Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication(s)

Metastatic carcinoma of the kidney

Protocol Number

CRAD001L2401

Protocol Title

An open-label, multi-center, expanded access study of everolimus in patients with metastatic carcinoma of the kidney who are intolerant of or have progressed despite any available vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor therapy

Clinical Trial Phase

IIIb

Phase of Drug Development

IIIb

Study Start/End Dates

16 Jul 2008 to 05 Aug 2010

Study Design/Methodology

This was an open-label, single-arm, multi-center, multinational study designed to evaluate additional safety of everolimus in adult patients with mRCC who were intolerant of or whose disease had progressed on any available prior VEGF receptor tyrosine kinase

inhibitor therapy. No other agents have demonstrated efficacy in this disease setting. As such, the elements of the trial design were consistent with the framework of a life-threatening disease with an unmet medical need.
Everolimus was provided until it became commercially available (not applicable in the UK and Norway) for this indication in each participating country or until 15-Jun-2010, whichever occurred first. A planned sample size of 1000 patients were chosen based on the expected accrual rates and the planned duration of the trial.
The primary focus of the study was the collection of safety data to fulfill international regulatory requirements. Patients were asked to visit the clinic monthly. A treatment cycle was 28 days, and study drug was to be administered daily during the cycle.

Centers

251 centers in 34 countries: Argentina (3), Australia (6), Austria (4), Belgium (7), Brazil (2), Canada (19), Columbia (1), Czech Republic (4), Finland (2), Germany (44), Greece (6), Hungary (3), Israel (5), Italy (43), Jordan (1), Republic of Korea (7), Lebanon (2), Mexico (2), Netherlands (7), Norway (3), Panama (1), Russia (4), Saudi Arabia (1), Singapore (1), Slovak Republic (1), Spain (26), Sweden (3), Switzerland (3), Taiwan (5), Thailand (2), Turkey (5), United Kingdom (14), United States (12), and Venezuela (2)

Objectives:

Primary Objective: to evaluate additional safety of RAD001 in patients with metastatic renal cell carcinoma (mRCC) who are intolerant of or whose disease has progressed despite any available prior VEGF receptor tyrosine kinase inhibitor therapy.

Secondary Objectives:

To evaluate the investigator's best overall response rate of RAD001 in patients with mRCC who are intolerant of or whose disease has progressed despite any available prior VEGF receptor tyrosine kinase inhibitor therapy.

To provide expanded access to RAD001 in patients with mRCC who are intolerant of or whose disease has progressed despite VEGF receptor tyrosine kinase inhibitor therapy, until the product is commercially available (not applicable in the UK and Norway) for mRCC in each participating country or until 15-Jun-2010.

Test Product (s), Dose(s), and Mode(s) of Administration

Everolimus 10 mg tablets orally once daily immediately after a meal.

Statistical Methods

No statistical hypotheses were tested in this study.

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Study Population: Key Inclusion/Exclusion Criteria

The study population was comprised of adult patients with mRCC who were intolerant of or who had progressed on any prior VEGF receptor-targeted therapy.

Inclusion Criteria

- ≥ 18 years of age, male or female.
- Histological or cytological confirmation of mRCC.
- Intolerant of or had progressed on or after stopping treatment with any available VEGF receptor tyrosine kinase inhibitor therapy.
- Measurable or non-measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) as determined by the Investigator.
- Karnofsky Performance Status ≥ 70%.
- Adequate bone marrow, liver, and renal function as defined in the protocol.
- Written informed consent according to local regulatory guidelines.

Exclusion Criteria

- Patients receiving chemotherapy, immunotherapy, radiation therapy or any other investigational agent (including pazopanib) within 4 weeks of the first dose of study drug, or sunitinib and/or sorafenib within 1 week of the first dose of everolimus.
- Radiotherapy (RT) given at low dose for palliative treatment of pre-existing painful bone metastasis was allowed within 4 weeks of the first dose as long as the patient had recovered from any toxicity associated with the RT and all blood counts are within protocol limits.
- Patients who have previously received everolimus or other mTOR inhibitors.
- Patients with known hypersensitivity to everolimus or other rapamycin analogs (sirolimus, temsirolimus), or to its excipients.
- Patients receiving systemic treatment with corticosteroids or another immunosuppressive agent; patients may receive low dose treatment of corticosteroids up to a maximum dose of 20 mg prednisone or steroid equivalent per day, if they are being given for disorders such as rheumatoid arthritis, asthma, or adrenal insufficiency; topical or inhaled corticosteroids are permitted.

Participant Flow Table

Patient disposition (Full analysis set)

	N = 1367
Patients	**n (%)**
Completed	269 (19.7)
Discontinued	1098 (80.3)
Primary reason for discontinuation*	
Adverse events	215 (15.7)
Abnormal laboratory values	12 (0.9)
Abnormal test procedure results	0
Patient withdrew consent	54 (4.0)
Lost to follow-up	9 (0.7)
Administrative problems	190 (13.9)
Death	45 (3.3)
Disease progression	565 (41.3)
Protocol deviation	8 (0.6)

* Discontinuation from study drug as reported on the End of Treatment CRF page.

Baseline Characteristics

Demographic and baseline characteristics (Full analysis set)

Baseline characteristic	N = 1367
Age [years]	
n	1367
Mean (SD)	62.0 (10.41)
Median	63.0
Min – Max	23 - 87
Age	
< 65 years	775 (56.7%)
≥ 65 years	592 (43.3%)
Sex	
Male	989 (72.3%)
Female	378 (27.7%)
Race	
Caucasian	1220 (89.2%)
Black	2 (0.1%)
Asian	114 (8.3%)
Native American	7 (0.5%)
Pacific Islander	1 (0.1%)
Other	23 (1.7%)
Ethnicity	
Hispanic/Latino	118 (8.6%)
Chinese	34 (2.5%)
Indian	4 (0.3%)
Japanese	0
Mixed ethnicity	2 (0.1%)
Other	1199 (87.7%)
Weight [kg]	
n	1315
Mean (SD)	76.50 (16.316)
Median	75.00
Min – Max	34.5 - 151.0
Height [cm]	
n	1274
Mean (SD)	170.6 (9.17)
Median	171.0
Min – Max	139 - 199

Primary Outcome Result

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result

Best overall tumor response as per the investigator (FAS)

	N = 1367
Best overall tumor response as per the Investigator	**n (%)**
Complete response	0
Partial response	23 (1.7)
Stable disease	705 (51.6)
Progressive disease	324 (23.7)
Unknown	315 (23.0)

Unknown = all cases not qualifying for a confirmed complete response or partial response and without stable disease after more than 6 weeks or early progression within the first 12 weeks.

Best overall tumor response was assessed using RECIST criteria.

Safety Results

SAEs occurring in at least 2 patients by PT, regardless of study drug relationship, by SOC and PT (Safety set)

System organ class Preferred term	N = 1367 n (%)
Patients with at least one serious event*	533 (39.0)
Respiratory, thoracic and mediastinal disorders	175 (12.8)
Dyspnoea	68 (5.0)
Pleural effusion	42 (3.1)
Pneumonitis	32 (2.3)
Respiratory failure	13 (1.0)
Interstitial lung disease	10 (0.7)
Pulmonary embolism	10 (0.7)
Haemoptysis	7 (0.5)
Acute respiratory failure	4 (0.3)
Cough	3 (0.2)
Acute respiratory distress syndrome	2 (0.1)
Dyspnoea exertional	2 (0.1)
Epistaxis	2 (0.1)
Pulmonary oedema	2 (0.1)
Infections and infestations	128 (9.4)
Pneumonia	64 (4.7)

System organ class Preferred term	N = 1367 n (%)
Urinary tract infection	15 (1.1)
Lower respiratory tract infection	9 (0.7)
Sepsis	9 (0.7)
Respiratory tract infection	8 (0.6)
Abdominal abscess	2 (0.1)
Cellulitis	2 (0.1)
Gastroenteritis	2 (0.1)
Gastrointestinal infection	2 (0.1)
Lobar pneumonia	2 (0.1)
Postoperative wound infection	2 (0.1)
Septic shock	2 (0.1)
Gastrointestinal disorders	107 (7.8)
Diarrhoea	23 (1.7)
Vomiting	15 (1.1)
Gastrointestinal haemorrhage	11 (0.8)
Nausea	11 (0.8)
Stomatitis	10 (0.7)
Abdominal pain	9 (0.7)
Ascites	8 (0.6)
Constipation	6 (0.4)
Gastrointestinal obstruction	6 (0.4)
Intestinal obstruction	4 (0.3)
Colitis	3 (0.2)
Gastritis	3 (0.2)
Pancreatitis	3 (0.2)
Abdominal pain upper	2 (0.1)
Gastrointestinal disorder	2 (0.1)
Haematemesis	2 (0.1)
Haematochezia	2 (0.1)
Haemorrhoids	2 (0.1)
Melaena	2 (0.1)
Tongue oedema	2 (0.1)
General disorders and administration site conditions	78 (5.7)
Pyrexia	23 (1.7)
General physical health deterioration	19 (1.4)
Fatigue	17 (1.2)
Asthenia	12 (0.9)
Oedema peripheral	5 (0.4)
Performance status decreased	3 (0.2)
Device occlusion	2 (0.1)
Non-cardiac chest pain	2 (0.1)
Pain	2 (0.1)

System organ class Preferred term	N = 1367 n (%)
Metabolism and nutrition disorders	71 (5.2)
Dehydration	17 (1.2)
Hypercalcaemia	15 (1.1)
Hyperglycaemia	13 (1.0)
Decreased appetite	8 (0.6)
Hyperkalaemia	7 (0.5)
Hyponatraemia	4 (0.3)
Diabetes mellitus	3 (0.2)
Hypoglycaemia	3 (0.2)
Hypokalaemia	3 (0.2)
Hypercholesterolaemia	2 (0.1)
Hypertriglyceridaemia	2 (0.1)
Hypophagia	2 (0.1)
Blood and lymphatic system disorders	61 (4.5)
Anaemia	56 (4.1)
Thrombocytopenia	2 (0.1)
Renal and urinary disorders	50 (3.7)
Renal failure acute	17 (1.2)
Renal failure	15 (1.1)
Haematuria	7 (0.5)
Azotaemia	4 (0.3)
Renal haemorrhage	2 (0.1)
Urinary retention	2 (0.1)
Musculoskeletal and connective tissue disorders	46 (3.4)
Back pain	12 (0.9)
Bone pain	8 (0.6)
Pain in extremity	5 (0.4)
Arthralgia	4 (0.3)
Flank pain	3 (0.2)
Musculoskeletal chest pain	3 (0.2)
Musculoskeletal pain	3 (0.2)
Intervertebral disc protrusion	2 (0.1)
Neck pain	2 (0.1)
Osteonecrosis of jaw	2 (0.1)
Nervous system disorders	42 (3.1)
Spinal cord compression	7 (0.5)
Cerebral haemorrhage	3 (0.2)
Epilepsy	3 (0.2)
Headache	3 (0.2)
Syncope	3 (0.2)
Cerebral infarction	2 (0.1)
Cognitive disorder	2 (0.1)

System organ class Preferred term	N = 1367 n (%)
Convulsion	2 (0.1)
Dizziness	2 (0.1)
Grand mal convulsion	2 (0.1)
Paraesthesia	2 (0.1)
Cardiac disorders	33 (2.4)
Atrial fibrillation	6 (0.4)
Pericardial effusion	4 (0.3)
Cardiac failure	3 (0.2)
Cardiac failure congestive	3 (0.2)
Cardio-respiratory arrest	3 (0.2)
Myocardial infarction	3 (0.2)
Acute myocardial infarction	2 (0.1)
Angina pectoris	2 (0.1)
Cardiac failure acute	2 (0.1)
Tachycardia	2 (0.1)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	19 (1.4)
Tumour pain	7 (0.5)
Metastatic pain	4 (0.3)
Tumour haemorrhage	3 (0.2)
Psychiatric disorders	16 (1.2)
Confusional state	9 (0.7)
Anxiety	2 (0.1)
Delirium	2 (0.1)
Hallucination	2 (0.1)
Vascular disorders	14 (1.0)
Thrombosis	3 (0.2)
Deep vein thrombosis	2 (0.1)
Hypertensive crisis	2 (0.1)
Injury, poisoning and procedural complications	12 (0.9)
Femur fracture	2 (0.1)
Spinal fracture	2 (0.1)
Investigations	12 (0.9)
Blood creatinine increased	9 (0.7)
C-reactive protein increased	2 (0.1)
Skin and subcutaneous tissue disorders	9 (0.7)
Decubitus ulcer	2 (0.1)
Rash	2 (0.1)
Rash erythematous	2 (0.1)
Rash pruritic	2 (0.1)
Hepatobiliary disorders	8 (0.6)
Cholecystitis	4 (0.3)
Jaundice	2 (0.1)

System organ class Preferred term	N = 1367 n (%)
Immune system disorders	2 (0.1)
Anaphylactic reaction	2 (0.1)

*Eight SAEs of death occurred before the trial cut-off date but were not reported in the clinical database as SAEs. However, programmatic SAE narratives for the eight deaths are included with the SAE listings. The 8 deaths occurred within the 28-day safety follow-up period and seven were assessed as being due to disease progression and one due to euthanasia.

SOCs are arranged in descending order of frequency; PTs are arranged in descending order of frequency inside each SOC.

Multiple episodes of an event are counted only once per patient, multiple events within a SOC are counted only once in the total row.

SAEs occurring prior to start of study drug or more than 28 days after the discontinuation of study treatment are not summarized.

Summary of deaths and adverse events (Safety set)

Summary of deaths and adverse events	N = 1367 n (%)
All deaths	226 (16.5)
On-treatment deaths[1]	170 (12.4)
Adverse events (AEs)[2]	1011 (74.0)
Grade 3-4 AEs	842 (61.6)
Suspected to be drug-related	530 (38.8)
Serious adverse events (SAEs)	533 (39.0)
Suspected to be drug-related	201 (14.7)
AEs leading to study drug discontinuation[3]	230 (16.8)
Other significant AEs	932 (68.2)
AEs requiring dose adjustment/temporary interruption of study drug	657 (48.1)
AEs requiring additional therapy[4]	791 (57.9)
Clinically notable AEs[5]	694 (50.8)

1. On-treatment deaths are those which occurred up to 28 days after the discontinuation of study treatment.
2. Grade 3 and 4 AEs, SAEs, and any AE that caused a change in study drug administration (including changes in the administered dose, temporary interruptions and treatment discontinuation) were collected and documented in the database.
3. Of the 230 patients discontinuing due to AEs, 215 of the discontinuation events were due to AEs, 12 of the discontinuation events were due to abnormal laboratory values, and 3 of the discontinuation events were due to disease progression as reported on the Adverse Events CRF page.

4. Additional therapy included all non-drug therapy and concomitant medications.
5. Clinically notable adverse events are the events for which there is a specific clinical interest in connection with everolimus or events which are similar in nature.

Adverse events occurring prior to start of study drug or more than 28 days after the discontinuation of study treatment are not summarized.

On-treatment deaths by SOC and PT (Safety set)

System organ class Preferred term	N = 1367 n (%)
Number of patients that died*	170 (12.4)
Study indication	120 (8.8)
Disease progression	120 (8.8)
Respiratory, thoracic and mediastinal disorders	19 (1.4)
Respiratory failure	9 (0.7)
Acute respiratory failure	2 (0.1)
Pneumonitis	2 (0.1)
Pulmonary embolism,	2 (0.1)
Acute respiratory distress syndrome	1 (0.1)
Dyspnoea	1 (0.1)
Pleural effusion	1 (0.1)
Respiratory distress	1 (0.1)
Infections and infestations	13 (1.0)
Pneumonia	9 (0.7)
Sepsis	2 (0.1)
Pneumonia streptococcal	1 (0.1)
Urinary tract infection	1 (0.1)

Cardiac disorders	6 (0.4)
Cardio-respiratory arrest	2 (0.1)
Myocardial infarction	2 (0.1)
Cardiac failure	1 (0.1)
Left ventricular failure	1 (0.1)
General disorders and administration site conditions	4 (0.3)
Sudden death	2 (0.1)
Euthanasia	1 (0.1)
General physical health deterioration	1 (0.1)
Renal and urinary disorders	4 (0.3)
Renal failure	2 (0.1)
Renal failure acute	2 (0.1)
Gastrointestinal disorders	1 (0.1)
Intestinal perforation	1 (0.1)
Injury, poisoning and procedural complications	1 (0.1)
Pneumonitis chemical	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)
Hyperglycaemia	1 (0.1)
Nervous system disorders	1 (0.1)
Cerebrovascular accident	1 (0.1)

SOCs are arranged in descending order of frequency; PTs are arranged in descending order of frequency inside each SOC.

On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment.

*Eight SAEs of death occurred before the trial cut-off date but were not reported in the clinical database as SAEs. The 8 deaths occurred within the 28-day safety follow-up period and seven were assessed as being due to disease progression and one due to euthanasia.

Other Adverse Events by System Organ Class

Adverse Events, Regardless of Study Drug Relationship, by System Organ Class and Worst CTC Grade (Safety Set)

N = 1367

System organ class	CTC grade 3 n (%)	CTC grade 4 n (%)	All grades* n (%)
Patients with at least one event	667 (48.8)	175 (12.8)	1011 (74.0)
Gastrointestinal disorders	182 (13.3)	15 (1.1)	302 (22.1)
Respiratory, thoracic and mediastinal disorders	156 (11.4)	39 (2.9)	301 (22.0)
General disorders and administration site conditions	166 (12.1)	19 (1.4)	266 (19.5)
Metabolism and nutrition disorders	196 (14.3)	27 (2.0)	262 (19.2)
Blood and lymphatic system disorders	161 (11.8)	42 (3.1)	240 (17.6)
Infections and infestations	118 (8.6)	17 (1.2)	185 (13.5)
Investigations	87 (6.4)	4 (0.3)	123 (9.0)
Musculoskeletal and connective tissue disorders	73 (5.3)	7 (0.5)	107 (7.8)
Skin and subcutaneous tissue disorders	37 (2.7)	1 (0.1)	81 (5.9)
Nervous system disorders	53 (3.9)	8 (0.6)	76 (5.6)
Renal and urinary disorders	37 (2.7)	16 (1.2)	68 (5.0)

Cardiac disorders	21 (1.5)	13 (1.0)	41 (3.0)
Vascular disorders	22 (1.6)	7 (0.5)	34 (2.5)
Psychiatric disorders	16 (1.2)	3 (0.2)	24 (1.8)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	13 (1.0)	5 (0.4)	23 (1.7)
Injury, poisoning and procedural complications	8 (0.6)	2 (0.1)	19 (1.4)
Hepatobiliary disorders	10 (0.7)	0	12 (0.9)
Reproductive system and breast disorders	3 (0.2)	0	7 (0.5)
Surgical and medical procedures	1 (0.1)	0	5 (0.4)
Ear and labyrinth disorders	2 (0.1)	0	4 (0.3)
Immune system disorders	2 (0.1)	1 (0.1)	4 (0.3)
Endocrine disorders	2 (0.1)	0	2 (0.1)
Eye disorders	0	0	1 (0.1)

* Only grade 3 and 4 AEs, SAEs, and any AE that caused a change in study drug administration (including changes in the administered dose, temporary interruptions and treatment discontinuation) were collected and documented in the database.

SOCs are arranged in descending order of frequency.

The event with maximum severity is counted for patients who experienced multiple episodes of an event; multiple events within a SOC are counted only once in each SOC.

Adverse events occurring prior to start of study drug or more than 28 days after the discontinuation of study treatment are not summarized.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Frequent AEs (incidence greater than 5% for all grades), regardless of study drug relationship, by PT and worst CTC grade (Safety set)

	N = 1367		
Preferred term	CTC grade 3 n (%)	CTC grade 4 n (%)	All grades* n (%)
Patients with at least one event	667 (48.8)	175 (12.8)	1011 (74.0)
Anaemia	142 (10.4)	41 (3.0)	202 (14.8)
Stomatitis	72 (5.3)	2 (0.1)	138 (10.1)
Dyspnoea	75 (5.5)	13 (1.0)	116 (8.5)
Fatigue	89 (6.5)	3 (0.2)	116 (8.5)
Pneumonitis	33 (2.4)	4 (0.3)	83 (6.1)
Hyperglycaemia	67 (4.9)	8 (0.6)	78 (5.7)
Pneumonia	50 (3.7)	7 (0.5)	71 (5.2)

* Only grade 3 and 4 AEs, SAEs, and any AE that caused a change in study drug administration (including changes in the administered dose, temporary interruptions and treatment discontinuation) were collected and documented in the database.

PTs are arranged in descending order of frequency over all grades.

The event with maximum severity is counted for patients who experienced multiple episodes of an event.

Adverse events occurring prior to start of study drug or more than 28 days after the discontinuation of study treatment are not summarized.

Other Relevant Findings

No other important or notable findings were reported in this study.

Conclusion:

This expanded access study confirms the safety and efficacy findings of the pivotal Phase III trial of everolimus in mRCC (Study RAD001C2240) in a larger population of patients from a wide range of centers and countries.

Date of Clinical Trial Report

03 Feb 2011