# A randomized phase II study to explore the efficacy and feasibility of upfront bi-monthly rotations between Everolimus and Pazopanib with sequential treatment of first line Pazopanib and second line Everolimus until progression in patients with advanced or metastatic clear cell renal cancer.

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Primary objectivesThe primary objective is to assess the progression-free survival (PFS) of patients who receive bi-monthly rotations of Pazopanib and Everolimus versus patients who receive Pazopanib as a first line treatment. Secondary…

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

## Summary

### ID

NL-OMON39600

**Source**
ToetsingOnline

**Brief title**
ROPETAR

### Condition

- Renal and urinary tract neoplasms malignant and unspecified

**Synonym**
Kidney cancer, Renal cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Werkgroep Immunotherapie Nederland voor Oncologie
**Source(s) of monetary or material Support:** GlaxoSmithKline,Novartis,Werkgroep immunotherapie Nederland voor Oncologie (verrichter)

## Intervention

**Keyword:** Clear cell renal cancer, Everolimus, Pazopanib, ROPETAR

## Outcome measures

### Primary outcome

Progression-free survival: PFS is defined as time to progressive disease per RECIST 1.1 or death whichever comes first in arm A (alternating schedule) and after Pazopanib monotherapy in arm B. Comparing time to first PD with time to first PD.

Patients who have not progressed or died at the date of the analysis cut-off or when they receive any further anticancer therapy will have their disease status censored at the time of the last adequate tumor assessment before the cut-off date or the anticancer therapy date.

### Secondary outcome

Time to second progression or death: defined as time to progressive disease per RECIST 1.1 on Everolimus monotherapy (when PD after 8 weeks Pazopanib) or on Pazopanib monotherapy (when PD after 8 weeks Everolimus) as second line treatment in arm A and time to progressive disease on Everolimus in arm B. Comparing time to 2nd PD with time to 2nd PD.

Quality of life and toxicity. Quality of life assessments and Common Toxicity

Criteria will be used.

Overall survival

Pharmacodynamic measurements and pharmacokinetic assessments at the switch of

Pazopanib and Everolimus and vice versa.

Genetic analysis of tumorbioppsies (optional).

# Study description

### Background summary

(Protocol chapter 1)The introduction of targeted agents in the treatment of clear cell renal cancer (ccRCC) has made a significant impact on survival of these patients. However, the optimal use of these agents is presently unclear. Current practice is to treat with VEGFR-TKI or mTOR inhibitors until progression and then continue with the next active agent. Although this strategy prolongs survival, side effects are substantial. Patient compliance to oral anti-cancer agents is an important issue and side effects are a factor in adherence to the prescribed treatment. From a biological perspective, TKI*s will most likely activate compensatory pathways which, may ultimately lead to the development of resistance. Recent studies suggest that resistance to treatment with TKI may be reversible after stopping treatment. There is therefore a rationale to alternate treatment to prevent or delay the occurrence of resistance.
Our hypothesis is that alternating Pazopanib and Everolimus in ccRCC may reduce side effects, improve tolerability and compliance of treatment and prolong progression free survival and overall survival compared to the standard of care. Pazopanib is registered as first line treatment of locally advanced or metastatic ccRCC. The continuous dosing schedule of Pazopanib provides a concomitant continuous therapeutic pressure on tumor cells. This makes Pazopanib the targeted agent of choice in this trial. In the current design it is avoided to start the alternating regimen with Everolimus because there are no data on Everolimus in first line treatment.

### Study objective

Primary objectives
The primary objective is to assess the progression-free survival (PFS) of patients who receive bi-monthly rotations of Pazopanib and Everolimus versus

patients who receive Pazopanib as a first line treatment.

Secondary objectives
The secondary objectives are time to second progression or death, overall survival, quality of life, toxicity of randomized patients receiving treatment as defined in arm A compared to arm B.
Other secondary objectives include pharmacodynamic measurements and pharmacokinetic assessments at the switch of Pazopanib and Everolimus and vice versa.
To develop biomarkers that may predict responsiveness to either of the agents used.

## Study design

This is an open-label, randomized phase II study to determine the feasibility of alternating cycles of treatment with Pazopanib and Everolimus compared to sequential treatment of Pazopanib followed by Everolimus.
The purpose of the study is to determine the progression free survival, feasibility and tolerability of the experimental arm compared to standard of care.
In the experimental arm (Arm A) alternating treatment will consist of repeating periods of 16 weeks of treatment consisting of 8 weeks of Pazopanib 800 mg qd followed by 8 weeks of Everolimus 10 mg qd until progression followed thereafter by Pazopanib or Everolimus monotherapy until second progression. The comparative arm (Arm B) will be the standard regimen of Pazopanib (800 mg qd continuously) until progression, followed thereafter by Everolimus (10 mg qd continuously) until progression.

## Intervention

In the experimental arm (Arm A) alternating treatment will consist of repeating periods of 16 weeks of treatment consisting of 8 weeks of Pazopanib 800 mg qd followed by 8 weeks of Everolimus 10 mg qd until progression followed thereafter by Pazopanib or Everolimus monotherapy until second progression. The comparative arm (Arm B) will be the standard regimen of Pazopanib (800 mg qd continuously) until progression, followed thereafter by Everolimus (10 mg qd continuously) until progression.

## Study burden and risks

The side effects of Pazopanib and Everolimus used as single agents have been well described. Outside study participation patients will be offered similar agents. The additive risk, for half of the participating patients, results from the alternating dosing schedule. The side effects of alternating Everolimus and Pazopanib is still unknown. The current guideline recommends starting with a

TKI in the first line followed by a mTOR inhibitor when progressive disease develops. This switch is generally well tolerated.
If the patient accepts tumorbiopsies at baseline and when progressive disease occurs the punction related complicationrate varies between 0-1,6% (Protocol chapter 12.6). Most common complications are bruising, bleeding which required bloodtransfusion and pneumothorax. This part is optional. It*s an invasive procedure in which the burden will greatly depend on the patient*s perception.

## 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

- Subjects must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow-up.;- Age >= 18 years.;- Histologically confirmed diagnosis of progressive metastatic clear cell

renal cell cancer defined as >10% of the tumor cells having the clear cell phenotype.;- Locally advanced (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV RCC according to AJCC staging).;- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.;- Measurable disease. ;- No prior systemic anti-cancer treatment against clear cell renal cancer.;- Adequate organ system function.;- A female is eligible to enter and participate in this study if she is of: Non-childbearing potential (physiologically or by using adequate contraception) .

## Exclusion criteria

- Malignancy within the previous 5 years.;- History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis.;- Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:
1)Active peptic ulcer disease.
2)Known intraluminal metastatic lesions with risk of bleeding.
3) Inflammatory bowel disease (e.g. ulcerative colitis, Crohn*s disease), or other gastrointestinal conditions with increased risk of perforation.
4)History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.;-Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:
1)Malabsorption syndrome.
2)Major resection of the stomach or small bowel.;-Presence of uncontrolled infection.;-Known past or present infection with Hepatitis B virus (HBV), Hepatitis C virus (HCV) or Human Immunodeficiency Virus (HIV).;-Corrected QT interval (QTc) > 480 msecs using Bazett*s formula.;-History of one or more of the following cardiovascular conditions within the past 6 months:
1)Cardiac angioplasty or stenting
2)Myocardial infarction
3)Stable or unstable angina pectoris.
4)Coronary artery bypass graft surgery.
5)Symptomatic peripheral vascular disease
6)Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA).;- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of >=160 mmHg or diastolic blood pressure (DBP) of >= 90mmHg].;- History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.;- Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any nonhealing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).;- Evidence of active bleeding or bleeding diathesis.;- Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.;- Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug.;- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject*s safety, provision of informed

consent, or compliance to study procedures.;- Unable or unwilling to discontinue use of prohibited medications or modify the dosing of interacting drugs as listed in Section 6.8.1. and 6.8.2 of the protocol.;- Pregnant or lactating female.;- Treatment with any of the following anti-cancer therapies: radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of Pazopanib OR chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy.

# Study design

## Design

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| Study phase: | 2 |
| 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): | 19-09-2012 |
| Enrollment: | 100 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Afinitor |
| Generic name: | Everolimus |
| 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: | 05-09-2011 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 03-11-2011 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 20-08-2012 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 31-08-2012 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 08-02-2013 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 15-03-2013 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 16-05-2013 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 19-02-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 24-02-2014 |

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| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 04-04-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 27-08-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 24-10-2014 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 10-04-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 20-04-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 29-07-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 07-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 03-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# 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 | EUCTR2011-000127-32-NL |
| ClinicalTrials.gov | NCT01408004 |
| CCMO | NL35303.041.11 |