Prediction of response to kinase inhibitors based on protein phosphorylation profiles in tumor tissue from advanced renal cell cancer patients

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To determine the relation between tumor tissue phosphoproteomic profiles and progression-free survival (PFS) in patients with advanced RCC

Ethical review   Approved WMO
Status   Completed
Health condition type   Renal and urinary tract neoplasms malignant and unspecified
Study type   Observational invasive

Summary

ID

NL-OMON37502

Source
ToetsingOnline

Brief title
Phosphoproteomics for prediction of response to treatment in kidney cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
kidney cancer, Renal cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Divisie I Beheer BV,VitrOmics Health

Services BV (VHS)

Intervention

Keyword: kinase inhibitors, phosphoproteomics, renal cell cancer, response prediction

Outcome measures

Primary outcome

Pretreatment tumor tissue phosphoproteomic profile, radiological response to

standard treatment, PFS.

Phosphoproteomic profiles will be determined from the tumor biopsy and

correlated to radiological response and PFS. Phosphotyrosine signaling pathways

aberrantly activated in individual subgroups, identified by unsupervised

hierarchical clustering, will be examined in relation to the clinical effect of

the different kinase inhibitors. The classifier will be based on activity of

one or multiple signaling pathways and protein networks and will be subjected

to an internal validation such as the ten-fold cross validation technique to

estimate its generalization performance.

Primary endpoint: Prediction accuracy of the phosphoproteomic classifier

Secondary outcome

-To determine the relation between pre-treatment PamChip kinase activity

profiling and PFS

-To determine whether genome-wide mutational profiles by Massively Parallel

Sequencing (MPS) can be related to PFS

-To determine whether both pre- and on-treatment serum proteomic profiles are

related to PFS

-To determine the value of the frequency and phenotype of immunoregulatory
cells in blood and tumor tissue for treatment response prediction.

-To determine the relation between genetic polymorphisms and pharmacokinetic
parameters (systemic and intratumoral drug concentrations) and PFS.

-To determine the value of tumor exosomes from urine and serum as potential
source of biomarkers.

Study description

Background summary

The rapid development of agents blocking kinases has established the use of
molecularly targeted therapy as the preferred treatment approach for patients
with metastatic renal cell cancer (RCC). Five kinase inhibitors (sunitinib,
everolimus, temsirolimus, sorafenib and pazopanib) are now approved for
clinical use. Response rates differ among these agents, importantly depending
on line of treatment. In first-line treatment sunitinib results in 47%
objective response rates, where in second-line after cytokines 34% responds.
Thus far, it is unclear which patient with advanced renal cell cancer will
respond to targeted therapy. In order to select patients for targeted
therapies, several profiling approaches have been explored but to date no
adequate and reliable test is available. It is assumed that responses to
targeted agents depend on specific receptor and protein signalling activities
in tumor tissues. Therefore, we propose that protein phosphorylation profiling
with phosphoproteomics may be a potential clinical diagnostic tool to predict
for tumor response to targeted therapy. This approach is expected to increase
efficacy, reduce costs and prevent toxicities from (ineffective) targeted
agents.

Study objective

To determine the relation between tumor tissue phosphoproteomic profiles and
progression-free survival (PFS) in patients with advanced RCC

Study design

Multicentered, observational study with non-therapeutic intervention prior to

standard treatment. The study consists of a training-phase and independent validation-phase. This protocol only covers the training phase, where a predictive classifier will be build. A feasibility analysis will be performed when 20 patients are included.

Study burden and risks

In this study, a fresh tumor biopsy from a metastasis or a primary tumor will be taken. In all subjects subsequent standard treatment will be initiated according to current clinical guidelines. In addition to this biopsy, collection of urine and blood is performed upon inclusion and the same procedure is optional on 2 other time points during treatment.

The tumor biopsy may cause physical discomfort and adverse events. Follow-up may include additional blood drawings before and during treatment which will be combined with laboratory analysis needed for routine outpatient clinic visits. Results of this study will be used for personalized treatment selection strategies that may increase response rates to standard therapy and prevent toxicity of ineffective therapy in renal cell carcinoma patients.

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

• Patients with advanced (unresectable and/or metastatic) renal cell cancer;
• Patients who will start treatment with sunitinib, pazopanib, sorafenib, axitinib or everolimus;
• At least one tumor lesion should be accessible for biopsy. Bone metastases are excluded as possible biopsy site;
• Age >- 18 years;
• Patients must have at least one measurable lesion. Lesions must be evaluated by CT-scan or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST);
• WHO performance status 0 - 2;
• Able to provide written informed consent;

Exclusion criteria

• Clinical findings associated with an unacceptably high tumor biopsy risk, according to the judgement of the investigator;
• Radiotherapy on target lesions during study or within 4 weeks of the start of study drug;
• Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study;

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-11-2012
Enrollment:	225
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Inlyta
Generic name:	axitinib
Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sutent
Generic name:	sunitinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Votrient
Generic name:	pazopanib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-05-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2012

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	EUCTR2011-006009-85-NL
CCMO	NL39036.029.12