Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00033
Edition Number	1
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A Phase III, Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of 10 mg ZD4054 in Combination with Docetaxel in Comparison with Docetaxel in Patients with Metastatic Hormone-resistant Prostate Cancer

Study dates:

First subject enrolled: 24 January 2008
Last subject last visit: 10 May 2011
Data cut off: 26 April 2011

Phase of development:

Therapeutic confirmatory (III)

[redacted]

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

Study centre(s)

This study was conducted in 152 hospital-based centres globally. This study was ongoing at the data cut-off for the clinical study report (CSR) (26 April 2011).

Publications

None at the time of writing this CSR.

Objectives and criteria for evaluation

The purpose of this synopsis is to report the results of the primary and secondary objectives.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To determine the effect of ZD4054 in combination with docetaxel on overall survival compared with docetaxel.	Assessment of OS, defined as time to death (from randomisation) from any cause.	Efficacy
Secondary	**Secondary**	
To assess the effect of ZD4054 in combination with docetaxel on progression free survival compared with docetaxel.	Clinical progression, defined as 1 of the following: • Four or more new bone lesions confirmed by either bone scan, CT scan or MRI • Increased pain • Skeletal Related Event • Appearance of new malignant soft tissue disease or objective progression of malignant soft-tissue disease assessed according to modified RECIST criteria • Death from any cause in absence of progression	Efficacy
To assess the safety and tolerability profile of ZD4054 in combination with docetaxel compared with docetaxel.	Adverse events, vital signs, laboratory data, ECGs, physical examination.	Safety
To assess the effect of ZD4054 in combination with docetaxel on skeletal-related events compared with docetaxel.	Skeletal-related events, defined as: • Pathologic fracture • Vertebral compression fracture not related to trauma • Prophylactic surgery or radiation for impending fracture or spinal cord compression • Spinal cord compression	Efficacy
To investigate the effect of ZD4054 in combination with docetaxel on time to PSA progression compared with docetaxel.	Time to PSA progression, defined as the time to the first PSA value >50% higher compared with baseline, seen in at least 2 consecutive PSA values.	Efficacy

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
To assess the effect of ZD4054 in combination with docetaxel on time to pain progression compared with docetaxel.	Time to pain progression, defined as significantly increased pain due to metastasis, defined as: • The initiation of opiate medication or an increase from baseline of analgesic use of at least 25% for a duration of 1 week or more with or without a change in BPI score. (Note that there must be a relationship between the pain and a metastatic site). • Pain due to metastasis that has an increase in the level of pain from baseline of at least 2 units (a movement from no/mild to moderate pain or moderate to severe pain) to a minimum score of 5 points in the worst pain item of the BPI, with no decrease in analgesic use. • Pain due to metastasis requiring radionuclide therapy, radiation therapy, surgery or continuous glucocorticoid therapy (which is not part of the standard docetaxel regime).	Efficacy
To assess the effects of ZD4054 in combination with docetaxel on pain response compared to docetaxel.	Pain response, defined as a decrease in worst pain item of the BPI of at least 2 points from baseline in patients who had a BPI score of ≥2 at baseline in the absence of increased analgesic use, OR a decrease from baseline of analgesic use of at least 25% for a duration of 1 week or more without an increase in BPI score.	Efficacy
To assess the effects of ZD4054 in combination with docetaxel on HRQoL compared to docetaxel.	FWB as recorded by the FWB domain of the FACT-P and the Total FACT-P score	PROs
To investigate the effect of ZD4054 in combination with docetaxel on PSA response compared to docetaxel.	PSA response, defined as a >50 % decrease in serum PSA from baseline on 2 occasions at least 2 weeks apart.	Efficacy

The exploratory objectives will not be discussed.
BPI Brief Pain Inventory; CT Computed tomography; ECG Electrocardiogram; FACT-P Functional assessment of cancer therapy for prostate cancer; FWB Functional well being; HRQoL Health-Related Quality of Life; MRI Magnetic resonance imaging; OS Overall survival; PSA Prostate-specific antigen; PRO Patient reported outcome; RECIST Response evaluation criteria in solid tumours.

Study design

This was a randomised, double-blind, parallel-group, multi-centre, 2-arm, placebo-controlled Phase III study to assess the efficacy and safety of ZD4054 10 mg in combination with docetaxel, compared with placebo in combination with docetaxel, in patients with metastatic hormone-resistant prostate cancer.

Target subject population and sample size

Patients with metastatic hormone-resistant prostate cancer who had rising serum prostate-specific antigen (PSA) levels despite medical or surgical castration.

A total of 1044 patients were planned to be recruited into this study.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength and route of administration	Manufacturer	Formulation number	Batch number
ZD4054	10 mg beige film coated tablet, once daily orally in tablet form	AstraZeneca	F13466	51227E07, 52640B07, 60666E08, 60667B08, 61728C08, 61730A08, 61729K08, 71352K09, 71354E09, 71355B09, TS29001
Placebo to match ZD4054	Beige film coated tablet, once daily orally in tablet form	AstraZeneca	F13544	51255J07, 52954D07, 60604B08, 52957F07, 60603E08, 61023I08, 61025C08, 70932G09
Docetaxel	75 mg/m^2 intravenously over 1 hour on Day 1of each 21-day cycle	NA	NA	NA
Dexamethasone	8 mg orally, 12 hours, 3 hours and 1 hour prior to each docetaxel infusion	NA	NA	NA
Prednisolone	5 mg orally, twice per day, on each day of the 21-day cycle	NA	NA	NA

NA Not applicable.

Docetaxel (75 mg/m^2) was administered intravenously over 1 hour on Day 1 of each 21-day cycle for up to 10 cycles.

Duration of treatment

Patients could continue on blinded ZD4054 10 mg/placebo with or without docetaxel, for as long as they met no withdrawal criteria.

Statistical methods

The primary analysis was to be performed when approximately 508 deaths had occurred. The primary endpoint for this study was overall survival (OS). The log rank test was used as the primary analysis to provide a comparison of treatment groups without adjusting for potential prognostic factors. Results were presented in terms of an estimate of the hazard ratio (HR; ZD4054 10 mg:placebo), associated confidence interval (CI) and p-value. A HR less than 1 indicated that, on average, OS was improved on ZD4054 10mg combination treatment compared to placebo.

To determine if there were any significant treatment-by-covariate interactions, using baseline prognostic covariates, an overall global interaction test was performed at the 10% level of significance for the Cox regression model for OS.

The nominal type I error rate used for this study was 5%. CIs were presented as 2-sided 95% CIs. The secondary endpoints were only to be tested if the primary endpoint (OS) was significant. A multiple-testing procedure to strongly control Type-I error at the overall alpha level was also implemented.

Subject population

In total, 1494 patients were enrolled into this study, 1052 patients were randomised (524 patients to ZD4054 10 mg and 528 patients to placebo) and, of these, 1048 patients received treatment (523 patients received ZD4054 10 mg and 525 patients received placebo).

At the time of data cut-off (26 April 2011), 171 of the 1052 patients randomised were still receiving ZD4054 10 mg/placebo, 286 patients were continuing in the study but off treatment and 595 patients had terminated the study.

Overall, the demographic and baseline characteristics were balanced across the treatment groups and representative of the target population.

Summary of efficacy results

In total, there were 557 (52.9%) deaths at the time of data cut-off (ie, 277 and 280 deaths in the ZD4054 10 mg and placebo groups, respectively). There was no difference in the primary objective of OS for patients in the ZD4054 10 mg group compared with the placebo group (HR 1.00, 95% CI: 0.84 to 1.18, p=0.9634). The median time to death was 20.0 and 19.2 months for the ZD4054 10 mg and placebo groups, respectively.

The result of a global interaction test indicated that there were no statistically significant treatment interactions with any of the baseline covariates (p=0.726).

No effect of ZD4054 10 mg was observed for any of the secondary endpoints.

Summary of safety results

Certain adverse events (AEs) were anticipated during the course of the study, either based on the pharmacological action of ZD4054 or due to docetaxel treatment. Pharmacological effects of ET_A antagonism by ZD4054 are largely the result of vasodilation and include headache, nasal congestion/rhinitis, peripheral oedema, reductions in blood pressure and reductions in haemoglobin; cardiac failure, whilst not a pharmacological effect of ZD4054, is an expected effect. Very common AEs (≥10% of patients) following treatment with docetaxel[1] include alopecia, anaemia, anorexia, asthenia, diarrhoea, dysgeusia, dyspnoea, febrile neutropenia, fluid retention, hypersensitivity, nail disorders, neutropenia, myalgia, nausea, pain, peripheral motor neuropathy, peripheral sensory neuropathy, pneumonia, sepsis, stomatitis and vomiting.

The most commonly reported AEs that occurred more frequently in the ZD4054 10 mg group than in the placebo group were pharmacologically mediated, principally headache, nasal congestion/rhinitis and peripheral oedema. Peripheral oedema is also an expected event with docetaxel. The frequency of peripheral oedema noted in this study (52.7% in the ZD4054 10 mg group versus 35.8% in the placebo group) was higher than that reported in a previous ZD4054 10 mg monotherapy study (44.3% in the ZD4054 10 mg group versus 19.0% in the placebo group). Relatively few of these AEs were assessed as being Common Terminology Criteria (CTC) Grade 3 or higher. However, anaemia and congestive heart failure (CHF) AEs (CHF; grouped term to include cardiac failure and related preferred terms) of CTC Grade 3 or higher were reported more commonly for patients in the ZD4054 10 mg group compared with the placebo group. More patients in the ZD4054 10 mg group developed CHF AEs compared with the placebo group (29 [5.6%] patients versus 9 [1.7%] patients). The cases of cardiac failure reported with ZD4054 10 mg in this study were largely managed by standard heart failure treatments; 2 cases were fatal. There was no evidence in this study to suggest that the addition of docetaxel to ZD4054 10 mg added to cardiac failure risk. The number of AE reports of pneumonia was higher, and the time to onset earlier, for patients receiving ZD4054 10 mg when compared to patients receiving placebo. However, the percentage of AE reports of pneumonia with a CTC Grade ≥3 (including an outcome of death), was similar for patients receiving ZD4054 10 mg and patients receiving placebo.

In total, there were 557 deaths (52.9%), of which the majority (79.5%) were due to prostate cancer; there were no imbalances between treatment groups in non-prostate cancer causes of death. Most patients had at least 1 AE; 96.4% in the ZD4054 10 mg group and 95.4% in the placebo group. AEs of CTC Grade 3 or higher were reported for 60.7% patients in the ZD4054 10 mg group and 60.4% patients in the placebo group. Serious adverse events (SAEs) were reported in 40.4% patients in the ZD4054 10 mg group and 37.3% patients in the placebo group. These included 71 (6.8%) patients who experienced AEs with an outcome of death (ie, 6.9% patients in the ZD4054 10 mg group and 6.7% patients in the placebo group). In total, 87 (16.7%) patients in the ZD4054 10 mg group and 76 (14.5%) patients in the

[1] Based on the docetaxel approved Summary of Product Characteristics.

placebo group discontinued treatment due to AEs. There were no 'other significant adverse events' identified in this study.

Reductions in haemoglobin, platelets and white blood cell parameters were a reflection of the vasodilatory effect of ZD4054 treatment. There were no other meaningful differences in laboratory safety parameter values between the treatment groups, and no clinically significant changes or individual abnormalities that raised any safety concerns.

No increase in mean weight was noted in the ZD4054 10 mg group, despite the higher incidence of peripheral oedema AEs reported in the ZD4054 10 mg group (52.7% versus 35.8%).

Small asymptomatic decreases from baseline in mean systolic blood pressure were observed, with no accompanying increases in pulse rate. As these were evident at Week 1, after the start of dosing and sustained during treatment, this suggests that they are also a consequence of the vasodilatory effect of ZD4054 treatment.

Overall, ZD4054 10 mg in combination with docetaxel was generally well tolerated in this patient population. The ZD4054 10 mg safety data were consistent with the findings of previous clinical studies, and there were no significant new concerns about the safety of ZD4054 10 mg in this patient population.

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