

TYPE OF CANCER: Non-Metastatic Hormone-Resistant Prostate Cancer
TYPE OF TRIAL: Phase III
TRIAL SPONSOR: Astra Zeneca

PRINCIPAL INVESTIGATOR: Nicholas Vogelzang, M.D.
CONTACT PERSON: Jacky Osorno
(702) 822-5393

STUDY SUMMARY

A Phase III, Randomized, 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.

TREATMENT OVERVIEW

- Patients will be randomized to receive either ZD4054 or Placebo 10 mg orally daily
- On treatment assessments will be performed every 4 weeks for the first 16 weeks of treatment, and then every 16 weeks for up to 5 years
- After disease progression, survival status will be assessed every 6 months

PRE-TREATMENT ASSESSMENTS

- Informed consent
- Medical and surgical history
- Physical exam
- Vital signs
- ECG
- Clinical chemistry
- Hematology
- Urinalysis
- Bone scintigraphy
- Tumor Assessment (by CT/MRI)
- Patient questionnaires
- Biomarker plasma sample (optional)

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

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 Organization (WHO) performance status 0 – 1
 8. Life expectancy of 6 months or more.

For inclusion in the genetic research, patients must fulfill the following criterion:

1. Provision of informed consent for genetic research.

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent to participate.

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) (QT_{cb}) >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. Hemoglobin (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 randomization 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.