AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00014
Edition Number	1
Date	1 February 2011

A Phase III, Randomised, Double-blind Study to Assess the Efficacy and Safety of 10 mg ZD4054 versus Placebo in Patients with Hormone-resistant Prostate Cancer and Bone Metastasis who are Pain Free or Mildly Symptomatic (data cut-off 16 July 2010)

Study dates: First patient enrolled: 20 November 2007
Last patient enrolled: 13 February 2009
Data cut-off: 16 July 2010

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centres

This study was conducted in 182 hospital-based centres in 27 countries in the world, including Europe, the Americas and Asia.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Primary and secondary objectives and outcome variables are summarised in Table S1 below.

Table S1 Primary and secondary objectives and outcome variables

	Objectives	Outcome variables
	Primary	**Primary**
	To determine the effect of ZD4054 on overall survival, defined as time to death (from randomisation) from any cause, compared to placebo.	Overall survival, defined as: time to death (from randomisation) from any cause
	Secondary	**Secondary**
1	To assess the effect of ZD4054 on progression free survival, defined as time from randomisation into the study until clinical progression of disease, compared to placebo.	Clinical progression, defined as any of: Increased pain[c]; Skeletal related event[d]; Objective progression[e]; Four or more new bone lesions confirmed by bone scan (with CT, MRI scan or x-ray as necessary); Death from any cause in the absence of progression.
2	To investigate the tolerability and safety profile of ZD4054 compared to placebo.	Incidence and severity of adverse events, vital signs, laboratory, ECG and physical examination findings.
3	To assess the effect of ZD4054 on time to use of opiates compared to placebo.	Time to use of opiate medication for duration of ≥1 week for pain due to prostate cancer metastasis; or death from any cause.
4	To assess the effect of ZD4054 on the incidence of skeletal related events compared to placebo.	Time to skeletal related events[d]; or death from any cause.
5	To investigate the effects of ZD4054 on bone metastases formation compared to placebo. [a]	Time to appearance of four or more new bone lesions confirmed by bone scan (with CT, MRI scan or x-ray as necessary); or death from any cause.
6	To assess the effects of ZD4054 on Health Related Quality of Life (HRQoL) compared to placebo.	TDS, calculated from FAPSI-8 of the FACT-P questionnaire. TDQoL calculated from total FACT-P.
7	To investigate the effect of ZD4054 on time to prostate-specific antigen (PSA) progression compared to placebo.	Time to PSA progression defined as: time to the first PSA value >50% higher than baseline, and an increase of at least 5 ng/mL, seen in ≥2 consecutive PSA values, ≥2 weeks apart; or death from any cause.
8	To assess the effects of ZD4054 on time to pain progression compared to placebo (composite). [a]	Time to pain progression (TPP), defined as: time to first assessment of an increased pain event[c]; or death from any cause.
9	To investigate the effects of ZD4054 on time to initiation of chemotherapy compared to placebo. [a]	Time from randomisation to first administration of chemotherapy; or death from any cause.
10	To investigate the PK characteristics of ZD4054.	To obtain estimates of PK variables, quantify variability and explore reasons for observed variability (covariate analysis).
11	To assess the effects of ZD4054 on time to patient reported pain progression compared to placebo. [b]	Time to patient reported pain progression (TPRPP), defined as time from date of randomisation to date of first assessment of a BPI[f] (Brief Pain Inventory) event, or death from any cause.

TDS: Time to deterioration of symptoms; FAPSI-8: 8-item FACT advanced prostate symptom index; FACT-P: Functional Assessment of Cancer Therapy for Prostate cancer; TDQoL: Time to deterioration of Quality of Life.

a Key Secondary Objective

b Objective added after the start of the study. See main Clinical Study Report (CSR) for details

c Increased pain, defined as:
- Patient requiring opiate medication for duration of ≥1 week for pain due to prostate cancer metastasis. Note that there must be a relationship between the pain and a metastatic site. If a patient started the study taking PRN opiates for non-disease-related symptoms, and subsequently developed pain due to prostate cancer metastasis, then progression was defined as an increase in opiate use for ≥1 week.
- Pain due to metastasis that has an increase in the worst pain item of the Brief Pain Inventory (BPI) from baseline to a minimum score of 5 with no decrease in analgesic use.
- Pain due to metastasis requiring radionuclide therapy, radiation therapy, or surgery.

d Skeletal related event, defined as: Pathologic fracture; vertebral compression fracture not related to trauma; prophylactic surgery or radiation for impending fracture or spinal cord compression; or spinal cord compression.

e Objective progression, defined as: Objective progression of visceral or nodal disease assessed according to modified RECIST criteria (including development of visceral or brain metastasis or malignant pleural effusion).

f BPI event defined as pain due to metastasis that has an increase in the worst pain item of the BPI from baseline to a minimum score of 5, which is the lowest score defined as moderate pain with no decrease in analgesic use.

Pharmacokinetic results reported separately from this Report, as documented in the Clinical Study Protocol (CSP).
Details of exploratory objectives are provided in the CSR; these results will be reported separately.

Study design

A randomised, double-blind, parallel-group, multi-centre, 2-arm, placebo-controlled study to assess the efficacy and safety of ZD4054 compared with placebo, both in combination with best supportive care (BSC). Patients were randomised (1:1) to receive either ZD4054 10 mg or placebo. In addition to study therapy, patients could receive castration therapy (either surgical or medical, including luteinising hormone-releasing hormone analogue (LHRHa), estramustine, megace and estradiol), and standard supportive/palliative treatment for prostate cancer, which could include: regular follow-up; bisphosphonates; or symptomatic therapy for pain control or urinary obstruction. Patients could also receive other therapies for progressive disease including chemotherapy, prednisolone, ketoconazole at the Investigator's discretion without the study treatment being considered to have failed and without the patient having to stop ZD4054 or placebo.

Target subject population and sample size

The patient population participating in this study was men with hormone resistant prostate cancer (HRPC) and bone metastases which were pain-free or mildly symptomatic and who had rising PSA levels despite medical or surgical castration. Study inclusion criteria specified that patients were to have: Histological or cytological confirmation of adenocarcinoma of the prostate; Documented evidence of bone metastasis on radionuclide bone scan (disease involvement <75% of the spine, pelvis and ribs in the anteroposterior (AP) or posteroanterior (PA) view; patients with ≤3 lesions seen on bone scan required CT scan, MRI, or X-ray to confirm); Biochemical progression of prostate cancer, documented while patient was castrate; Asymptomatic or mild pain from prostate cancer, defined as a score of ≤2 in the worst pain item of the BPI; Surgically castrated or continuously medically castrated (serum testosterone ≤2.4 nmol/L (70 ng/dL)); World Health Organization (WHO) performance status 0 to 1; and Life expectancy of ≥6 months.

At least 580 patients were planned to be recruited into this study. The formal analysis was planned for when a minimum of 263 deaths had occurred. Based on a recruitment period of 18 months and a median overall survival for the placebo group of approximately 19 months (Tannock I et al 2004; N

Engl J Med; 351:1502-12), it was estimated that 263 deaths would occur approximately 30 months after the first patient entered the study. If the true hazard ratio for ZD4054 versus placebo is 0.67, then the analysis will have 90% power to demonstrate a statistically significant effect in overall survival at the 5% significance level.

Investigational product and comparator: dosage, mode of administration and batch numbers

ZD4054 10 mg tablets administered orally once daily at approximately the same time each morning. Batch numbers: 5122-4C07/5K07/7E07; 5264-0B07/2G07; 6062-3H08/5B08; 60667B08; 6172-7F08/8C08; 71352K09.
Placebo tablets to match ZD4054, administered orally once daily at approximately the same time each morning. Batch numbers: 51255J07; 5295-4D07/7F07; 6060-3E08/4B08; 61025C08; 70932G09.

Duration of treatment

Patients were to receive ZD4054 10 mg or placebo until a discontinuation criterion was met (ie, voluntary discontinuation, safety concerns, severe protocol non-compliance, lost to follow-up, incorrect enrolment or disease progression). Blinded study drug could be continued at Investigator discretion following disease progression.

Statistical methods

The primary endpoint for this study was overall survival (OS). A hierarchal testing strategy was introduced to prioritise the interpretation of the secondary efficacy endpoints. The 3 key secondary endpoints to be tested if the primary endpoint of OS was significant were: time to pain progression (composite), time to development of new bone metastases and time to chemotherapy. The remaining secondary endpoints were analysed in a hierarchical manner to address issues of multiplicity (for details see the Clinical Study Report [CSR]).

A log rank test was performed for the primary analysis of OS based on the intent-to-treat (ITT) population. Results were presented in terms of an estimate of the hazard ratio (ZD4054:placebo), associated confidence intervals (CI) and p-value. The number of events at the time of analysis, as well as point estimates of the median, lower and upper quartile for OS were presented for each treatment group, and OS displayed graphically using Kaplan-Meier plots. Subgroup analyses investigating the effect of pre-defined prognostic factors on OS were performed using the Log Rank test and presented as a Forest plot. The secondary efficacy variables were analysed using the same methods as the primary variable.

Subject population

Patient disposition (data cut-off 16 July 2010), key demographic data, and number of patients in each population analysed are summarised in Table S2. In total, 594 patients were randomised at 182 centres in 27 countries. Overall the treatment groups were well balanced at baseline with regards to demographic and patient characteristics, disease characteristics, medical and surgical history, and use of previous anti-cancer treatment modalities. The vast majority of patients were being managed by LHRHa plus anti-androgen therapy; 33% had prior bisphosphonate use. Concomitant medication usage post-randomisation, including anti-cancer treatments and opiates, was comparable across the

treatment groups and was considered to reasonably reflect best supportive care in accordance with current clinical practice. Most patients were pain free at study entry and were of normal performance status. Median PSA was 53 ng/mL, but with a very wide range; 83% patients had ≤20 bone metastases. Therefore the patient population participating in this study was considered to be typical of a population of men in the early stages of metastatic HRPC, and representative of the intended target population.

Table S2 Patient disposition, demographics and analysis sets

	ZD4054 10 mg	Placebo	Total
Disposition			
Patients enrolled n	-	-	896
Patients randomised n (%)	299 (100)	295 (100)	594 (100)
Patients who received treatment n (%)	298 (99.7)	295 (100)	593 (99.8)
Patients ongoing at data cut-off n (%)	73 (24.4)	70 (23.7)	143 (24.1)
Patients who discontinued treatment n (%)	225 (75.3)	225 (76.3)	450 (75.8)
Continuing study, stopped study drug at data cut-off n (%)	79 (26.4)	71 (24.1)	150 (25.3)
Terminated study n (%)	147 (49.2)	154 (52.2)	301 (50.7)
Demographics			
Mean age: (range) years	70.2 (46 - 90)	70.9 (46 - 95)	70.5 (46 - 95)
Sex: male n (%)	299 (100)	295 (100)	594 (100)
Race: White n (%)	191 (63.9)	189 (64.1)	380 (64.0)
Race: Asian n (%)	101 (33.8)	99 (33.6)	200 (33.7)
Analysis sets			
Full analysis set n	299	295	594
Safety analysis set n	298	295	593

Asian: Asia (including Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, Philippine Islands, Thailand, Vietnam)
Data cut-off 16 July 2010.

Summary of efficacy results

In total, 283/594 death events (47.6%) had occurred at the time of data cut-off (ie, 136/299 and 147/295 deaths for ZD4054 10 mg and placebo, respectively). There was no significant difference in overall survival for patients in the ZD4054 10 mg group compared to placebo (HR 0.87, 95.2% CI 0.69 to 1.10, p=0.2401). The median time to death was 24.5 and 22.5 months for ZD4054 10 mg and placebo, respectively. Median duration of follow-up was balanced between treatment groups (17.81 and 17.87 months for patients in the ZD4054 10 mg and placebo groups, respectively). The effect was generally consistent across known prognostic factors and regions. There was no statistically significant difference between ZD4054 10 mg and placebo for the key secondary variables: time to pain progression (composite); time to development of new bone metastasis; or time to chemotherapy. None of the remaining secondary variables showed a significant difference.

Summary of safety results

Overall, ZD4054 10 mg was generally well tolerated in this patient population. The most commonly reported adverse events (AEs) were pharmacologically-mediated, principally peripheral oedema, headache and nasal congestion/rhinitis, and occurred more frequently in the ZD4054 group than with placebo. Relatively few of these AEs were assessed as being CTC grade 3 or higher. However anaemia, cardiac failure and pleural effusion AEs of CTC grade 3 or higher were reported more commonly for patients on ZD4054 compared with placebo. More patients on ZD4054 developed congestive heart failure (CHF; grouped term to include cardiac failure and related preferred terms) compared with placebo (17 (5.7%) vs 5 (1.7%)). CHF events were manageable, reversible in most cases, and none were fatal. AEs of alopecia and neutropenia were considered to be attributable to chemotherapy rather than to ZD4054, as their incidence was notably reduced when comparing AEs reported before and after the initiation of chemotherapy.

In total, there were 283 death events (48%), of which the majority (78%) were due to prostate cancer; there were no imbalances in non-prostate cancer causes of death. Serious AEs were infrequent, with anaemia, cardiac failure and pneumonia as the most commonly reported following ZD4054 treatment. Relatively few patients discontinued treatment due to AEs. The most common AEs resulting in discontinuation of ZD4054 treatment were peripheral oedema, cardiac failure and nasal congestion. Although more patients on ZD4054 discontinued treatment due to AEs compared with placebo, the excess on ZD4054 over placebo was largely accounted for by treatment discontinuations due to pharmacologically-mediated AEs (ie, peripheral oedema, headache, nasal congestion/rhinitis).

In general, there were no differences in laboratory safety parameters between the treatment groups, and no clinically significant changes noted or individual abnormalities that raised any safety concerns. Sustained decreases in mean haemoglobin (Hb) levels from baseline were observed for patients on ZD4054 that were early in onset from start of dosing, and were consistent with the prevalence of anaemia AEs reported in this group. This was considered to be a manifestation of a haemodilutional effect secondary to pharmacologically-mediated vasodilatation, as decreases in other haematology parameters were also observed. Decreases from baseline in mean systolic and diastolic blood pressures, also evident from start of dosing and sustained throughout, further support that this is a consequential effect of the vasodilatory properties of ZD4054. Overall, there were no new concerns about the safety of ZD4054 in this patient population.