A randomized, open label, multi-center phase II study to compare bevacizumab plus RAD001 versus interferon alfa-2a and bevacizumab for the first-line treatment of patients with metastatic clear cell carcinoma of the kidney

Published: 15-04-2009
Last updated: 24-01-2024

• To estimate the difference in the efficacy and safety of RAD001 10 mg p.o. daily dose in combination with bevacizumab 10 mg/kg administered intravenously every two weeks for first-line treatment of patients with metastatic carcinoma of the kidney...

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

Summary

ID

NL-OMON34911

Source
ToetsingOnline

Brief title
RECORD-2

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
renal cell cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: bevacizumab, interferon alfa 2a, kidney carcinoma, RAD001

Outcome measures

Primary outcome

Primary:

To assess the treatment effect on progression-free survival (PFS) of patients who receive RAD001 plus bevacizumab versus patients who receive IFN plus bevacizumab, in order to estimate the chance of success of a possible subsequent phase III study.

Secondary outcome

Secondary:

• To estimate the overall survival (OS) treatment effect in patients who receive RAD001 plus bevacizumab versus patients who receive IFN plus bevacizumab.

• To estimate the objective response rate and response duration differences in patients who receive RAD001 plus bevacizumab versus patients who receive IFN plus bevacizumab.

• To describe the safety profile of RAD001 plus bevacizumab versus IFN plus bevacizumab.

• To estimate patient reported outcomes on quality of life (QoL) from patients

treated with RAD001 plus bevacizumab versus patients treated with IFN plus bevacizumab.

• To measure the exposure of RAD001 in patients randomized to the treatment combination of RAD001 plus bevacizumab.

Exploratory:

• To determine the effects of RAD001 on plasma angiogenic molecules e.g., VEGF, basic FGF, PLGF, sVEGFR1, and sVEGFR2 and other markers of hypoxia e.g., LD isoenzyme 5 and carbonic anhydrase IX (CA9).

• To characterize pre-treatment tumor samples by immunohistochemical and genetic analyses for activation of the mTOR and angiogenic/hypoxia pathways.

• Relationships between response and RAD001 Cmin will be explored. RAD001 Cmin represents the minimum exposure of the drug in blood during daily administration. Exploration of the relationship between RAD001 Cmin and response helps to determine the minimum effective concentration of RAD001 in the target patient population.

Study description

Background summary

RAD001 (everolimus) is a derivative of rapamycin which acts as a signal transduction inhibitor. Its target is mTOR (mammalian target of rapamycin), a key protein kinase regulating cell growth, proliferation and survival. The mTOR pathway activity is modulated by the PI3K/AKT pathway, a pathway known to be dysregulated in numerous human cancers.
RAD001 is being investigated as an anticancer agent based on its potential to

act:
• directly on the tumor cells by inhibiting tumor cell growth and proliferation
• indirectly by inhibiting angiogenesis leading to reduced tumor vascularity
(via potent inhibition of tumor cell HIF-1 activity and vascular endothelial growth factor (VEGF) production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as
well as modulation of VEGFR signaling in endothelial cells. RAD001 is approved since 2003 in more than 60 countries (trade name: Certican®) for the prevention of organ rejection in patients with renal and cardiac transplantation.
Bevacizumab (Avastin®) is a recombinant humanized monoclonal IgG1 antibody that binds and prevents the interaction of VEGF to
its receptors VEGF receptors-1 and -2 (also known as Flt-1 and KDR or Flk-2.2). Bevacizumab has been approved since 2003 for the treatment of metastatic colorectal cancer in combination with chemotherapy; approvals for the treatment of metastatic breast and non-small cell lung cancer have more recently been added in many countries.

Based on the results from a randomized, double blind phase III trial of first-line bevacizumab plus interferon alfa-2a (IFN) versus IFN in patients with metastatic renal cell cancer, bevacizumab received approval in December 2007 in the EU for this indication. Bevacizumab is not yet approved in the US for the treatment of metastatic renal cell cancer. 641 patients were treated in this study in 18 countries. The objective response rate was 30.6% for bevacizumab plus IFN compared to 12.4% IFN and a progression-free survival of 10.2 months for bevacizumab plus IFN compared to 5.4 months for IFN (Escudier, et al 2007). Patients receiving bevacizumab plus IFN experienced the following Grade 3/4 adverse events: fatigue 12%, asthenia 10%,proteinuria 7%, neutropenia 4%, and bleeding, hypertension influenza-likesyndrome, anorexia, and anemia (all 3% each).
Phase 1 and 2 studies investigating the combination of RAD001 and bevacizumab are ongoing. To date, full dose of bevacizumab 10 mg/kg, i.v. every 2 weeks and full dose of RAD001 10 mg, p.o. daily given together has shown to be tolerable. An ongoing Phase II trial of RAD001 and bevacizumab in patients with advanced clear cell cancer of the kidney has enrolled 44 patients to date; 30 of which were treatment naive. Patient accrual is still ongoing for the cohort of patients with prior treatment. Preliminary data from 28 of 30 patients with no prior treatment showed: 6 partial responses, 15 stable disease, 2 progressive disease, 5 unevaluable, and 2 not yet available (Hainsworth, Sarah Cannon Cancer Center, direct communication on September 6, 2007; study title: Phase II study of bevacizumab and everolimus (RAD001) in the treatment of advanced renal cell carcinoma (RCC)).
A Phase 1 dose-escalation study of bevacizumab, RAD001, and erlotinib in patients with advanced-stage solid tumor demonstrated that the combination of RAD001 and bevacizumab was well tolerated, allowing full doses of both agents to be administered. The study included four dose levels:

Bevacizumab RAD001 Erlotinib
Dose Level 1 10 mg/kg every 2 wks 5 mg/day *
Dose Level 2 10 mg/kg every 2 wks 10 mg/day *
Dose Level 3 10 mg/kg every 2 wks 10 mg/day 75 mg/day
Dose Level 4 5 mg/kg every 2 wks 5 mg/day 75 mg/day

A total of 20 patients received bevacizumab and RAD001. Fifteen patients were treated in Dose Level 2 (bevacizumab 10 mg/kg every 2 weeks and RAD001 10 mg daily), and no dose-limiting toxicities were seen at this dose level (Bendell, 2007). The most common adverse events were mild or moderate mucositis, fatigue, rash, and musculo-skeletal pain. In the group of patients who received RAD001 and bevacizumab (20), there were six Grade 3 events, one of each of the following: proteinuria, deep vein thrombosis, cardiac ischemia, liver enzyme elevation, partial bowel obstruction, and rash. There were three Grade 4 events, one of each of the following: proteinuria, left ventricular thrombus, and left ventricular systolic dysfunction (Bendell, 2007).

Study objective

• To estimate the difference in the efficacy and safety of RAD001 10 mg p.o. daily dose in combination with bevacizumab 10 mg/kg administered intravenously every two weeks for first-line treatment of patients with metastatic carcinoma of the kidney compared to treatment with IFN dose escalating from 3 MIU (million international unit) during week one of
treatment, 6 MIU during week two of treatment, and 9 MIU during week 3 and subsequently (if tolerated), given subcutaneously three times weekly in combination with bevacizumab 10 mg/kg administered intravenously every two weeks.

Rationale:
• RAD001 has a potential to act directly on the tumor cells as well as indirectly by inhibiting angiogenesis.
• RAD001 has shown anti-tumor activity in patients with renal cell carcinoma in phase I and II clinical trials.
• Bevacizumab interferes with angiogenesis by blocking the interaction of VEGF with its receptors.
• mTOR inhibition by RAD001 affects a different biochemical pathway than VEGF inhibition by bevacizumab.
• RAD001 and bevacizumab exhibit non-overlapping toxicity profiles.

Study design

This is a randomized, open-label, multi-center phase II study. The estimated progression-free survival (PFS) treatment effect from this study will be used to calculate a predictive power. This predictive power will be used to estimate the

chance that a possible subsequent phase III study would demonstrate a significant improvement in PFS.
The final analysis of this phase II study will be performed when a total of 230 PFS events (per independent central radiological review) are observed in the Full Analysis Set (FAS) population. Assuming a study duration of 24 months, a total of 360 patients must be randomized, which includes 10% of patients lost to follow up during the study. See Statistical Methods section for additional details. As part of safety monitoring, an early safety analysis is planned when safety
listings on the first 100 randomized patients who have been treated for at least 1 cycle are available. This study will be supported by a independent central radiology panel for efficacy and safety (assessing non-infectious pneumonitis), central laboratory for analysis of blood samples, and IVRS for randomization.

Stratification: For randomization and primary efficacy analyses, patients will be stratified according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria for treatment-naïve patients (favorable vs. intermediate vs. poor risk groups, based on Karnofsky performance, time from initial diagnosis to treatment < 1 year, LDH, hemoglobin, and corrected serum
calcium laboratory values reported by the central laboratory).
Randomization ratio: 1:1
Screening phase: Screening evaluations will be performed within 21 days prior to the first dose of the study treatment (Day -20 to Day 0).
Baseline phase: Baseline evaluations will be performed within 1 week prior to the first dose of study treatment (Day -6 to Day 0). Baseline tumor assessment will be acceptable within 35 days prior to treatment start (Day -34 to Day 0).
Treatment phase/duration of treatment: Patients will receive their first dose of study drugs (IFN or RAD001 and bevacizumab) on Day 1, Cycle 1. All patients will be treated with either RAD001 10 mg, p.o. daily plus bevacizumab 10 mg/kg, i.v. every two weeks or IFN dose escalating from 3 MIU during week one, 6 MIU during week two, and 9 MIU during week 3 of treatment and subsequently (if tolerated), s.c. three times per week plus bevacizumab 10 mg/kg, i.v. every two weeks until tumor progression (by RECIST criteria, as assessed by the investigator), unacceptable toxicity, death, or discontinuation from the study for any other reason. The combination of IFN and bevacizumab should be continued as long as the patient does not have disease progression and tolerates the combination. When bevacizumab and IFN are given on the same day, IFN will be administered after the bevacizumab. On the days of PK blood sampling, the dose of RAD001 will be taken at the center after the PK blood sampling.
Tumor assessments will be performed every 12 weeks (± 1 week) from randomization until the start of another anticancer therapy. A partial or complete response warrants confirmation no sooner than 4 weeks and no later than 6 weeks after its initial observation.
6 Month Follow-up period: Any patient who is discontinued from study treatment for any reason will continue to have tumor assessments every 12 weeks (± 1

week) until the patient starts another anticancer therapy. The investigator or his/her designee will continue collecting information on the initiation of additional anticancer therapies until the date of data cutoff for the final analysis. All new anticancer therapy therapies after the last dose of study treatment will be recorded on the appropriate CRF.
Patients who have ongoing hypertension at the end-of-treatment visit or who experience a new hypertensive event during the 6 month follow-up period will have their blood pressure and use of anti-hypertensive medications monitored. Monitoring will take place at the 3 month follow-up and 6 month follow-up visits or until blood pressure returns to within
normal range (systolic blood pressure <= 140 mmHg and diastolic blood pressure <= 90 mmHg).
• Patients who have ongoing proteinuria events at the end-of-treatment visit or who experience a new proteinuria event during the 6 month follow-up period will be monitored for 24-hour urine collection at the 3 Month Followup and 6 Month Follow-up visits or until total 24-hour urine protein improves to <= 1g.
• An adverse event of wound healing complication, gastrointestinal perforations, and arterial thromboembolic event, irrespective of causal relationship, should be reported during the 6 month follow-up period. Patients who have ongoing wound healing complications at the end-oftreatment visit or who experience a new wound healing event during the 6
month follow-up period will have their wound healing complications monitored every 4 weeks until the events have resolved.
28 Day Follow-up Visit: All patients will have a follow-up visit scheduled 28 days after the end-of-treatment visit to follow for AEs and SAEs that may have occurred after discontinuation from the study. 3 Month & 6 Month Follow-up Visits: All patients will have a 3 month followup and a 6 month follow-up visits scheduled after the end-of-treatment visit to
monitor for hypertension, proteinuria, wound healing complication, gastrointestinal perforations, surgical procedure, major injury, and arterial thromboembolic event, irrespective of causal relationship. Any major injury or surgical procedure must be reported during the follow-up period.
Central radiological review: The primary analysis of PFS will be based on an independent central radiology review. All CT scans, MRIs, bone scans, and MRI-Quickscans (at baseline only) obtained at baseline, during the treatment period, and after the study treatment discontinuation until patient starts another anticancer therapy will be sent to the independent central radiologist.
Survival data collection: After the 6 month follow-up period or patient*s last visit, all patients will be followed every 2 months for survival up to 2 years after the last patient is randomized to the study.

Intervention

Study treatment will start on Day 1, Cycle 1 until progression of disease (per the investigator), unacceptable toxicity, death or discontinuation from the study for any other reason. A treatment cycle consists of 4 continuous weeks (or 28

continuous days) of study treatment.

Arm 1:
RAD001 :10 mg/day, p.o., daily (two 5 mg tablets)
Bevacizumab: 10 mg/kg, i.v., every 2 weeks

Arm 2:
IFN: Week 1: 3 MIU, Week 2: 6 MIU, Week 3: 9 MIU, Subsequently: 9 MIU (if tolerated) s.c., 3 times weekly (administered after bevacizumab if given on same day)
Bevacizumab: 10 mg/kg, i.v., every 2 weeks

Study burden and risks

This research study may involve unpredictable risks to the participants.
The most common possible side effects of the study drug RAD001 are skin changes (rash) including redness, itching or irritation, mouth lining changes (stomatitis) manifested as redness, irritation, swelling in the mouth or mouth ulcers, fatigue, nausea, decrease of appetite (anorexia), headache, vomiting, diarrhea, constipation, abdominal distension and occasionally infections. There could be a lowering of the number of red blood cells, white blood cells and platelets as well as lowering in levels of some electrolytes (potassium, sodium, calcium, magnesium or phosphate) in the blood. The levels of glucose, lipids (triglycerides and cholesterol) or liver enzymes (transaminases)in the blood could increase (increased levels of cholesterol are an important factor of risk of heart disease), and therefore the blood glucose, lipid and liver enzymes levels will be regularly monitored in this study.
RAD001 may be associated with changes within lungs such as inflammation (pneumonitis). Some patients have no symptoms associated with lung changes, while others may develop a cough and/or shortness of breath.
RAD may predispose bleeding specially when number of platelets in the blood is low. Very rarely, RAD001 may cause toxicity to your kidneys and the levels of blood creatinine in your blood could increase. Therefore, blood creatinine levels will be regularly monitored in this study.
Please also see section E9 of this form.

Contacts

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Eligibility criteria

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

Inclusion criteria

1. Age >= 18 years old
2. Patients with metastatic renal cell carcinoma and with histological or cytological confirmation of clear cell RCC (pathology report based on the tissue from the original diagnosis of renal cell cancer is acceptable). Any percentage of clear cell histology is acceptable.
3. Patients with at least one measurable lesion at baseline as per the RECIST criteria. If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper) in clear focus to allow the size of the lesion(s) to be determined from the photograph.
4. Patients with progressive metastatic renal cell carcinoma (by RECIST criteria) requiring treatment.
5. Patients who had a prior partial or complete nephrectomy. Partial nephrectomy is allowed only if the resection margins were clearly negative.
6. Patients with a Karnofsky Performance Status >=70%.
7. Adequate bone marrow function as shown by: ANC >= 1.5 x 109/L, Platelets >= 100 x 109/L, Hb >9 g/dL.
8. Adequate liver function: serum bilirubin: <= 1.5 x ULN, ALT and AST <= 2.5x ULN. Patients with known liver metastases: AST and ALT <= 5x ULN.
9. Adequate renal function: serum creatinine <= 2.0 x ULN.
10. INR and PTT <= 1.5 (Anticoagulation is allowed if target INR <= 1.5 on a stable dose of warfarin or on a stable dose of LMW heparin for >2 weeks at time of randomization.)
11. Adequate lipid profile: total cholesterol < 300 mg/dL and triglyceride < 200 mg/dL.
12. Women of childbearing potential must have had a negative serum pregnancy test 72 hours prior to the administration of the study treatment start.
13. Patients who give a written informed consent obtained according to local guidelines.

Exclusion criteria

1. Patients within 4 weeks post-major surgery (e.g., intra-thoracic, intraabdominal or intra-pelvic), open biopsy, or significant traumatic injury to avoid wound healing complications. Minor procedures and percutaneous biopsies or placement of vascular access device require 7 days prior to study entry.
2. Patients who had radiation therapy within 4 weeks prior to start of study treatment (palliative radiotherapy to bone lesions allowed within 2 weeks prior to study treatment start).
3. Patients in anticipation of the need for major surgical procedure during the course of the study.
4. Patients with a serious non-healing wound, ulcer, or bone fracture.
5. Patients with a history of seizure(s) not controlled with standard medical therapy.
6. Patients who have received prior systemic treatment for their metastatic RCC. Adjuvant immunotherapy (vaccines acceptable, but no cytokines) completed 3 months prior to study treatment start is acceptable.
7. Patients who received prior therapy with VEGF pathway inhibitor (even in the adjuvant setting), such as sunitinib, sorafenib, and bevacizumab.
8. Patients who have previously received systemic mTOR inhibitors (sirolimus, temsirolimus, everolimus).
9. Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients.
10. Patients with evidence of current central nervous system (CNS) metastases or spinal cord compression.
11. Patients with a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment.
12. Patients with proteinuria at screening as demonstrated by either:
- Urine protein: creatinine (UPC) ratio >= 1.0 at screening.
- Urine dipstick for proteinuria >= 2+ (patients discovered to have >=2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate <= 1g of protein in 24 hours to be eligible).
13. Patients with inadequately controlled hypertension (defined as a blood pressure of > 150 mmHg systolic and/or > 100 mmHg diastolic on medication), or any prior history of hypertensive crisis or hypertensive encephalopathy.
14. Patients receiving ongoing or with recent (within 10 days prior to study treatment start) need for full therapeutic dose of oral or parenteral anticoagulants or chronic daily treatment with aspirin (> 325 mg/day) or clopidogrel (>75 mg/day).
15. Patients receiving chronic systemic treatment with corticosteroids (dose of >= 10 mg/day methylprednisone equivalent) or another immunosuppressive agent. Inhaled and topical steroids are acceptable.
16. Patients with a known history of HIV seropositivity.
17. Patients with hypersensitivity to IFN or any component of the product.
18. Patients with an active, bleeding diathesis or coagulopathy or recurrent thromboembolism (>1 episode of DVT/PE during the past year).
19. Patients who have any severe and/or uncontrolled medical conditions or other conditions

that could affect their participation in the study such as:
- unstable angina pectoris, symptomatic congestive heart failure (NYHA II, III, IV), myocardial infarction <= 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia, cerebrovascular accidents <= 6 months before study treatment start,
- severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or 02 saturation that is 88% or less at rest on room air,
- poorly controlled diabetes as defined by fasting serum glucose >2.0 x ULN,
- any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study,
- nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study treatment, such as severe hypertension that is not controlled with medical management and thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication,
- liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis or chronic persistent hepatitis.
20. Patients who have a history of another primary malignancy and off treatment for <= 3 years, with the exception of non-melanoma skin cancer and carcinoma in situ of the uterine cervix.
21. Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Oral contraceptives are not acceptable.
22. Patients who are using other investigational agents or who had received investigational drugs <= 4 weeks prior to study treatment start.
23. Patients unwilling to or unable to comply with the protocol.

Study design

Design

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):	16-09-2009
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	bevacizumab
Generic name:	Avastin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	interferon alfa-2a
Generic name:	Roferon-a
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	RAD001
Generic name:	Certican
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	15-04-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-06-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-09-2009
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-02-2012

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	2008-000077-38
ClinicalTrials.gov	NCT00719264
CCMO	NL25381.058.08