Sponsor

Novartis

Generic Drug Name

RAD001 (Everolimus)

Therapeutic Area of Trial

Non Small Cell Lung Cancer (NSCLC)

Approved Indication

- Approved for Progressive Neuroendocrine Tumors of Pancreatic Origin (PNET) in unresectable, locally advanced or metastatic disease.
- Advanced renal cell carcinoma after Failure of Treatment Failure with Sunitinib or Sorafenib.
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) that cannot be surgically removed.

Study Number

CRAD001C2112

Title

A phase I study investigating the combination of RAD001 with pemetrexed in patients with advanced Non Small Cell Lung Cancer (NSCLC) previously treated with chemotherapy.

Phase of Development

Phase I

Study Start/End Dates

19 Dec 2006 First patient screened

10 Oct 2008 Last patient completed core treatment stage

14 Jan 2010 Last data from extension treatment stage

Study Design/Methodology

This was an open-label, multi-center, dose-escalation Phase I study of everolimus in combination with pemetrexed in patients with NSCLC previously treated with one regimen of standard chemotherapy. The study plan was to investigate two different dosing schedules of everolimus (daily and weekly) in combination with the standard 21-day cyclic administration of pemetrexed. Up to four individual dose levels of everolimus in the daily arm (2.5mg, 5mg, 7.5mg and 10mg) and up to three dose levels in the weekly arm (20mg, 30mg and 50mg) were planned to be explored.

On Day 1 of each cycle, patients received 500 mg/m^2 pemetrexed administered as a 10-minute continuous i.v. infusion in 100mL normal saline (NS) directly after everolimus dosing, except in cycle 1 when no everolimus was administered on day 1. In both treatment arms, everolimus dosing began on Day 2 of Cycle 1. Weekly dosing of everolimus mid-cycle was administered on Days 8 and 15.

Patients received a maximum of six cycles of everolimus in combination with pemetrexed during the core treatment stage. Following completion of the core treatment stage of the study (or if chemotherapy was discontinued early), three treatment options were available for the patient:

• Extension of combined pemetrexed and everolimus;

• Everolimus monotherapy;

• Pemetrexed treatment alone.

All study treatment in the extension stage of the study could continue until there was evidence of progressive disease or unacceptable toxicity occurred.

Centers

5 centers in 3 countries: Australia (2), Belgium (1), Germany (2)

Publication

The publication of the study results is currently ongoing.

Objectives

Primary objective(s)

- To establish the feasible dose levels/regimens of everolimus combined with the standard pemetrexed regimen in patients with NSCLC previously treated with one regimen of chemotherapy based on the evaluation of safety.

Secondary objective(s)

- To assess the ability to deliver the standard pemetrexed treatment when administered in combination with everolimus.
- To assess the pharmacokinetics (PK) of everolimus in NSCLC patients treated with the combination everolimus and pemetrexed and to estimate the PK interaction between everolimus and pemetrexed.
- To assess the clinical efficacy of combined administration of different everolimus dose levels/regimens with standard pemetrexed treatment based on the evaluation of overall tumor response according to the RECIST (response evaluation criteria for solid tumors).

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

Everolimus was supplied by Novartis as tablets in 3 different dosage strengths, 2.5, 5 and 10 mg. The tablet (or tablets as appropriate for the dose) was taken orally with a glass of water at the same time of the day, approximately one hour before the ingestion of food, or 2 hours after the last meal.

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

Commercially available pemetrexed (Alimta®) was supplied to the sites for use in this study and 500 mg/m^2 was administered on Day 1 of each cycle as a 10-minute continuous i.v. infusion in 100mL normal saline.

Criteria for Evaluation

Primary variables

- The primary variable used in the time-to-event model was time-to-DLT, defined as the time from date of treatment start to the date of the DLT. The primary endpoint was expressed in terms of the probability of the End-of-Cycle 1 DLT rate falling within prespecified intervals and was estimated via a Bayesian time-to-event model.

Secondary variables

- Cumulative relative dose intensity (RDI) as predicted by a Bayesian mixed-effects model, where the model provided the probability that the RDI falls within the optimal/suboptimal intervals.
- Non-compartmental PK parameters as follows:
  - $AUC_{0\text{-}tlast}$ The AUC from time zero to the last measurable concentration sampling time in a dosing interval (t_{last}) (mass x time x volume^{-1}) (everolimus and pemetrexed)
  - $AUC_{0\text{-}\tau}$ The area under the concentration-time curve during a dosing interval (τ) (mass x time x volume^{-1}) (everolimus only)
  - CL/F (L/h)* Apparent oral clearance = dose/$AUC_{0\text{-}\tau}$ (volume x time^{-1}) (everolimus only)
  - CL/F (L/h/m2) Apparent oral clearance normalized to BSA = dose/($AUC_{0\text{-}\tau}$*BSA) (volume x time^{-1} x BSA^{-1}) (everolimus only)
  - C_{max} The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1}) (everolimus and pemetrexed)
  - C_{min} Pre-dose trough concentration (mass x volume^{-1}) (everolimus and pemetrexed)
  - C_{avg} Average concentration during a dosing interval = $AUC_{0\text{-}tlast}/t_{last}$ (mass x volume^{-1}) (everolimus and pemetrexed)
  - T_{max} The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time) (everolimus only)
- Evaluation of overall objective tumor response rate according to RECIST.

Safety and tolerability

- Collection of all adverse events (AEs) including all DLTs, serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. This included the regular monitoring of hematology, blood chemistry and urine performed at each study laboratory and regular assessments of vital signs, physical condition and body weight.

Statistical Methods

To address the primary objective of the study, a Bayesian time-to-event model of the rate of DLT was used for the dose escalation process. Dose escalation decision-making were made based on the distribution of the probability of the End-of-Cycle-1 DLT rate as derived from the model (the primary endpoint). A Bayesian model for the relative dose intensity (RDI) of the chemotherapy agents, based on the overall RDI of pemetrexed, was used in the assessment of the secondary objective related to RDI.

All data marked as core in the database were included in the core outputs. The summary of results described here refers to core outputs, except for efficacy analysis which combined core and extension data. In the core outputs, all summaries were provided split by regimen, schedule (i.e. treatment arm) and everolimus dose level. Unless otherwise stated, continuous data were summarized using descriptive statistics such as mean, standard deviation, median and range; categorical data were summarized using contingency tables with frequency and percentages.

Study Population:

Inclusion Criteria

- Histologically or cytologically confirmed diagnosis of advanced (stage IIIB/IV) NSCLC
- Age ≥ 18 years
- World Health Organization (WHO) performance status grade ≤ 1
- Only one prior regimen of chemotherapy for the treatment of advanced NSCLC and recovered from the side effects of such therapy
- Adequate bone marrow function as shown by:
  - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin (Hb) > 9g/dL
- Adequate liver function as shown by:
  - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (or ≤ 5 x ULN if hepatic metastases are present)
  - Total bilirubin ≤ 1.5 x ULN
- Adequate renal function as shown by:
  - Creatinine clearance (CrCl) ≥ 45 mL/min
- Negative serum pregnancy test at screening for all women of child-bearing potential
- Written informed consent obtained according to local guidelines.

Exclusion Criteria

- Patients with a history of another primary malignancy ≤ 5 years still requiring treatment, with the exception of inactive basal or squamous cell carcinoma of the skin or cervical cancer *in situ*.
- Patients who received any investigational drug ≤ 5 half lives, or 4 weeks for antibodies,

or who had not recovered from side effects of such therapy;

- Patients who received any systemic anticancer therapy after completion of 1st-line chemotherapy regimen for advanced NSCLC.
- Patients who had not recovered from the side effects of any major surgery or required major surgery during the course of the study;
- Patients who received wide field radiation therapy to the bone marrow within 4 weeks or limited radiation therapy for palliation within 2 weeks prior to first study treatment.
- Patients receiving chronic treatment with steroids or another immunosuppressive agent.
- Patients who received prior therapy with everolimus or other mTOR inhibitors.
- Patients being treated with drugs known to be strong inhibitors or inducers of isoenzyme CYP3A.
- Patients with symptomatic, leptomeningeal or uncontrolled brain metastases, or any severe and/or uncontrolled medical conditions as defined in the protocol, or impairment of gastrointestinal function or gastrointestinal disease that could significantly alter the absorption of everolimus.
- Patients who have any severe and/or uncontrolled medical conditions such as:
  - unstable angina pectoris, unstable angina, or symptomatic congestive heart failure,
  - ventricular arrhythmias, active ischemic heart disease, myocardial infarction ≤ 6
  - months prior to allocation, serious uncontrolled cardiac arrhythmia or uncontrolled
  - hypertension
  - uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
  - active or uncontrolled severe infection
  - chronic liver or renal disease.
- Having impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome).
- Patients with active respiratory, skin, mucosal, renal, neurological or ocular disorders of grade > 1.
- Patients with grade 3 hypercholesterolemia / hypertriglyceridemia or ≥ grade 2 hypercholesterolemia / hypertriglyceridemia with history of coronary artery disease (despite lipid lowering treatment if given).
- Patients with a known history of Human Immunodeficiency Virus seropositivity.
- Women who are pregnant or breast feeding; or women who are able to conceive and are unwilling to practice an effective method of birth control (see Section 8.2).
- Patients who have a history of non-compliance to medical regimens or patients unwilling or unable to comply with the protocol.

Number of Subjects

Patient disposition (Full Analysis Set)

Regimen: Continuous	Daily				
	RAD001 2.5mg + Pemetrexed N=5 n (%)	RAD001 5mg + Pemetrexed N=12 n (%)	RAD001 7.5mg + Pemetrexed N=4 n (%)	RAD001 10mg + Pemetrexed N=3 n (%)	All QD patients N=24 n (%)
Enrolled	5 (100.0)	12 (100.0)	4 (100.0)	3 (100.0)	24 (100.0)
Completed 6 cycles	1 (20.0)	5 (41.7)	1 (25.0)	0	7 (29.2)
Entered extension phase*	0	5 (100.0)	0	0	5 (71.4)
Discontinued	4 (80.0)	7 (58.3)	3 (75.0)	3 (100.0)	17 (70.8)
Adverse Event(s)	0	2 (16.7)	2 (50.0)	0	4 (16.7)
Abnormal laboratory value(s)	2 (40.0)	0	0	0	2 (8.3)
Lost to follow-up	0	0	0	0	0
Administrative problems	0	0	0	0	0
Death	0	0	0	0	0
New cancer therapy	0	0	0	0	0
Disease progression	2 (40.0)	5 (41.7)	1 (25.0)	3 (100.0)	11 (45.8)
Entered extension phase#	1 (25.0)	1 (14.3)	1 (33.3)	0	3 (17.6)

Regimen: Continuous	Weekly		
	RAD001 30mg + Pemetrexed N=6 n (%)	RAD001 50mg + Pemetrexed N=13 n (%)	All QW patients N=19 n (%)
Enrolled	6 (100.0)	13 (100.0)	19 (100.0)
Completed 6 cycles	2 (33.3)	3 (23.1)	5 (26.3)
Entered extension phase*	2 (100.0)	2 (66.7)	4 (80.0)
Discontinued	4 (66.7)	10 (76.9)	14 (73.7)
Adverse Event(s)	0	2 (15.4)	2 (10.5)
Abnormal laboratory value(s)	0	1 (7.7)	1 (5.3)
Lost to follow-up	0	0	0
Administrative problems	0	1 (7.7)	1 (5.3)
Death	0	1 (7.7)	1 (5.3)
New cancer therapy	0	1 (7.7)	1 (5.3)
Disease progression	4 (66.7)	4 (30.8)	8 (42.1)
Entered extension phase#	0	2 (20.0)	2 (14.3)

*Percentage of patients entering extension who completed 6 cycles in core phase.

#Percentage of patients who entered extension having discontinued core phase.

Demographic and Background Characteristics (Full Analysis Set)

Regimen: Continuous	Daily				
	RAD001 2.5mg + Pemetrexed N=5 n (%)	RAD001 5mg + Pemetrexed N=12 n (%)	RAD001 7.5mg + Pemetrexed N=4 n (%)	RAD001 10mg + Pemetrexed N=3 n (%)	All QD patients N=24 n (%)
Sex					
Female	3 (60.0)	3 (25.0)	2 (50.0)	2 (66.7)	10 (41.7)
Male	2 (40.0)	9 (75.0)	2 (50.0)	1 (33.3)	14 (58.3)
Baseline age (years)					
< 65	4 (80.0)	7 (58.3)	4 (100.0)	2 (66.7)	17 (70.8)
>= 65	1 (20.0)	5 (41.7)	0	1 (33.3)	7 (29.2)
Age (years)					
n	5	12	4	3	24
Mean	55.8	63.8	52.0	63.0	60.0
SD	11.39	7.92	5.29	3.00	8.97
Median	58.0	63.5	53.0	63.0	59.5
Range	37 - 68	52 - 74	45 - 57	60 - 66	37 - 74
WHO PS [1]					
0	2 (40.0)	4 (33.3)	1 (25.0)	0	7 (29.2)
1	3 (60.0)	8 (66.7)	3 (75.0)	3 (100.0)	17 (70.8)

Regimen: Continuous	Weekly		
	RAD001 30mg + Pemetrexed N=6 n (%)	RAD001 50mg + Pemetrexed N=13 n (%)	All QW patients N=19 n (%)
Sex			
Female	2 (33.3)	6 (46.2)	8 (42.1)
Male	4 (66.7)	7 (53.8)	11 (57.9)
Baseline age (years)			
< 65	3 (50.0)	10 (76.9)	13 (68.4)
>= 65	3 (50.0)	3 (23.1)	6 (31.6)
Age (years)			
n	6	13	19
Mean	62.7	58.5	59.8
SD	12.03	9.58	10.27
Median	65.5	59.0	60.0
Range	43 - 74	36 - 72	36 - 74
WHO PS [1]			
0	0	8 (61.5)	8 (42.1)
1	6 (100.0)	5 (38.5)	11 (57.9)

[1]Key: 0=Fully active, able to carry out normal activity without restriction, 1=Restricted in physical strenuous activity but ambulatory and able to carry work of a light or sedentary nature e.g. light house work, office work.

Primary Objective Results

Posterior end-of-Cycle 1 DLT rate based on the Bayesian model (Dose-determining Population)

	Daily				Weekly	
	RAD001 2.5 mg N= 5	RAD001 5 mg N= 12	RAD001 7.5 mg N= 4	RAD001 10 mg N= 3	RAD001 30 mg N= 5	RAD001 50 mg N= 12
Mean	0.103	0.167	0.225	0.280	0.068	0.123
SD	0.045	0.050	0.071	0.103	0.034	0.053
Median	0.098	0.161	0.217	0.264	0.063	0.116
Probability of under dosing [0%, 20%)	0.968	0.753	0.406	0.238	0.998	0.916
Probability of targeted toxicity [20%, 35%)	0.032	0.246	0.538	0.543	0.002	0.082
Probability of excessive toxicity [35%, 60%)	0.0	0.001	0.056	0.212	0.0	0.002
Probability of unacceptable toxicity [60%,100%]	0.0	0.0	0.0	0.007	0.0	0.0

Based on a combination of the statistical output from the time-to-event model, the RDI model and the clinical opinion of the investigators, 5mg/daily and 50mg/weekly were considered to be the feasible dose levels of RAD001 that could be administered with pemetrexed.

Dose limiting toxicities (DLTs) during Cycles 1-6 (Dose-determining Population)

Cycle	DLT	Daily				
		RAD001 2.5mg + Pemetrexed N=5 n (%)	RAD001 5mg + Pemetrexed N=12 n (%)	RAD001 7.5mg + Pemetrexed N=4 n (%)	RAD001 10mg + Pemetrexed N=3 n (%)	All QD patients N=24 n (%)
1	No. of patients exposed	5	12	4	3	24
	No. of patients with DLT	0	2 (16.7)	2 (50)	2 (66.7)	6 (25)
	No. of DLTs	0	2	4	2	8
2	No. of patients exposed	5	10	3	3	21
	No. of patients with DLT	0	1 (10)	1 (33.3)	0	2 (9.5)
	No. of DLTs	0	2	1	0	3
3	No. of patients exposed	3	6	1	2	12
	No. of patients with DLT	1 (33.3)	1 (16.7)	0	0	2 (16.7)
	No. of DLTs	1	1	0	0	2
4	No. of patients exposed	2	6	1	2	11
	No. of patients with DLT	0	2 (33.3)	0	0	2 (18.2)
	No. of DLTs	0	2	0	0	2
5	No. of patients exposed	1	5	1	0	7

	No. of patients with DLT	0	2 (40)	0	0	2 (28.6)	
	No. of DLTs	0	2	0	0	2	
6	No. of patients exposed	1	5	1	0	7	
	No. of patients with DLT	0	0	0	0	0	
	No. of DLTs	0	0	0	0	0	

Cycle	DLT	Weekly		
		RAD001 30mg + Pemetrexed N=5 n (%)	RAD001 50mg + Pemetrexed N=12 n (%)	All QW patients N=17 n (%)
1	No. of patients exposed	5	12	17
	No. of patients with DLT	0	2 (16.7)	2 (11.8)
	No. of DLTs	0	2	2
2	No. of patients exposed	5	10	15
	No. of patients with DLT	0	1 (10)	1 (6.7)
	No. of DLTs	0	1	1
3	No. of patients exposed	4	8	12
	No. of patients with DLT	0	2 (25)	2 (16.7)
	No. of DLTs	0	3	3
4	No. of patients exposed	4	6	10
	No. of patients with DLT	0	0	0
	No. of DLTs	0	0	0
5	No. of patients exposed	2	4	6
	No. of patients with DLT	0	1 (25)	1 (16.7)
	No. of DLTs	0	1	1
6	No. of patients expose	2	4	6
	No. of patients with DLT	0	0	0
	No. of DLTs	0	0	0

-The denominator for cycle rate is the number of patients who reached that cycle (i.e. have at least one administration of any study drug during that cycle).

- Total includes all DLT's over all cycles.

Secondary Objective Results

RDI Model Results

The probability that the RDI of pemetrexed fell within the optimal interval (RDI ≥80%) was ≥97% for all everolimus dose levels within each of the daily and weekly dosing schedules. These results ratified the conclusions drawn about the feasible dose levels as described above.

PK

Statistical analysis of dose proportionality for everolimus, by PK parameter, regimen and schedule (Safety Population)

			90% CI	
Treatment	**PK parameter (units) [1]**	**Estimate of Beta**	**Lower**	**Upper**
Regimen: Continuous Schedule: Daily (N=24)				
RAD001 alone	$AUC_{0\text{-}last}$ (ng.h/mL)	0.46	-0.081	1.004
	AUC_{tau} (ng.h/mL)	0.54	0.134	0.946
	C_{max} (ng/mL)	0.65	-0.097	1.396
RAD001 + Pemetrexed	$AUC_{0\text{-}last}$ (ng.h/mL)	1.06	0.220	1.902
	AUC_{tau} (ng.h/mL)	1.13	0.388	1.881
	C_{max} (ng/mL)	1.14	0.357	1.919
Regimen: Continuous Schedule: Weekly (N=19)				
RAD001 alone	$AUC_{0\text{-}last}$ (ng.h/mL)	1.07	0.165	1.970
	AUC_{tau} (ng.h/mL)	1.07	0.165	1.967
	C_{max} (ng/mL)	0.31	-0.179	0.804
RAD001 + Pemetrexed	$AUC_{0\text{-}last}$ (ng.h/mL)	0.55	-1.740	2.834
	AUC_{tau} (ng.h/mL)	0.52	-1.818	2.852
	C_{max} (ng/mL)	-0.28	-1.937	1.370

[1] The log-transformed PK parameter is modeled by means of power model of log-actual dose at sample time, by treatment, regimen and schedule. Samples with zero actual dose (treatment interrupted or discontinued) were excluded.

- Everolimus C_{max} increased less than dose-proportionally in the weekly dosing schedule, which is in accordance with previous everolimus weekly dose results.
- Everolimus PK parameters $AUC_{0\text{-}tlast}$, AUC_{tau} and C_{max} demonstrated less than dose-proportional increases with increasing daily doses, while everolimus PK was dose-proportional across the daily and weekly dosing schedules, when administered in combination with pemetrexed. However, a wide confidence interval associated with the PK parameters renders these results inconclusive.
- Everolimus did not exert any notable impact on pemetrexed exposure.
- Pemetrexed influenced everolimus PK at the everolimus dose of 2.5 mg/day and 50 mg/week, however due to the lack of sufficient samples and high variability of data the cause of this interaction could not be determined.
- Concomitant administration of CYP3A4 substrates did not have an impact on everolimus pre-dose concentrations in this study.

Summary statistics for everolimus C_{min} (ng/mL) by regimen, schedule and dose level (Safety Population)

RAD	Profile	Raw statistics			Intra-patient CV% [2]	Inter-Patients CV% [3]
Dose (mg)	**Day/Cycle**	**n**	**Mean**	**SD**		
Regimen: Continuous Schedule: Daily (N = 24)						
0	D1 C2	1	0.45			

	D1 C4	1	0.38				
	Overall	2	0.42	0.049	---	---	
2.5	D8 C1	6	6.15	2.968			
	D1 C2	4	4.27	2.449			
	D1 C3	1	10.70	---			
	D1 C4	3	5.27	4.000			
	D1 C5	2	8.08	6.116			
	D1 C6	2	5.54	2.348			
	Overall	7	5.98	3.270	41.6	69.8	
5	D8 C1	8	9.89	5.152			
	D1 C2	6	13.49	8.194			
	D1 C3	4	6.84	4.044			
	D1 C4	3	5.41	3.184			
	D1 C5	3	10.83	6.935			
	D1 C6	3	11.82	7.449			
	Overall	10	10.06	6.159	35.8	68.0	
7.5	D8 C1	1	12.10	----			
	D1 C2	1	10.89	----			
	D1 C3	1	12.20	----			
	D1 C4	1	15.70	----			
	D1 C5	1	14.10	----			
	D1 C6	1	11.20	----			
	Overall	1	12.70	1.850	---	----	
10	D8 C1	1	9.46	----			
	D1 C2	1	10.60	----			
	D1 C3	1	7.69	----			
	D1 C4	1	10.30	----	---	----	
	Overall	1	9.51	1.307	---	----	
Regimen: Continuous Schedule: Weekly (N = 19)							
20	D8 C1	1	0.57	----	---	----	
	Overall	1	0.57	----	---	---	
30	D8 C1	5	0.95	0.349			
	D1 C2	4	0.80	0.476			
	D1 C3	1	0.36	----			
	D1 C4	3	0.48	0.271			
	D1 C5	2	0.39	0.006			
	D1 C6	2	0.51	0.013			
	Overall	5	0.68	0.368	44.1	49.5	
50	D8 C1	9	2.20	1.993			
	D1 C2	8	1.97	2.301			
	D1 C3	6	0.97	0.643			
	D1 C4	5	1.07	0.638			
	D1 C5	3	0.69	0.048			
	D1 C6	3	0.67	0.252			
	Overall	10	1.50	1.610	35.8	119.3	

[1] The log-transformed PK parameter is modeled by means of a mixed model with patient as a random effect and time as a fixed effect.

[2] Intra-patient CV: calculated from the variance of the residual error of the model, by means of formula: CV = sqrt(exp(within subject variance)-1)*100

[3] Inter-patient CV: calculated from the variance of the residual error of the model, by means of formula: CV = sqrt(exp(within subject variance+between subject variance)-1)*100.

Statistical analysis of the drug interaction for everolimus by PK parameter, regimen, schedule and dose level (Safety Population)

RAD Dose (mg)	PK Parameter (units) [1]	Profile Day/Cycle	n	Geometric mean [2]	Ratio of geometric means [3]		Intra-Patients CV% [4]
					Ratio	90% CI	
Regimen: Continuous Schedule: Daily (N = 24)							
2.5	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	6	255.52			
		B: D1 C2 (test)	4	102.19	0.40	(0.22, 0.74)	---
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	6	268.02			
		B: D1 C2 (test)	4	109.48	0.41	(0.23, 0.72)	---
	C_{max} (ng/mL)	A: D8 C1 (ref)	6	30.45			
		B: D1 C2 (test)	5	11.08	0.36	(0.15, 0.90)	---
5	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	10	309.35			
		B: D1 C2 (test)	9	220.20	0.71	(0.46, 1.11)	---
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	9	369.45			
		B: D1 C2 (test)	8	271.03	0.73	(0.48, 1.12)	---
	C_{max} (ng/mL)	A: D8 C1 (ref)	10	35.65			
		B: D1 C2 (test)	9	23.87	0.67	(0.34, 1.32)	---
7.5	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	1	613.65			
		B: D1 C2 (test)	1	408.87	0.67	(0.20, 2.22)	----
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	1	613.65			
		B: D1 C2 (test)	1	409.53	0.67	(0.21, 2.09)	---
	C_{max} (ng/mL)	A: D8 C1 (ref)	1	109.00			
		B: D1 C2 (test)	1	36.80	0.34	(0.04, 2.56)	---
10	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	1	642.09			

		B: D1 C2 (test)	1	512.42	0.80	(0.24, 2.66)	47.1	
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	1	638.47				
		B: D1 C2 (test)	1	511.89	0.80	(0.26, 2.52)	45.0	
	C_{max} (ng/mL)	A: D8 C1 (ref)	1	115.00				
		B: D1 C2 (test)	1	58.80	0.51	(0.07, 3.88)	72.7	
Regimen: Continuous Schedule: Weekly (N = 19)								
20	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	1	3100.50				
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	1	3101.02				
	C_{max} (ng/mL)	A: D8 C1 (ref)	1	138.00				
30	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	4	3151.05				
		B: D1 C2 (test)	3	2372.61	0.75	(0.30, 1.92)	---	
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	4	3157.25				
		B: D1 C2 (test)	3	2380.27	0.75	(0.29, 1.96)	---	
	C_{max} (ng/mL)	A: D8 C1 (ref)	5	228.37				
		B: D1 C2 (test)	4	128.53	0.56	(0.27, 1.16)	---	
50	$AUC_{0\text{-}last}$ (ng.h/mL)	A: D8 C1 (ref)	7	6394.02				
		B: D1 C2 (test)	7	3175.56	0.50	(0.26, 0.97)	72.0	
	AUC_{tau} (ng.h/mL)	A: D8 C1 (ref)	7	6402.65				
		B: D1 C2 (test)	7	3133.92	0.49	(0.25, 0.96)	73.9	
	C_{max} (ng/mL)	A: D8 C1 (ref)	9	236.88				
		B: D1 C2 (test)	10	111.20	0.47	(0.29, 0.77)	66.3	

[1] The log-transformed PK parameter is modeled by means of a linear model including terms for treatment (i.e. combination or alone), dose and treatment*dose interaction, and patient as a random effect.

[2] The geometric mean is obtained by back-transforming on the original scale the mean of the log-transformed PK parameters.

[3] Comparison of interest: B/A (test/ref).

[4] Intra-patient CV: calculated from the variance of the residual error of the model, by means of the formula: CV = SQRT(EXP(variance)-1)*100.

Best Overall Response (Full Analysis Set)

Regimen: Continuous	Daily				
Best overall response	RAD001 2.5mg + Pemetrexed N=5 n (%)	RAD001 5mg + Pemetrexed N=12 n (%)	RAD001 7.5mg + Pemetrexed N=4 n (%)	RAD001 10mg + Pemetrexed N=3 n (%)	All QD patients N=24 n (%)
Complete response (CR)	0	0	0	0	0
Partial response (PR)	1 (20.0)	3 (25.0)	0	0	4 (16.7)
Stable disease (SD)	1 (20.0)	4 (33.3)	2 (50.0)	0	7 (29.2)
Progressive disease (PD)	2 (40.0)	4 (33.3)	1 (25.0)	2 (66.7)	9 (37.5)
Unknown (UNK)	1 (20.0)	1 (8.3)	1 (25.0)	1 (33.3)	4 (16.7)
Objective response rate (ORR) (CR or PR)	1 (20.0)	3 (25.0)	0	0	4 (16.7)
95% CI of ORR	[0.5, 71.6]	[5.5, 57.2]	[0.0, 60.2]	[0.0, 70.8]	[4.7, 37.4]
Disease control rate (DCR) (CR or PR or SD)	2 (40.0)	7 (58.3)	2 (50.0)	0	11 (45.8)
95% CI of DCR	[5.3, 85.3]	[27.7, 84.8]	[6.8, 93.2]	[0.0, 70.8]	[25.6, 67.2]

Regimen: Continuous	Weekly		
Best overall response	RAD001 30mg + Pemetrexed N=6 n (%)	RAD001 50mg + Pemetrexed N=13 n (%)	All QW patients N=19 n (%)
Complete response (CR)	0	0	0
Partial response (PR)	0	2 (15.4)	2 (10.5)
Stable disease (SD)	2 (33.3)	3 (23.1)	5 (26.3)
Progressive disease (PD)	4 (66.7)	6 (46.2)	10 (52.6)
Unknown (UNK)	0	2 (15.4)	2 (10.5)
Objective response rate (ORR) (CR or PR)	0	2 (15.4)	2 (10.5)
95% CI of ORR	[0.0, 45.9]	[1.9, 45.4]	[1.3, 33.1]
Disease control rate (DCR) (CR or PR or SD)	2 (33.3)	5 (38.5)	7 (36.8)
95% CI of DCR	[4.3, 77.7]	[13.9, 68.4]	[16.3, 61.6]

The best overall response is determined based on investigator assessments of overall lesion response as recorded in the eCRF.

The Clopper-Pearson method is used to determine the confidence intervals.

Note: Based on core data only,

- 1 patient in RAD001 (everolimus) 2.5mg is PR at the end of the extension while being SD at end of core. This patient was never treated with RAD in the extension.

- 1 patient in RAD001 5mg is SD at the end of the extension while being UNK at end of core. This patient was never treated with RAD in the extension.

-1 patient in RAD001 50mg is PD at the end of the extension while being UNK at end of core. This patient was never treated with RAD in the extension.

Safety Results

Number of patients with most frequent (greater than or equal to 20% incidence across all patients) adverse events by primary system organ class and preferred term (Safety Population)

Regimen: Continuous	Daily				
Primary system organ class Preferred Term	RAD001 2.5mg + Pemetrexed N=5 n (%)	RAD001 5mg + Pemetrexed N=12 n (%)	RAD001 7.5mg + Pemetrexed N=4 n (%)	RAD001 10mg + Pemetrexed N=3 n (%)	All QD patients N=24 n (%)
Patients with AE(s)	5 (100.0)	12 (100.0)	4 (100.0)	3 (100.0)	24 (100.0)
General disorders and administration site conditions	4 (80.0)	10 (83.3)	4 (100.0)	3 (100.0)	21 (87.5)
Fatigue	3 (60.0)	7 (58.3)	3 (75.0)	3 (100.0)	16 (66.7)
Pyrexia	2 (40.0)	4 (33.3)	4 (100.0)	1 (33.3)	11 (45.8)
Mucosal inflammation	1 (20.0)	3 (25.0)	1 (25.0)	1 (33.3)	6 (25.0)
Gastrointestinal disorders	5 (100.0)	10 (83.3)	2 (50.0)	2 (66.7)	19 (79.2)
Nausea	3 (60.0)	4 (33.3)	1 (25.0)	1 (33.3)	9 (37.5)
Stomatitis	4 (80.0)	2 (16.7)	1 (25.0)	0	7 (29.2)
Diarrhea	2 (40.0)	6 (50.0)	1 (25.0)	0	9 (37.5)
Vomiting	1 (20.0)	3 (25.0)	1 (25.0)	0	5 (20.8)
Constipation	1 (20.0)	3 (25.0)	1 (25.0)	0	5 (20.8)
Abdominal Pain Upper	2 (40.0)	2 (16.7)	1 (25.0)	0	5 (20.8)
Skin and subcutaneous tissue disorders	5 (100.0)	11 (91.7)	4 (100.0)	1 (33.3)	21 (87.5)
Rash	5 (100.0)	8 (66.7)	3 (75.0)	1 (33.3)	17 (70.8)
Dry skin	1 (20.0)	3 (25.0)	1 (25.0)	0	5 (20.8)
Blood and lymphatic system disorders	2 (40.0)	10 (83.3)	4 (100.0)	2 (66.7)	18 (75.0)
Neutropenia	2 (40.0)	8 (66.7)	4 (100.0)	2 (66.7)	16 (66.7)
Anemia	0	6 (50.0)	1 (25.0)	2 (66.7)	9 (37.5)
Thrombocytopenia	0	4 (33.3)	2 (50.0)	2 (66.7)	8 (33.3)
Leukopenia	0	5 (41.7)	0	2 (66.7)	7 (29.2)
Lymphopenia	0	3 (25.0)	0	2 (66.7)	5 (20.8)
Metabolism and nutrition disorders	2 (40.0)	9 (75.0)	3 (75.0)	3 (100.0)	17 (70.8)
Anorexia	1 (20.0)	7 (58.3)	2 (50.0)	2 (66.7)	12 (50.0)
Hyperglycemia	0	3 (25.0)	0	1 (33.3)	4 (16.7)
Respiratory, thoracic and mediastinal disorders	4 (80.0)	9 (75.0)	3 (75.0)	1 (33.3)	17 (70.8)
Dyspnea	2 (40.0)	3 (25.0)	2 (50.0)	0	7 (29.2)
Cough	2 (40.0)	4 (33.3)	1 (25.0)	0	7 (29.2)
Epistaxis	2 (40.0)	5 (41.7)	0	1 (33.3)	8 (33.3)
Nervous system disorders	3 (60.0)	7 (58.3)	1 (25.0)	0	11 (45.8)
Headache	1 (20.0)	4 (33.3)	0	0	5 (20.8)
Investigations	1 (20.0)	5 (41.7)	0	3 (100.0)	9 (37.5)
Aspartate aminotransferase	0	4 (33.3)	0	2 (66.7)	6 (25.0)

increased					
Alanine aminotransferase increased	0	3 (25.0)	0	2 (66.7)	5 (20.8)

Regimen: Continuous	**Weekly**		
Primary system organ class **Preferred Term**	**RAD001 30mg + Pemetrexed N=6 n (%)**	**RAD001 50mg + Pemetrexed N=13 n (%)**	**All QW patients N=19 n (%)**
Patients with AE(s)	6 (100.0)	13 (100.0)	19 (100.0)
General disorders and administration site conditions	4 (66.7)	11 (84.6)	15 (78.9)
Fatigue	1 (16.7)	7 (53.8)	8 (42.1)
Pyrexia	3 (50.0)	4 (30.8)	7 (36.8)
Mucosal inflammation	1 (16.7)	2 (15.4)	3 (15.8)
Gastrointestinal disorders	6 (100.0)	9 (69.2)	15 (78.9)
Nausea	4 (66.7)	4 (30.8)	8 (42.1)
Stomatitis	3 (50.0)	6 (46.2)	9 (47.4)
Diarrhea	2 (33.3)	4 (30.8)	6 (31.6)
Vomiting	1 (16.7)	4 (30.8)	5 (26.3)
Constipation	0	2 (15.4)	2 (10.5)
Abdominal Pain Upper	0	0	0
Skin and subcutaneous tissue disorders	4 (66.7)	9 (69.2)	13 (68.4)
Rash	3 (50.0)	8 (61.5)	11 (57.9)
Dry skin	1 (16.7)	0	1 (5.3)
Blood and lymphatic system disorders	4 (66.7)	11 (84.6)	15 (78.9)
Neutropenia	4 (66.7)	9 (69.2)	13 (68.4)
Anemia	0	8 (61.5)	8 (42.1)
Thrombocytopenia	1 (16.7)	5 (38.5)	6 (31.6)
Leukopenia	0	5 (38.5)	5 (26.3)
Lymphopenia	0	4 (30.8)	4 (21.1)
Metabolism and nutrition disorders	4 (66.7)	11 (84.6)	15 (78.9)
Anorexia	3 (50.0)	7 (53.8)	10 (52.6)
Hyperglycemia	1 (16.7)	6 (46.2)	7 (36.8)
Respiratory, thoracic and mediastinal disorders	4 (66.7)	10 (76.9)	14 (73.7)
Dyspnea	2 (33.3)	6 (46.2)	8 (42.1)
Cough	1 (16.7)	4 (30.8)	5 (26.3)
Epistaxis	1 (16.7)	1 (7.7)	2 (10.5)
Nervous system disorders	3 (50.0)	3 (23.1)	6 (31.8)
Headache	1 (16.7)	2 (15.4)	4 (15.8)
Investigations	1 (16.7)	6 (46.2)	7 (36.8)
Aspartate aminotransferase increased	0	4 (30.8)	4 (21.1)
Alanine aminotransferase increased	1 (16.7)	3 (23.1)	4 (21.1)

Primary system organ classes and preferred terms within primary system organ class are sorted by descending frequency across all patients.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

CTC grade 3 or 4 adverse events (greater than or equal to 10% incidence) regardless of study treatment relationship by primary system organ class and preferred term (Safety Population)

Regimen: Continuous	**Daily**				
Primary system organ class **Preferred term**	**RAD001 2.5 mg + Pemetrexed N=5 n (%)**	**RAD001 5 mg + Pemetrexed N=12 n(%)**	**RAD001 7.5 mg + Pemetrexed N=4 n (%)**	**RAD001 10 mg + Pemetrexed N=3 n (%)**	**All QD patients N=24 n (%)**
Any primary system organ class	5 (100)	10 (83.3)	4 (100)	2 (66.7)	21 (87.5
Blood and lymphatic system disorder	2 (40)	8 (66.7)	4 (100)	2 (66.7)	16 (66.7
Neutropenia	2 (40)	7 (58.3)	4 (100)	2 (66.7)	15 (62.5
Thrombocytopenia	0	3 (25.0)	2 (50.0)	0	5 (20.8)
Leucopenia	0	3 (25.0)	0	1 (33.3)	4 (16.7)
Anemia	0	1 (8.3)	0	1 (33.3)	2 (8.3)
Febrile neutropenia	0	0	1 (25.0)	1 (33.3)	2 (8.3)
Granulocytopenia	0	1 (8.3)	0	1 (33.3)	2 (8.3)
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1 (8.3)	2 (50.0)	0	4 (16.7)
Dyspnea	1 (20.0)	1 (8.3)	2 (50.0)	0	4 (16.7)
Pleural effusion	1 (20.0)	0	0	0	1 (4.2)
Gastrointestinal disorders	1 (20.0)	0	0	1 (33.3)	2 (8.3)
Anal pruritis	0	0	0	1 (33.3)	1 (4.2)
Painful defaecation	0	0	0	1 (33.3)	1 (4.2)
Vomiting	1 (20.0)	0	0	0	1 (4.2)
General disorders and administration site conditions	1 (20.0)	2 (16.7)	0	1 (33.3)	4 (16.7)
Fatigue	0	1 (8.3)	0	1 (33.3)	2 (8.3)
Metabolism and nutrition disorders	1 (20.0)	2 (16.7)	0	0	3 (12.5)
Polydipsia	1 (20.0)	0	0	0	1 (4.2)
Skin and subcutaneous tissue disorders	0	1 (8.3)	1 (25.0)	1 (33.3)	3 (12.5)
Pruritus	0	1 (8.3)	1 (25.0)	1 (33.3)	3 (12.5)
Rash	0	1 (8.3)	1 (25.0)	1 (33.3)	3 (12.5)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (25.0)	0	1 (4.2)
Tumor pain	0	0	1 (25.0)	0	1 (4.2)
Renal and urinary disorders	0	0	0	1 (33.3)	1 (4.2)
Dysuria	0	0	0	1 (33.3)	1 (4.2)
Reproductive system and	0	0	0	1 (33.3)	1 (4.2)

breast disorders						
Vulvovaginal pruritis	0	0	0	1 (33.3)	1 (4.2)	

Regimen: Continuous	**Weekly**		
Primary system organ class **Preferred term**	**RAD001 30 mg + Pemetrexed N=6 n(%)**	**RAD001 50 mg + Pemetrexed N=13 n(%)**	**All QW patients N=19 n (%)**
Any primary system organ class	5 (83.3)	9 (69.2)	14 (73.7)
Blood and lymphatic system disorder	4 (66.7)	7 (53.8)	11 (57.9)
Neutropenia	4 (66.7)	7 (53.8)	11 (57.9)
Thrombocytopenia	1 (16.7)	2 (15.4)	3 (15.8)
Leucopenia	0	3 (23.1)	3 (15.8)
Anemia	0	3 (23.1)	3 (15.8)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	3 (23.1)	5 (26.3)
Dyspnea	1 (16.7)	3 (23.1)	4 (21.1)
Pleural effusion	1 (16.7)	1 (7.7)	2 (10.5)
Gastrointestinal disorders	1 (16.7)	3 (23.1)	4 (21.1)
Stomatitis	0	3 (23.1)	3 (15.8)
Abdominal pain	1 (16.7)	0	1 (5.3)
Ileus	1 (16.7)	0	1 (5.3)
General disorders and administration site conditions	0	2 (15.4)	2 (10.5)
Fatigue	0	2 (15.4)	2 (10.5)
Skin and subcutaneous tissue disorders	0	1 (7.7)	1 (5.3)
Rash	0	1 (7.7)	1 (5.3)
Reproductive system and breast disorders	1 (16.7)	0	1 (5.3)
Benign prostatic hyperplasia	1 (16.7)	0	1 (5.3)

Primary system organ classes and preferred terms within primary system organ class are sorted by descending frequency across all patients.
- The totals in primary system organ classes include all CTC grade 3/4 events in that class.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row

Deaths, other serious or clinically significant adverse events or related discontinuations (Safety Population)

Regimen: Continuous	**Daily**				
	RAD001 2.5mg + Pemetrexed N=5 n (%)	RAD001 5mg + Pemetrexed N=12 n (%)	RAD001 7.5mg + Pemetrexed N=4 n (%)	RAD001 10mg + Pemetrexed N=3 n (%)	All QD patients N=24 n (%)
All deaths [1]	0	1 (8.3)	0	1 (33.3)	2 (8.3)

On treatment deaths [2]	0	0	0	0	0	
Serious adverse events	2 (40.0)	6 (50.0)	2 (50.0)	0	10 (41.7)	
Adverse events leading to any study treatment discontinuation	2 (40.0)	3 (25.0)	2 (50.0)	0	7 (29.2)	
Adverse events of grade 3-4	5 (100.0)	10 (83.3)	4 (100.0)	2 (66.7)	21 (87.5)	
Clinically notable adverse events	5 (100.0)	11 (91.7)	4 (100.0)	3 (100.0)	23 (95.8)	

Regimen: Continuous	**Weekly**		
	RAD001 30mg + Pemetrexed N=6 n (%)	**RAD001 50mg + Pemetrexed N=13 n (%)**	**All QW patients N=19 n (%)**
All deaths [1]	2 (33.3)	2 (15.4)	4 (21.1)
On treatment deaths [2]	0	1 (7.7)	1 (5.3)
Serious adverse events	2 (33.3)	6 (46.2)	8 (42.1)
Adverse events leading to any study treatment discontinuation	0	4 (30.8)	4 (21.1)
Adverse events of grade 3-4	5 (83.3)	9 (69.2)	14 (73.7)
Clinically notable adverse events	6 (100.0)	12 (92.3)	18 (94.7)

[1] Includes all deaths regardless of whether they are within 28 days of last treatment
[2] Death occurring not more than 28 days after the end of study treatment
Categories are not mutually exclusive;
Adverse events occurring more than 28 days after end of treatment are not summarized;
Clinically notable adverse events are the events for which there is a specific clinical interest in connection with RAD001 (everolimus) or events which are similar in nature.

Date of Clinical Trial Report

07 Feb 2011

Date Inclusion on Novartis Clinical Trial Results Database

25 Jul 2011

Date of Latest Update