

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

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23305

Source

NTR

Brief title

SOPRANO

Health condition

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

Sponsors and support

Primary sponsor: VU University Medical Center

Source(s) of monetary or material Support: It is an investigator initiated study

Intervention

Outcome measures

Primary outcome

-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.

Secondary outcome

Escalation cohorts:

-To determine the pharmacokinetic behaviour of sorafenib and its major active metabolite pyridine N-oxide.

-To determine a recommended phase II plasma sorafenib AUC0-12h.

Expansion cohort:

-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 description

Background summary

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 AUC_{0-12h} 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 AUC_{0-12h}.
- 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 AUC_{0-12h} 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 AUC_{0-12h}. The escalation cohorts consist of 3-6 patients per exposure level starting with the target plasma sorafenib AUC_{0-12h} level of 25-50 mg/L/h. After the determination of the maximum tolerated AUC_{0-12h}, 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 AUC_{0-12h} for further assessment of safety and preliminary exploration of efficacy.

Study objective

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 AUC_{0-12h} between patients treated at the same dose level.

Study design

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 AUC_{0-12h}, 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 AUC_{0-12h} 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.

Intervention

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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Eligibility criteria

Inclusion criteria

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 \geq 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status of \leq 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 \geq 5,6 mmol/L
 - b. Absolute neutrophil count (ANC) \geq $1,5 \times 10^9/l$
 - c. Platelet count \geq $100 \times 10^9/l$
 - d. Total bilirubin \leq 1.5 times the upper limit of normal (ULN). Patients with known Gilbert's disease who have serum bilirubin \leq 3x ULN may be enrolled.
 - e. ALT and AST \leq 2.5 x ULN (in case of liver metastases: \leq 5 times ULN).
 - f. Serum creatinine \leq 1.5 x ULN or creatinine clearance \geq 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).

Exclusion criteria

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 ≤ 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 $\leq 160/95$ 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 \geq 8 weeks prior to the screening radiographic study
- d. Discontinuation of corticosteroids and anticonvulsants \geq 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 proarrhythmic potential (such as sotalol, haloperidol, flecainide) is not permitted during the study.

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

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL
Recruitment status: Recruiting
Start date (anticipated): 01-09-2015
Enrollment: 40
Type: Anticipated

Ethics review

Positive opinion
Date: 18-11-2015
Application type: First submission

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
NTR-new	NL5444
NTR-old	NTR5571
Other	: 2015.224

Study results

Summary results

-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.