# Onderzoek naar het effect van OATP1B blokkade op de stofwisseling van sorafenib (Nexavar®) bij volwassen patiënten met kanker.

No registrations found.

| | |
|---|---|
| **Ethical review** | Positive opinion |
| **Status** | Recruitment stopped |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON23851

**Source**
NTR

**Brief title**
SORA-RIFA

**Health condition**

Solid tumors treated with sorafenib (Nexavar®) mono therapy.

### Sponsors and support

**Primary sponsor:** Erasmus Medical Center; Department of Medical Oncology
**Source(s) of monetary or material Support:** Erasmus Medical Center; Department of Medical Oncology

### Intervention

### Outcome measures

**Primary outcome**

To determine the influence of OATP1B inhibition, through rifampicin exposure, on the metabolism and plasma pharmacokinetics of sorafenib and its metabolites.

**Secondary outcome**

1. To compare the incidence and severity of side effects of treatment with sorafenib in the absence and presence of rifampicin (interim-analysis after 4 patients).

2. To study the influence of genetic polymorphisms in OATP1B involved in the metabolism of sorafenib.

3. To assess the degree of CYP3A induction after administration of rifampicin for two days by measuring midazolam clearance.

# Study description

**Background summary**

Rationale: Sorafenib is a multi-targeted tyrosine kinase inhibitor, which has been approved for irresectable hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC). It is known that sorafenib is predominantly metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and UDP-glucuronosyltransferase 1A9 (UGT1A9). In pre-clinical research mice with mutated organic anion transporting polypeptides (OATP) 1B2 prove to have an eight-fold increase of sorafenib plasma concentrations. Therefore this study aims to observe the effect of these transporters on sorafenib metabolism by inhibiting it with rifampicin and by analyzing germline pharmacogenetics of the OATP genes.

Objective: Primary objective is to determine the influence of OATP1B inhibition, through rifampicin exposure, on the metabolism and plasma pharmacokinetics of sorafenib and its metabolites.

Secondary objectives are to compare the incidence and severity of side effects of treatment with sorafenib in the absence and presence of rifampicin (interim-analysis after 4 patients), to study the influence of genetic polymorphisms in OATP1B involved in the metabolism of sorafenib, according to protocol METC 02.1002, and to assess the degree of CYP3A induction after administration of rifampicin for two days by measuring midazolam clearance.
Study design: This is a single- center, randomized cross- over pharmacokinetic study.

Study population: Patients will be recruited from a population of cancer patients with solid tumors treated with sorafenib.
Intervention: Patients that are regularly treated with sorafenib for at least 14 days will be admitted to the hospital for pharmacokinetic blood sampling on day 2 and day 11. Patients will receive rifampicin 600 mg orally prior to the pharmacokinetic blood sampling on days 1 and 2 in arm A and on days 10 and 11 in arm B, in order to assess the influence of OATP1B

blockage on sorafenib pharmacokinetics. Furthermore, patients will be challenged with a midazolam test (2,5 mg intravenously) during each hospital admission in order to assess the degree of CYP3A induction due to rifampicin.
Main study parameters/endpoints: As primary endpoint, pharmacokinetics of sorafenib with and without preceding OATP1B inhibition by rifampicin will be compared. Secondary endpoints include the analysis of side effects after rifampicin administration and the influence of germline genetic polymorphisms in OATP1B on sorafenib pharmacokinetics. Finally, CYP3A induction due to rifampicin will be assessed by observing the clearance of midazolam.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients on regular treatment with sorafenib will be admitted to the hospital on two different days, during which pharmacokinetic blood withdrawals and a midazolam clearance test (MCT) will be performed. In advance of one of the hospital admissions (depending on randomization), patients are challenged with rifampicin 600 mg on two consecutive days. Patients do not benefit individually from this study. Major risks to be expected are side effects of one of the investigational medicinal products, for which patients will be carefully observed.

### Study objective

Recent pre-clinical experiments demonstrated that sorafenib in Oatp1b2(-/-) mice had 8-fold increased sorafenib-glucuronide blood concentrations.OATP1B1 and 1B3 are highly expressed in the human liver and facilitate the hepatocellular uptake of several substrates before metabolism and efflux from the liver. Because sorafenib is subject to an enterohepatic recirculation, OATP1B deficiency in human possibly results in altered sorafenib (parent drug) concentrations. If rifampicin is used as OATP inhibitor, and not as CYP3A4 inducer, sorafenib concentrations may increase indirectly. This study should help to provide further insights into the variability in antitumor activity and side effects in sorafenib-treated patients.

### Study design

Within 2 weeks patients will be admitted twice for pharmacokinetic sampling

### Intervention

1. Administration of rifampicin and midazolam.

2. Bloodwithdrawal for pharmacokinetics of sorafenib and midazolam.

## Contacts

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# Eligibility criteria

## Inclusion criteria

• Age ≥18 years;

• Histological/ cytological confirmed diagnosis of cancer treated with sorafenib monotherapy

• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. (see appendix A);

• A stable dose of sorafenib for at least 2 weeks (to guarantee steady-state);

• Adequate hematological functions, absolute neutrophil count (ANC)> 1.0 x 109/L, platelet count ≥ 100 × 109/L);

• Adequate renal and hepatic functions defined as serum creatinin <1.25 x ULN; total bilirubin <1.25 x ULN; asparate aminotransferase (AST) and alanine aminotransferase (AST) ≤ 5 x ULN;
• PTT ≤ 1.5×ULN and INR < 1.5;

• Signed informed consent and amenable to compliance with protocol schedules and testing;

• For patients with reproductive potential a reliable method of contraception (excluding oral contraceptive) must be used.

## Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation

in this study:

• Pregnant or child nursing patients;

• Serious illness or medical unstable condition requiring treatment, symptomatic CNS-metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;

• Major surgery within 2 weeks prior to start of the protocol;

• Radiotherapy within the last 2 weeks before start of this study;

• Patients who had a liver transplantation prior to sorafenib treatment;

• Patients who receive therapeutic anticoagulation therapy. Low dose, non- therapeutic anticoagulation (e.g., low dose warfarin) for catheter prophylaxis only will be permitted;

• Patients who receive anti-retroviral therapy for Human Immunodeficiency Virus (HIV). Prophylactic antiviral therapy to prevent Hepatitis B virus (HBV) reactivation or cytokine therapy (e.g. interferon) for Hepatitis C virus infection is allowed;

• Use of CYP3A4 inhibiting or inducing medication;

• Concurrent medication or supplements which can interact with sorafenib.

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | N/A , unknown |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 12-08-2013 |
| Enrollment: | 9 |

Type: Actual

## Ethics review

Positive opinion
Date: 08-08-2013

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 | NL3945 |
| NTR-old | NTR4110 |
| Other | MEC ErasmusMC : MEC 2013-194 |
| ISRCTN | ISRCTN wordt niet meer aangevraagd. |

## Study results

**Summary results**
N/A