Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Advanced Hepato-Cellular Carcinoma (HCC)

Approved Indication

- Postmenopausal women with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, after prior endocrine therapy.
- Patients with advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin.
- Patients with advanced renal cell carcinoma.
- Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.
- Patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC).
- For the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogenic renal or cardiac transplant. In kidney and heart transplantation, in combination with ciclosporin for microemulsion and corticosteroids.
- For the prophylaxis of organ rejection in patients receiving a hepatic transplant. In combination with tacrolimus and corticosteroids.

Study Number

CRAD001O2101

Title

A phase I open-label/phase II randomized, double-blind, multicenter study investigating the combination of RAD001 and sorafenib (Nexavar®) in patients with advanced hepatocellular carcinoma

Phase of Development

Phase I/II

Study Start/End Dates

03-Dec-2008 to 17-Jun-2011

Study Design/Methodology

Phase I was an open-label, non-randomized, multicenter dose-defining study combining daily oral everolimus plus daily oral sorafenib in patients with advanced hepatocellular carcinoma (HCC). This study used a sequential dose-escalation design based on an adaptive 4-parameter Bayesian logistic regression model with overdose control. The dose-escalation criteria guided everolimus dose modifications in order to determine the Maximum Tolerated Dose (MTD). As part of the identification of the MTD, assessment of safety and tolerability of the everolimus and sorafenib combination treatment was used to define the Dose Limiting Toxicities (DLTs).

DLTs were pre-defined Adverse Events (AEs) occurring within the first 28 days after the first dose of combination treatment. Other safety assessments and the pharmacokinetic (PK) profile of everolimus and sorafenib were taken into account at dose-defining decision time-points, but were not formally included in the statistical model. Thirty patients were allocated, in sequential cohorts, to Phase I.

Phase II was to be a randomized, blinded, parallel, two-arm multicenter study estimating the relative efficacy of the MTD combination treatment identified in Phase I versus that of sorafenib alone in terms of hazard ratio (HR) of time to progression based on Response Evaluation Criteria in Solid Tumors (RECIST). However, the inability to achieve what was deemed a biologically effective dose of everolimus in combination with sorafenib precluded progression to Phase II in this study.

Centres

International, multicenter trial

Publication

None

Objectives

Primary objective(s)

Phase I:

To characterize the safety and tolerability of daily everolimus in combination with daily sorafenib and to determine the MTD of the combination of everolimus plus sorafenib to bring forward into Phase II.

Phase II:

To estimate the hazard ratio of the treatment effect as a measure of anti-tumor activity in terms of time to progression of the combination of everolimus plus sorafenib, at the MTD level, as compared to sorafenib alone.

Secondary objective(s)

Phase I:

- To describe the efficacy of the combination of everolimus plus sorafenib at the explored dose-levels in terms of best overall response as defined by Response Evaluation Criteria in Solid Tumors (RECIST)
- To assess the safety and tolerability of the combination of everolimus plus sorafenib as measured by the rate and severity of adverse events (AEs)
- To determine the steady state exposure of everolimus at pre-dose and 1 hour and 2 hours post-dose at the explored combination dose-levels using concentrations at pre-dose (C_{min}) and at 1 hour (C_{1h}) and 2 hours (C_{2h}) post-dose.

Phase II:

- To describe the clinical efficacy of the study treatment in terms of the following endpoints according to RECIST: Best overall response and progression-free survival (PFS)
- To compare overall survival (OS) of everolimus plus sorafenib with sorafenib alone.

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

Once daily oral tablets of everolimus 2.5 mg and 5.0 mg;

Once daily oral tablets of sorafenib as 200 mg

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

Not applicable

Criteria for Evaluation

Primary variables

The primary variable used in the statistical model was the occurrence of a DLT (DLT/no DLT) within the first 28 days of combination treatment. The primary endpoint was expressed in terms of the probability of the DLT rate falling within pre-specified toxicity intervals as estimated by the Bayesian 4-parameter logistic regression model. A DLT was defined as toxicity occurring within the first 28 days of combination treatment that was considered possibly or probably related to therapy. Exceptions to the DLT definition were alopecia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, hand and foot syndrome, hypertension, hypersensitivity, and/or nausea/vomiting. A DLT met the following criteria:

- Grade 3 or 4 non-hematologic toxicity defined as:
  - any Grade 3 or 4 toxicity requiring 7 or more days to resolve to Grade ≤ 1 despite medical therapy
  - reactivation of HBV or HCV
  - bilirubin increase greater than 2 x upper limit of normal (ULN)
  - creatinine increase greater than 2 x ULN
  - any toxicity requiring 7 or more days of treatment interruption
- Grade 3 or 4 hematologic toxicity defined as:
  - any Grade 4 hematologic toxicity
  - Grade 3 thrombocytopenia with bleeding or Grade 3 anemia requiring transfusion or Grade 3 neutropenia with fever
  - any Grade 3 hematologic toxicity which persisted for > 7 days and required dose interruption for more than 7 days to resolve to a Grade ≤ 1

Secondary variables

Evidence of clinical efficacy was evaluated using overall response rate based on Novartis RECIST guidelines. Only patients with measurable disease (the presence of at least one measurable lesion) at Baseline were included in the study. Tumor assessments were performed at Screening to determine patient eligibility. Both measurable and non-measurable lesions were assessed and target lesions identified prior to enrollment. The same methods of assessment (CT or MRI scan) and the same techniques were used to characterize each identified and reported lesion at Baseline and during follow-up. PFS and OS were also analyzed.

Safety and tolerability

Safety assessments consisted of collecting all AEs/Serious Adverse Events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry, and urine parameters; the assessment of World Health Organization(WHO) performance status; screening for possible hepatitis infection; and regular

assessments of vital signs, physical condition and body weight. Safety and tolerability were assessed according to Common Terminology Criteria for Adverse Events.

Statistical Methods

The primary variable used in the statistical model was the occurrence of a DLT (DLT/no DLT) within the first 28 days of combination treatment. The primary endpoint was expressed in terms of the probability of the DLT rate falling within pre-specified toxicity intervals as estimated by the Bayesian 4-parameter logistic regression model. The model included all patients eligible to be included in the dose-determining population at any of the dose-levels tested. The final recommended dose level was based on considerations of the MTD estimated by the Bayesian model and on an overall assessment of safety taking into consideration tolerability data from the entire study at all of the different dose-levels tested. PFS was defined as the time from date of first study treatment to the date of the first documented disease progression (as per RECIST) or death due to any cause. OS was defined as the time from date of start of treatment to date of death due to any cause. The Kaplan-Meier estimates of PFS and OS were provided for each combination of doses.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

All inclusion and exclusion criteria were applicable for both Phase I and Phase II.

- Male or female patients ≥ 18 years old with ability to take oral drugs
- Diagnosis of advanced HCC according to the American Association for the Study of Liver Diseases guidelines
- HCC stage B or C according to the Barcelona Clinic Liver Cancer (BCLC) staging system
- No previous systemic therapy for HCC (tamoxifen was allowed as previous systemic therapy)
- Measurable disease according to RECIST, i.e. at least one measurable lesion. This lesion should not have been previously treated with local therapy. A treated lesion could be used where these lesions were the only lesions available for evaluation and had shown definite progression since the last local treatment. Local therapy must have been completed at least four weeks prior to baseline evaluation.
- Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Child-Pugh Class A status only (5-6 points) with no encephalopathy and no ascites (ascites controlled by diuretics was also excluded in this study). Child-Pugh status was to be calculated based on clinical findings and laboratory results during the screening period.
- Patients positive for Hepatitis B virus (HBV)-DNA and/or Hepatitis B surface Antigen (HBsAg) at Baseline must be treated prophylactically with anti-virals for at least 1-2 weeks prior to receiving study drug at Visit 2
- The following laboratory parameters at Visit 2:
  - absolute neutrophil count ≥ 1.5 x 10^9/L

- platelets ≥ 100,000 x 10^6/L
- hemoglobin ≥ 9 g/dL
- serum aspartate aminotransferase (AST) and alanine amino-transferase (ALT) ≤ 5 x
- the upper limit of normal (ULN)
- serum creatinine ≤ 1.5 x ULN

- Ability to understand and willingness to sign a written informed consent and to be able to follow the visit schedule

Exclusion criteria:

- Patients currently receiving any anti-cancer therapy or who had received any local anticancer therapy ≤ 4 weeks prior to baseline computed tomography (CT)/magnetic resonance imaging (MRI) scan at Visit 2
- Active bleeding during the last 30 days prior to Visit 1 including variceal bleeding (esophageal varices should be treated according to standard practice e.g. ligation/banding and procedure completed 30 days prior to Visit 1)
- Patients with a known hypersensitivity to everolimus or known hypersensitivity to sorafenib or contradictions to sorafenib based on the local sorafenib label
- Known previous/current malignancy requiring treatment within ≤ 3 years except for cervical carcinoma in situ, basal cell carcinoma, and superficial bladder carcinoma
- Known history of human immunodeficiency virus (HIV) seropositivity (HIV testing is not mandatory)
- Any severe and/or uncontrolled medical conditions including:
  - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to Visit 1, serious uncontrolled cardiac arrhythmia, uncontrolled hypertension
  - Previous transient ischemic attack, cerebrovascular accident, symptomatic peripheral vascular disease within 6 months prior to Visit 1
  - Patients with active alcohol intake
  - Uncontrolled diabetes as defined by HbA1c > 8%
  - Greater or equal Grade 3 hypercholesterolemia/hypertriglyceridemia or ≥ Grade 2 hypercholesterolemia/hypertriglyceridemia with history of coronary artery disease (despite lipid-lowering treatment if given)
  - Acute and chronic, active infectious disorders and nonmalignant medical illnesses that were uncontrolled or whose control would be jeopardized by the complications of study therapy, in the opinion of the Investigator, with the exception of chronic HBV or HCV infections
  - Impairment of gastrointestinal function or patients who had gastrointestinal disease that may have significantly altered the absorption of study drugs (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)

- Significant deterioration of lung function, defined as any of the following: 30% decrease in predicted lung volumes, and/or 30% decrease in DLCO, and/or ≤ 88% O_2 saturation at rest on room air
- Patients receiving chronic treatment with corticosteroids (except for intermittent topical or local injection or aldosterone) or another immunosuppressive agent
- Patients treated with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A unless the drugs were medically necessary and no substitutes were available. If there were no acceptable substitutes, special precautions were to be taken in these patients
- Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug or who had not recovered from surgery
- Female patients who were pregnant or breast feeding, or adults of reproductive potential not employing an effective method of birth control. Adequate contraceptives were to be used throughout the trial and for 3 months after last study drug administration in both sexes. Women of childbearing potential were to have a negative serum pregnancy test within 72 hours prior to administration of everolimus and/or sorafenib.
- Patients who had received an investigative drug or therapy within 30 days prior to Visit 1
- Patients unwilling or unable to comply with the protocol, in the opinion of the Investigator.

Number of Subjects

Patient Disposition (All patients):

Patients	Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)	Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)	All patients N=62 n (%)
Screened[1]			62 (100.0)
Screen-failed[1]			32 (51.6)
Enrolled [2]	16 (100.0)	14 (100.0)	30 (100.0)
Exposed	16 (100.0)	14 (100.0)	30 (100.0)
Completed [3]	13 (81.3)	8 (57.1)	21 (70.0)
Discontinued [4]	16 (100.0)	14 (100.0)	30 (100.0)
Adverse event(s)	1 (6.3)	4 (28.6)	5 (16.7)
Withdrew consent	2 (12.5)	1 (7.1)	3 (10.0)
Disease progression[3]	13 (81.3)	8 (57.1)	21 (70.0)
Protocol deviation(s)	0	1 (7.1)	1 (3.3)

1. Patients screened or who were screen failures are reported overall and not by cohort. The denominator for number of patients screened and screen-failed is the number of patients screened.

2. Enrolled patients were allocated to a treatment cohort and had received at least one dose of study drug /study treatment.

3. Completed patients met the endpoint of disease progression or death.

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

The denominator for all categories other than screened and screen-failed is the number of enrolled patients.

Demographic and Background Characteristics

Demographic summary (FAS):

	Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)	Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)	All patients N=62 n (%)
Sex			
Male	15 (93.8%)	11 (78.6%)	26 (86.7%)
Female	1 (6.3%)	3 (21.4%)	4 (13.3%)
Age (years)			
n	16	14	30
Mean ± SD	56.8 ± 11.99	63.8 ± 8.45	60.0 ± 10.91
Median	57.5	62.5	62.0
Minimum - maximum	36 - 71	49 - 77	36 - 77
Age category			
< 35 years	0	0	0

≥ 35 - < 55 years	7 (43.8%)	3 (21.4%)	10 (33.3%)
≥ 55 - < 65 years	3 (18.8%)	5 (35.7%)	8 (26.7%)
≥ 65 years	6 (37.5%)	6 (42.9%)	12 (40.0%)
Race			
Caucasia	3 (18.8%)	5 (35.7%)	8 (26.7%)
Asian	13 (81.3%)	9 (64.3%)	22 (73.3%)
Weight (kg)			
n	16	14	30
Me n ± SD	69.51 ± 16.776	70.49 ± 13.475	69.97 ± 15.073
Median	67.50	68.75	68.25
Minimum - maximum	51.8 - 118.5	55.0 - 99.5	51.8 - 118.5
ECOG status			
0 to 1	16 (100.0%)	14 (100.0%)	30 (100.0%)
History of hepatitis			
HBV	11 (68.8%)	9 (64.3%)	20 (66.7%)
HCV	2 (12.5%)	2 (14.3%)	4 (13.3%)
Child-Pugh class			
A	16 (100.0%)	14 (100.0%)	30 (100.0%)

Primary Objective Result(s)

Duration of exposure to study drug (safety population):

Exposure categories	**Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16**	**Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14**
< 1 month	0	2 (14.3%)
1 – 3 months	8 (50.0%)	8 (57.1%)
> 3 – 6 months	5 (31.3%)	3 (21.4%)
> 6 months	3 (18.8%)	1 (7.1%)
Duration of exposure (days)		
n	16	14
Mean ± SD	131.3 ± 106.03	80.2 ± 55.78
Median	88.5	60.0
Minimum -maximum	33 - 393	24 - 238

A patient was counted only once in each exposure category.
Duration of exposure is calculated as the number of days from the first dose to the last dose of any component of study treatment.

Dose limiting toxicities by dose cohort (dose determining population):

	Everolimus 2.5 mg qd + sorafenib 400 mg bid	**Everolimus 5.0 mg qd + sorafenib 400 mg bid**

	N=12 n (%)	N=13 n (%)
Experienced a DLT	1 (8.3)	6 (46.2)
Dose limiting toxicity type		
Hyperbiliubinemia greater than 2 x ULN	0	1 (7.7)
Grade 3 AST[1] elevation with drug interruption for more than 7 days	1 (8.3)	0
Grade 4 thrombocytopenia	0	1 (7.7)
Grade 3 thrombocytopenia with bleeding[2]	0	2 (15.4)
Grade 3 thrombocytopenia lasting > 7 days + drug interruption for > 7 days	0	2 (15.4)

1. AST, aspartate aminotransferase

2. One patient had Grade 1 gastrointestinal hemorrhage and one patient had Grade 1 epistaxis

A DLT was defined as a pre-specified AE occurring within the first 28 days after administration of the first dose of combination treatment

Secondary Objective Result(s)

Best overall response by phase I dose cohort (FAS):

Best overall response[1]	**Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)**	**Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)**
Complete response (CR)	0	0
Partial response (PR)	0	0
Stable disease (SD)	10 (62.5)	6 (42.9)
Progressive disease	5 (31.3)	6 (42.9)
Unknown	1 (6.3)	2 (14.3)
Disease Control Rate (DCR)		
(CR + PR + SD)	10 (62.5)	6 (42.9)
95% CI for DCR	[35.4; 84.8]	[17.7; 71.1]

1. As per the Investigator's evaluation of overall response

Progression-free survival in phase I (FAS):

Progression-free survival	**Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)**	**Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)**
Number of PFS events[1]	14 (87.5%)	11 (78.6%)
Number of progressions	13 (81.3%)	9 (64.3%)
Number of deaths	1 (6.3%)	2 (14.3%)
Number censored	2 (12.5%)	3 (21.4%)
Kaplan-Meier estimates [95% CI] (days) for :		
25th percentile for PFS [95% CI]	68.0 [36, 109]	53.0 [32, 56]
Median PFS [95% C.I.]	136.0 [56, 164]	56.0 [50, 232]
75th percentile for PFS [95% CI]	164.0 [109, 387]	232.0 [56, 325]

1. If a patient had documented progressive disease before death, then PFS event was progression.

Overall survival in phase I (FAS):

Overall survival (days)	**Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)**	**Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)**
Number of deaths	12 (75.0%)	9 (64.3%)
Number censored	4 (25.0%)	5 (35.7%)
Kaplan-Meier estimates [95% C.I.] at:		

25th percentile for OS [95% C.I.]	136.0 [103, 170]	113.0 [32, 325]
Median OS [95% C.I.]	225.0 [128, 465]	355.5 [69, NE]
75th percentile for OS [95% C.I.]	465.0 [225, 786]	NE [325, NE]
NE, not evaluable		

Safety Results

Adverse Events by System Organ Class:

Incidence of AEs irrespective of study drug relationship, by primary SOC (safety population):

Primary system organ class	Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)	Everolimus 5.0 mg qd + sorafenib 400 mg bid N =14 n (%)
Any primary system organ class	16 (100%)	16 (100%)
Gastrointestinal disorders	16 (100.0)	13 (92.9)
Skin and subcutaneous tissue disorders	16 (100.0)	12 (85.7)
General disorders and administration site conditions	9 (56.3)	11 (78.6)
Metabolism and nutrition disorders	9 (56.3)	11 (78.6)
Blood and lymphatic system disorders	9 (56.3)	9 (64.3)
Respiratory, thoracic and mediastinal disorders	6 (37.5)	8 (57.1)
Investigations	11 (68.8)	7 (50.0)
Musculoskeletal and connective tissue disorders	8 (50.0)	6 (42.9)
Nervous system disorders	3 (18.8)	6 (42.9)
Inf ctions and infestations	6 (37.5)	4 (28.6)
Vascular disorders	3 (18.8)	4 (28.6)
Renal and urinary disorders	5 (31.3)	2 (14.3)
Psychiatric disorders	4 25.0)	2 (14.3)
Eye disorders	3 (18.8)	1 (7.1)
Hepatobiliary disorders	2 (12.5)	1 (7.1)
Reproductive system and breast disorders	2 (12.5)	1 (7.1)
Cardiac disorders	1 (6.3)	1 (7.1)
Injury, poisoning and procedural complications	0	1 (7.1)

Primary system organ classes are sorted by descending frequency in the everolimus highest dose group (5.0 mg qd).

A patient with multiple AEs within a primary 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 AEs Overall by Preferred Term n (%)

Frequently reported AEs, irrespective of study drug relationship, by PT (safety population):

Preferred term with an incidence ≥ 20%	Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)	Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)
Any preferred term	16 (100.0)	14 (100.0)
Diarrhoea	10 (62.5)	10 (71.4)
Palmar-plantar erythrody aes hesia syndrome	11 (68.8)	9 (64.3)
Thrombocytopenia	7 (43.8)	8 (57.1)
Decreased appetite	7 (43.8)	7 (50.0)
Rash	7 (43.8)	7 (50.0)
Pyrexia	4 (25.0)	6 (42.9)
Stomatitis	3 (18.8)	6 (42.9)
Neutropenia	2 (12.5)	6 (42.9)
Constipation	4 (25.0)	5 (35.7)
Fatigue	4 (25.0)	5 (35.7)
Hypokalaemia	2 (12.5)	5 (35.7)
Alopecia	6 (37.5)	4 (28.6)
Hypertension	2 (12.5)	4 (28.6)
Dizziness	1 (6.3)	4 (28.6)
Cough	5 (31.3)	3 (21.4)
Nausea	3 (18.8)	3 (21.4)
Blood bilirubin increased	2 (12.5)	3 (21.4)
Headache	2 (12.5)	3 (21.4)
Weight decreased	1 (6.3)	3 (21.4)
Dysphonia	0	3 (21.4)
Abdominal pain	8 (50.0)	2 (14.3)
Aspartate aminotransferase increased	6 (37.5)	2 (14.3)

Preferred terms are presented by descending frequency in the highest dose everolimus group (5.0 mg qd).

A patient with multiple AEs within a preferred term is counted only once.

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

Serious Adverse Events and Deaths

Number of patients who died, had SAEs, discontinued because of an AE, had grade 3-4 AEs, or had a clinically notable AE (safety population):

AE category	Everolimus 2.5 mg qd + sorafenib 400 mg bid N=16 n (%)	Everolimus 5.0 mg qd + sorafenib 400 mg bid N=14 n (%)
All deaths	12 (75.0)	9 (64.3)
On-treatment deaths[1]	1 (6.3)	3 (21.4)
Serious adverse events	10 (62.5)	7 (50.0)
Adverse events of grade 3-4	11 (68.8)	14 (100.0)
Adverse events leading to discontinuation[2]	2 (12.5)	4 (28.6)
Clinically notable adverse events[3]	16 (100.0)	11 (78.6)

Categories are not mutually exclusive.

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

1. On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment.
2. As reported on the AE CRF page
3. Clinically notable adverse events are AEs for which there is a specific clinical interest in connection with and based on previous experience with everolimus treatment, or AEs which are similar but not identical in nature.

Date of Clinical Trial Report

15-Nov-2011

Date Inclusion on Novartis Clinical Trial Results Database

26-Jan-2012

Date of Latest Update