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

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To Assess the Efficacy and Safety of Once-daily Orally Administered ZD4054 10 mg in Non-metastatic Hormone-resistant Prostate Cancer Patients compared to placebo.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive and genitourinary neoplasms gender unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON32304

Source
ToetsingOnline

Brief title
D4320C00015 or Enthuse M0

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC
- Genitourinary tract disorders NEC

Synonym
hormone resistent prostate cancer

Research involving

Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Door de opdrachtgever/sponsor AstraZeneca

Intervention

Keyword: Cancer, Hormone-resistant, Non-metastatic, Prostate

Outcome measures

Primary outcome

1. To determine the effect of ZD4054 on overall survival compared to placebo

Overall survival, defined as time to death (from randomisation) from any cause

2. To assess the effect of ZD4054 on progression free survival compared to

placebo

Progression free survival 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 (confirmed, if <=3 lesions, by CT,

MRI or x-ray)

• Development of malignant visceral disease on CT/MRI

• Death in absence of progression

N.B. Local recurrence of disease resulting in urinary retention and

loco-regional node involvement is not classified as progression

Secondary outcome

1. To investigate the tolerability and safety profile of ZD4054

Safety and tolerability in terms of incidence and severity of adverse events, vital signs, laboratory data, electrocardiogram (ECG) and physical examination findings

2. To investigate the effect of ZD4054 on time to prostate-specific antigen (PSA) progression compared to placeboTime to PSA progression, defined as the time to the first PSA value >50% from baseline, seen in at least two consecutive PSA values

3. To assess the effects of ZD4054 on Health-related Quality of Life (HRQOL) compared to placebo
Functional well being (FWB) as recorded by the FWB domain of the FACT-P and the total FACT-P score

4. 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

Exploratory objectives and outcome variables:

1. To assess the effects of ZD4054 on health status compared to placebo
Measured by EQ-5D (EuroQol-5 Dimension)

2. To assess the effects of ZD4054 on the plasma concentration of brain natriuretic peptide (BNP) and explore its utility to predict development of cardiac failure

Plasma concentration of BNP and incidence of cardiac failure

3. To collect serum samples for investigation of exploratory biomarkers

Blood samples may be collected for exploratory biomarker research. Future analysis may aim to determine the effect of study treatments versus placebo on serum biomarkers, their correlation to disease progression / response to therapy or an improved understanding of disease progression

4. To collect prostate cancer tissue (eg, from diagnostic samples and / or on study TURP or biopsies) from consenting patients and store for further investigation

Available tumour specimens may be collected for exploratory biomarker research. Future analysis may aim to determine the effect of biomarkers on clinical outcomes and response to study treatments versus placebo

5. To collect an optional pharmacogenetics sample from consenting patients and store for further investigation

A blood sample may be collected to study polymorphisms in the genes involved in the response to ZD4054

Study description

Background summary

The main purpose of this study is to assess the effect of ZD4054 on progression free survival (PFS) and Overall Survival (OS) compared to placebo (reflecting standard care alone) in men with non-metastatic hormone-resistant prostate cancer. Information about the pre-clinical and clinical studies to date for ZD4054 is covered in detail in the Investigator Brochure (IB). The IB is intended to facilitate the investigator*s understanding of the compound for clinical studies in which the product is administered in tablet form.

1.1.1 Prostate cancer
Even though radiation therapy and radical prostatectomy provide excellent cancer control for men with prostate cancer, prostate-specific antigen (PSA) recurrence develops in up to 35% of patients within 10 years of their primary therapy (Freedland et al 2005, Hanks et al 2002). In a large retrospective study, the median time from biochemical recurrence to metastasis was 8 years and the time from metastasis to death, 5 years (Pound et al 1999). For men who go on to develop metastatic disease, PSA recurrence is clearly the first indication that the cancer has returned, and investigators are currently initiating therapy with rising PSA before metastases are evident. There is no standard therapy for men with a PSA-only recurrence; a number of therapies are presently being evaluated, along with watchful waiting. A major treatment modality used in these men is hormonal therapy consisting of either a luteinising hormone releasing hormone analogue (LHRHa) alone or in combination with an anti-androgen. Despite the ability of hormonal therapy to slow or reverse the PSA rise in these men, in the vast majority PSA does eventually start to rise and the prostate cancer becomes hormone-resistant prostate cancer (HRPC). Due to the large number of men living with prostate cancer today (230,000 new cases/year in the US and 30,000 new cases /year in the UK (Cancer Research UK, American Cancer Society), a large number of men advance into a state of HRPC.

1.1.2 Endothelin and endothelin receptors
Three endothelin isoforms have been characterised (ET-1, ET-2 and ET-3), and 2 receptors (ETA and ETB). ET-1, originally identified as a potent vasoconstrictor, has been implicated in various aspects of tumour progression, including proliferation, apoptosis, angiogenesis (Dawas et al 1999), bone remodelling in metastatic disease (Kozawa et al 2000), and modification of tumour blood flow (Chaplin et al 1998). The predominant actions of ET-1 appear to be mediated via the ETA receptor (Levin 1995). There is also evidence suggesting that the ETA receptor is involved in mediating nociceptive effects associated with ET-1 and in stimulating proliferation and differentiation of osteoblasts. ETA receptor blockade reduces the formation of bone metastases in vivo. There has been particular interest in the role of ET-1 in prostate

cancer (reviewed by Nelson and Carducci 2000). Elevated levels of circulating ET-1 have been found in men with metastatic prostate cancer, as has over-expression of the ETA receptor in prostate cancer cells and down-regulation of the ETB receptor, which is thought to induce cell apoptosis and acts as a clearance mechanism for plasma ET-1 (Fukuroda et al 1994). The ideal profile proposed for an endothelin antagonist for use in the treatment of prostate cancer is a specific ETA receptor antagonist which has no inhibitory activity at the ETB receptor. This should block the cell proliferation and survival signals mediated by ETA receptor, while allowing the beneficial ETB receptor mediated tumour cell apoptosis and ET-1 clearance.

Study objective

To Assess the Efficacy and Safety of Once-daily Orally Administered ZD4054 10 mg in Non-metastatic Hormone-resistant Prostate Cancer Patients compared to placebo.

Study design

This is a randomised, double-blind, parallel-group, multi-centre, 2-arm, Phase III study to assess the efficacy and safety of 10 mg ZD4054 in comparison with placebo, in patients with non-metastatic hormone-resistant prostate cancer. Randomisation will be 1:1, stratified by centre, and patients will be randomised to either ZD4054 or placebo.

Intervention

Patients will be randomised to either ZD4054 or placebo

Study burden and risks

See protocol section 3.2.2 Risk/benefit and ethical assessment

ZD4054 has been studied in a number of clinical studies to date with over 200 patients being exposed to drug in the Phase II setting. The most common adverse effects, principally headache, rhinitis, oedema reflect the pharmacology of the drug and are manageable and considered tolerable rather than significant safety concerns. An increased reporting of cardiac failure was seen compared with placebo in one previous study, this was also reported with another endothelin receptor antagonist, atrasentan. The reported incidence of cardiac failure as a serious adverse event is low at approximately 5%. Investigators and patients will be made aware of safety profile from previous studies and advised on management approaches for adverse effects (see Section 3.10).
The onset of metastatic prostate cancer is associated with deterioration in quality of life, development of symptoms, particularly pain and urinary

problems, and life expectancy is reduced. Given the potential to delay the onset of metastatic disease and ultimately improve survival in men with hormone-resistant prostate cancer, the benefits of studying ZD4054 are considered to outweigh the risks involved. Furthermore, it is considered appropriate to study ZD4054 in comparison with placebo in large scale Phase III studies given that patients under study are not being deprived of any active proven therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of informed consent
2. Male, aged 18 years or older
3. Histological or cytological confirmation of adenocarcinoma of the prostate

4. No evidence of metastatic disease, local recurrence or pelvic lymph node disease on:
* CT scan of chest
* CT scan or MRI of abdomen/pelvis
* Bone scan
5. Biochemical progression of prostate cancer, documented while the patient is castrate. Diagnostic studies will be performed to rule out local recurrence as the cause of the rising PSA if there is suspicion of a prostatic bed/pelvic lymph node:
* Biochemical progression is defined as at least 2 stepwise increases in PSA over a period of >=1 month (values do not need to be consecutive but 2 values that have increased since the previous highest value are required) with at least 14 days between each measurement irrespective of assay or laboratory
* Historical values may be used
* The last PSA must be an increase of >=50 % of the first PSA value of the 3 values or an absolute increase of >=10 ng/mL over the initial PSA
* The final PSA value must be >=1.2 ng/mL in patients who have had a radical prostatectomy and >=5 ng/mL in all other patients
6. Surgically castrated or continuously medically castrated with serum testosterone <=2.4 nmol/L (70 ng/dL), with stable treatment for 8 weeks.
7. World Health Organisation (WHO) performance status 0 - 1
8. Life expectancy of 6 months or more.;For inclusion in the genetic research, patients must fulfil the following criterion:
1. Provision of informed consent for genetic research.

Exclusion criteria

1. Current use (from the time that written informed consent is given) of any opiates, with the exception of opiates taken PRN for non-disease-related symptoms
2. Definitive therapy to treat the patient*s primary prostate cancer (prostatectomy, radiotherapy, cryotherapy) within 3 months prior to study entry
3. Prior cytotoxic chemotherapy (such as paclitaxel, docetaxel and mitoxantrone) for the treatment of recurrent prostate cancer (prior estramustine therapy is allowed), as well as other targeted cancer therapies (such as EGF, EGFR, VEGF and VEGFR)
4. Use of intravenous bisphosphonates within 6 weeks prior to start of study treatment. Oral bisphosphonates for prevention and/or treatment of osteoporosis are permitted. Oral bisphosphonate dose must be stable for a minimum of 4 weeks prior to starting study treatment. Intravenous bisphosphonates are permitted after disease progression, however dose must be stable within trial
5. Use of potent CYP450 inducers (such as phenytoin, rifampicin, carbamazepine and phenobarbitone, St John*s Wort) within 2 weeks prior to start of study treatment. Dexamethasone will be allowed if the investigator feels it is necessary but is encouraged to use a different form of steroid treatment wherever possible
6. Use of systemic retinoids within 2 weeks prior to starting study treatment
7. Have received investigational drug in another clinical study of anticancer therapy, within 4 weeks prior to starting study treatment
8. Prior therapy with endothelin receptor antagonists or family history of hypersensitivity to

endothelin antagonists
9. History of past or current epilepsy, epilepsy syndrome, or other seizure disorder
10. Stage II, III or IV cardiac failure (classified according to New York Heart Association (NYHA) classification) or myocardial infarction within 6 months prior to study entry
11. QT interval corrected for heart rate (by Bazett*s correction) (QTcB) >470 msec
12. Previous history or presence of another malignancy, other than prostate cancer or treated squamous/basal cell carcinoma of the skin, within the last 5 years
13. In the opinion of the investigator, any evidence of severe or uncontrolled systemic disease (eg, currently unstable or uncompensated respiratory, cardiac, hepatic or renal disease) or evidence of any other significant clinical disorder or laboratory finding that makes it undesirable for the patient to participate in the study
14. Haemoglobin (Hb) <9 g/dL. Concomitant use of erythropoietin or blood transfusions is allowed
15. Serum bilirubin greater than 1.5 times the upper limit of normal (ULN). This will not apply to patients with Gilbert*s syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician
16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the ULN
17. Creatinine clearance of <50 mL/minute, determined using the Cockcroft-Gault equation or by 24-hour creatinine clearance
18. Patients who discontinue after randomisation cannot be re-enrolled. Patients who fail to meet the inclusion/exclusion criteria may be reconsidered once for participation in the study. Patients who are re-enrolled must re-consent and will be assigned a new enrolment number
19. Involvement in the planning and conduct of the study (ICON and AstraZeneca staff or staff at the study site). ;The following are regarded as exclusion criteria for genetic research:
1. The patient has undergone a previous bone marrow transplant
2. The patient has undergone a whole blood transfusion in the preceding 90 days.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-12-2007
Enrollment:	129
Type:	Anticipated

Ethics review

Approved WMO Date:	03-01-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-08-2008
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2008
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-07-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-10-2010

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-003224-38-NL
CCMO	NL20291.091.07