic characteristics		
Mean age (range) (years)	67 (52-84)	71 (56-85)
Race: Caucasian	20 (100)	10 (91)
Black	0 (0)	1 (9)
Patient Disposition		
Patients enrolled[a]	33	
Patients who failed screening	2	
Patients randomised	20 (100)	11 (100)
Patients who received treatment (IP and docetaxel)	20 (100)	11 (100)
Patients who discontinued IP and docetaxel	17 (85)	10 (91)
Patients who discontinued IP / docetaxel	17 (85) / 20 (100)	10 (91) / 11 (100)
Disease progression	11 (55) / 6 (30)	7 (64) / 4 (36)
Adverse event	3 (15)[e,f] / 4 (20)	0 (0) / 0 (0)
Other	0 (0) / 7 (35)	2 (18)[g,h] / 5 (45)
Patient withdrawal of consent to treatment	3 (15) / 3 (15)	1 (9) / 2 (18)
[b,c]Patients continuing in study, off IP	1 (5)	0 (0)
Patients who discontinued study:	16 (80)	10 (91)
Disease progression	10 (50)	7 (64)
Other – completed 10 cycles	0 (0)	1 (9)[g]
Other - Adverse event	2 (10)[e]	0 (0)
Patient lost to follow-up	1 (5)[d]	0 (0)
Analysis sets		
Patients included in Safety Analysis set	20	11
Patients included in Full Analysis set (ITT)	20	11
Patients included in Objective Response analysis set	9	6
Patients included in PRO analysis set	18	11
Patients included in Bone analysis set	17	9

IP – Investigational Product; ITT – Intention to treat; PRO - Patient Reported Outcomes
Data cut-off: 10 December 2008
a Informed consent received
b Patients E0112005 (ZD4054), E0302010 (ZD4054), E0550005 (ZD4054), and E0550001 (Placebo) – continuing in study at data cut-off - discontinued docetaxel, ongoing ZD4054/placebo treatment.
c Patient E0112004 continuing in study, off treatment
d Patient E0302002 discontinued ZD4054 and docetaxel treatment; subsequently lost to follow-up
e Deaths: Patient E0552001 (cardiac failure); Patient E0552003 (diabetic coma)
f Patient E0109003 discontinued ZD4054 due to nausea AE; discontinued docetaxel due to disease progression; subsequently discontinued study due to disease progression
g Patient E0109001 discontinued IP as patient found to be on placebo when unblinded; discontinued study as completed 10 cycles of treatment
h Patient E0109002 discontinued IP as patient found to be on placebo when unblinded; subsequently voluntary discontinuation from study.

Summary of efficacy and pharmacodynamic results (Part B - *final* analysis; data cut-off 10 December 2008)

Table S2 provides an overview of the efficacy and pharmacodynamic results obtained from the *final* analysis, which are described in further detail below.

Table S2 Summary of efficacy and pharmacodynamic parameters (Part B)

Category	Number (%) of patients	
	ZD4054	Placebo
Objective Response Rate	2 / 9 (22%)	1 / 6 (17%)
PSA Response Rate	17 / 20 (85%)	8 / 11 (73%)
PSA doubling	2 / 20 (10%)	4 / 11 (36%)
New bone lesions appearance	6 / 20 (30%)	5 / 11 (45%)
Worsening of existing bone lesions	1 / 17 (6%)	0 / 9 (0%)

Data cut-off:10 December 2008

Objective response rate was assessed only in patients with measurable malignant soft tissue disease at baseline. Two patients demonstrated an Objective response on ZD4054+docetaxel, and one patient on placebo+docetaxel; the difference in the proportion of responders was 0.06 with a 80% CI (-0.23, 0.30).

PSA response was defined as decrease relative to baseline of ≥50% documented on at least 2 separate occasions, at least 2 weeks apart. For the ITT population, 85% of patients on ZD4054+docetaxel, and 73% of patients on placebo+docetaxel demonstrated a PSA response; the difference in the proportion of responders between the treatment groups was 0.12, with a 80% CI (-0.06, 0.33).

There was an immediate and steady decrease in PSA levels from baseline for the ZD4054+docetaxel group; the decrease in the placebo+docetaxel group occurred, but with a lag time of approximately 12 weeks until any evident decreases were observed. Median PSA levels remained below baseline levels during the course of the study. Two patients on ZD4054+docetaxel exhibited a PSA doubling of their baseline level, compared with 4 patients on placebo+docetaxel. PSA doubling time (alternative method: PSADT) did not add to the interpretation of PSA data as most patients did not demonstrate a doubling of their PSA.

Six patients in the ZD4054+docetaxel group and 5 patients in the placebo+docetaxel group had new confirmed bone lesion(s). Of those patients with bone lesions present at baseline, one patient on ZD4054+docetaxel demonstrated a confirmed worsening of their existing bone lesions from baseline.

Overall serum CTX (C-terminal cross linking telopeptide) remained unchanged, whilst BAP (bone-specific alkaline phosphatase) and PINP (procollagen type I N propeptide) fell modestly and similarly in both treatment arms, indicating reduced bone turnover and formation. Urinary NT_X (urinary type I collagen-cross-linked N telopeptide) levels appeared to fall in the placebo+docetaxel group, but remained constant in the ZD4054+docetaxel group, suggesting reduced bone loss with docetaxel alone.

Pain levels at baseline were low and remained low over the course of the study on both treatment arms.

Summary of safety results (Part B - *final* analysis; data cut-off 10 December 2008)

Overall, no unusual or unexpected AEs/SAEs were observed following treatment with ZD4054 and/or docetaxel, with no evidence to suggest that ZD4054 had increased the severity or frequency of AEs commonly associated with docetaxel therapy. No significant changes in the safety profile of ZD4054 in combination with docetaxel have emerged upon further exposure since the *primary* analysis, indicating that tolerability to combination therapy remains good. Although a high number of AEs were reported, this is expected in this patient population receiving chemotherapy. The most commonly reported AEs were typically those that are pharmacologically mediated by ZD4054 (eg, headache, oedema peripheral/fluid retention, nasal congestion, nausea/vomiting, dyspnoea), and other known AEs associated with docetaxel treatment (eg, fatigue, neutropenia, leukopenia, alopecia, nausea/vomiting, paraesthesia, infections). There were 2 deaths in the ZD4054+docetaxel group (diabetic coma, cardiac failure) - neither was considered by the Investigator to be causally related to study treatment, and both patients had significant co-morbidities. Few SAEs were reported, although at a higher incidence in the ZD4054+docetaxel group (25% vs 18% placebo+docetaxel). The majority of SAEs were not considered by the Investigator to be causally related to study treatment. Three patients (all received ZD4054+docetaxel) experienced cardiac/ischaemic SAEs (ie, acute myocardial infarction / ECG T wave abnormal; cardiac failure (death, as mentioned above); cerebrovascular accident, also CTC grade 1 cardiac failure) – each of these patients had existing co-morbid conditions. Few patients discontinued study treatment due to AEs.

Mean haemoglobin (Hb) levels were reduced by approximately 15 g/L from baseline in patients receiving ZD4054+docetaxel; the rapid onset of this reduction suggests a haemodilutional effect, possibly as a consequence of the vasodilatory effect of ZD4054 leading to increased fluid volume. Hence AEs of anaemia were also commonly reported during this study. There were no clinically important changes noted in any of the clinical laboratory safety parameters, with no individual abnormalities that raise any safety concerns. Small asymptomatic decreases from baseline in mean systolic and diastolic blood pressure are consistent with findings of previous ZD4054 studies; the fact that they are evident early and persist during treatment suggests that they are a consequence of the vasodilatory activity of ZD4054. There were no clinically important ECG findings. There were no consistent trends regarding changes from baseline weight over time. Overall, there were no new concerns about the safety of ZD4054 in this patient population, either alone or in combination with docetaxel..