# Phase III randomized sequential open-label study to evaluate the efficacy and safety of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the treatment of advanced / metastatic renal cell carcinoma

Published: 05-07-2012
Last updated: 28-04-2024

Primary:To evaluate if progression-free survival from randomization to progression or death during second-line therapy (total PFS) of sorafenib followed by pazopanib is non-inferior compared to pazopanib followed by sorafenib.Secondary:1. Time from...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Renal and urinary tract neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON43677

**Source**
ToetsingOnline

**Brief title**
SWITCH 2 Study

### Condition

- Renal and urinary tract neoplasms malignant and unspecified

**Synonym**
advanced / metastatic renal cell carcinoma, advanced/ disseminated renal cell kidney cancer

**Research involving**

Human

## Sponsors and support

**Primary sponsor:** Dekan der Fakultät für Medizin der Technischen Universität München
**Source(s) of monetary or material Support:** Dekan der Fakultät für Medizin der Technischen Universität München

## Intervention

**Keyword:** advanced/metastatic renal cell carcinoma, pazopanib, phase III, sorafenib

## Outcome measures

### Primary outcome

Total Progression Free Survival

### Secondary outcome

1. Time from randomization to progression during second-line therapy (total TTP)

2. Time to first-line treatment failure (progression, death, discontinuation

due to toxicity) descriptively in each arm

3. PFS in first-line and second-line treatment, descriptively

4. Overall survival, descriptively (data cut-off same as for primary endpoint)

5. Disease Control Rate (DCR); Response rates in first-line and in second-line

(CR, PR, SD according to RECIST criteria)

6. Health-related Quality of Life (FACIT-F, FKSI-10)

7. Veiligheid en verdraagbaarheid

# Study description

### Background summary

Renal cell carcinoma (RCC) is the most common cancer of the kidney and accounts for 2 % of all cancers. Up to 30% of patients with RCC present with metastatic

disease. When distant metastases are present, disease-free survival is poor. Surgical resection is the mainstay of treatment. Even in patients with disseminated tumor, surgical resection of tumor mass may have a positive impact on survival. RCC is highly resistant to chemotherapy.
Approximately 50 % of patients with RCC develop metastatic disease. The median survival of these patients is approximately 1 year, and survival at 2 years is 10 % or less in most studies. Metastatic RCC is resistant to chemotherapy.

Spontaneous regressions have been reported in some patients.

Interleukin-2 (IL-2) and interferon alpha-2a (IFN -2a) have shown tumor response. However, i. v. IL-2 induces severe side effects. Only 20 % of the patients benefit from high-dose IL-2 and/or IFN -2a.

Median overall survival (OS) following progression after cytokine therapy is approximately 10 to13 months, and no effective treatment was available until a few years ago for patients whose disease progresses after an initial response or who did not respond to cytokine therapy.

A growing understanding of the underlying biology of RCC has identified vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), mTOR (mammalian target of rapamycin), and a number of other hypoxia-inducible proteins as logical therapeutic targets. In fact, while IFN(interferon)-based immunotherapy and high-dose immunotherapy with intravenous interleukin-2 represented the standard of care until the past few years, agents such as sorafenib, sunitinib, pazopanib, bevacizumab (in combination with IFN), emsirolimus, and everolimus now dominate the treatment in mRCC.

Sorafenib and pazopanib are both effective and promising treatments for advanced RCC. Both drugs are registered for this indication. No prospective comparative data in advanced RCC (or other indications) have been published. As sequential therapy is now the standard of treatment for advanced RCC it is important to evaluate in clinical trials what the value of different sequential strategies is. As there are no data yet on the sequential use of sorafenib followed by pazopanib or vice versa, this sequence, however, will most certainly be used in daily practice, it is required to examine efficacy and safety of this sequential approach in a clinical trial in a randomized setting.

**Study objective**

Primary:
To evaluate if progression-free survival from randomization to progression or death during second-line therapy (total PFS) of sorafenib followed by pazopanib is non-inferior compared to pazopanib followed by sorafenib.

Secondary:

1. Time from randomization to progression during second-line therapy (total TTP)
2. Time to first-line treatment failure (progression, death, discontinuation due to toxicity) descriptively in each arm
3. PFS in first-line and second-line treatment, descriptively
4. Overall survival, descriptively (data cut-off same as for primary endpoint)
5. Disease Control Rate (DCR); Response rates in first-line and in second-line (CR, PR, SD according to RECIST criteria)
6. Health-related Quality of Life (FACIT-F, FKSI-10)
7. Veiligheid en verdraagbaarheid

**Study design**

This study is a sequential, randomized, open-label (1:1), multicenter phase III study starting in first-line of metastatic / advanced RCC using in the experimental arm sorafenib until progression followed by pazopanib and in the control arm pazopanib until progression followed by sorafenib.
Sorafenib-patients will switch to pazopanib and vice versa, with a treatment-free period of at least seven and up to maximum 28 days after confirmed first-line treatment failure, in order to avoid additive toxicity. In general, the first-line treatment should be continued until progression (RECIST 1.1). However, if patients do not tolerate the first-line medication (sorafenib or pazopanib) because of toxicity, they may cross-over to the secondline therapy (pazopanib or sorafenib) despite the lack of progression, if an appropriate attempt according to a specific dose reduction / interruption scheme has been made to cope with the toxicity and try to resume first line therapy, if deemed appropriate with a reduced dose. In case of discontinuation of first-line treatment because of toxicity, patients will be enrolled for the second-line treatment, onlyafter non-hematological toxicity has resolved to grade *1 and hematological toxicity to grade *2. As an exception, patients who refuse to be treated further with the first-line regimen due to intolerability despite having no progression may be crossed over to the second-line treatment, if they consent and are in general compliance.
Any cross-over, also without progression, requires a CT scan, which is in this case also considered the baseline scan for the second-line treatment.
One cycle is of four weeks duration. Patients will undergo a CT/MRI scan after every second cycle (i.e. after 8 weeks each), which will be evaluated according to RECIST 1.1 criteria. There will be no continuation of the same study medication beyond progression in both first- or second-line therapy.
After the study reached its primary endpoint cut off, i.e. after 383 disease progressions under second-line therapy have occurred, clean data for these patients exist and a statistical analysis has been performed data collection will be stopped. After that the trial is terminated and a close-out visit will be performed. Remaining patients will be treated outside the study and will be censored in the analysis.

**Intervention**

Arm 1:
Sorafenib 400 mg bid orally until progression or intolerable toxicity, followed by pazopanib 800 mg once daily orally until progression or intolerable toxicity

Arm 2:
Pazopanib 800 mg once daily orally until progression or intolerable toxicity, followed by Sorafenib 400 mg bid orally until progression or intolerable toxicity

During first- and second-line, treatment visits are scheduled in weeks 0, 2, 4, 8, 12, and every 4 weeks thereafter, with tumor assessments and electrocardiogram after every second cycle (every 8 weeks).

**Study burden and risks**

Study assessments will be performed at screening, CxD1, C1D15, C1D3, CxD28 (only the even numbered cycles), stop first line therapy. Treatment duration will continue until disease progression, unacceptable toxicity, patient withdrawal of consent, death, or discontinuation from the study for any other reason, whereupon all patients will complete the End of Treatment visit ± 7 days after last study medication. FU will take place every 3 months
Please refer to the Flowchart of the protocol.
Risks:
*Toxicity due to the use of the studymedication.
*Reaction to the use of contrast fluid (used for CT/MRI scans
*Possible side effects of blood sampling (bruises, bleeding, bloodclots, infection)
*Exposure to radiation with X-rays

# 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. Patients with metastatic / advanced RCC (all histologies), who are not suitable for cytokine therapy and for whom study medication constitutes first-line treatment. For cytokine-unsuitability at least one of the following criteria must be fulfilled*:
* Age 66 to 88 years
* Non-clear cell histology RCC
* Intermediate risk according to MSKCC score
* ECOG * 1 and> 1 organ metastasis + < 24 months between diagnosis and establishing indication for interleukin-2-therapy
* ECOG * 1 and *unable to carry on normal activity or do active work* (Karnofsky Index 70%)
* Creatinine * 1x ULN and < 2x ULN
* Total bilirubin * 1x ULN and < 1.5x ULN
* Present autoimmune disease
* Patients who might require steroids
* Hypersensitivity against cytokines
* Severe organic disease, not interfering with other in-/exclusion criteria of the Switch-2 study
* Non-symptomatic brain metastases
* Severe lung disease (e.g. PAH, COPD) with Pa O2 < 60 mmHg on rest
2. Age * 18 and * 85 years
3. Karnofsky Index * 70% (see appendix *15.1 Performance Status (ECOG, Karnofsky)*)
4. MSKCC prognostic score (2004), low or intermediate (see appendix *15.2 Motzer Scoring*)
5. Life expectancy of at least 12 weeks
6. Subjects with at least one uni-dimensional (for RECIST 1.1, see appendix *15.3 RECIST 1.1) measurable lesion. Lesions must be measured by CT/MRI-scan

7. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to start of therapy:
* Hemoglobin > 9.0 g/dl
* Absolute neutrophil count (ANC) >1,500/*l
* Platelet count * 100,000/*l
* Total bilirubin < 1.5x the upper limit of normal (Note: Subjects with Gilbert*s Syndrome are eligible if their total bilirubin is <3.0 X ULN and direct bilirubin is * 35%.)
* ALAT and ASAT < 2.5x upper limit of normal (Note: concomitant elevations in bilirubin and ASAT/ALAT above 1.0x upper limit of normal are not permitted).
* Alkaline phosphatase < 4x upper limit of normal
* PT-INR/aPTT < 1.2x upper limit of normal [Patients who are being therapeutically anticoagulated with an agent such as coumadin or heparin will be allowed to participate provided that their INR is stable and within the recommended range for the desired level of anticoagulation and no prior evidence of underlying abnormality in these parameters exists.]
* Serum creatinine < 2 x upper limit of normal
8. Written Informed Consent

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*Based on references:
o Kirchner H., H. Heinzer, J. Roigas und F. Overkamp: Differentialtherapie beim metastasierenden Nierenzellkarzinom. Der Onkologe 2008; 14: 191-197;
o SmPC of interleukin-2
o SmPC of interferon alfa -2a

## Exclusion criteria

1. History of cardiac disease: congestive heart failure >NYHA class 2 or with LVEF at baseline echocardiography < 50% (echocardiography is optional); active CAD (MI more than 6 months prior to study entry is allowed); cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
2. Uncontrolled hypertension (defined as blood pressure * 150 mmHg systolic and/or * 90 mmHg diastolic on medication).
3. History of HIV infection or chronic hepatitis B or C
4. Active clinically serious infections (> grade 2 NCI-CTC version 4.03)
5. Symptomatic metastatic brain or meningeal tumors (unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry)
6. Patients with seizure disorder requiring medication (such as steroids or antiepileptics)
7. Patients with evidence or history of bleeding diathesis
8. History of organ allograft
9. Major surgery within 4 weeks of start of study
10. Autologous bone marrow transplant or stem cell rescue within 4 months before study start.

11. Any significant condition that increases the risk for bleeding, including, but not limited to active peptic ulcer disease, inflammatory bowel disease, known intraluminal or endobronchial metastatic lesions and/or lesions infiltrating major pulmonary vessels with risk of bleeding, presence of non-healing wound or trauma within 4 weeks prior to first dose of investigational drug
12. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep vein thrombosis (DVT) within the past 6 months (Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible)
13. Corrected QT Interval (QTc) > 480 msecs
14. Untreated hypothyroidism
15. Patients undergoing renal dialysis
16. Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumors [Ta, Tis & T1] or any cancer curatively treated > 3 years prior to study entry
17. Pregnant or breast-feeding patients. 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 use adequate barrier birth control measures (with a Pearl Index < 1) during the course of the trial and 3 months after the completion of trial.
18. Substance abuse, medical, psychological or social conditions that may interfere with the patient*s participation in the study or evaluation of the study results
19. Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study
20. Patients unable to swallow oral medications
21. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product
22. Known allergy to Votrient® or Nexavar®(i.e. to active substance or one of the constituents)
23. Prior exposure to study drugs.
24. Investigational drug therapy within 4 weeks of study entry.
25. Use of biologic response modifiers, such as G-CSF and other hematopoietic growth factors, within 3 weeks of study entry.
26. Radiotherapy within 3 weeks of start of study drug and planned radiotherapy during the study
27. Concomitant medication: Any condition at the discretion of the investigator that precludes compliance with concomitant therapy restrictions described below:
Non-permitted medication:
a. Other anticancer chemo-, cytokine- or targeted therapy for RCC, as well as other investigational drug therapy.
b. Any St. John*s wort containing remedy
For further details also refer to chapters 7.1.3 / 7.2.3.
To be used with caution:
a. Co-administration of pazopanib with medicines that increase gastric pH should be avoided.
* Proton-pump inhibitor (PPI): If the concomitant use of a proton-pump

inhibitor (PPI) is medically necessary, it is recommended that the dose of pazopanib be taken without food once daily in the evening concomitantly with the PPI.
* H2-receptor antagonist: If the concomitant administration of an H2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H2-receptor antagonist.
* Short-acting antacids: Pazopanib should be administered at least 1 hour before or 2 hours after administration of short-acting antacids.
b. Anticoagulants: Pazopanib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.
c. Hypoglycemic therapy including insulin: Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.
d. Simvastatin: Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations and should be undertaken with caution and close monitoring.
e. Strong CYP3A4 inhibitors* (e.g. grapefruit juice, star fruit or star fruit juice, Seville orange, antibiotics, protease inhibitors, antifungals, antidepressants) should be avoided during pazopanib treatment.
f. CYP3A4 inducers* should be avoided during pazopanib treatment, unless use of the drug is essential and no substitute is available.

# Study design

## Design

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|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 02-01-2013 |
| Enrollment: | 45 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Nexavar |
| Generic name: | sorafinib |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Votrient |
| Generic name: | pazopanib |
| Registration: | Yes - NL intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 05-07-2012 |
| Application type: | First submission |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 19-10-2012 |
| Application type: | First submission |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 29-04-2013 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 24-03-2014 |
| Application type: | Amendment |

| | |
|---|---|
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 08-04-2014 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 05-12-2014 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 11-12-2014 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 20-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 15-12-2015 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 08-07-2016 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |
| Approved WMO Date: | 06-09-2016 |
| Application type: | Amendment |
| Review commission: | METC Noord-Holland (Alkmaar) |

# 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 | EUCTR2011-004396-36-NL |
| ClinicalTrials.gov | NCT00732914 |
| CCMO | NL40447.094.12 |