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

Published: 18-09-2007
Last updated: 09-05-2024

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

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Genitourinary tract disorders NEC
Study type	Interventional

Summary

ID

NL-OMON31111

Source
ToetsingOnline

Brief title
D4320C00014

Condition

- Genitourinary tract disorders NEC

Synonym
Hormoon-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, Prostate, prostate-cancer

Outcome measures

Primary outcome

To determine the effect of ZD4054 on overall survival, defined as time to death

(from randomisation) from any cause, compared to placebo

Secondary outcome

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

2. To investigate the tolerability and safety profile of ZD4054 compared to

placebo

3. To assess the effect of ZD4054 on time to use of opiates compared to placebo

4. To assess the effect of ZD4054 on the incidence of skeletal related events

compared to placebo

5. To investigate the effects of ZD4054 on bone metastases formation compared

to placebo

6. To assess the effects of ZD4054 on Health Related Quality of Life (HRQOL)

compared to placebo

7. To investigate the effect of ZD4054 on time to prostate-specific antigen

(PSA) progression compared to placebo

8. To assess the effects of ZD4054 on time to pain progression compared to placebo

9. To investigate the effects of ZD4054 on time to initiation of chemotherapy compared to placebo

10. To investigate the pharmacokinetic characteristics of ZD4054

Exploratory objectives:

1. To assess the effects of ZD4054 on health status compared to placebo

2. To explore the relationship between pharmacokinetic and pharmacodynamic measurements

3. 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

4. To collect optional serum samples for investigation of exploratory biomarkers

5. To collect optional prostate cancer tissue (eg, from TURP or biopsies) from consenting patients and store for further investigation

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

Study description

Background summary

ZD4054, a specific endothelin receptor-A (ETA) antagonist, is currently being developed as a potential treatment for hormone-resistant prostate cancer.

Prostate cancer is a leading cause of cancer death worldwide. Bone metastases will develop in the majority of men with advanced prostate cancer and are a major cause for the morbidity associated with advanced prostate cancer. Initial treatment of advanced disease is via suppression of testicular androgen production, either
alone or in combination with an anti-androgen but nearly all men with metastases will eventually experience disease progression despite this treatment. Patients with hormone-resistant prostate cancer have a poor prognosis.

Although docetaxel is widely approved to manage this population of patients, it must be noted that this is a chemotherapy regime with its attendant toxicity issues. Furthermore, there remains controversy over the appropriate time to initiate docetaxel.
AZ4054 has the potential to improve survival in men with metastatic prostate cancer without the toxicity associated with chemotherapy

Study objective

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

Study design

Phase III

Randomised (1:1), double-blind
2 treatment grouos:
Group A: AZ4054 10mg
Group B: placebo

Intervention

Patients will receive ZD4054 10mg or placebo

Study burden and risks

Burden for the patient:

Blood sampling: 14x
ECG: 4x
CT or MRI scan: 2x
Bone scan: 2x
Abovementioned data presume a patient whom receives study medication during 12 months and has a 18 months follow up period

Risks of the research medication:
In earlier research, the most frequently reported side effects were headache, rhinitis (blocked nose, which can be caused by allergies or other factors), nausea, vomiting and oedema (swelling of the body).

Side effects which are less likely to occur while the research medication is being taken are arthralgia (pain in your joints), dyspnoea (shortness of breath), myalgia (muscle pain), skin rash and erythemia (redness of the skin due to the accumulation of blood in the blood vessels. In earlier research, when compared with the placebo, there were occurrences of back pain, a slight increase in the diastolic blood pressure (at rest) and an increased risk of heart failure.

In a small number of cases deviations in the blood picture were recorded, such as an increase in transaminases (indicators of liver function), anaemia (lower number of red blood cells) and less haemoglobin (a protein in red blood cells which carries oxygen).

The research medication which is being used for this research may entail other risks which are unknown at the present time.

Other risks
When blood samples are being taken, the subject may have the following side effects: a feeling of weakness, inflammation of the vein, pain, blue spots or bruises at the location of the puncture. There is also a slight risk of infection.

After the ECG (electrocardiogram) there may be irritation of the skin at the place where the electrodes were applied.

A CT scan is a generally used diagnostic standard procedure. During this test, one is exposed to a small quantity of radiation. Although all the radiation one receives during your lifetime accumulates, small doses do not represent a significant health risk.

An MRI scan is a generally used standard procedure. There are no known dangers or side effects of an MRI scan. Since during the scan patients must lie in a large cylinder, some people can however experience a feeling of claustrophobia (phobia of small or enclosed spaces).

The bone scan is a generally used diagnostic procedure to track down metastases in the skeleton. The amount of radioactivity from the radionuclide substance injected is not enough to constitute a significant risk to your health.

Contacts

Public
Astra Zeneca

Forskargatan 18
Sodertalje SE-15185
SE
Scientific
Astra Zeneca

Forskargatan 18
Sodertalje SE-15185
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:
1. Provision of informed consent
2. Male, aged 18 years or older
3. Histological or cytological confirmation of adenocarcinoma of the prostate
4. Documented evidence of bone metastasis on radionuclide bone scan. Patients must have 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 will require a CT scan, MRI or x-ray to confirm
5. Biochemical progression of prostate cancer, documented while the patient is castrate:
- 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. Asymptomatic or mild pain from prostate cancer, defined as a score of <=2 in the worst pain item of the BPI
7. Surgically castrated or continuously medically castrated with serum testosterone <=2.4 nmol/L (70 ng/dL)
8. World Health Organisation (WHO) performance status 0 - 1
9. Life expectancy of 6 months or more.;For inclusion in the genetic component of the study, patients must fulfil the following criterion:
1. Provision of informed consent for genetic research.

Exclusion criteria

1. Radiotherapy to bone lesion or prostatic bed within 4 weeks of starting study treatment
2. Current use (from the time that written informed consent is given) of any opiates, with the exception of opiates taken PRN for pain not directly related to prostate cancer
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. Systemic radionuclide therapy (ie, strontium chloride Sr89, 186Relabeled HEDP, or 153Sm-EDTMP pentasodium) within 12 weeks of starting study treatment
5. Use of potent CYP450 inducers (such as phenytoin, rifampicin, carbamazepine, phenobarbitone and St John*s Wort) within 2 weeks of starting 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 of starting study treatment
7. Have received investigational drug in another clinical study of anticancer therapy, within 4 weeks of starting study treatment
8. Prior therapy with endothelin receptor antagonists or family history of hypersensitivity to endothelin antagonists
9. Neurological symptoms or signs consistent with acute or evolving spinal cord compression. If a patient has neurologic symptoms, an MRI must be performed that demonstrates no impending or actual spinal cord compression. Stable, previously treated patients are allowed
10. Symptomatic peripheral neuropathy of CTCAE grade 2 or higher
11. Known or suspected central nervous system metastases
12. History of past or current epilepsy, epilepsy syndrome, or other seizure disorder
13. 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
14. QT interval corrected for heart rate eg, by Bazett*s correction >470 msec
15. 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

16. 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
17. Hemoglobin (Hb) <9 g/dL. Concomitant use of erythropoietin or blood transfusions is allowed
18. Serum bilirubin >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 haemolysis or hepatic pathology), who will be allowed in consultation with their physician
19. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the ULN or 5 times the ULN in the presence of liver metastasis
20. Creatinine clearance of <50 mL/minute, determined using the Cockcroft-Gault equation or by 24-hour creatinine clearance
21. 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 be re-consented and will be assigned a new enrolment number
22. Involvement in the planning and conduct of the study (applies to ICON and AstraZeneca staff or staff at the study site).;The following is regarded as an exclusion criterion 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):	01-10-2007

Enrollment:	40
Type:	Anticipated

Ethics review

Approved WMO Date:	18-09-2007
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-10-2007
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-12-2007
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2008
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:	25-03-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2010
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)

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	EUCTR2007-003227-20-NL
CCMO	NL19123.091.07