Phase I study of nelfinavir in combination with temsirolimus in the treatment of patients with advanced cancers, including second line renal cell cancer

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Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON33441

Source
ToetsingOnline

Brief title
I-NET

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, metastatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Wyeth,Wyeth Pharmaceuticals BV;Spicalaan 31;2132 JG Hoofddorp

Intervention

Keyword: malignancy, nelfinavir, pharmacokinetics, temsirolimus

Outcome measures

Primary outcome

- pharmacokinetics (steady state concentration) and toxicity/feasibility of

the combination of temsirolimus and nelfinavir

Secondary outcome

- tumor response

- duration of response

- time to progression

- toxicity profile

- level of PI3K /Akt/mTOR cascade activation in white blood cells

- gene profile of drug elimination gene polymorphism of the patients and its

association with the pharmacokinetic profile

Study description

Background summary

In the past decade, the characterization of human tumours at the molecular level has considerably improved. This has led to the development of targeted therapeutics that inhibit specific molecules and pathways involved in oncogenesis. One of the key pathways that is dysregulated in cancer is the phosphatidylinositol 3*-kinase (PI3K)/Akt/mTOR pathway. This pathway is important for cell growth and survival. In most cancer types this pathway is

over-activated leading to proliferation and survival of malignant cells.
Inhibition of this pathway is therefore of great therapeutic potential.
Both temsirolimus and nelfinavir are agents with PI3K /Akt/mTOR inhibiting activity. The main active metabolite of temsirolimus is sirolimus that decreases mTOR activity. Inhibition of mTOR activity results in G1 phase cell cycle arrest and subsequent inhibition of tumour growth. An other effect is growth factor downregulation and inhibition of angiogenesis. In addition, mTOR inhibition may exert its anti-tumour effect by inducing apoptosis.
Although inhibitors of mTOR demonstrated clinical activity in tumor types like, mantle cell lymphoma, endometrial carcinoma, and neuro-endocrine tumors, most malignancies are resistant by feedback PI3 kinase activation. Resent data suggest that this tumor escape mechanism can be overcome by dual inhibition of mTOR and PI3 kinase.
Nelfinavir is a well known human immuno-deficiency protease inhibitor with PI3kinase inhibiting activity, via inhibition of Akt, downstream the PI3kinase cascade. Nelfinavir is able to inhibit Akt at concentrations that are achieved in HIV patients at standard antiviral doses. Nelfinavir is therefore a feasible and generally well tolerated agent to be used in combination with temsirolimus to overcome resistance of mTOR inhibition.
Simultaneous inhibition of mTOR/PI3kinase pathway by temsirolimus and nelfinavir is a promising strategy to treat cancer.

Study objective

- The primary objective is to determine the dose limiting toxicity and the maximum tolerated dose and recommended dose of the combination of temsirolimus weekly and nelfinavir orally BID to patients with advanced solid tumors.
- Secondary objective is to establish the effect of functional genetic polymorphisms of drug metabolizing genes on the pharmacokinetics and pharmacodynamics of temsirolimus and nelfinavir (pharmacogenetics).
- to establish the time to disease progression, toxicity profile
- To establish the relationship between pharmacokinetics, antitumor effect and biomarker investigations of the treatment with temsirolimus and nelfinavir

Study design

This is a phase 1 non-randomized, single center trial.
The study is designed to define the maximum tolerated dose by dose escalation of temsirolimus and nelfinavir. There will be dose escalation of temsirolimus and nelfinavir.

Design (treatment schedule)
Day 1: patients will be treated with nelfinavir BID, orally. Blood samples will be drawn for pharmacokinetics.
Day 4: patients will be treated with temsirolimus intravenously. Blood samples will be drawn for pharmacokinetics.

Day 11: patients will be treated with combination of BID nelfinavir orally and weekly temsirolimus intravenously.
Dose escalation will take place between cohorts in case the prior cohorts tolerates the treatment well as defined in the protocol.

Intervention

Treatment with BID nelfinavir orally
Treatment with weekly temsirolimus intravenously
Blood sampling

Study burden and risks

The burden for the patient may be the experience of side effects of the study medication: nausea, vomiting, diarrhea, fatigue, anorexia, bone marrow suppression, pneumonitis, dyslipidemia, skin reactions, increase in liver enzymes. Patients will be checked regularly for development of these side effects. Both temsirolimus and nelfinavir are known agents with an acceptable toxicity profile.
Other burden for the patient will be the admission at the hospital for blood samples and other investigations. To reduce the total time of admission the investigations will be planned in a way that reduces the burden to a minimum. Hospital admission will take place twice for the pharmacokinetic blood sampling of a duration of 24 hours. In case the patient prefers to come to the hospital twice within 24 hours then an overnight admission would not be necessary. Other outpatient visits will take place following standard of care. Temsirolimus treatment will take place on a weekly bases following standard procedures.
The benefit for the participant of this trial is the option to be treated for a disease (advanced/metastatic malignancies) for which there is no standard systemic anticancer treatment available.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ
Nederland
Scientific
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ

Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients with histological or cytological confirmed malignancies
· ECOG / WHO performance status of 0-2
· Age 18 years
· Life expectancy of at least 3 months
· Minimal acceptable safety laboratory values defined as
· WBC 3.0 x 109 /L
· Platelet count 100 x 109 /L
· Hepatic function as defined by serum bilirubin 1.5 x ULN, ALT or AST 2.5 x ULN, in case of liver metastases 5 x ULN
· Renal function as defined by creatinine < 150*mol/L
· Able and willing to give written informed consent according to ICH/GCP, and national/local regulations.
· Able to swallow and retain oral medication
· Able and willing to undergo blood sampling for pharmacokinetic and pharmacogenetic analysis
· Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Exclusion criteria

- Patients with known alcoholism, drug addiction and/or psychotic disorders in the history that are not suitable for adequate follow up
· Women who are pregnant or breast feeding
· Women of childbearing potential who refuse to use a reliable contraceptive method

throughout the study
· Serious concomitant systemic disorder that would compromise the safety of the patient, at the discretion of the investigator
· Any other medical condition that would interfere with study procedures and/or decrease safety of the protocol treatment
· Concomitant use of strong CYP3A4 inhibitors, CYP3A4 inducers or CYP substrates (see section 1)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2009
Enrollment:	21
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Nelfinavir mesylate
Generic name:	Viracept
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Temsirolimus
Generic name:	Torisel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-04-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2008-007774-38-NL
CCMO	NL26658.018.09