Everolimus (RAD001, Afinitor®) and Cyclophosphamide in Castration and Docetaxel resistant Prostate Cancer, a proof of principle Phase II study.

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Ethical review	Not approved
Status	Will not start
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON35076

Source
ToetsingOnline

Brief title
Metronomic treatment of castration resistant prostate cancer

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Cancer of the prostate, prostatic neoplasm.

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut

Source(s) of monetary or material Support: instituut zelf

Intervention

Keyword: castration resistance, cyclophosphamide, Evrolimus, metronomic therapy, mTOR inhibition, Prostate cancer, signal transduction

Outcome measures

Primary outcome

In order to investigate the mTOR inhibition in the prostate by Everolimus and

the possible synergistic interaction with low dose, metronomic, oral

Cyclophosphamide treatment, phophorylation of 4eBP1 and p70S6K will be assessed

in prostate biopsies of prostate cancer patients.

Secondary outcome

PSA response

Toxicity of the combined Everolimus and Cyclophosphamide treatment

Study description

Background summary

progress has been made in the last decades in the treatment of other prevalent solid tumors, such as breast and colorectal cancer. New treatment modalities and new drug regimens have been developed which resulted in increased median survival and better quality of life of patients affected by these diseases. However, the prognosis of patients with prostate cancer, which is irresponsive to castration, is very poor and has not changed in recent years. There is an urgent need for new treatment modalities that will improve the quality of life and life span of prostate cancer patients.

Study objective

The primary objective is to study whether treatment with the mTOR inhibitor Everolimus results in an objectable change in phosphorylation of the selected downstream effectors 4eBP1 and p70S6K in human prostate cancer biopsies.

A secondary objective is to study tolerability and PSA response of the combination of continuous low-dose cyclophosphamide and Everolimus.

Study design

This is a phase II study.
Patients with a rising PSA under castrate serum testosterone levels and previously treated with Docetaxel might be eligible for this study. Baseline investigations will include prostate biopsies and blood analysis, physical examination, recording of medical history, concomitant drug use and ECOG performance status (Appendix 2). After 2 weeks of lead-in Everolimus treatment, prostate biopsies and blood analysis and physical examination will be performed and toxicity score, concomitant drug use and ECOG performance status will be recorded. Everolimus treatment will be combined with cyclophosphamide once daily 50 mg from week 3 on. Patients will visit their physician every 2 weeks during the first 8 weeks of treatment followed by every 4 weeks, for history taking, physical examination (including ECOG performance status), laboratory tests and recording of toxicity. In order to monitor for, subclinical, non-infectious pneumonitis, a Chest X-ray will be made every 8 weeks during treatment. Patients will continue this treatment until PSA progression, disease progression or > grade 3 toxicity.

Intervention

Everolimus treatment will be prescribed at two dose levels. The first ten included patients will be treated at a dose of 5 mg once daily. In case of * 20 % Grade 3 toxicity after 6 weeks of treatment (2 weeks Everolimus single agent and 4 weeks combined Everolimus and cyclophosphamide treatment), the Everolimus dose will be increased to 10 mg per day for the next 10 patients.
Besides, prostate biopties will be taken prior- and after four weeks of Everolimus alone treatment.

Study burden and risks

Patients wil visit their physician every two weeks during the fisrst eight weeks and every four weeks thereafter. There will be more laboratort tests then there would be outside this study. There is a significant chance that patients will experience side effects of the treatment. In a pilot studie to combination of Everolimus and Cyclophosphamide lymphopenia, neutropenia, thrombopenia, anaemia and fatiue were most frequently described. Besides, prostate biopties will be taken prior- and after four weeks of Everolimus alone treatment. Some patients describe taking prostate biopsies as painfull. Possible risks include bleeding or infection of the prostate.
Benefit for the patient might be a palliative effect of the treatment or complaints might be postponed.

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

- Prostate cancer diagnosis and a rising PSA under castrate serum testosterone levels (2 rises in a period of at least 3 months), PSA > 10ng/ml.
- At least one prior cycle of Docetaxel treatment.
- ECOG performance status 0-2.
- Locally accessible prostate cancer for TRUS-guided biopsies.
- Written informed consent.
- Laboratory requirements:
a) Hematology:
* Hemoglobin > 5 mmol/L
* Platelet count * 100,000/*L
* No leucopenia
b) Hepatic function:

* AST and ALT * 2.5 times upper limit of normal (ULN)
* Bilirubin * 1.5 times ULN
c) Renal function:
* Calculated GFR (Cockroft) * 60 ml/min
* PT/PTT normal (no anticoagulants)
- Fertile patients must use effective contraception during and for 6 months after completion of
study therapy.

Exclusion criteria

- Small cell pathology.
- Allergy to Everolimus or cyclophosphamide or components of Afinitor ® or Endoxan ®.
- Co-medication interfering with CYP3A4 activity.
- Gastrointestinal (GI) disease, condition, or symptoms that may significantly impair GI function
and alter the absorption of Everolimus, including any of the following:
o Ulcerative disease
o Vomiting
o Diarrhea
o Malabsorption syndrome
- Other active malignancy or malignancy at * 30% risk for relapse after completion of therapy,
except nonmelanoma skin cancer .
- Recent (within 2 weeks) surgery.
- Uncontrolled concurrent illness including, but not limited to, any of the following:
o Ongoing or active infection (e.g., bacterial, viral or fungal)
o Severely impaired lung function
o Uncontrolled diabetes (fasting serum glucose > 1.5 times ULN)
o Liver disease (e.g., cirrhosis, chronic active hepatitis, or chronic persistent hepatitis)
o Symptomatic congestive heart failure
o Unstable angina pectoris
o Cardiac arrhythmia
- Lower urinary tract obstruction not treated with bladder catheterisation.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Cyclophosphamide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Everolimus (RAD001, Afinitor®)
Generic name:	Everolimus (RAD001, Afinitor®)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	29-10-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Not approved

Date:	10-12-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2010-018772-24-NL
CCMO	NL31523.031.10