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RAD001 Plus Best Supportive Care (BSC) Versus BSC Plus Placebo in Patients With Metastatic Carcinoma of the Kidney Which Has Progressed After Treatment With Sorafenib and/or Sunitinib (RECORD-1)

This study has been completed.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT00410124

First received: December 11, 2006
Last updated: December 7, 2012
Last verified: December 2012
History of Changes

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Purpose

To assess whether daily treatment with **RAD001** could slow the growth and spread of metastatic carcinoma of the kidney. The safety of **RAD001** was also to be studied in this trial.

Condition	Intervention	Phase
Metastatic Renal Cell Carcinoma	Drug: **RAD001** Drug: Placebo	**Phase 3**

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Randomized, Double-blind, Placebo-controlled, Multicenter Phase III Study to Compare the Safety and Efficacy of **RAD001** Plus Best Supportive Care (BSC) Versus BSC Plus Placebo in Patients With Metastatic Carcinoma of the Kidney Which Has Progressed on VEGF Receptor Tyrosine Kinase Inhibitor

Resource links provided by NLM:

MedlinePlus related topics: Cancer Kidney Cancer

Drug Information available for: Sirolimus Everolimus Temsirolimus

Genetic and Rare Diseases Information Center resources: Kidney Cancer Renal Cancer

U.S. FDA Resources

Further study details as provided by Novartis:

Primary Outcome Measures:

- Progressive Free Survival (PFS) in Patients Who Receive **RAD001** Plus Best Supportive Care(BSC) Versus Patients Who Receive Matching Placebo Plus BSC [Time Frame: Time from randomization to dates of disease progression, death from any cause or last tumor assessment reported between date of first patient randomized until 28Feb2008 cut of date.] [Designated as safety issue: Yes]

  Progression Free survival is defined as the time from randomization to the date of first documented disease progression or death from any cause. The primary statistical analysis of PFS was based on central radiological assessments using a one-sided stratified log-rank test.

Radiological assessments: every 8 weeks (+/-1 week) during the first year and every 12 weeks (+/- 1 week) during the second year and thereafter and at the end of the study. Kaplan-Meier methodology was used to estimate the median PFS for each treatment group.

Secondary Outcome Measures:

- Overall Survival (OS) Assessed by the Monthly Overall Survival Assessments [Time Frame: Assessed every month up to 2 years after the last patient was randomized into the study from the date of randomization to the time of death. (Data cutoff was 15Nov2009)]
  [Designated as safety issue: Yes]

  Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. Kaplan-Meier methodology was used to estimate the median overall survival for each treatment group

- Best Overall Response Rate in Patients Who Receive **RAD001** Plus BSC Versus Matching Placebo Plus BSC [Time Frame: Time from randomization to dates of disease progression, death from any cause or last tumor assessment reported, between date of first patient randomized until 28Feb2008 cutoff date] [Designated as safety issue: No]

  The Best Overall Response rate (BOR) is defined as the percentage of patients having achieved confirmed Complete Response + Partial Response. Complete Response (CR) = at least two determinations of CR at least 4 weeks apart before progression. • Partial response (PR) = at least two determinations of PR or better at least 4 weeks apart before progression. Radiological assessments: every 8 weeks (+/-1 week) during the first year and every 12 weeks (+/- 1 week) during the second year and thereafter and at the end of the study.

- Duration of Response in Patients Who Receive **RAD001** Plus BSC Versus Placebo Plus BSC [Time Frame: Time from randomization to dates of disease progression, death from any cause or last tumor assessment reported, between date of first patient randomized until 28Feb2008 cutoff date] [Designated as safety issue: No]

  Duration of overall response (CR or PR) applies only to patients whose Best Overall Response (BOR) was Complete Response (CR) or Partial Response (PR). The start date is the date of first documented response (CR or PR) and the end date is the date of event defined as the first documented progression or death. Radiological assessments: every 8 weeks (+/-1 week) during the first year and every 12 weeks (+/- 1 week) during the second year and thereafter and at the end of the study.

- Analysis of Time to Definitive Deterioration of the Global Health Status/QoL Scale(QL) Scores of the EORTC QLQ-30 Questionnaire by at Least 10 Percent Using Kaplan Meier Method, by Treatment. [Time Frame: Baseline and every 28 days under treatment and at discontinuation from RAD001" until 28Feb2008 cutoff date] [Designated as safety issue: No]

  The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items. Global health status / QoL scale (QL), consisting of 2 questions each scored from 1 (very poor) to 7 (excellent), and with possible scores ranging from 2 to 14. Higher score indicates better functioning. Definitive deterioration by at least 10% is defined as a decrease in score by at least 10% compared to baseline, with no increase above this threshold observed during the course of the study. A single measure reporting a decrease of at least 10% is considered definitive only if it is the last one available for the patient. Time to definitive deterioration is the number of days between the date of randomization and date of assessment at which definitive deterioration is seen.

- Time to Definitive Deterioration of the FKS-DRS Risk Score by at Least 2 Score Units Using Kaplan-Meier Method, by Treatment.
  [Time Frame: Baseline and every 28 days under treatment and at discontinuation from RAD001" until 28Feb2008 cutoff date]
  [Designated as safety issue: No]

  The Functional Assessment of Cancer Therapy - Kidney Symptom Index, Disease Related Symptoms (FKSI-DRS) is a set of items to assess symptoms experienced by patients with advanced kidney cancer. These symptoms include fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. There were 4 response categories (1=Not at all, 2= A little, 3=Quite a bit, 4=Very much), sum of item responses can range from 0 to 36. "0"= severely symptomatic patient and the highest score is an asymptomatic patient. Definitive deterioration of the FKSI-DRS score was defined as a decrease by at least 2 units compared to baseline, with no later increase above this threshold observed during the study. A single measure reporting a decrease of at least 2 units was considered definitive only if it is the last one available for the patient. Time to definitive deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen.

- Time to Definitive Deterioration of the Physical Functioning Scale (PF)Score of the EORTC QLQ-C30 Questionnaire by at Least 10 Percent Using Kaplan_Meier Method, by Treatment. [Time Frame: Baseline and every 28 days under treatment and at discontinuation from RAD001" until 28Feb2008 cutoff date] [Designated as safety issue: No]

  The EORTC QLQ-C30 contains 30 items. These include five functional scales (physical, role, emotional, social and cognitive functioning), three symptom scales fatigue, pain, nausea, and vomiting), a global health status/QoL scale, and six single items (dyspnea, diarrhea, constipation, anorexia, insomnia and financial impact). Physical Functioning (PF) sub-scale, consisting of 5 questions each scored from 1 (not at all) to 4 (very much), and with possible values ranging from 5 to 20. Definitive deterioration by at least 10% is defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the course of the study. A single measure reporting a decrease of at least 10% is considered definitive only if it is the last one available for the patient. Time to definitive deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen.

- Pharmacokinetics of **RAD001**:Peak Concentration in a Dosing Interval (C-max); Pre-dose Concentration at 24-h Time Point in Dosing Interval

(C-min) and Average Concentration in a Dosing Interval =(C-avg) [Time Frame: At pre-dose and post-dose: 1 hour, 2 hour, 5 hour, 24 hour of Cycle 1 Day1, Cycle 1 Day 15 and at pre-dose from Cycle 2(day1) and all subsequent treatment cycles up until data cut-off 28 Feb 2008.] [Designated as safety issue: No]

Blood samples will be collected by direct venipuncture during regularly scheduled visits according to the collection plan provided in the study protocol. C-avg= Area under curve (AUC) in a dosing interval from time-zero to time of the last quantifiable concentration (AUC0-tlast)/ time of the last quantifiable concentration in a dosing interval (tlast)

- Pharmacokinetics of **RAD001**: Time at Which C-Max Occurs (t-Max) [Time Frame: At pre-dose and post-dose: 1 hour, 2 hour, 5 hour, 24 hour of Cycle 1 Day 1, Cycle 1 Day 15 and at pre-dose of From Cycle 2 (Day 1) and all subsequent treatment cycles until data cut-off 28Feb2008.] [Designated as safety issue: No]

  Blood samples will be collected by direct venipuncture during regularly scheduled visits according to the collection plan provided in the study protocol.

- Pharmacokinetics of **RAD001**: Area Under Curve (AUC) in a Dosing Interval From Time-zero to Time of the Last Quantifiable Concentration. (AUC 0-tlast) [Time Frame: At pre-dose and post-dose: 1 hour, 2 hour, 5 hour, 24 hour of Cycle 1 Day 1, Cycle 1 Day 15 and at pre-dose from Cycle 2 (Day 1) and all subsequent treatment cycles until data cut-off 28Feb2008.] [Designated as safety issue: No]

  Blood samples will be collected by direct venipuncture during regularly scheduled visits according to the collection plan provided in the study protocol.

- Pharmacokinetics of **RAD001**: Time of the Last Quantifiable Concentration in a Dosing Interval - (Tlast) [Time Frame: At pre-dose and post-dose: 1 hour, 2 hour, 5 hour, 24 hour of Cycle 1 Day 1, Cycle 1 Day 15 and at pre-dose from Cycle 2 (Day 1) and all subsequent treatment cycles until data cut-off 28Feb2008.] [Designated as safety issue: No]

  Blood samples will be collected by direct venipuncture during regularly scheduled visits according to the collection plan provided in the study protocol.

- Pharmacokinetics of **RAD001**: Apparent Systemic Clearance From Blood Following Extravascular Administration (CL/F) [Time Frame: At pre-dose and post-dose: 1 hour, 2 hour, 5 hour, 24 hour of Cycle 1 Day 1, Cycle 1 Day 15 and at pre-dose from Cycle 2 (Day 1) and all subsequent treatment cycles until data cut-off 28Feb2008.] [Designated as safety issue: No]

  Blood samples will be collected by direct venipuncture during regularly scheduled visits according to the collection plan provided in the study protocol.Apparent oral clearance of RAD001 (CL/F) was calculated using AUC in a dosing interval of 24 hours (AUC0-24hours) value on Day 15 as: CL/F = dose/ AUC0-τ

- Pharmacokinetics of **RAD001**: Normalized to Body Surface Area (CL/F) [Time Frame: At pre-dose and post-dose: 1 hour, 2 hour, 5 hour, 24 hour of Cycle 1 Day 1, Cycle 1 Day 15 and at pre-dose from Cycle 2 (Day 1) and all subsequent treatment cycles until data cut-off 28Feb2008.] [Designated as safety issue: No]

  Blood samples will be collected by direct venipuncture during regularly scheduled visits according to the collection plan provided in the study protocol.

Enrollment:	416
Study Start Date:	November 2006
Study Completion Date:	October 2011
Primary Completion Date:	February 2008 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: **RAD001** +BSC The study drugs were self administered by the patients. Patients were instructed to take the study drug as specified in the protocol. Patients were instructed to take two tablets (5 mg each) by mouth every day. Tablets were to be taken one tablet after another with a glass of water, at the same time each day in a fasting state or with a light fat-free meal. If disease progression occurred, patients were unblinded and if they were receiving **RAD001**, they would discontinue the study. Otherwise, they would be given the option to continue in the extension open label phase of 2 tablets of **RAD001** 5mg by mouth every day.	Drug: **RAD001** The dose of **RAD001** was 10 mg/day. Patients were instructed to take two tablets (5 mg each) by mouth every day. Other Name: **Everolimus**
Placebo Comparator: Placebo (plus BSC) Patients received matching placebo of **RAD001** tablets twice a day along with Best Supportive Care. With the documented disease progression, the investigator could unblind the patient. If unblinded patient was receiving placebo treatment, they were given the option to continue in the extension open label phase of 2 tablets of **RAD001** 5mg by mouth every day.	Drug: Placebo

Eligibility

Ages Eligible for Study: 18 Years to 85 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Patients with metastatic carcinoma and with histological or cytological confirmation of clear cell RCC (tissue from the original diagnosis of renal cell cancer is acceptable).
- The date of progression on sunitinib and/or sorafenib must be within 6 months.
- Patients may have received one or both agents
- Prior therapy with cytokines (i.e., IL-2, Interferon) and/or VEGF-ligand inhibitors (i.e., bevacizumab) are permitted.
- Prior vaccine therapy in the adjuvant setting is permitted.
- Patients with at least one measurable lesion at baseline as per the Response evaluation criteria in solid tumors (RECIST) criteria, either on physical exam or as determined by Computer Tomography (CT) Scan or Magnetic Resonance Imaging (MRI).
- Patients with a Karnofsky Performance Status ≥70%.
- Adequate bone marrow, liver and renal function.
- Patients with a life expectancy ≥ 3 months.
- Women of childbearing potential must have had a negative serum or urine pregnancy test 48 hours prior to the administration of the first study treatment.
- Patients who give a written informed consent obtained according to local guidelines

Exclusion Criteria:

- Patients currently receiving chemotherapy, immunotherapy, or radio-therapy or who have received these within 4 weeks of study entry
- Patients who have previously received mTOR inhibitors.
- Patients with a known hypersensitivity to RAD001 or other rapamycins (sirolimus, temsirolimus) or to its excipients.
- Patients with untreated CNS metastases or who are neurologically unstable despite treatment of the CNS metastases. (Patients with treated CNS metastases, who are neurologically stable off of corticosteroids, are eligible to enter study).
- Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent
- Patients with a known history of HIV seropositivity.
- Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumadin)
- Patients who have any severe and/or uncontrolled medical conditions
- Patients who have a history of another primary malignancy ≤ 3 years, with the exception of non-melanoma skin cancer, and carcinoma in situ of uterine cervix
- 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.
- Patients who are using other investigational agents or who had received investigational drugs ≤ 4 weeks prior to randomization
- Patients unwilling to or unable to comply with the protocol

Other protocol-defined inclusion/exclusion criteria may apply.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00410124

Show 93 Study Locations

Sponsors and Collaborators

Novartis Pharmaceuticals

Investigators

Study Director: Novartis Pharmaceuticals Novartis Pharmaceuticals

More Information

No publications provided by Novartis

Additional publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Stein A, Bellmunt J, Escudier B, Kim D, Stergiopoulos SG, Mietlowski W, Motzer RJ; RECORD-1 Trial Study Group. Survival prediction in everolimus-treated patients with metastatic renal cell carcinoma incorporating tumor burden response in the RECORD-1 trial. Eur Urol. 2013 Dec;64(6):994-1002. doi: 10.1016/j.eururo.2012.11.032. Epub 2012 Nov 21.

Stein A, Wang W, Carter AA, Chiparus O, Hollaender N, Kim H, Motzer RJ, Sarr C. Dynamic tumor modeling of the dose-response relationship for everolimus in metastatic renal cell carcinoma using data from the phase 3 RECORD-1 trial. BMC Cancer. 2012 Jul 23;12:311. doi: 10.1186/1471-2407-12-311.

Porta C, Calvo E, Climent MA, Vaishampayan U, Osanto S, Ravaud A, Bracarda S, Hutson TE, Escudier B, Grünwald V, Kim D, Panneerselvam A, Anak O, Motzer RJ. Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 Trial. Eur Urol. 2012 Apr;61(4):826-33. doi: 10.1016/j.eururo.2011.12.057. Epub 2012 Jan 5.

Calvo E, Escudier B, Motzer RJ, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Ravaud A, Kim D, Panneerselvam A, Anak O, Figlin RA. Everolimus in metastatic renal cell carcinoma: Subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. Eur J Cancer. 2012 Feb;48(3):333-9. doi: 10.1016/j.ejca.2011.11.027. Epub 2011 Dec 30.

White DA, Camus P, Endo M, Escudier B, Calvo E, Akaza H, Uemura H, Kpamegan E, Kay A, Robson M, Ravaud A, Motzer RJ. Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. Am J Respir Crit Care Med. 2010 Aug 1;182(3):396-403. doi: 10.1164/rccm.200911-1720OC. Epub 2010 Mar 1.

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A; RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56. Epub 2008 Jul 22.

Responsible Party:	Novartis (Novartis Pharmaceuticals)
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Study First Received:	December 11, 2006
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Last Updated:	December 7, 2012
Health Authority:	United States: Food and Drug Administration

Keywords provided by Novartis:
advanced kidney cancer
everolimus
kidney cancer
oral therapy

Additional relevant MeSH terms:

Everolimus
Sirolimus
Carcinoma
Carcinoma, Renal Cell
Neoplasms, Glandular and Epithelial
Neoplasms by Histologic Type
Neoplasms
Adenocarcinoma
Kidney Neoplasms
Urologic Neoplasms
Urogenital Neoplasms
Neoplasms by Site
Kidney Diseases
Urologic Diseases
Immunosuppressive Agents
Immunologic Factors
Physiological Effects of Drugs
Pharmacologic Actions
Antibiotics, Antineoplastic
Antineoplastic Agents
Therapeutic Uses
Antifungal Agents
Anti-Infective Agents
Anti-Bacterial Agents

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