Sorafenib administered using a high-dose, pulsatile regimen in patients with advanced solid malignancies: a phase I exposure escalation study

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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45075

Source
ToetsingOnline

Brief title
The SOPRANO study

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Divisie 1 Beheer BV

Intervention

Keyword: dose titration, high-dose, phase I study, sorafenib

Outcome measures

Primary outcome

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 outcome

- 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 description

Background summary

Preclinical research showed improved efficacy of sorafenib when given in a high-dose, weekly, 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.

Study objective

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. 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.

Intervention

A pretreatment and on-treatment tumor biopsy will be performed, the second along with a skin biopsy on Day 15 of treatment for patients entering the expansion cohort. This is to to gain more insight in the biological effects of the drug. These biopsies are optional for patients in the escalation cohort.
In addition, for pharmacokinetic analysis venapunctures will be performed and also punctures of the finger tip.

Study burden and risks

The most common side effects of sorafenib reported in previous clinical trials (observed in at least 10% of the patients) are hypertension, fatigue, diarrhea, nausea, vomiting, mucositis, hair changes, skin rash (such as hand and foot syndrome), taste alteration and loss of appetite.
Venapunctures, punctures of the fingertip, skin and tumor biopsies may be painful for the patient. Risks are dependent on the nature and location of the puncture/biopsy. In general, bleeding or inflammation may occur. Literature reports <1% risk of serious complications from primary tumor biopsies.

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

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 (see appendix III; at least 1 target or non-target lesion for the dose escalation cohorts; at least 1 target lesion the for dose expansion cohorts).
4. Patients must have documented radiographic or clinical progressive disease.
5. Age * 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status of * 1 (appendix IV).
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 * 5,6 mmol/L
b. Absolute neutrophil count (ANC) * 1,5 x 10*9/l
c. Platelet count * 100 x 10*9/l
d. Total bilirubin * 1.5 times the upper limit of normal (ULN). Patients with known Gilbert*s disease who have serum bilirubin * 3x ULN may be enrolled.
e. ALT and AST * 2.5 x ULN (in case of liver metastases: * 5 times ULN).
f. Serum creatinine * 1.5 x ULN or creatinine clearance * 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 * 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 * 8 weeks prior to the screening radiographic study
d. Discontinuation of corticosteroids and anticonvulsants * 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.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-11-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	01-06-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-07-2015
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2017
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	EUCTR2015-001379-37-NL
CCMO	NL53039.029.15