Targeted therapy selection based on tumor tissue kinase activity profiles for patients with advanced solid malignancies, an exploratory study

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To select targeted treatment based on ex vivo kinase activity inhibition profiles to targeted agents of tumor tissue from patients with advanced cancer for whom no standard treatment is available.

Ethical review	Approved WMO
Status	Completed
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON34546

Source
ToetsingOnline

Brief title
Therapy selection in advanced cancer patients based on kinase profiling

Condition

- Metastases

Synonym
Advanced solid tumors, metastasized or inoperable 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 BV

Intervention

Keyword: Individualized medicine, Kinome profiling, Targeted therapy, Tyrosine kinase inhibitor

Outcome measures

Primary outcome

The primary objective is to determine the clinical benefit rate (CBR) of this therapy selection approach, defined by the number of patients demonstrating either a complete or partial response or stable disease after 12 weeks of treatment. Available phase I data of several registered tyrosine kinase inhibitors have shown CBR*s of approximately 10% in patients with advanced solid malignancies excluding renal cell carcinoma, hepatocellular carcinoma and GIST. Based on these data, we expect to increase CBR by ex vivo analysis and therapy selection to 25%.

Secondary outcome

1. To compare progression free survival (PFS) using a kinase inhibitor treatment regimen selected by kinase profiling with the PFS of the most recent treatment regimen on which the patient progressed (i.e., patients are their own controls).

2. To determine the relation of Comparative Genomic Hybridization (CGH)-profiles with response to kinase inhibitors.

3. To determine the relation of serum and tissue kinome proteomic and activity profiles with response to kinase inhibitors and survival.

4. To correlate the frequency and phenotype of immunoregulatory cells in blood

and tumor tissue with response to kinase inhibitors.

5. To correlate individual pharmacodynamics with response to kinase inhibitors.

Study description

Background summary

In the past decade multiple agents that target specific signalling proteins important for tumor growth and angiogenesis have been developed and have reached clinical approval. Thus far, it is unclear which patients will respond to these agents and why targeted agents are only effective in a subgroup of cancer patients. Adequate diagnostic tools to predict whether a patient will respond are not yet available. It is of crucial importance to develop new clinical tests to determine which patients will respond to these targeted agents. In order to select patients for a targeted therapy, several profiling approaches have been explored but to date no adequate and reliable test to predict for response is available. It is assumed that responses to these agents depend on specific receptor and protein signalling activities in tumor tissues. We hypothesize that inhibitory activity of tyrosine kinase inhibitors on kinase activity in a tumor biopsy will correlate to and predict for response to treatment. Therefore, we propose that kinase activity profiling may be a potential clinical diagnostic tool to predict for tumor response to targeted therapy with tyrosine kinase inhibitors (TKI*s).

Study objective

To select targeted treatment based on ex vivo kinase activity inhibition profiles to targeted agents of tumor tissue from patients with advanced cancer for whom no standard treatment is available.

Study design

Non-randomized intervention study.

Intervention

Patients will undergo a tumor biopsy for *ex vivo* treatment of this tumor tissue with clinically available targeted (antiangiogenic) tyrosine kinase inhibitors, such as sunitinib, sorafenib and erlotinib. Inhibition of the kinase activity profiles of ex vivo treated samples will be determined by comparison to their untreated control. If incubation with a targeted agent results in significant signal inhibition, treatment with the most potent inhibitor in this assay will be proposed to the patient. In case of equal

inhibition, the least toxic agent will be selected for treatment.

Study burden and risks

Enrolment in this study will require a tumor biopsy prior to treatment with tyrosine kinase inhibitors. If a tumor biopsy is technically feasible, patients can be given study information for this study. This biopsy and, if necessary, supporting procedures may cause physical discomfort.
In general reversible side effects of the kinase inhibitor and adverse events as a consequence of the tissue biopsy may occur.
During therapy, follow-up will include laboratory analysis on regular visits to the outpatient clinic according to standard treatment with these type of agents.

As a result of the *personalized* therapy selection, advanced cancer patients lacking standard treatment options may benefit from potential disease regression or stabilization by agents that have shown to be able to result in clinical benefit in other tumor types.
In general, identifying additional treatment options that are likely to be effective beforehand may increase life expectancy of advanced cancer patients and will prevent toxicity of therapy that turns out to be ineffective or from which efficacy may not be expected, such as in phase I clinical studies with experimental agents. In addition, this response predicting strategy may be more cost-effective.

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

Advanced solid malignancy, minimum age 18 years, no standard therapeutic options available, life expectancy of at least 12 weeks, measurable disease with at least one lesion assessable for biopsy.

Exclusion criteria

Cardiovascular conditions including congestive heartfailure NYHA class >2, recent myocardial infarction or uncontrolled coronary artery disease, uncontrolled hypertension; uncontrolled infections; anticancer treatment during study or within 4 weeks of start of study treatment.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-09-2010
Enrollment:	43

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sutent
Generic name:	sunitinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tarceva
Generic name:	erlotinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tykerb
Generic name:	lapatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-06-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	24-01-2011
Application type:	Amendment
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	EUCTR2010-019982-27-NL
CCMO	NL32011.029.10