Kinaseprofiling voor therapieselectie bij uitbehandelde kankerpatiënten.

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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).

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON22647

Bron
NTR

Verkorte titel
TSAP

Aandoening

Gemetastaseerde solide tumoren
Vergevorderde (uitgezaaide of inoperabele) kanker
Advanced solid tumors
Metastasized or inoperable cancer

Ondersteuning

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Overige ondersteuning: Vitromics BV

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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. Targeted agents induce responses in a subgroup of cancer patients only, and adequate diagnostic tools to predict whether a patient will respond to targeted treatments are not yet available. It is of crucial importance to develop new clinical tests to determine which patients will respond to specific targeted agents. In order to select patients for targeted therapies, several profiling approaches have been explored but to date no adequate and reliable test to predict for response is available. Each patient has a unique genomic and proteomic tumor profile. It is assumed that responses to targeted agents depend on specific receptor and protein signalling activities in tumor tissues. Therefore, we propose that kinase activity profiling may be a potential clinical diagnostic tool to predict for tumor response to targeted therapy with TKI’s.

Doel van het onderzoek

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).

Onderzoeksopzet

Upon informed consent for participation in this trial, a tumor biopsy of either the primary tumor or a metastasis will be performed for ex vivo analysis. If this procedure demonstrates significant inhibition of kinase activity compared to the untreated sample, the patient will receive treatment with the most potent kinase inhibitor in this assay.

Patients will be monitored by outpatient clinic visits and laboratory analysis on a 1- to 3-weekly basis.

Treatment will continue until disease progression.

Onderzoeksproduct en/of interventie

Patients will undergo a tumor biopsy for 'ex vivo' treatment of this tumor tissue with clinically available targeted 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 of 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.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Patients presenting with an advanced (unresectable and/or metastatic) solid malignancy for whom no standard treatment is available;

2. Patients should have received at least one prior standard medical treatment regimen for their advanced disease;

3. Patients with progressive disease within 12 weeks prior to the start of study medication based on radiological assessment;

4. At least one tumor lesion should be assessable for biopsy to perform kinase activity analysis;

5. Age ≥ 18 years;

6. Histological or cytological documentation of cancer is required;

7. Patients with at least one measurable lesion. Lesions must be evaluated by CT-scan or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST);

8. WHO performance status 0 - 2;

9. Life expectancy of at least 12 weeks;

10. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:

A. Hemoglobin ≥ 5.6 mmol/L;

B. Absolute neutrophil count (ANC) ≥ 1,500/mm3;

C. Platelet count ≥ 100*109/l;

D. Total bilirubin ≤ 1.5 times the upper limit of normal;

E. ALT and AST ¡Ü 2.5 x upper limit of normal (≤ 5 x upper limit of normal for subjects with liver involvement of their cancer);

F. Serum creatinine ≤ 1.5 x upper limit of normal or a calculated creatinine clearance ≥ 50 ml/min;

G. Activated partial thromboplastin time < 1.25 x ULN;

H. Prothrombin time or INR < 1.25 x ULN.

11. Patients should be able to swallow oral medication;

12. Written informed consent.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. History of cardiac disease:

A. Congestive heart failure >NYHA class 2;

B. Active Coronary Artery Disease (myocardial infarction more than 6 months prior to screening is allowed);

C. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted);

D. Uncontrolled hypertension. Blood pressure must be ≤160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 3 separate measurements on at least 2 separate days.

2. Uncontrolled infections (> grade 2 NCI-CTC version 3.0);

3. Subjects with serious non-healing wound, ulcer, or bone fracture;

4. History or clinical evidence of CNS disease, including primary brain tumor and brain metastases;

5. Clinical findings associated, in the judgment of the investigator, with an unacceptably high tumor biopsy risk;

6. Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must agree to use adequate barrier birth control measures (e.g., cervical cap, condom, and diaphragm) during the course of the trial. Oral birth control methods alone will not be considered adequate on this study, because of the potential pharmacokinetic interaction between study drug and oral contraceptives. Concomitant use of oral and barrier contraceptives is advised. Contraception is necessary for at least 6 months after receiving the study kinase inhibitor;

7. Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks of the start of study drug;

8. Radiotherapy on target lesions during study or within 4 weeks of the start of study drug. Palliative radiotherapy will be allowed;

9. Concomitant use of dexamethasone, anti-convulsants and anti-arrhythmic drugs other than digoxin or beta blockers;

10. Major surgery within 28 days of start of treatment. The surgical wound should be fully healed prior to the start of study drug. In subjects who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed;

11. Substance abuse, medical, psychological or social conditions that may interfere with the

subject's participation in the study or evaluation of the study results;

12. Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-09-2010
Aantal proefpersonen:	43
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	04-08-2010
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL2353
NTR-old	NTR2460
Ander register	METC VUmc : 2010/124
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A