Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication

Metastatic renal cell cancer

Protocol Number

CRAD001L2101

Protocol Title

A phase Ib, multi-center, open-label study to evaluate the safety of RAD001 (everolimus) in Chinese patients with metastatic renal cell cancer who are intolerant of or who have progressed despite treatment with vascular endothelial growth factor-targeted therapies

Clinical Trial Phase

Ib

Phase of Drug Development

Phase IV

Study Start/End Dates

13 May 2010 to 13 Dec 2013

Study Design/Methodology

This was an open-label, single arm, multi-center study to evaluate the safety of everolimus in Chinese patients with metastatic renal cell cancer who were intolerant of or who had progressed despite prior treatment with vascular endothelial growth factor-targeted therapies. All patients were treated with everolimus 10 mg daily until tumor progression, unacceptable toxicity, death, or discontinued the study for any other reason. A treatment cycle consisted of 28 days.

Centers

7 centers in China

Publication

Guo J, Huang Y, Zhang X, et al (2013) Safety and efficacy of everolimus in Chinese patients with metastatic renal cell carcinoma resistant to vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy: an open-label phase 1b study. BMC Cancer; 13:136.

Objectives:

Primary Objective:

- To evaluate the safety and tolerability profile of everolimus (10 mg daily dose) in Chinese patients who were intolerant of or who had progressed on or after vascular endothelial growth factor-targeted therapy.

Secondary objectives:

- To evaluate disease control rate, best overall response rate and progression free survival
- To evaluate overall survival

Test Product, Dose, and Mode of Administration

Everolimus 5 mg tablets administered orally at a dose of 10 mg/day.

Statistical Methods

Analysis of primary variable (Safety): Safety analyses were performed in the safety population and were focused on adverse events with a recorded severity of grade 3 or 4 and on serious adverse events. Frequency counts and exact 95% confidence interval estimates were provided. Specific groupings of clinically notable adverse events were summarized and the number of patients with at least one event in each grouping was reported. Laboratory data was summarized in terms of frequency distribution of patients by the worst common terminology criteria grade experienced during the treatment, based on the availability of laboratory normal ranges.

Analysis of secondary variable (Efficacy): Efficacy was evaluated in the full analysis set by estimating disease control rate, overall response rate, progression free survival and overall survival and performed according to response evaluation criteria in solid tumors.

Progression-free survival and overall survival were analyzed using Kaplan-Meier method.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients of Chinese origin who were ≥ 18 years old.
- Patients with histologically or cytologically confirmed metastatic renal cell carcinoma.
- Patients who were intolerant of or who had progression on or after stopping treatment with vascular endothelial growth factor-targeted therapies within six months. Note: Prior treatment with vaccine therapy in the adjuvant setting and prior treatment with cytokines (i.e., interleukin-2, Interferon) or chemotherapy was permitted.

- Patients with at least 1 measurable lesion determined according to the response evaluation criteria in solid tumors guidelines.
- Patients with history of brain metastasis who were clinically judged by the investigator as neurologically stable following definitive radiation or surgery and do not require corticosteroids may be enrolled in the study.
- Patients with a Karnofsky Performance Status ≥ 70%.
- Patients with adequate bone marrow function defined as absolute neutrophil count ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin >9 g/dL.
- Patients with adequate liver function defined as serum bilirubin ≤ 1.5 x upper limit of normal, alanine aminotransferase and aspartate aminotransferase ≤ 2.5 x upper limit of normal. Patients with known liver metastases who had an aspartate aminotransferase and alanine aminotransferase ≤ 5x upper limit of normal.
- Patients with adequate renal function which was defined as serum creatinine ≤ 2 x upper limit of normal.
- Women of childbearing potential must have had a negative serum pregnancy test within 14 days prior to the administration of everolimus.
- Patients must give written informed consent according to local guidelines.

Exclusion criteria

- Patients who had received chemotherapy, immunotherapy, radio-therapy or any other investigational agent (including pazopanib, axitinib) within four weeks of study entry, or have received sunitinib® and/or sorafenib® within two weeks of the first dose of everolimus.
- Patients who had previously received everolimus or other mammalian target of rapamycin inhibitors.
- Patients with a known hypersensitivity to everolimus or other rapamycin analogs (sirolimus, temsirolimus), or to its excipients.
- Patients who had history of another primary malignancy ≤ 3 years, with the exception of non-melanoma skin cancer, and carcinoma in situ of uterine cervix.
- Patients receiving chronic and systemic treatment with corticosteroids or another immunosuppressive agent. Patients may receive low dose treatment of corticosteroids with a maximum dose of 20 mg prednisone or 10 mg dexamethasone per day, if they were being given for disorders such as rheumatoid arthritis, asthma, or adrenal insufficiency. Topical or inhaled corticosteroids were permitted.
- Patients with a clinically significant active bleeding diathesis.
- Patients with known human immunodeficiency virus seropositivity, hepatitis B or C seropositivity. Patients with prior hepatitis B vaccination may be entered in the study after review of hepatitis test results by the investigator.

- Patients who had undergone major surgery within four weeks prior to starting study drug (e.g., intra-thoracic, intra-abdominal, or intra-pelvic), open biopsy, or significant traumatic injury, or who had not recovered from the side effects of any of the above.
- Patients with any severe and/or uncontrolled medical conditions such as: unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months, serious uncontrolled cardiac arrhythmia, uncontrolled hypercholesterolemia (>300 mg/dL or 7.75 mmol/L),uncontrolled diabetes (fasting glucose >2 x upper limit of normal), an active or uncontrolled severe infection, cirrhosis, chronic or persistent active hepatitis.
- Female patients who were pregnant or breast feeding, or adults of reproductive potential who were not using effective birth control methods. If barrier contraceptives were used, they were continued throughout the study by both sexes, and up to eight weeks after ending treatment. Hormonal contraceptives were not acceptable as a sole method of contraception.

Participant Flow Table

Patient disposition - Full Analysis Set

	Everolimus 10 mg/day N=64 n (%)
Ongoing*	1 (1.6)
Discontinued study treatment [1]	63 (98.4)
Disease progression	30 (46.9)
Adverse Event(s)	17 (26.6)
Subject withdrew consent	7 (10.9)
Death	4 (6.3)
Protocol deviation	2 (3.1)
Abnormal laboratory value(s)	2 (3.1)
Lost to follow-up	1 (1.6)
Entered post-treatment evaluation [2]	54 (84.4)
Discontinued from post-treatment evaluations [3]	54 (100.0)
Follow-up phase completed as per protocol	33 (61.1)
New cancer therapy	11 (20.4)
Death	7 (13.0)
Disease progression	1 (1.9)
Lost to follow-up	1 (1.9)
Protocol deviation	1 (1.9)

	Everolimus 10 mg/day N=64 n (%)

[1] Per 'End of Treatment' page. All percentages in this section use N as the denominator

[2] Percentages of patients who entered post-treatment evaluation use N as the denominator. All subsequent percentages use the number of those who entered post-treatment evaluation as the denominator.

[3] Per 'Study Evaluation Completion' page.

*The last ongoing patient was discontinued from the study due to withdrawal of consent and received the last dose of everolimus on 15-Nov-2013. After the last dose of everolimus, the 28 day safety follow-up was completed as per protocol, and the patient's last visit was on 13-Dec-2013. The new data collected from this last ongoing patient did not impact efficacy and safety conclusions of the study.

Baseline Characteristics

Demographic characteristics - Full Analysis Set

	Everolimus 10 mg/day N=64
Age (years)	
N	64
Mean (standard deviation)	52.78 (10.86)
Median	51.50
Range	19.0 - 75.0
Age, n (%)	
<65	58 (90.6)
≥65	6 (9.4)
Gender, n (%)	
Male	44 (68.8)
Female	20 (31.3)
Race, n (%)	
Asian	64 (100)
Ethnicity, n (%)	
Chinese	64 (100)

Summary of Efficacy

Primary Outcome Result

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Analysis of progression-free survival using Kaplan-Meier method - Full Analysis Set

	Everolimus 10 mg/day N=64 n (%)
No. of PFS events, n (%)	41 (64.1)
Progression	30 (46.9)
Death	11 (17.2)
No. censored	23 (35.9)
Kaplan-Meier estimates [95% CI] at:	
4 months	61.6 [47.3;73.1]
6 months	51.7 [37.5;64.1]
12 months	38.2 [24.1;52.1]
Median PFS [95% CI] (months)	6.93 [3.71;12.52]

Best overall response - Full Analysis Set

Best overall response	**Everolimus 10 mg/day N=64 n (%)**
Complete Response (CR)	0
Partial Response (PR)	3 (4.7)
Stable Disease (SD)	39 (60.9)
Progressive Disease (PD)	8 (12.5)
Unknown	14 (21.9)
Response analysis	
Objective Response Rate ORR (CR or PR)	3 (4.7)
95% CI for ORR	[1.0; 13.1]
Disease Control Rate DCR (CR or PR or SD)	42 (65.6)
95% CI for DCR	[52.7; 77.1]

The exact 95% CI (Clopper and Pearson) is shown.
Best Overall Response Unknown includes patients with no tumor assessments recorded.

Analysis of overall survival using Kaplan-Meier method - Full Analysis Set

	Everolimus 10 mg/day N=64
No. of deaths, n (%)	43 (67.2)
No. of censored, n (%)	21 (32.8)
Kaplan-Meier estimates [95% CI] at:	
4 months	82.6 [70.7;89.9]
6 months	76.1 [63.6;84.9]

	Everolimus 10 mg/day N=64
12 months	56.4 [43.1;67.7]
18 months	42.4 [29.7;54.5]
24 months	30.1 [18.5;42.5]
Median OS [95% CI] (months)	13.54 [10.71;19.65]

Summary of Safety

Safety Results

Adverse events regardless of relationship to study drug by system organ class - Safety Set

System organ class	Everolimus 10 mg/day N=64 n (%)
Any system organ class	62 (96.9)
Metabolism and nutrition disorders	55 (85.9)
Investigations	48 (75.0)
Blood and lymphatic system disorders	47 (73.4)
Gastrointestinal disorders	45 (70.3)
General disorders and administration site conditions	41 (64.1)
Respiratory, thoracic and mediastinal disorders	39 (60.9)
Skin and subcutaneous tissue disorders	32 (50.0)
Infections and infestations	28 (43.8)
Musculoskeletal and connective tissue disorders	18 (28.1)
Nervous system disorders	15 (23.4)
Psychiatric disorders	8 (12.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (10.9)
Renal and urinary disorders	7 (10.9)
Cardiac disorders	6 (9.4)
Hepatobiliary disorders	6 (9.4)
Eye disorders	5 (7.8)
Ear and labyrinth disorders	4 (6.3)
Injury, poisoning and procedural complications	4 (6.3)
Vascular disorders	3 (4.7)
Endocrine disorders	2 (3.1)

System organ classes are sorted by descending frequency (any common terminology criteria grade).
A patient with multiple adverse events within a system organ class is counted only once
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Most frequently reported (in at least 10% of patients in all grades) adverse events regardless of relationship to study drug by preferred term - Safety Set

	Everolimus 10 mg/day N=64		
Preferred term	**All grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Any preferred term	62 (96.9)	34 (53.1)	18 (28.1)
Anaemia	42 (65.6)	11 (17.2)	3 (4.7)
Hypertriglyceridaemia	35 (54.7)	4 (6.3)	0
Mouth ulceration	34 (53.1)	2 (3.1)	0
Hyperglycaemia	33 (51.6)	8 (12.5)	0
Hypercholesterolaemia	32 (50.0)	0	0
Pyrexia	28 (43.8)	1 (1.6)	0
Blood lactate dehydrogenase increased	25 (39.1)	1 (1.6)	1 (1.6)
Cough	22 (34.4)	1 (1.6)	0
Gamma-glutamyltransferase increased	21 (32.8)	9 (14.1)	0
Blood creatinine increased	20 (31.3)	0	1 (1.6)
Fatigue	20 (31.3)	1 (1.6)	0
Rash	20 (31.3)	0	0
Aspartate aminotransferase increased	19 (29.7)	0	0
Alanine aminotransferase increased	16 (25.0)	1 (1.6)	0
Epistaxis	15 (23.4)	1 (1.6)	0
Hypocalcaemia	14 (21.9)	0	0
Interstitial lung disease	14 (21.9)	1 (1.6)	0
Leukopenia	14 (21.9)	0	0
Pruritus	14 (21.9)	0	0
Oedema peripheral	13 (20.3)	2 (3.1)	0
Platelet count decreased	13 (20.3)	1 (1.6)	0
Blood alkaline phosphatase increased	12 (18.8)	1 (1.6)	0
Diarrhoea	12 (18.8)	1 (1.6)	0
Dyspnoea	12 (18.8)	1 (1.6)	4 (6.3)
Hypokalaemia	11 (17.2)	0	3 (4.7)
Lymphopenia	10 (15.6)	4 (6.3)	0
Dizziness	9 (14.1)	0	0
Nasopharyngitis	9 (14.1)	0	0
Insomnia	8 (12.5)	0	0
Blood creatinine phosphokinase increased	7 (10.9)	0	0
Chest discomfort	7 (10.9)	1 (1.6)	1 (1.6)
Decreased appetite	7 (10.9)	1 (1.6)	0
Haemoglobin decreased	7 (10.9)	2 (3.1)	0
Headache	7 (10.9)	0	0

Preferred term	Everolimus 10 mg/day N=64 All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Hyponatraemia	7 (10.9)	5 (7.8)	0
Nausea	7 (10.9)	0	0
Pleural effusion	7 (10.9)	4 (6.3)	0
Upper respiratory tract infection	7 (10.9)	0	0
White blood cell count increased	7 (10.9)	0	0

Preferred terms are sorted by descending frequency of all grades.
A patient with multiple occurrences of an adverse event is counted only once, by the worst grade.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Adverse events with suspected relationship to study drug, by system organ class - Safety Set

System organ class	Everolimus 10 mg/day N=64 n (%)
Any system organ class	60 (93.8)
Metabolism and nutrition disorders	50 (78.1)
Investigations	43 (67.2)
Blood and lymphatic system disorders	40 (62.5)
Gastrointestinal disorders	40 (62.5)
Skin and subcutaneous tissue disorders	29 (45.3)
Respiratory, thoracic and mediastinal disorders	26 (40.6)
General disorders and administration site conditions	18 (28.1)
Infections and infestations	6 (9.4)
Hepatobiliary disorders	4 (6.3)
Vascular disorders	3 (4.7)
Eye disorders	2 (3.1)
Musculoskeletal and connective tissue disorders	2 (3.1)
Renal and urinary disorders	2 (3.1)
Cardiac disorders	1 (1.6)
Ear and labyrinth disorders	1 (1.6)
Endocrine disorders	1 (1.6)
Nervous system disorders	1 (1.6)
Psychiatric disorders	1 (1.6)

System organ classes are sorted by descending frequency (any common terminology criteria grade).
A patient with multiple adverse events within a system organ class is counted only once.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Most frequently reported (in at least 10% of patients in all grades) adverse events with suspected relationship to study drug, by preferred term – Safety Set

Preferred term	Everolimus 10 mg/day N=64 All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any preferred term	60 (93.8)	32 (50.0)	5 (7.8)
Anaemia	36 (56.3)	9 (14.1)	3 (4.7)
Hypertriglyceridaemia	35 (54.7)	4 (6.3)	0
Mouth ulceration	33 (51.6)	2 (3.1)	0
Hypercholesterolaemia	32 (50.0)	0	0
Hyperglycaemia	31 (48.4)	7 (10.9)	0
Rash	20 (31.3)	0	0
Gamma-glutamyltransferase increased	18 (28.1)	8 (12.5)	0
Aspartate aminotransferase increased	15 (23.4)	0	0
Blood creatinine increased	15 (23.4)	0	1 (1.6)
Interstitial lung disease	14 (21.9)	1 (1.6)	0
Alanine aminotransferase increased	13 (20.3)	1 (1.6)	0
Platelet count decreased	13 (20.3)	1 (1.6)	0
Pruritus	13 (20.3)	0	0
Leukopenia	11 (17.2)	0	0
Pyrexia	11 (17.2)	0	0
Blood lactate dehydrogenase increased	10 (15.6)	0	0
Cough	8 (12.5)	1 (1.6)	0
Epistaxis	7 (10.9)	1 (1.6)	0

Preferred terms are sorted by descending frequency of all grades.

A patient with multiple occurrences of an adverse event is counted only once, by the worst grade.

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Summary of deaths and AEs –Safety set

Category	Everolimus 10 mg/day N=64 n (%)
All deaths	43 (67.2)
On-treatment deaths [1]	8 (12.5)
Adverse events (AEs)	62 (96.9)
Suspected to be drug-related	60 (93.8)
Grade 3-4 AEs	52 (81.3)
Suspected to be drug-related	37 (57.8)
Clinically notable AEs*	59 (92.2)
Serious adverse events (SAEs)	28 (43.8)

Category	**Everolimus 10 mg/day N=64 n (%)**
Suspected to be drug-related	11 (17.2)
AEs leading to discontinuation	19 (29.7)
Suspected to be drug-related	13 (20.3)
Other significant AEs	56 (87.5)
AEs requiring dose interruption and/or reduction	35 (54.7)
AEs requiring additional therapy	55 (85.9)

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

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Additional therapy includes all non-drug therapy and concomitant medications.

*The AE groupings consist of adverse events for which there is a specific clinical interest in connection with everolimus or adverse events which are similar in nature.

Conclusion:

- The benefit of treatment with everolimus which has been observed in this study is comparable with the one observed in the Phase III registration study (RAD001C2240). This study showed that everolimus 10 mg daily given orally provides a positive clinical benefit when administered to patients with metastatic renal cell cancer who are intolerant of or who have progressed despite treatment with vascular endothelial growth factor-targeted therapies. The efficacy variables including response rate, disease control rate, estimated median progression free survival and median overall survival were comparable with those observed in RAD001C2240 study.
- Overall, the safety findings of everolimus given at 10 mg/day orally are consistent with previous experiences in the Phase III registration study and the Phase I study in Chinese patients. Generally, everolimus was well tolerated and there were no unexpected safety findings reported in this study. Adverse events related to treatment with everolimus can be managed effectively with dose modification or supportive intervention. Based on the pivotal Phase III study in advanced renal cell carcinoma, a guidance regarding the appropriate management of everolimus-related adverse events was developed.
- Evaluation of the overall finding should take into consideration the sample size of both studies and the patient population of the current study, which included heavily pre-treated patients with abnormal laboratory values often reported at baseline. Nevertheless, no serious clinical concerns were raised despite the higher incidence rates of certain adverse events as they were mainly grade 1 and 2.
- In conclusion, there were no untoward effects or new events reported in the current study that would considerably affect the established safety profile of everolimus or later the benefit-risk. The findings of this study confirm that the administration of everolimus is safe and efficacious in Chinese patients with metastatic renal cell carcinoma.

Date of Clinical Trial Report

04 July 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

24 July 2014

Date of Latest Update

Reason for Update