Onderzoek met hoge dosis sorafenib bij patiënten met solide tumoren gedoseerd op basis van de sorafenib bloedspiegels.

Gepubliceerd: 18-11-2015 Laatst bijgewerkt: 18-08-2022

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

Samenvatting

ID

NL-OMON23305

Bron
NTR

Verkorte titel
SOPRANO

Aandoening

advanced and metastasized solid malignancies, sorafenib, altered dosing schedule, dose titration, phase I study

Ondersteuning

Primaire sponsor: VU University Medical Center
Overige ondersteuning: It is an investigator inititiated study

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

-To determine the maximum tolerated sorafenib plasma AUC0-12h of high-dose sorafenib when administered in a weekly, pulsatile schedule.
-To assess the safety and tolerability of high-dose, pulsatile sorafenib titrated on the target AUC0-12h.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Preclinical research showed improved efficacy of sorafenib when given in a high-dose, pulsatile schedule compared with conventional (lower dose) continuous scheduling as a result of higher peak concentrations in the tumor. In this phase I study patients will be treated with high-dose, pulsatile sorafenib in exposure escalation cohorts. Exposure escalations cohorts are based on a target plasma AUC0-12h and are used instead of conventional dose escalation cohorts because the effect of a drug is dependent of its AUC levels and large differences in plasma sorafenib AUC0-12h have previously been shown between patients treated at the same dose level.

Primary Objectives:

-To determine the maximum tolerated plasma AUC0-12h of high-dose sorafenib administered in a weekly, pulsatile schedule.

-To assess the safety and tolerability of high-dose, pulsatile sorafenib.

Secondary Objectives:

-To determine the pharmacokinetic behaviour of sorafenib and its major active metabolite pyridine N-oxide when administered in a weekly, pulsatile schedule.

-To determine a recommended phase II plasma AUC0-12h of high-dose sorafenib in a weekly pulsatile schedule.

-Preliminary assessment of the efficacy of high-dose, pulsatile sorafenib administered at the maximum tolerated plasma AUC0-12h.

-To determine the skin and intratumoral concentrations of sorafenib and their correlation with the plasma and whole blood concentrations.

-To select 1-2 optimal time points from the AUC0-12h data to determine sorafenib exposure in a high-dose, pulsatile schedule using a finger puncture.

Study design: A single center, open-label, phase I study of high-dose, pulsatile sorafenib administered in exposure escalation cohorts.

Study population: Adult patients with locally advanced or metastatic disease for whom no standard therapy exists.
Treatment: Patients will be treated in exposure escalation cohorts with high-dose sorafenib administered in a weekly pulsatile schedule. Using pharmacokinetic monitoring, the sorafenib dose will be adjusted to a target plasma AUC0-12h. The escalation cohorts consist of 3-6 patients per exposure level starting with the target plasma sorafenib AUC0-12h level of 25-50 mg/L/h. After the determination of the maximum tolerated AUC0-12h, 10 additional patients will be entered into an expansion cohort. In the expansion cohort the patients will be treated with a weekly pulse of sorafenib at the maximum tolerated AUC0-12h for further assessment of safety and preliminary exploration of efficacy.

Doel van het onderzoek

Our hypothesis is that high-dose, pulsatile sorafenib may exhibit improved efficacy with an acceptable toxicity profile compared to standard continuous dosing. AUC escalation cohorts are used instead of the conventional dose escalation cohorts, because the latter have shown large differences in plasma sorafenib AUC0-12h between patients treated at the same dose level.

Onderzoeksopzet

In each exposure level 3-6 patients are treated and at least 48 hours will intervene between the enrolment of the first patient and subsequent patients. The exposure limiting toxicity period is during the first 42 days from start of treatment. After the determination of the maximum tolerated AUC0-12h, 10 additional patients will be entered into an expansion cohort. In the expansion cohort the patients will be treated with a weekly pulse of sorafenib at the maximum tolerated AUC0-12h for further assessment of safety and preliminary exploration of efficacy.Response will be assessed clinically and through radiographic tumor assessments (mainly CT scans, but this may also include MRI scans, bone scans and other imaging modalities as required).
Evaluation by CT scan will be required at fixed time-points: pretreatment, at 8 weeks, at 16 weeks and thereafter every 8 weeks during treatment until progressive disease. Treatment with high-dose, pulsatile sorafenib will be continued until disease progression or until any other medical or patient-related reason for discontinuation. Follow up will end when progressive disease has been established and/or death of the patient, or upon patient request.

Onderzoeksproduct en/of interventie

Patients will be treated in exposure escalation cohorts with high-dose sorafenib administered in a weekly pulsatile schedule. Using pharmacokinetic monitoring, the sorafenib dose will be adjusted to a target plasma AUC0-12h. The escalation cohorts consist of 3-6 patients per exposure level starting with the target plasma sorafenib AUC0-12h level of 25-50 mg/L/h. After the determination of the maximum tolerated AUC0-12h, 10 additional patients will be entered into an expansion cohort. In the expansion cohort the patients will be treated with a weekly pulse of sorafenib at the maximum tolerated AUC0-12h for further assessment of

safety and preliminary exploration of efficacy.

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Histological or cytological documentation of incurable locally advanced or metastatic solid malignancy for which no standard therapy exists.

2. Patients eligible for the expansion cohort must be willing to undergo tumor and skin biopsies, while tumor and skin biopsies are optional for patients enrolled in the escalation cohort. Primary tumor or metastatic site must be accessible for biopsy. Bone metastases are excluded as a biopsy site.

3. Evaluable disease by RECIST version 1.1. criteria

4. Patients must have documented radiographic or clinical progressive disease.

5. Age ¡Ý 18 years.

6. Eastern Cooperative Oncology Group (ECOG) performance status of ¡Ü 1.

7. Normal 12-lead ECG (clinically insignificant abnormalities permitted), and left ventricular ejection fraction (LVEF) > 50% evaluated by multigated acquisition scan (MUGA) or echocardiogram.

8. Normal or regulated thyroid function - supplementation or blocking drugs permitted.

9. Urine analysis: no clinically significant abnormalities.

10. Albumin higher than 25 g/L.

11. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 14 days prior to screening:

a. Hemoglobin ¡Ý 5,6 mmol/L

b. Absolute neutrophil count (ANC) ¡Ý 1,5 x 10*9/l

c. Platelet count ¡Ý 100 x 10*9/l

d. Total bilirubin ¡Ü 1.5 times the upper limit of normal (ULN). Patients with known Gilbert¡¯s disease who have serum bilirubin ¡Ü 3x ULN may be enrolled.

e. ALT and AST ¡Ü 2.5 x ULN (in case of liver metastases: ¡Ü 5 times ULN).

f. Serum creatinine ¡Ü 1.5 x ULN or creatinine clearance ¡Ý 50 ml/min (based on MDRD).

g. PT-INR/PTT < 1.5 x ULN, unless coumarin derivatives are used.

h. Activated partial thromboplastin time < 1.25 x ULN (therapeutic anticoagulation therapy is allowed, if this treatment can be interrupted for a biopsy as judged by the treating physician).

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Evidence of a significant uncontrolled concomitant disease, such as cardiovascular disease (including stroke, New York Heart Association Class III or IV cardiac disease or myocardial infarction within 6 months prior to screening, unstable arrhythmia, clinically significant valvular heart disease and unstable angina); nervous system, pulmonary (including obstructive pulmonary disease and history of symptomatic bronchospasm), renal, hepatic, endocrine, or gastrointestinal disorders; or a serious non-healing wound or fracture.

2. Prior radiotherapy in the abdominal or thoracic area or in > 3 vertebrae in the spine (if long interval since previous radiotherapy or radiotherapy in ¡Ü 3 vertebrae, eligibility will be decided on an individual basis by the primary investigator).

3. Poorly controlled hypertension despite adequate blood pressure medication. Blood pressure must be ¡Ü 160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 2 separate measurements.

4. Seizure disorders requiring anticonvulsant therapy.

5. Major surgery, other than diagnostic surgery, within 4 weeks prior to day 1, without complete recovery.

6. Known active bacterial, viral, fungal, mycobacterial, or other infection (including HIV and atypical mycobacterial disease, but excluding fungal infection of the nail beds).

7. Known hypersensitivity to sorafenib or to its excipients.

8. Presence of any significant central nervous system or psychiatric disorder(s) that would interfere with the patient¡¯s compliance.

9. Drug or alcohol abuse.

10. Any evidence of a disease or condition that might affect compliance with the protocol or interpretation of the study results or render the patient at high risk from treatment complications.

11. Unwillingness or inability to comply with study and follow-up procedures.

12. Chemotherapy, radiotherapy, or biologic therapy within the previous 4 weeks; Nitrosoureas or mitomycin C within the previous 6 weeks; Investigational agents within the previous 4 weeks.

13. Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis.

14. Untreated or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).

15. Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:

a. Presence of evaluable or measurable disease outside the CNS

b. Radiographic demonstration of stabilization upon completion of CNS-directed therapy and no evidence of interim progression between completion of CNS-directed therapy and the screening radiographic study

c. Completion of radiotherapy ¡Ý 8 weeks prior to the screening radiographic study

d. Discontinuation of corticosteroids and anticonvulsants ¡Ý 4 weeks prior to the screening

radiographic study

16. 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, or 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 protein kinase inhibitor.

17. Concomitant medication with drugs having proarrythmic potential (such as sotalol, haloperidol, flecainide) is not permitted during the study.

Note: Prior sorafenib therapy does not constitute an exclusion criterion.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-09-2015
Aantal proefpersonen:	40
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	18-11-2015

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	NL5444
NTR-old	NTR5571
Ander register	: 2015.224

Resultaten

Samenvatting resultaten

-Honeywell R, Yarzadah K, Giovannetti E, et al. Simple and selective method for the determination of various tyrosine kinase inhibitors used in the clinical setting by liquid chromatography tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878:1059-68.
-Pécuchet N, Lebbe C, Mir O, et al. Sorafenib in advanced melanoma: a critical role for pharmacokinetics? Br J Cancer. 2012;107:455-61.
-Strumberg D, Clark JW, Awada A, et al. Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. Oncologist. 2007;12:426-37.
-Wang X, Zhang L, Goldberg SN, et al. High dose intermittent sorafenib shows improved efficacy over conventional continuous dose in renal cell carcinoma. J Transl Med. 2011;9:220. doi: 10.1186/1479-5876220.