A Phase II Study of PHA-739358 in Patients with Metastatic Hormone Refractory Prostate Cancer.

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1) To assess the antitumor activity of PHA-739358 administered as IV infusion according to two different dose schedules in metastatic HRPC patients progressing on standard docetaxel-based chemotherapy.2) To have a precise idea of the antitumor…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Prostatic disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON31740

Source
ToetsingOnline

Brief title
AURA-6202-007

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
HRPC/ hormone refractory prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Nerviano Medical Sciences Srl, Italy
Source(s) of monetary or material Support: Nerviano MS

Intervention

Keyword: hormone refractory, PHA-739358, prostate cancer

Outcome measures

Primary outcome

PSA response rate within the first three months of treatment, defined as proportion of patient achieving at least a 50% PSA decline from baseline confirmed by a second PSA value, 4 or more weeks later.

Secondary outcome

Secondary:

* Duration of PSA response: defined as time from date of first 25% PSA decline from baseline to the date of first PSA rise by 50% above the nadir, provided that the increase is of at least 2 ng/ml or back to the baseline.

* 30% PSA reduction: defined as proportion of patient achieving at least a 30% PSA decline from baseline confirmed by a second PSA value, 4 or more weeks later.

* PSA velocity: i.e. rate of change in PSA levels during the first 3 months of treatment.

* Progression Free Survival (PFS): defined as the time from the date of randomization to the date of first documentation of progression, or of death due to any cause, whichever comes first. Progression of disease will be defined as described in the full protocol.

* Objective tumor response rate: proportion of patients with measurable disease at baseline achieving partial or complete overall best response according to RECIST criteria.

* Clinical benefit rate: proportion of patients with pain score >= 2 on a 10-point pain intensity scale and/or analgesic score >= 1 on a 5-point analgesic scale at baseline achieving a clinical benefit defined as:

• a >= 2-point decrease of pain score during treatment accompanied by stable or reduced analgesic score as compared to baseline, lasting at least 2 weeks

or

• a >= 1-point decrease of analgesic score accompanied by stable/ reduced pain score as compared to baseline, lasting at least 2 weeks

and

• performance status score unchanged or decreased versus baseline.

* Overall Safety profile: characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 3.0), timing and relationship to study therapy of adverse events and laboratory abnormalities. Dose delays/reductions will be used as an additional parameter to evaluate schedule tolerability.

Study description

Background summary

PHA-739358 is a small ATP competitive molecule that selectively inhibits Aurora A, B and C kinases, a family of proteins that regulate different steps in the mitotic and meiotic processes, and that are overexpressed in several cancers, including prostate cancer. PHA-739358 antitumor activity has been shown in several in vitro and in vivo studies where tumor growth inhibition, regressions and cures were observed. In the murine transgenic prostate carcinoma TRAMP model, tumor regression >80% was seen in 3 out of 16 animals and disease stabilizations in 10 out of 16 animals treated with PHA-739358.
Thus far, 6 clinical studies with PHA-739358 have been activated including two phase I dose escalation studies in solid tumors testing two different treatment

schedules (6-h IV infusion on days 1, 8, and 15 every 4 weeks and 24-h IV infusion on day 1 every 2 weeks), two phase I dose escalation studies in hematological malignancies, one pilot phase II study in CML and one phase II study in various solid tumors that has just started.
Clinical experience with PHA-739358 is too limited to draw any conclusion as regards its potential in HRPC (4 heavily pretreated patients enrolled in phase I , one showing a partial PSA decline (39%) and 4-month disease stabilization). However, available data on overexpression of the PHA-739358 target in prostate cancer samples, the tumor regressions/stabilizations observed with PHA-739358 in the TRAMP model in vivo, together with the predictable, manageable and reversible toxicities observed thus far in patients with solid tumors, support proceeding with clinical investigations of this new agent in HRPC patients progressing during or after standard, taxotere-based, 1st-line chemotherapy for which no standard therapy is available.

Study objective

1) To assess the antitumor activity of PHA-739358 administered as IV infusion according to two different dose schedules in metastatic HRPC patients progressing on standard docetaxel-based chemotherapy.
2) To have a precise idea of the antitumor activity of PHA-739358 in the selected patient population (patients are stratified based on PSA response to previous docetaxel based therapy), a control group has been inserted in step 2: mitoxantrone plus prednisone or an approved 2nd-line treatment if any agent is registered for this indication before the 2nd step of the study is activated.

Study design

This will be a Phase II, multi-center open-label, randomized study of PHA-739358 in approximately 118 adult patients with metastatic HRPC progressing on/after standard, docetaxel-based, 1st-line chemotherapy for HRPC. Randomization will be stratified according to PSA response to prior docetaxel-based therapy (50% decrease or more versus less than 25%). The study will consist of two steps:
• In the first step of the study 58 patients will be randomized to one of two PHA-739358 dose schedules in a 1:1 ratio, i.e. 330 mg/m2 administered as 6-h IV Infusion on Days 1, 8, and 15 of a 28-day cycle (Arm A) or 500 mg/m2 administered as 24-h IV infusion on Days 1 and 15 of a 28-day cycle (Arm B). The dose intensity for the two schedules tested is equivalent: 990 and 1000 mg/m2/28-day cycle for arm A and B, respectively. For each PHA-739358 treatment schedule a two-step Simon*s Mini Max design will be used, allowing early termination at the first step in case of inactivity of one or both schedules. At completion of the first step, the best PHA-739358 schedule will be selected for proceeding to the 2nd step based on the observation of the number of PSA responses required to proceed (at least 3 out of 29 patients per arm) and

taking into consideration treatment effect on other efficacy and safety secondary end-points points.
• Assuming at least one of the two PHA-739358 dose schedules meets the requirements for proceeding to the 2nd-step of the study, a second randomization will take place where 54 patients will be randomized in a 1:1 ratio to the PHA-739358 selected schedule or a control treatment (mitoxantrone plus prednisone). The inclusion of a control group in this second step of the study is aimed at keeping under control potential biases in the selection of study population that may affect the observed outcome. In the theoretical situation that before the start of the second part of the study another second line treatment becomes available (following registration and if available) the study design will be adapted and an amendment will be submitted to the Ethics Committee.

Intervention

PHA-739358 will be dosed based on the patient's body surface area. De dose in arm A is 330 mg/m2 administered on day 1, 8 and 15 (6 hours infusion) or in arm B 500mg/m2 administered on day 1 and day 15 (24 hours infusion) in a 28-day cycle. In the absence of hematloogical toxicity greater then Grade 1 (exclusing nause, vomiting and) in cycle 1 the dose may be increased to 400mg/m2 in arm A and to 580mg/m2 in arm B.

Study burden and risks

Patients will undergo a full medical examination including a X-ray of the thorax. An electrocardiogram (ECG) and a scan (MUGA) to monitor the hartfunction will be done. Also CT or MRI imaging is done to measure the tumor size. This will be repeated every two cycles. Also a bonescan will be made to measure the extension (bone metastasis) of the disease. This will be repeted every 12 weeks. Furthermore blood samples will be taken for laboratory analysis. In all patients frequent blood samples will be drawn (at least 2 times per 28 weeks). There is a risk for pain or bruising at the location of blood sampling. Cardiac function will be monitored at regualar intevals with MUGA scan.

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. Adult (age >= 18 years) male patients.
2. Histologically confirmed diagnosis of adenocarcinoma of the prostate.
3. Metastatic (stage D3 according to Jewett Staging System).
4. Hormone-refractory disease, progressing after 1st-line docetaxel-based chemotherapy. For patients with measurable disease, progression will be defined by RECIST criteria. For patients without any measurable disease, appearance of new bone lesions at bone scan and PSA progression, according to recommendations from the Prostate-Specific Antigen Working Group, will be required.
5. Patients receiving corticosteroids requested for concomitant disease other than HRPC should continue treatment at the same dose.
6. Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks prior to enrollment.
7. Patients who have not undergone surgical castration must continue on primary androgen deprivation with LHRH analogue, if any, and testosterone must be < 50 ng/dL.
8. Prior radiotherapy is allowed provided that no more than 25% of bone marrow reserve has been irradiated and a minimum of 4 weeks have elapsed between the end of prior radiotherapy and the entry into the trial.
9. ECOG performance status 0-2.
10. Life expectancy of at least 3 months.
11. Resolution of all acute toxic effects (excluding alopecia) of any prior surgery, radiotherapy, radio-surgery or chemotherapy to NCI CTC (Version 3.0) Grade >= 1.
12. Required baseline laboratory data include:

Absolute Neutrophils Count (ANC) >= 1.500/mm3 (>= 1,5 x 109/L)
Platelets >= 100.000/mm3 (>= 100 x 109/L)
Hemoglobin >= 10,0 g/dL
Serum Creatinine <=1,5 mg/dL (<=133 *mol/L)
Serum Albumin >= 3,0 g/dL
Total Serum Bilirubin <= 1,5 x ULN
Liver Transaminases (AST/ALT) <= 2,5 x ULN; <= 5 x ULN if livermetastasis are present
Alkalische fosfatase (ALP) <= 2,5 x ULN; <= 5 x ULN if bonemetastasis are present
AST/ALT = aspartate aminotransferase/alanine aminotransferase, ULN = upper normal limit
13. Signed and dated informed consent indicating that the patient is aware of the neoplastic nature of his disease and has been informed of the procedures to be followed, the experimental nature of the therapy, potential benefits, side effects, discomforts, risks, and alternative treatments.
14. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study indications or procedures.

Exclusion criteria

1. Current enrollment in another therapeutic clinical trial.
2. Use of other investigational drugs (drugs not marketed for any indication) within 30 days prior to treatment.
3. More than one prior chemotherapy line.
4. Known brain or leptomeningeal disease (baseline computerized tomography [CT] or Magnetic Resonance Imaging [MRI] scan of the brain required only in case of clinical suspicion of central nervous system metastases.
5. Other prior malignancy, except for adequately treated basal or squamous cell skin cancer or superficial bladder cancer, or any other cancer from which the patient has been disease-free for 5 years or greater.
6. Prior treatment with radiopharmaceuticals (e.g. Strontium-89, Samarium-153) within 8 weeks prior to enrollment.
7. Major surgery, within 4 weeks or not fully recovered prior to Day 1.
8. Patients must agree to have no intention to father a child during the study and in the following 3 months after the end of the treatment.
9. Uncontrolled hypertension with blood pressure exceeding 160/100 mmHg (Stage 2 hypertension according to the JNC 7/ NIH USA 2003 guideline).
10. Any of the following in the past 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis.
11. Cardiac dysrhythmias Grade >= 2 according to NCI CTCAE version 3.0.
12. Known active infections, including HIV positivity.
13. History of allergic reactions to a similar structural compound, biological agent, or formulation.
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or

may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-02-2008
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	geen
Generic name:	geen

Ethics review

Approved WMO

Date:	11-12-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	11-01-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-06-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2006-006136-21-NL
CCMO	NL19674.078.07