Sponsor

Novartis

Generic Drug Name

Everolimus

Therapeutic Area of Trial

Renal cell carcinoma

Approved Indication

- Indicated for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, after prior endocrine therapy.
- Indicated for the treatment of patients with advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin.
- Indicated for the treatment of patients with advanced renal cell carcinoma.
- Indicated for the treatment of patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.
- Indicated for the treatment of patients with TSC who have subependymal giant cell astrocytoma (SEGA) not requiring immediate surgery

Protocol Number

CRAD001C2240

Title

A randomized, double-blind, placebo-controlled, multicenter phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy

Phase of Development

Phase III

Study Start/End Dates

06-Dec-2006 to 27-Oct-2011 (first patient first visit to last patient last visit)

Study Design/Methodology

This was a prospective, randomized, double-blind, multicenter, placebo-controlled, parallel group phase III study designed to evaluate the safety and efficacy of RAD001 in patients with mRCC whose disease had progressed on VEGFr TKI therapy.

Eligible patients randomized in a 2:1 ratio to everolimus versus matching placebo, for the double-blind phase of the study. There were up to five different phases in the study: screening/baseline, blinded treatment, open-label RAD001, follow-up and the extension portion of the study.

The study used a group-sequential design with 2 planned interim analyses and a final analysis. The first and second interim analyses were to be executed when approximately 30% and 60% of 290 PFS events required for the final analysis had been reached respectively. The IDMC, based on a review of safety and/or efficacy data gathered at each interim analysis, could recommend stopping the study either for outstanding efficacy or for futility. If the study was not stopped at one of the two planned interim analyses, then a final analysis would be performed at the time when approximately 290 PFS events had been observed.

At the first occurrence of radiologically documented, disease progression according to RECIST guidelines, the investigator could unblind the patient and if the patient was receiving placebo, the investigator could offer treatment with active RAD001 during the open-label phase of the study.

During the conduct of the study, the double blinded phase was stopped due to outstanding efficacy shown in the second interim analysis (data up to 28-Feb-2008, complete study was unblinded at this date). When the study was terminated on 28-Feb-2008, patients who had been receiving RAD001, and also patients who had been receiving placebo in the double-blind phase of the study, were enrolled in the extension phase to receive open-label RAD001.

Centers

Eighty-six centers in ten countries: Australia (5), Canada (7), France (8), Germany (5), Italy (8), Poland (4), Spain (5), Netherlands (4), Japan (14) and the USA (26).

Publication

None

Outcome measures

Primary outcome measures

- Determination and comparison of progression free survival in patients who received RAD001 plus best supportive care (BSC) versus patients who received Matching Placebo plus BSC.

Secondary outcome measures

- Comparison of overall survival for patients who received RAD001 plus BSC versus patients who receive Matching Placebo plus BSC
- Comparison of objective response rate and duration in patients who received RAD001 plus BSC versus patients who receive Matching Placebo plus BSC
- Duration of response compared between treatment arms
- Time to definitive deterioration of the Global health status / QoL scale (QL) score of the

EORTC QLQ-C30 by at least 10% from baseline

- Time to definitive deterioration of the FKSI-DRS score by at least 2 score units from baseline
- Time to definitive deterioration of the physical functioning scale (PF) score of the EORTC QLQ-C30 by at least 10% from baseline
- Pharmacokinetics (PK) of RAD001 in patients with metastatic renal cell cancer (mRCC).
- Safety profile of RAD001

Test Product, Dose, and Mode of Administration

Oral tablets of everolimus 5 mg each; two tablets were to be taken one tablet after another with a glass of water, at the same time each day in a fasting state or with a light fat-free meal.

Statistical Methods

The Full Analysis Set (FAS population) was defined as all randomized patients. Following the intent-to-treat principle, patients were analyzed according to the treatment and stratum they were assigned to at randomization. The Safety population was defined as all patients who received at least one dose of study drug and who had at least one valid post-baseline safety assessment.
The open-label period population included only patients who received at least one dose of open-label RAD001 and had at least one safety or efficacy assessment during the open-label period.

The primary endpoint was progression-free survival (PFS), defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. The primary analysis of PFS was based on central radiological assessments.

The primary statistical analysis to compare PFS was performed using a one-sided log-rank test stratified by strata defined by the MSKCC risk criteria. In each treatment group, the Kaplan-Meier estimate of the PFS survival function was estimated. Median PFS for each treatment group was obtained along with 95% confidence intervals, 25% and 75% percentiles are also given. Kaplan-Meier estimates with 95% confidence intervals at 4, 6 and 12 months were summarized.
The hazard ratio of the treatment effect estimated in a stratified Cox proportional hazard model, using the strata defined by the MSKCC criteria, was provided with two-sided 95% confidence interval.

Two interim analyses were planned in the protocol: the first interim analysis was planned after observing approximately 30% (~87 PFS events) and the second after observing approximately 60% (~174 PFS events), of the targeted number of 290 PFS events (per central radiology review) required for the final statistical analysis. Both interim analyses were to allow for stopping for lack of efficacy (futility) and for outstanding efficacy.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients were included who met the following criteria:

- Age ≥ 18 years old
- Patients with metastatic carcinoma and with histological or cytological confirmation of clear-

cell RCC (tissue from the original diagnosis of renal cancer is acceptable).

- Patients must have progression on or within 6 months of stopping treatment with a VEGFr TKI (sunitinib and/or sorafenib). Patients may have received one or both agents.
- Prior therapy with cytokines (i.e., IL-2, interferon) and/or VEGF-ligand inhibitors (i.e. bevacizumab) are permitted.
- Prior vaccine therapy in the adjuvant setting is permitted.
- Patients with at least one measurable lesion at baseline as per the RECIST criteria, either on physical exam or as determined by Computer Tomography (CT) Scan or Magnetic Resonance Imaging (MRI). If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper or a ruler) in clear focus to allow the size of the lesion(s) to be determined from the photograph.
- Patients with a Karnofsky Performance Status ≥ 70%.
- Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb > 9 g/dL.
- Adequate liver function: serum bilirubin: ≤ 1.5 x ULN, ALT and AST ≤ 2.5x ULN. Patients with known liver metastases: AST and ALT ≤ 5x ULN.
- Adequate renal function: serum creatinine ≤ 1.5 x ULN.
- Patients with a life expectancy ≥ 3 months. Life expectancy should be judged in relation to other determining patient eligibility factors such as laboratory results, Karnofsky Performance Status etc.)
- Women of childbearing potential must have had a negative serum or urine pregnancy test within 7 days prior to the administration of the first study treatment .
- Patients who give a written informed consent obtained according to local guidelines

Exclusion Criteria

Patients were excluded who met the following criteria:

- Patients receiving chemotherapy, immunotherapy, or radio-therapy or who have received these ≤4 weeks prior to Visit 1. The wash-out period for sunitinib and/or sorafenib is at least 2 weeks from the first dose of the study medication.
- Patients who have previously received mTOR inhibitors.
- Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent
- Patients with a known history of HIV seropositivity
- Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumadin)
- Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients.
- Patients with untreated CNS metastases or who have received treatment for CNS metastases within 6 months of study entry. Patients with treated CNS metastases, who were neurologically stable and off of corticosteroids for more than 6 months prior to study entry, could enter the study.
- Patients who have any severe and/or uncontrolled medical conditions such as:

- unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia,
- uncontrolled diabetes as defined by fasting serum glucose >1.5x ULN.
- active or uncontrolled severe infection.
- cirrhosis, chronic active hepatitis or chronic persistent hepatitis
- severely impaired lung function

- Patients who have a history of another primary malignancy ≤ 3 years, with the exceptions of non-melanoma skin cancer, and carcinoma in situ of uterine cervix
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes.
- Patients using other investigational agents or who had received investigational drugs ≤ 4 weeks prior to Visit 1.
- Patients unwilling to or unable to comply with the protocol.

Participant Flow

Patient disposition, by treatment-FAS (Core Phase double-blind 15 months)

Labels as per rando	RAD001 +BSC	Placebo + BSC	Total
STARTED	277 [1]	139	416
COMPLETED AS PER FINAL PRIMARY ANALYSIS	62	2	64
COMPLETED	75 [2]	6 [3]	81
ONGOING	13	4	17
DISCONTINUED	202	133 from Placebo	335
REASONS FOR DISCONTINUATION			
Adverse Events	36	2	38
Abnormal Lab Values	1	0	1
Abnormal Test Procedures	0	0	0
Protocol Deviation	2	1	3
Subject Withdrew Consent	13	2	15
Lost to Follow-Up	4	0	4
Death	7	4	11
Administrative problems	2	0	2
Disease Progression	137	124	261
Missing	0	0	0

[1] Started indicates randomized (FAS) and treated.
[2] Patients ongoing/completed double blind phase had option entering extension phase continuing RAD001.
[3] All patients ongoing/completed/not completed in core had option to enter extension taking RAD001.

Patient disposition, by treatment-FAS (Extension Phase)

Labels as per rando	RAD001 +BSC	Placebo + BSC	Total

STARTED	67	111[1]	178
ONGOING	0	0	0
DISCONTINUED from RAD	67	111 from RAD	178
REASONS FOR DISCONTINUATION			0
Adverse Events	7	19	26
Abnormal Lab Values	0	1	1
Abnormal Test Procedures	0	1	1
Subject Withdrew Consent	1	1	2
Lost to Follow-Up	0	0	0
Death	2	10	12
Disease Progression	56	78	134
Missing	1	0	1
Final Primary Analysis	0	1	1
Subject's condition no longer requires study drug	1	0	1
[1] Patients on placebo in core received RAD001 in extension phase			

Baseline Characteristics

Demographic and baseline characteristics, by treatment-FAS

Variable		RAD001 10mg/day (plus BSC) N=277	Placebo (plus BSC) N=139	All patients N=416
Gender – n (%)	Female	61 (22.0)	33 (23.7)	94 (22.6)
	Male	216 (78.0)	106 (76.3)	322 (77.4)
Age group – n (%)	< 65	165 (59.6)	98 (70.5)	263 (63.2)
	≥ 65	112 (40.4)	41 (29.5)	153 (36.8)
Age (years)	Mean	60.66	59.27	60.20
	SD	10.355	9.585	10.114
	Median	61.00	60.00	61.00
	Minimum	27.0	29.0	27.0
	Maximum	85.0	79.0	85.0
Race – n (%)	Asian	16 (5.8)	11 (7.9)	27 (6.5)
	Black	2 (0.7)	3 (2.2)	5 (1.2)
	Caucasian	246 (88.8)	121 (87.1)	367 (88.2)
	Missing	4 (1.4)	1 (0.7)	5 (1.2)
	Native American	1 (0.4)	0 (0.0)	1 (0.2)
	Other	8 (2.9)	3 (2.2)	11 (2.6)
Ethnicity - n (%)	Hispanic/Latino	14 (5.1)	3 (2.2)	17 (4.1)
	Indian (Indian subcontinent)	1 (0.4)	1 (0.7)	2 (0.5)
	Japanese	15 (5.4)	9 (6.5)	24 (5.8)

	Missing	26 (9.4)	13 (9.4)	39 (9.4)
	Mixed ethnicity	1 (0.4)	1 (0.7)	2 (0.5)
	Other	220 (79.4)	112 (80.6)	332 (79.8)
BMI (kg/m2)	n	268	136	404
	Mean	26.31	26.22	26.28
	SD	5.009	4.329	4.786
	Median	25.60	25.30	25.50
	Minimum	15.9	17.9	15.9
	Maximum	47.5	40.2	47.5
Karnofsky PS n (%)	100	78 (28.2)	41 (29.5)	119 (28.6)
	90	98 (35.4)	53 (38.1)	151 (36.3)
	80	72 (26.0)	30 (21.6)	102 (24.5)
	70	28 (10.1)	15 (10.8)	43 (10.3)
	Missing	1 (0.4)	0 (0.0)	1 (0.2)
MSKCC risk group n (%)	Favorable risk	81 (29.2)	39 (28.1)	120 (28.8)
	Intermediate risk	156 (56.3)	79 (56.8)	235 (56.5)
	Poor risk	40 (14.4)	21 (15.1)	61 (14.7)

Note: MSKCC risk group given as assigned at randomization

Outcome measures

Primary Outcome Results

Analysis of PFS based on central radiology review using the Kaplan-Meier method, by treatment-FAS (Double blind phase)

	RAD001 10mg/day (plus BSC) N=277	Placebo (plus BSC) N=139	p-value [1]	Hazard ratio [2] [95% CI] RAD001 / Placebo
No. of PFS events n (%)	155 (56.0)	111 (79.9)	<0.001	0.33 [0.25,0.43]
Progression	134 (48.4)	103 (74.1)		
Death	21 (7.6)	8 (5.8)		
No. censored	122 (44.0)	28 (20.1)		
Kaplan-Meier estimates [95% CI] at:				
4 months	55.9 [49.5;62.3]	14.5 [7.8; 21.1]		
6 months	35.6 [28.8; 42.3]	9.0 [3.4; 14.7]		
12 months	8.0 [NA; 20.4]	NA		
25th percentile for PFS [95% CI] (months)	2.46 [2.00;3.22]	1.74 [1.64;1.77]		
Median PFS [95% CI] (months)	4.90 [3.98;5.52]	1.87 [1.84;1.94]		
75th percentile for PFS [95% CI] (months)	10.58 [7.29;11.86]	3.61 [2.89;3.78]		

[1] p-value is obtained from the stratified Log-Rank test

[2] Hazard ratio is obtained from stratified Cox model

Analysis of PFS based on investigator using Kaplan-Meier method, by treatment – FAS (Double blind phase)

	RAD001 10mg/day (plus BSC) N=277	Placebo (plus BSC) N=139	p-value [1]	Hazard ratio [2] [95% CI] RAD001 / Placebo
No. of PFS events n (%)	170 (61.4)	129 (92.8)	<0.001	0.32 [0.25,0.41]
Progression	152 (54.9)	121 (87.1)		
Death	18 (6.5)	8 (5.8)		
No. censored	107 (38.6)	10 (7.2)		
Kaplan-Meier estimates [95% CI] at:				
4 months	62.7 [56.7;68.6]	19.4 [12.7;26.1]		
6 months	41.8 [35.4;48.2]	8.6 [3.6;13.6]		
12 months	17.7 [9.9;25.6]	NA		
25th percentile for PFS [95% CI] (months)	2.66 [2.07;3.52]	1.66 [1.58;1.77]		
Median PFS [95% CI] (months)	5.49 [4.63;5.82]	1.87 [1.84;2.23]		
75th percentile for PFS [95% CI] (months)	9.23 [7.62;12.81]	3.71 [3.52;4.27]		

[1] p-value is obtained from the stratified Log-Rank test
[2] Hazard ratio is obtained from stratified Cox model

Secondary Outcome Results

Analysis of overall survival using the Kaplan-Meier method, by treatment – FAS (Double blind phase)

	RAD001 10mg/day (plus BSC) N=277	Placebo (plus BSC) N=139	p-value [1]	Hazard ratio [2] [95% CI] RAD001/ Placebo
No. of OS events - n (%)	85 (30.7)	48 (34.5)	0.137	0.82 [0.57,1.17]
No. of censored	192 (69.3)	91 (65.5)		
Kaplan-Meier estimates [95% CI] at:				
4 months	90.0 [86.4;93.6]	86.0 [80.2;91.9]		
6 months	79.3 [74.3;84.2]	76.7 [69.5;83.9]		
12 months	53.7 [43.9;63.6]	53.5 [40.7;66.3]		
25th percentile for OS [95% CI] (months)	6.83 [5.88;8.80]	6.14 [5.09; 8.05]		
Median OS [95% CI] (months)	NA [11.43; NA]	13.01 [10.09;NA]		
75th percentile OS [95% CI] (months)	NA	NA [13.01; NA]		

[1] p-value is obtained from the stratified Log-Rank test
[2] Hazard ratio is obtained from stratified Cox model

Best overall response rates as per central radiology review, by treatment – FAS (Double blind phase)

Best overall response	RAD001 10mg/day (plus BSC) N=277 n (%)	Placebo (plus BSC) N=139 n (%)
Complete Response (CR)	0 (0.0)	0 (0.0)

Partial Response (PR)	5 (1.8)	0 (0.0)
Stable Disease (SD)	185 (66.8)	45 (32.4)
Progressive Disease (PD)	57 (20.6)	74 (53.2)
Unknown	30 (10.8)	20 (14.4)
Response analysis		
Objective Response Rate ORR (CR or PR)	5 (1.8)	0 (0.0)
95% CI for ORR	[0.6; 4.2]	[NA;NA]

Exact binomial 95% confidence interval is used

Analysis of overall survival using the Kaplan-Meier method and Cox's proportional hazard model, by treatment – FAS (extension phase)

	RAD001 10mg/day (plus BSC) N=277	Placebo (plus BSC) N=139	p-value [1]	Hazard ratio [2] [95% CI] RAD001 / Placebo
No. of OS events - n (%)	209 (75.5)	103 (74.1)	0.183	0.90 [0.71,1.14]
No. of censored	68 (24.5)	36 (25.9)		
Kaplan-Meier estimates [95% CI] at:				
6 months	78.4 [73.5;83.3]	77.3 [70.3;84.3]		
12 months	55.6 [49.7;61.5]	53.4 [44.9;61.8]		
18 months	43.0 [37.1;48.9]	37.2 [29.0;45.5]		
24 months	29.2 [23.8;34.6]	25.4 [17.9;32.9]		
25th percentile for OS [95% CI] (months)	6.83 [5.85;8.15]	6.47 [5.16;8.05]		
Median OS [95% CI] (months)	13.57 [11.96;17.87]	13.01 [10.09;16.66]		
75th percentile OS [95% CI] (months)	27.83 [23.46;NA]	24.64 [20.17;NA]		

[1] p-value is obtained from the stratified Log-Rank test using strata defined by MSKCC risk criteria.
[2] Hazard ratio is obtained from stratified Cox model using strata defined by MSKCC risk criteria.

Duration of Response in Patients Who Receive RAD001 Plus BSC Versus Placebo Plus BSC

	RAD001 +BSC	Placebo + BSC
Number of Participants Analyzed	5	0
Duration of Response in Patients Who Receive RAD001 Plus BSC Versus Placebo Plus BSC *[units: months]* Number (95% Confidence Interval)	NA (NA to NA) [1]	

[1] No duration of response result due to small number of responders.

Analysis of Time to Definitive Deterioration of the Global Health Status/QoL Scale(QL)

Scores of the EORTC QLQ-30 Questionairre by at Least 10 Percent Using Kaplan Meier Method, by Treatment.

	RAD001 +BSC	**Placebo + BSC**
Number of Participants Analyzed	277	139
Analysis of Time to Definitive Deterioration of the Global Health Status/QoL Scale(QL) Scores of the EORTC QLQ-30 Questionairre by at Least 10 Percent Using Kaplan Meier Method, by Treatment. *[units: scores on a scale]* Median (95% Confidence Interval)	4.76 (3.71 to 6.47)	3.91 (2.79 to NA) [1]
[1] Upper limit was beyond the timeframe of the analysis..		

Time to Definitive Deterioration of the FKS-DRS Risk Score by at Least 2 Score Units Using Kaplan-Meier Method, by Treatment.

	RAD001 +BSC	**Placebo + BSC**
Number of Participants Analyzed	277	139
Time to Definitive Deterioration of the FKS-DRS Risk Score by at Least 2 Score Units Using Kaplan-Meier Method, by Treatment. *[units: months]* Median (95% Confidence Interval)	4.76 (3.75 to 7.39)	3.84 (2.04 to 4.57)

Time to Definitive Deterioration of the Physical Functioning Scale (PF)Score of the EORTC QLQ-C30 Questionnaire by at Least 10 Percent Using Kaplan_Meier Method, by Treatment.

	RAD001 +BSC	**Placebo + BSC**
Number of Participants Analyzed	277	139
Time to Definitive Deterioration of the Physical Functioning Scale (PF)Score of the EORTC QLQ-C30 Questionnaire by at Least 10 Percent Using Kaplan_Meier Method, by Treatment. *units: scores on a scale]* Median (95% Confidence Interval)	5.06 (3.78 to 7.39)	4.57 (2.79 to NA) [1]
[1] Upper limit could not be calculated.		

Everolimus pharmacokinetic parameters on Cycle 1 Day 1 and Cycle 1 Day 15 after receiving 10 mg daily doses of everolimus (Double blind phase)

	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	$AUC_{0-\tau}$ (ng.h/mL)	CL/F (L/h)	CL/F[1] ($L/h/m^2$)	C_{avg} (ng/mL)	Tlast (h)
Day 1 (n = 13)	68.1 +/- 29.8 (43.7%)	1.0 (1.0-2.0)	7.9 +/- 3.4 (43.3%)	455.0 +/- 168.5 (37.0%)			19.0 +/- 7.0	24.0 (24.0-24.0)
Day 15 (n =12)	76.7 +/- 39.3 (51.2%)	1.0 (1.0-5.0)	19.8 +/- 12.3 (61.8 %)	729.1 +/- 262.7 (36.0%)	15.4 +/- 5.3 (34.3%)	7.5 +/- 2.3 (30.1%)	30.4 +/- 10.9	24.0 (24.0-24.0)

Summary statistics: median (range) for t_{max} and mean ± SD (CV%) for all other PK parameters.

[1]. Normalized to body surface area (m^2)

[2] CL/F was calculated using steady state (Day 15) ($AUC_{0-\tau}$) data only

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and by treatment - safety population (Double blind phase)

Primary system organ class	RAD001 10mg/day (plus BSC) N=274 n (%)	Placebo (plus BSC) N=137 n (%)
Any primary system organ class	265 (96.7)	128 (93.4)
Gastrointestinal disorders	223 (81.4)	68 (49.6)
General disorders and administration site conditions	217 (79.2)	84 (61.3)
Skin and subcutaneous tissue disorders	165 (60.2)	29 (21.2)
Respiratory, thoracic and mediastinal disorders	176 (64.2)	49 (35.8)
Metabolism and nutrition disorders	155 (56.6)	37 (27.0)
Blood and lymphatic system disorders	133 (48.5)	25 (18.2)
Musculoskeletal and connective tissue disorders	118 (43.1)	47 (34.3)
Nervous system disorders	106 (38.7)	38 (27.7)
Infections and infestations	101 (36.9)	25 (18.2)
Investigations	81 (29.6)	19 (13.9)
Psychiatric disorders	46 (16.8)	14 (10.2)
Renal and urinary disorders	42 (15.3)	13 (9.5)
Eye disorders	31 (11.3)	1 (0.7)
Vascular disorders	27 (9.9)	11 (8.0)
Cardiac disorders	27 (9.9)	4 (2.9)
Injury, poisoning and procedural complications	25 (9.1)	7 (5.1)
Ear and labyrinth disorders	12 (4.4)	5 (3.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (4.4)	3 (2.2)
Reproductive system and breast disorders	12 (4.4)	0 (0.0)
Hepatobiliary disorders	10 (3.6)	3 (2.2)
Endocrine disorders	5 (1.8)	1 (0.7)

Immune system disorders	2 (0.7)	0 (0.0)
Congenital, familial and genetic disorders	1 (0.4)	0 (0.0)
Surgical and medical procedures	0 (0.0)	1 (0.7)

A patient with multiple AEs within a SOC is counted only once. AEs occurring more than 28 days after the end of treatment are not included. SOC are shown in order of decreasing frequency in the RAD001 treatment group.

Frequent adverse events (≥ 10% in any treatment group), regardless of study drug relationship, by preferred term and treatment – safety population (Double blind phase)

Preferred Term	RAD001 10mg/day (plus BSC) N=274 n (%)	Placebo (plus BSC) N=137 n (%)
Anemia	103 (37.6)	20 (14.6)
Stomatitis	103 (37.6)	9 (6.6)
Asthenia	91 (33.2)	31 (22.6)
Fatigue	84 (30.7)	37 (27.0)
Cough	82 (29.9)	22 (16.1)
Diarrhea	81 (29.6)	9 (6.6)
Rash	80 (29.2)	9 (6.6)
Nausea	72 (26.3)	26 (19.0)
Anorexia	69 (25.2)	19 (13.9)
Edema peripheral	68 (24.8)	11 (8.0)
Dyspnea	65 (23.7)	20 (14.6)
Vomiting	56 (20.4)	16 (11.7)
Hypercholesterolemia	55 (20.1)	3 (2.2)
Pyrexia	54 (19.7)	12 (8.8)
Constipation	53 (19.3)	24 (17.5)
Headache	51 (18.6)	12 (8.8)
Mucosal inflammation	51 (18.6)	2 (1.5)
Epistaxis	49 (17.9)	0
Hypertriglyceridemia	40 (14.6)	3 (2.2)
Pruritus	37 (13.5)	9 (6.6)
Dry skin	35 (12.8)	7 (5.1)
Back pain	34 (12.4)	15 (10.9)
Hyperglycemia	33 (12.0)	3 (2.2)
Arthralgia	28 (10.2)	14 (10.2)
Dysgeusia	28 (10.2)	3 (2.2)
Pain in extremity	28 (10.2)	9 (6.6)

preferred terms are sorted by descending frequency in the RAD001 group

Number of patients who died, had an SAE, discontinued because of an AE, had a grade 3/4 AE or had a clinically notable AE, by treatment - safety population (Double blind phase)

	RAD001 10mg/day (plus BSC) N=274 n (%)	Placebo (plus BSC) N=137 n (%)
On-treatment death[1]	21 (7.7)	7 (5.1)

Serious adverse event	110 (40.1)	31 (22.6)
Adverse event of grade 3-4	178 (65.0)	39 (28.5)
Adverse event leading to discontinuation	38 (13.9)	4 (2.9)
Clinically notable adverse event	237 (86.5)	53 (38.7)

Categories are not mutually exclusive
Deaths occurring more than 28 days after discontinuation of study treatment or patients entering open-label RAD001 are not summarized

Adverse events, regardless of study drug relationship, by primary system organ class (safety population) (extension phase)

Primary system organ class	All patients N=385 n (%)
Any primary system organ class	377 (97.9)
General disorders and administration site conditions	324 (84.2)
Gastrointestinal disorders	310 (80.5)
Respiratory, thoracic and mediastinal disorders	264 (68.6)
Metabolism and nutrition disorders	233 (60.5)
Skin and subcutaneous tissue disorders	230 (59.7)
Blood and lymphatic system disorders	193 (50.1)
Musculoskeletal and connective tissue disorders	191 (49.6)
Infections and infestations	161 (41.8)
Nervous system disorders	156 (40.5)
Investigations	136 (35.3)
Psychiatric disorders	76 (19.7)
Renal and urinary disorders	75 (19.5)
Cardiac disorders	49 (12.7)
Eye disorders	48 (12.5)
Vascular disorders	48 (12.5)
Injury, poisoning and procedural complications	41 (10.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	27 (7.0)
Ear and labyrinth disorders	24 (6.2)
Hepatobiliary disorders	20 (5.2)
Reproductive system and breast disorders	19 (4.9)
Endocrine disorders	10 (2.6)
Immune system disorders	6 (1.6)
Congenital, familial and genetic disorders	2 (0.5)
Social circumstances	1 (0.3)

Frequent adverse events (≥ 10%), regardless of study drug relationship, by preferred term – safety population (extension phase)

Preferred Term	All patients N=385 n (%)
Anemia	157 (40.8)
Stomatitis	140 (36.4)
Asthenia	130 (33.8)
Cough	129 (33.5)
Fatigue	129 (33.5)

Diarrhea	119 (30.9)
Rash	112 (29.1)
Decreased appetite	110 (28.6)
Edema peripheral	108 (28.1)
Dyspnea	107 (27.8)
Nausea	107 (27.8)
Pyrexia	89 (23.1)
Constipation	85 (22.1)
Vomiting	85 (22.1)
Hypercholesterolemia	81 (21.0)
Mucosal inflammation	80 (20.8)
Headache	69 (17.9)
Epistaxis	63 (16.4)
Hypertriglyceridemia	62 (16.1)
Arthralgia	59 (15.3)
Back pain	56 (14.5)
Pruritus	55 (14.3)
Dry skin	52 (13.5)
Hyperglycemia	51 (13.2)
Pain in extremity	51 (13.2)
Dysgeusia	46 (11.9)
Weight decreased	46 (11.9)
Abdominal pain	43 (11.2)
Insomnia	41 (10.6)
Aphthous stomatitis	39 (10.1)

Number of patients who died, had an SAE, discontinued because of an AE, had a grade 3/4 AE or had a clinically notable AE - safety population (extension phase)

	All patients N=385 n (%)
All deaths	290 (75.3)
On-treatment death [1]	47 (12.2)
SAEs, regardless of relationship to study treatment	191 (49.6)
SAEs, with suspected relationship to study treatment	72 (18.7)
AEs of grade 3-4, regardless of relationship to study treatment	280 (72.7)
AEs of grade 3-4, with suspected relationship to study treatment	166 (43.1)
AEs leading to discontinuation	68 (17.7)
Clinically notable AEs	342 (88.8)

Categories are not mutually exclusive.
[1] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
Clinically notable adverse events are the events for which there is a specific clinical interest in connection with RAD001 or events which are similar in nature

Number of patients who died, had an SAE, discontinued because of an AE, had a grade 3/4 AE or had a clinically notable AE - safety population (updated data from end of the extension phase of the study, 15-Nov-2009 to the actual last patient last visit, 27-Oct-2011)

	All patients N=9
Deaths	0
SAEs, regardless of relationship to study treatment	4
Discontinuation from study	
Due to study termination	1
Due to disease progression	1
Clinically notable AEs	3

Other Relevant Findings

None

Date of Clinical Trial Report

01-Oct-2008 (Double blind phase)

26-May-2010 (extension phase)

Date Inclusion on Novartis Clinical Trial Results Database

23-Oct-2012

Date of Latest Update