AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	ZD4054
Study Code	D4320C00015
Edition Number	1
Date	20 October 2011

A Phase III, Randomised, Placebo-controlled, Double-blind Study to Assess the Efficacy and Safety of Once-daily Orally Administered ZD4054 10 mg in Non-metastatic Hormone-resistant Prostate Cancer Patients

Study dates:
First patient enrolled: 15 January 2008
Last patient last visit: 3 May 2011
Data cut-off for early analysis: 1 October 2010
Data cut-off for final analysis: 27 June 2011

Phase of development:
Therapeutic confirmatory (III)

International Co-ordinating Investigator:
[redacted]

Sponsor's Responsible Medical Officer:
[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 417 hospital-based centres globally.

Publications

Yu EY, Nathan FE, Higano CS. Detection of metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic castration-resistant prostate cancer (CRPC) [abstract]. J Clin Oncol 2011;29:4655.

Objectives and criteria for evaluation

The purpose of this synopsis is to report the results of the primary objectives of overall survival (OS) and progression-free survival (PFS) based on an early analysis data cut-off date (1 October 2010) and to report the full safety results up to the final data cut-off (27 June 2011). Only the primary objectives of OS and PFS were analysed for this study; the secondary (efficacy) and exploratory objectives will not be discussed.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To determine the effect of ZD4054 on OS compared to placebo	OS defined as time to death (from randomisation) from any cause
To assess the effect of ZD4054 on PFS compared to placebo	PFS defined as the time from randomisation until documentation of progressive metastatic disease Progression defined as any of: • One or more new bone lesions on bone scan[a] (confirmed, if ≤3 lesions, by computer tomography [CT], magnetic resonance imaging [MRI] or x-ray) • Development of malignant visceral disease on CT/MRI • Death in absence of progression N.B. Any local recurrence of disease or loco-regional lymph node involvement was not classified as progression. Prostate cancer involving pelvic lymph nodes below the aortic bifurcation was classified as loco-regional disease. Any enlargement of distant lymph nodes above the aortic bifurcation to >2 cm by visual estimation was considered as progression
Secondary	**Secondary**
To investigate the tolerability and safety profile of ZD4054	Safety and tolerability in terms of incidence and severity of adverse events (AEs), vital signs, laboratory data, electrocardiogram (ECG) and physical examination findings
To investigate the effect of ZD4054 on time to prostate-specific antigen (PSA) progression compared to placebo	Time to PSA progression, defined as the time to the first PSA value ≥50% from baseline, seen in at least two consecutive PSA values
To assess the effects of ZD4054 on Health-Related Quality of Life compared to placebo	Functional well being (FWB) as recorded by the FWB domain of the functional assessment of cancer therapy for prostate cancer (FACT-P) and the total FACT-P score

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
To investigate the effect of ZD4054 on time to symptomatic progression compared to placebo	Time to symptomatic progression, defined as time to pain requiring opiate analgesia due to metastatic disease

[a] In the event that bone scans could not be performed due to a Technetium-99 radioisotope shortage, guidance was provided in the clinical study protocol.

The secondary efficacy and exploratory objectives will not be discussed.

Study design

This was a randomised, double-blind, parallel-group, multi-centre, 2-arm, Phase III study to assess the efficacy and safety of ZD4054 10 mg monotherapy in comparison with placebo in patients with non-metastatic hormone-resistant prostate cancer (HRPC).

Results from an earlier Phase III ZD4054 monotherapy study, in patients with HRPC and bone metastasis, showed a lack of efficacy. This prompted an early analysis being carried out for Study D4320C00015 (data cut-off: 1 October 2010), to determine if it should continue on the basis of efficacy. AZ formulated a continue-stop decision matrix for this study, based on the hazard ratio (HR) for the co-primary objectives of OS and PFS for the early analysis. On reviewing the unblinded data from the early analysis, the Independent Data Monitoring Committee (IDMC) ruled that the criteria for stopping the study were met and Study D4320C00015 was, therefore, terminated early on the grounds of futility. This decision was communicated to all sites by 7 February 2011. All patients were discontinued from study treatment and procedures, and only safety data were subsequently collected up until the final data cut-off (27 June 2011).

Target subject population and sample size

Approximately 1500 patients with non-metastatic HRPC and rising serum prostate-specific antigen (PSA) levels, despite medical or surgical castration, were to be recruited.

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	51224C07, 52641J07, 52642G07, 60623H08, 60662F08, 61727F08, 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, 61025C08, 61023I08, 60603E08, 70932G09

Patients were randomised 1:1 and received either ZD4054 10 mg, or placebo, given orally once daily in tablet form.

Duration of treatment

Patients could continue on randomised study treatment after disease progression unless or until another discontinuation criterion had been met.

Statistical methods

The co-primary endpoints for this study were OS and PFS. To preserve the study significance level at 5%, the significance level was set at 4% for OS and 1% for PFS. A total of 590 deaths were required. If the true HR for ZD4054 10 mg versus placebo was 0.75 then the study would have had 90% power to demonstrate a statistically significant effect in OS at the 4% significance level. With a total of 1500 patients, a recruitment period of approximately 33 months from January 2008 and a median OS for the placebo group of approximately 47 months, it was estimated that 590 deaths would occur approximately 62 months after the first patient entered the study.

An early analysis of OS and PFS was performed to assess whether there was a reasonable chance that this study could meet its co-primary objectives (data cut-off: 1 October 2010). Both OS and PFS were analysed using a log rank test. The number of events at the time of the early analysis was presented together with an estimate of the HR (ZD4054:placebo), 95% confidence interval (CI) and p-value.

Subject population

In total, 2577 patients were enrolled into this study, 1421 patients were randomised (705 patients to the ZD4054 10 mg group and 716 patients to the placebo group) and, of these,

1415 patients received treatment (703 patients in the ZD4054 10 mg group and 712 patients in the placebo group).

At the time of final data cut-off (27 June 2011), all patients had discontinued study treatment and terminated from the study.

Overall, treatment groups were generally well balanced with regard to disposition and were representative of the target population.

Summary of efficacy results

The efficacy results are based on the early analysis (data cut-off: 1 October 2010).

The HR for OS was 1.13 and met the criteria for stopping the study early (HR 1.13, 95% CI 0.73 to 1.76, p=0.5891) and the HR for PFS was ≥0.8 (HR 0.89, 95% CI 0.71 to 1.12, p=0.3296).

As the HR for OS was >1.1 and the HR for PFS was ≥0.8, the IDMC, in accordance with the pre-specified Decision Matrix, ruled that the criteria for stopping the study were met and Study D4320C00015 was, therefore, terminated early on the grounds of futility.

Summary of safety results

The safety results are based on the final data cut-off (27 June 2011).

Certain AEs were anticipated during the course of the study based on the pharmacological action of ZD4054. Pharmacological effects of endothelin A (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 (Hb); cardiac failure, whilst not a pharmacological effect of ZD4054, is an expected effect.

Overall, ZD4054 10 mg monotherapy was generally well tolerated in this patient population. 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 and peripheral oedema. Few of these pharmacologically mediated events were assessed as being Common Terminology Criteria (CTC) Grade 3 or higher, or serious adverse events (SAEs). Overall, the frequency of CTC Grade 3 or higher AEs was similar in both groups (24.5% in the ZD4054 10 mg group versus 21.9% in the placebo group). More patients in the ZD4054 10 mg group had congestive heart failure (CHF) AEs (CHF; grouped term to include cardiac failure and related preferred terms) compared with the placebo group (28 [4.0%] versus 10 [1.4%] patients). CHF events were manageable and reversible in most cases; there were no fatal cases in the ZD4054 10 mg group.

In total, there were 128 deaths (9.0%), of which the majority (69.5%) were due to prostate cancer; there were no imbalances between treatment groups in non-prostate cancer causes of death. Most patients reported at least 1 AE; 86.9% of patients in the ZD4054 10 mg group and 78.7% of patients in the placebo group. AEs of CTC Grade 3 or higher were reported for

24.5% of patients in the ZD4054 10 mg group and 21.9% of patients in the placebo group. Overall, SAEs were reported in 19.8% of patients in the ZD4054 10 mg group and 18.7% of patients in the placebo group. These included 14 (2.0%) patients in each group who experienced AEs with an outcome of death. A higher number of patients in the ZD4054 10 mg group discontinued treatment due to AEs compared with the placebo group (23.0% versus 6.2%). This was largely accounted for by treatment discontinuations due to pharmacologically mediated AEs, principally headache, nasal congestion and peripheral oedema. There were no 'other significant AEs' identified in this study.

Reductions in Hb, platelet count and white cell count in patients receiving ZD4054 10 mg were noted, and these were likely to be a reflection of haemodilution, as a result of the vasodilatory effect of ZD4054. There were no other clinically relevant changes in laboratory safety parameter values between the treatment groups, and no clinically significant changes or individual abnormalities that raised any safety concerns.

No consistent increases in mean weight were noted in the ZD4054 10 mg group, despite the higher incidence of peripheral oedema AEs reported in the ZD4054 10 mg group (37.7% versus 11.9%).

Small asymptomatic decreases from baseline in mean systolic and diastolic blood pressure were observed, with no accompanying increases in pulse rate. As these were evident at Week 4, after the start of dosing and sustained during treatment, this suggests that they are a consequence of the vasodilatory effect of ZD4054 10 mg.

In general, the safety findings from this study were consistent with those seen previously with ZD4054 10mg in this patient population. The safety profile of ZD4054 10 mg is largely a reflection of its vasodilatory effects of ET_A antagonism.

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