An open-label, multicenter phase II study to compare the efficacy and safety of RAD001 as first-line followed by second-line sunitinib versus sunitinib as first-line followed by second-line RAD001 in the treatment of patients with metastatic renal cell carcinoma

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To evaluate the probability that the progression free survival (PFS) in the first-line treatment with RAD001 is non-inferior to the first-line treatment with sunitinib for patients with metastatic renal cell carcinoma (primary objective)....

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

Summary

ID

NL-OMON36802

Source
ToetsingOnline

Brief title
Record-3

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer of the kidney, metastatic Renal Cell Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: mRCC, RAD001, Sunitinib

Outcome measures

Primary outcome

The primary efficacy endpoint is Progression Free Survival (PFS) during or

after first-line of both treatments (PFS-1L) according to the RECIST criteria.

Secondary outcome

* Progression Free Survival (PFS) of both arms, for first- and second-line

combined (PFS-C) after the second-line treatment

* To compare safety profiles of both drugs within the 2 lines strategies

* To compare Quality of Life (QoL) according to the FKSI-DRS and EORTC QLQ-C30

questionnaires for both arms of treatment

* To compare Overall Survival (OS) between the 2 treatment arms

* Objective Response Rate (ORR) and duration of response according to RECIST

during first-line treatment

* Assess plasma/serum changes in biomarkers of angiogenesis pre- and post

treatment (VEGFA, VEGFD, sVEGFR2, sVEGFR3, bFGF, PLGF, sVEGFR1, ckit, PDGF)

Study description

Background summary

The past 5 years have seen a dramatic expansion of therapeutic options in the treatment of metastatic renal cell carcinoma. The introduction of VEGF targeted therapies such as sorafenib, sunitinib, bevacizumab and mTOR inhibitors temsirolimus and everolimus have completely changed the treatment paradigm. Despite this progress, metastatic RCC still remains a fatal disease and the development of new treatments are needed to help improve the outcome for these patients.

RAD001 (everolimus, Afinitor®) is an oral mTOR inhibitor. It targets mTOR, a key protein kinase in regulating cell growth, proliferation and survival. The anticancer activity has recently been confirmed in a phase 3 study. In this study RAD001 significantly prolonged the progression-free-survival compared to placebo (median PFS of 4,9 vs. 1,87 months) in patients with mRCC which had progressed on sunitinib, sorafenib or both.

Sunitinib is an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (PDGFR-*, VEGFR2, c-KIT). In a phase 3 study, sunitinib significantly prolonged progression-free-survival compared to IFN-* in mRCC patients who had not received previous systemic therapy (median PFS of 11 vs. 5 months).

RAD001 and temsirolimus have both been combined with sunitinib in phase I trials, but due to toxicity concomitant use of these agents is not recommended.

RAD001 and sunitinib have been studied in phase 2 trials as single agents for mRCC patients who had previously received cytokines therapies. The PFS reported was prolonged relative to historical controls.

Therefore, the rationale for sequencing RAD001 and sunitinib is warranted to investigate the efficacy and safety of both agents as first-line and second-line treatment in mRCC and to evaluate the feasibility of a phase III study with RAD001 to demonstrate significant improvement as a first-line treatment over sunitinib in patients with mRCC.

Study objective

To evaluate the probability that the progression free survival (PFS) in the first-line treatment with RAD001 is non-inferior to the first-line treatment with sunitinib for patients with metastatic renal cell carcinoma (primary objective). Additionally, the purpose is to compare the PFS combined after the second-line and to evaluate the safety profile of RAD001 and sunitinib in both the first-line and second-line therapy setting.

Study design

In a phase II, open-label, multi-centre, international, non-inferiority trial patients will be randomized to receive either 10 mg RAD001 p.o (continuous) followed by sunitinib 50 mg p.o. (4 weeks on/2 weeks off) or vice versa. Patients will be stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) Risk Criteria.

Treatment with RAD001 and sunitinib should be continued as long as the patient is not progressing and tolerates the study treatment.

Patients will be eligible to cross over to the second-line medication and will stop second-line medication in case of documented disease progression or in case of discontinuation due to unacceptable toxicity or for other reasons (for example withdrawal of consent).

Intervention

Patients will be instructed to use RAD001 10 mg daily oral dose or sunitinib 50 mg oral dose 4 weeks on/2 weeks off. The duration of 1 cycle is 42 days.

Study burden and risks

After the screeningsperiod patients have to visit the hospital every 1st and 28th day of each treatment cycle (1st and 2nd line) which consists of 42 days. Tumor evaluations will be performed before the start of first-line study medication and every 12 weeks during both 1st and 2nd line treatment, until progression of disease. When discontinued for reasons other than disease progression, tumor evaluations have to be continued until disease progression or until initiation of another anti-cancer therapy.
Before cross-over to the second-line of medication, patients have to repeat the specified baseline assessments. Baseline tumor evaluations for the second-line period will only be necessary if the time between the last tumor evaluation (which lead to documentation of disease progression in 1st line) and start of 2nd line treatment is greater than 35 days.
After completion or discontinuations of both lines of study medication, all patients will return for an end-of treatment visit.
Patients who permanently discontinue with the study will have a safety follow-up visit 28 days after the last dose of medication and they will be followed for survival after 28 days and thereafter each 2 months for up to 3 years after the last patient is randomized to the study.
Use of RAD001 might cause side effects.

Contacts

Public

Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Patients with advanced renal cell carcinoma of a histological or cytological confirmation of clear cell (or with a component of clear cell) or patients with non-clear cell renal carcinoma.
* Patients with nephrectomy (partial or total) or without nephrectomy.

Exclusion criteria

* Patients who have received prior systemic treatment for their metastatic RCC.
* Patients who have previously received systemic mTOR inhibitors (sirolimus, temsirolimus, everolimus) or VEGF inhibitors.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-04-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sutent
Generic name:	Sunitinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-11-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-02-2010
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-03-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-04-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-08-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	21-03-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-03-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	23-01-2012
Application type:	Amendment
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

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	EUCTR2009-011056-21-NL
ClinicalTrials.gov	NCT00903175
CCMO	NL29936.068.09