Sponsor

Novartis

Generic Drug Name

Everolimus/RAD001

Therapeutic Area of Trial

Non-small cell lung cancer (NSCLC)

Approved Indication

- Hormone receptor-positive advanced breast cancer in postmenopausal women, in conjunction with an aromatase inhibitor which is used for hormonal anticancer therapy.
- Advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin.
- Advanced renal cell carcinoma.
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS)
- For the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. In kidney and heart transplantation, everolimus should be used in combination with ciclosporin for microemulsion and corticosteroids.
- For the prophylaxis of organ rejection in patients receiving a hepatic transplant. In liver transplantation, everolimus should be used in combination with tacrolimus and corticosteroids.

Protocol Number

CRAD001C2111

Title

A combined Phase 1 and 2 study investigating the combination of RAD001 and erlotinib in patients with advanced NSCLC previously treated only with chemotherapy

Phase of Development

Phase I/II

Study Start/End Dates

14-Jun-2005 to 30-Mar-2011

Study Design/Methodology

Phase 1 was an open-label, non-randomized, multi-center study combining daily and weekly everolimus with daily erlotinib with a sequential dose-escalation design. Doses available for

investigation included: everolimus - 2.5 mg once daily (o.d.), 5 mg o.d., 10 mg o.d., 20 mg/week, 30 mg/week, 50 mg/week and erlotinib: 50 mg o.d., 75 mg o.d., 100 mg o.d., 150 mg o.d.

Phase 2 was an open-label, randomized, multi-center and parallel group study of the combined treatment of everolimus and erlotinib combination schedule(s) *vs* treatment with erlotinib alone in the same patient population as phase 1.

Centres

14 centres in 5 countries: France (2), Canada (3), United States (7), Denmark (1), Russia (1)

Publication

None

Outcome measures

Primary outcome measures

Phase 1

- Rate of dose limiting toxicities (DLTs)
- PK drug-drug interaction

The PK parameters provided for everolimus included $AUC_{0\text{-}tlast}$, AUC_{inf}, C_{max}, C_{min}, t_{max}, CL/F (L/h), CL/F ($L/h/m^2$) and $T_{1/2}$ (h) for patients receiving weekly doses of everolimus. The PK parameters provided for erlotinib and its principal metabolite (OSI-420) included $AUC_{0\text{-}tlast}$, AUC_{inf}, C_{max}, C_{min}, t_{max}, CL/F (L/h), CL/F ($L/h/m^2$) and $T_{1/2}$ (h) for everolimus weekly dose.

The effect of the co-administration of everolimus with erlotinib (Day 8) on the pharmacokinetics ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, C_{max}) of everolimus will be informally assessed by comparing the pharmacokinetics of everolimus when co-administered with erlotinib with historical data from everolimus mono-therapy trials.

Phase 2

Disease Control Rate (DCR) at 3 months as a measure of anti-tumor activity in patients who receive everolimus (daily and/or weekly schedule) together with daily erlotinib as compared to the DCR at 3 months in patients who receive erlotinib alone.

Secondary outcome measures

Phase 1

Clinical efficacy of everolimus and erlotinib combination schedule(s), based on evaluation of objective response rate (ORR) and early progression rate (EPR)

Phase 2

- clinical efficacy of all study treatments in terms of ORR, progression-free survival (PFS) and overall survival (OS)
- the safety profile of all study treatments
- trough levels for erlotinib and everolimus administered at daily schedule
- potential molecular markers
- tumor metabolic response with FDG-PET imaging

Test Product, Dose, and Mode of Administration

Everolimus oral tablets of 2.5 mg and 5 mg strengths and erlotinib oral tablets of 25 mg, 100 mg, and 150 mg strength.

Statistical Methods

Data from all centers that participated in the protocol were used; if a patient discontinued study treatment his/her data were still analyzed. Separate outputs were produced for phase 1, phase 2, and also a phase 2 final update subset of tables, figures and listings (TFLs), which were considered a key subset of the original phase 2 outputs. In the phase 1 outputs, all summaries were provided for the continuous regimen, for each of the daily and weekly schedules, at each dose level investigated. In the phase 2 and phase 2 final update outputs, all summaries were provided by treatment arm.

Phase 1: The secondary efficacy endpoints ORR and EPR were derived based on the best overall lesion response (BOR). Tumor response was assessed by the investigator (recorded in the CRF) and also based on a re-calculated response.

Phase 2: The primary efficacy endpoint was DCR at 3 months. The primary source of information for efficacy purposes at the interim futility analysis and final analysis was the investigator overall lesion response. This response was consistently used as a primary source since it was used for patient management. Secondary analyses were based on the Novartis re-calculated lesion response, and also a central radiology review. The primary efficacy decision-rule was based on the assessment of the chance that the experimental arm (combined treatment with everolimus and erlotinib) ensured at least a clinically significant treatment benefit of 15% over the control arm (erlotinib alone) in terms of DCR at 3 months. If the chance that the experimental arm ensured this or a higher benefit was above 40% (level of proof of efficacy), then it was to be identified as efficacious. The probability that the difference (experimental vs. control) in DCR at 3 months exceeds a given threshold (i.e. that the experimental is better than the control) was estimated using the posterior distribution based on a standard Bayesian conjugate Beta-Binomial model

Safety was analyzed using descriptive statistics to summarize the incidences of AEs and laboratory findings.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patients with advanced NSCLC (unresectable or metastatic)
- Age ≥ 18 years old
- Pathologic confirmation of NSCLC (must include accurate histology in phase 2 part of the study)
- Patients entered on the phase 2 part of the study must have had at least 1 measurable site of disease according to RECIST criteria that had not been previously irradiated. If the patient had previous radiation to the marker lesion(s), there must have been evidence of progression since the radiation
- Previous chemotherapy treatment for advanced disease with documented tumor progression (serial CT scans demonstrating progressive disease according to RECIST must be available) despite ≤ 2 chemotherapy schedules for treatment of advanced disease (previous therapy for

localized disease is not counted), 1 of which must have included cisplatin or carboplatin

- More than 2 weeks since any major surgery, completion of radiation, or completion of all prior chemotherapy (adequately recovered from the acute toxicities of any prior therapy)
- WHO performance status ≤ 2 in the phase 1 part of the study
- WHO performance status ≤ 1 in the phase 2 part of the study
- Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin > 9 g/dL
- Adequate liver function as shown by serum: bilirubin grade ≤ 2 and transaminases activity ≤ 3 x ULN (with the exception of serum transaminases (< 5 x ULN) if the patient had liver metastases)
- Signed informed consent

Exclusion criteria

- Concurrent therapy with agents otherwise used in treatment of cancer (for example, methotrexate for rheumatoid arthritis)
- Treatment with any other investigational drugs within the preceding 4 weeks
- Prior treatment with an EGFR inhibitor (either a small molecule EGFR-TK inhibitor or anti-EGFR antibody)
- Chronic treatment with steroids or another immunosuppressive agent
- Leptomeningeal or uncontrolled brain metastases, including patients who continue to require glucocorticoids or intrathecal chemotherapy for brain or leptomeningeal metastases (documented by lumbar puncture)
- Malignancies other than lung cancer within the past 2 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin
- Other concurrent severe and/or uncontrolled medical disease which could have compromised participation in the study (i.e. uncontrolled diabetes, uncontrolled hypertension, severe infection, severe malnutrition, unstable angina, or congestive heart failure - New York Heart Association Class III or IV, ventricular arrhythmias active ischemic heart disease, myocardial infarction within 6 months, chronic liver or renal disease, active upper GI tract ulceration)
- A known history of HIV or previous seropositivity for the virus
- Patients with active skin, mucosa, ocular or GI disorders of grade > 1
- Impairment of gastrointestinal function or gastrointestinal disease that could significantly alter the absorption of everolimus or erlotinib (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
- Women who were pregnant or breast feeding, or women able to conceive and unwilling to practice an effective method of birth control (women of childbearing potential must have had a negative urine or serum pregnancy test within 7 days prior to administration of everolimus or erlotinib)
- History of noncompliance to medical regimens

- Patients unwilling to or unable to comply with the protocol

Participant Flow

Patient disposition - n (%) of patients by schedule and dose − phase 1 (FAS)

	RAD 5/o.d + ERL 100 N=15 n (%)	RAD 5/q.o.d + ERL 100 N=12 n (%)	RAD 2.5/o.d + ERL 100 N=13 n (%)	RAD 2.5/o.d + ERL 150 N=13 n (%)	RAD 5/o.d + ERL 75 N=13 n (%	RAD 5/o.d + ERL 150 N=8 n (%)	RAD 30/wk + ERL 150 N=6 n (%)	RAD 50/wk + ERL 150 N=14 n (%)	Total Daily N=74 n (%)	Total Weekly N=20 n (%)	Total N=94 n (%)
Ongoing at 17DEC2009	0	0	0	1 (7.7)	0	1 (12.5)	0	1 (7.1)	2 (2.7)	1 (5.0)	3 (3.2)
Discontinuations by reason	15 (100)	12 (100)	13 (100)	12 (92.3)	13 (100)	7 (87.5)	6 (100)	13 (92.9)	72 (97.3)	19 (95.0)	91 (96.8)
Adverse Event(s)	3 (20.0)	4 (33.3)	1 (7.7)	5 (38.5)	3 (23.1)	1 (12.5)	3 (50.0)	4 (28.6)	17 (23.0)	7 (35.0)	24 (25.5)
Abnormal laboratory value(s)	0	0	0	0	0	0	0	0	0	0	0
Abnormal test procedure result(s)	0	0	1 (7.7)	0	0	0	0	0	1 (1.4)	0	1 (1.1)
Protocol violation	0	0	0	0	0	0	0	0	0	0	0
Subject withdrew consent	0	0	1 (7.7)	0	1 (7.7)	0	0	2 (14.3)	2 (2.7)	2 (10.0)	4 (4.3)
Lost to follow-up	0	0	0	0	0	0	0	0	0	0	0
Administrative problems	0	0	0	0	0	0	0	0	0	0	0
Death	0	0	1 (7.7)	0	0	0	0	0	1 (1.4)	0	1 (1.1)
Disease progression	12 (80.0)	8 (66.7)	9 (69.2)	7 (53.8)	9 (69.2)	6 (75.0)	3 (50.0)	7 (50.0)	51 (68.9)	10 (50.0)	61 (64.9)

Patient disposition - n (%) of patients, by treatment - phase 2 (FAS)

	RAD001 5mg/o.d. + erlotinib 150mg N=66 n (%)	Erlotinib 150mg N=67 n (%)
Ongoing at 27JUN2009	**10 (15.2)**	**13 (19.4)**
Discontinuations by reason	**56 (84.8)**	**53 (79.1)**
Adverse Event(s)	7 (10.6)	3 (4.5)
Abnormal laboratory value(s)	0	0
Abnormal test procedure result(s)	0	0
Protocol violation	1 (1.5)	0
Subject withdrew consent	8 (12.1)	2 (3.0)
Lost to follow-up	0	0
Administrative problems	0	2 (3.0)
Death	1 (1.5)	0
Disease progression	39 (59.1)	46 (68.7)

Baseline Characteristics

Demographic summary by schedule and dose - phase 1 (FAS)

	RAD 5/o.d + ERL 100 N=15	RAD 5/q.o.d + ERL 100 N=12	RAD 2.5/o.d + ERL 100 N=13	RAD 2.5/o.d + ERL 150 N=13	RAD 5/o.d + ERL 75 N=13	RAD 5/o.d + ERL 150 N=8	RAD 30/wk + ERL 150 N=6	RAD 50/wk + ERL 150 N=14	Total Daily N=74	Total Weekly N=20	Total N=94
Age – years											
Mean (SD)	63.7 (9.0)	60.3 (13.2)	60.8 (9.4)	60.9 (8.9)	60.8 (9.5)	60.1 (7.1)	60.0 (8.2)	58.9 (9.6)	61.2 (9.50)	59.2 (9.04)	60.8 (9.4)
Median (min, max)	63.0 (49, 75)	60.0 (35, 75)	59.0 (44, 74)	58.0 (50, 77)	63.0 (45, 75)	60.5 (45, 70)	57.5 (54, 76)	58.0 (46, 77)	60.5 (35, 77)	58.0 (46, 77)	59.5 (35, 77)
Sex – n (%)											
Male	10 (66.7)	5 (41.7)	6 (46.2)	5 (38.5)	9 (69.2)	5 (62.5)	5 (83.3)	8 (57.1)	40 (54.1)	13 (65.0)	53 (56.4)
Female	5 (33.3)	7 (58.3)	7 (53.8)	8 (61.5)	4 (30.8)	3 (37.5)	1 (16.7)	6 (42.9)	34 (45.9)	7 (35.0)	41 (43.6)
Race – n (%)											
Caucasian	15 (100)	11 (91.7)	12 (92.3)	11 (84.6)	12 (92.3)	8 (100)	6 (100)	13 (92.9)	69 (93.2)	19 (95.0)	88 (93.6)
Black	0	1 (8.3)	0	0	0	0	00	0	1 (1.4)	0	1 (1.1)
Asian	0	0	1 (7.7)	2 (15.4)	0	0	0	0	3 (4.1)	0	3 (3.2)
Native Ameri-can	0	0	0	0	0	0	0	0	0	0	0
Pacific Islander	0	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	1 (7.7)	0	0	1 (7.1)	1 (1.4)	1 (5.0)	2 (2.1)
Ethnicity – n (%)											
Hispanic/Latino	0	0	0	0	1 (7.7)	0	0	0	1 (1.4)	0	1 (1.1)
Chinese	0	0	1 (7.7)	2 (15.4)	0	0	0	0	3 (4.1)	0	3 (3.2)
Indian*	0	0	0	0	0	0	0	1 (7.1)	0	1 (5.0)	1 (1.1)
Japanese	0	0	0	0	0	0	0	0	0	0	0
Mixed Ethnicity	0	0	0	0	0	0	0	0	0	0	0
Other	15 (100)	12 (100)	11 (84.6)	10 (76.9)	12 (92.3)	12 (92.3)	6 (100)	12 (85.7)	66 (89.2)	18 (90.0)	84 (89.4)
Missing	0	0	1 (7.7)	1 (7.7)	0	2 (25.0)	0	1 (7.1)	4 (5.4)	1 (5.0)	5 (5.3)

*Indian subcontinent

Demographic summary by dose - phase 2 (FAS)

	RAD001 5mg/o.d. + erlotinib 150mg N=66	Erlotinib 150mg N=67
Age (years)		

Mean (SD)	58.6 (9.9)	59.7 (10.6)
Median (min, max)	60.0 (28 – 77)	60.5 (35 - 80)
Sex - n (%)		
Male	36 (54.5)	33 (49.3)
Female	30 (45.5)	33 (49.3)
Race - n (%)		
Caucasian	54 (81.8)	57 (85.1)
Black	4 (6.1)	6 (9.0)
Asian	7 (10.6)	2 (3.0)
Native American	0	0
Pacific Islander	1 (1.5)	0
Other	0	1 (1.5)
Ethnicity - n (%)		
Hispanic/Latino	0	0
Chinese	3 (4.5)	2 (3.0)
Indian*	0	0
Mixed Ethnicity	0	0
Other	54 (81.8)	51 (76.1)
Missing	7 (10.6)	13 (19.4)

*Indian subcontinent

Outcome measures

Primary Outcome Result(s)

Number of patients with DLT events by primary system organ class and preferred term, by schedule and dose – phase 1 (Safety population)

System organ class preferred term	Total Daily N=74 n (%)	Total Weekly N=20 n (%)	Total N=94 n (%)
Patients with AEs	15 (20.3)	3 (15.0)	18 (19.1)
Gastrointestinal disorders	**9 (12.2)**	**0**	**9 (9.6)**
Diarrhoea	3 (4.1)	0	3 (3.2)
Dysphagia	1 (1.4)	0	1 (1.1)
Nausea	1 (1.4)	0	1 (1.1)
Stomatitis	5 (6.8)	0	5 (5.3)
Vomiting	1 (1.4)	0	1 (1.1)
Skin and subcutaneous tissue disorders	**5 (6.8)**	**3 (15.0)**	**8 (8.5)**
Dermatitis acneiform	0	2 (10.0)	2 (2.1)
Dry skin	1 (1.4)	0	1 (1.1)
Palmar-plantar erythrodysaesthesia syndrome	1 (1.4)	0	1 (1.1)
Rash	3 (4.1)	1 (5.0)	4 (4.3)
Blood and lymphatic system disorders	**1 (1.4)**	**0**	**1 (1.1)**
Neutropenia	1 (1.4)	0	1 (1.1)
Infections and infestations	**1 (1.4)**	**0**	**1 (1.1)**
Dermatitis infected	1 (1.4)	0	1 (1.1)

Skin infection	1 (1.4)	0	1 (1.1)

System organ classes are ordered by descending frequency across the doses.
A patient with multiple adverse events within a primary system organ class is counted only once within that class.
A patient with multiple adverse events may be counted in more than one system organ class.

Descriptive statistics for RAD001 PK profile parameters, pre-amendment 1, by profile day and dose - phase 1 (Safety population)

		RAD 5/o.d + ERL 100 N=6		RAD 5/q.o.d + ERL 100 N=12	
PK Parameter (units)	**Profile Day**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
$AUC_{0\text{-}inf}$ (ng.h/mL)	1	6	194.87 ± 60.284	11	184.25 ± 141.985
	8	5	201.13 ± 64.361	10	247.95 ± 108.532
	22	2	227.66 ± 78.212	10	407.49 ± 206.792
$AUC_{0\text{-}tlast}$ (ng.h/mL)	1	6	154.1 ± 43.627	10	143.17 ± 95.08
	8	6	244.57 ± 215.555	10	182.77 ± 86.592
	22	1	173.61	10	255.7 ± 99.86
CL/F (L/h)	1	6	34.69 ± 10.0117	11	55.841 ± 48.8478
	8	6	29.169 ± 13.169	10	33.855 ± 15.9406
	22	1	29.358	10	23.07 ± 11.2174
CL/F ($L/h/m^2$)	1	6	18.933 ± 5.8357	11	29.977 ± 23.9682
	8	6	15.641 ± 6.6257	10	19.373 ± 11.4189
	22	1	14.334	10	12.626 ± 6.1897
C_{max} (ng/mL)	1	6	27.83 ± 8.783	11	24.12 ± 15.619
	8	6	35.1 ± 11.239	10	30.85 ± 18.38
	22	2	34.25 ± 2.758	10	33.31 ± 10.418
C_{min} (ng/mL)	1	6	2.382 ± 0.8436	10	2.431 ± 1.9534
	8	6	9.942 ± 18.5157	10	2.64 ± 0.7656
	22	2	3.62 ± 0.099	10	4.047 ± 2.3856

Day 1 (D1): Everolimus alone
Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for erlotinib PK profile parameters, pre-amendment 1, by profile day and dose - phase 1 (Safety population)

		RAD 5/o.d + ERL 100 N=6		RAD 5/q.o.d + ERL 100 N=12	
PK Parameter (units)	**Profile Day**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
$AUC_{0\text{-}inf}$ (ng.h/mL)	5	2	4612.66 ± 3024.522	8	53256.56 ± 116137.585
	8	5	17159.5 ± 7912.057	9	36586.57 ± 29816.619
	22	2	25572.04 ± 6298.495	8	74297.82 ± 81518.006

$AUC_{0\text{-}tlast}$ (ng.h/mL)	8	5	9083.51 ± 2155.612	9	15133.39 ± 8056.218
	22	2	14654.11 ± 318.351	8	23879.71 ± 13170.937
CL/F (L/h)	8	5	11.757 ± 3.9346	9	8.423 ± 4.3591
	22	2	6.946 ± 0.0665	8	6.417 ± 6.3873
CL/F ($L/h/m^2$)	8	5	6.401 ± 2.3284	9	4.484 ± 1.7578
	22	2	3.546 ± 0.251	8	3.352 ± 3.0488
C_{max} (ng/mL)	5	5	628.8 ± 253.319	10	842.5 ±466.203
	8	5	614.8 ± 13.609	11	1082.64 ± 500.05
	22	2	945.5 ± 58.69	9	1508.22 ± 562.325
C_{min} (ng/mL)	5	2	262 ± 370.524	7	387.571 ± 187.6884
	6	4	309.75 ± 99.9746	4	676.25 ± 628.4777
	8	6	591.745 ± 851.8479	11	530.273 ± 365.3952
	22	2	410.5 ± 107.4802	10	964.025 ± 759.0936

Day 5 (D5): Erlotinib alone
Day 6 (D6): Erlotinib alone
Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for OSI-420 PK profile parameters, pre-amendment 1, by profile day and dose - phase 1 (Safety population)

		RAD 5/o.d + ERL 100 N=6		RAD 5/q.o.d + ERL 100 N=12	
PK Parameter (units)	**Profile Day**	**n**	**Mean ± SD**	**n**	**Mean**
$AUC_{0\text{-}inf}$ (ng.h/mL)	5	2	216.89 ± 91.453	8	934.95 ± 545.536
	8	3	1002.66 ± 842.084	9	6485.47 ± 14370.004
	22	2	2506.13 ± 631.916	8	5480.9 ± 5573.983
$AUC_{0\text{-}tlast}$ (ng.h/mL)	8	2	835.03 ± 359.235	9	1253.82 ± 990.396
	22	2	1447.98 ± 122.719	8	2245.69 ± 1384.991
CL/F (L/h)	5	0		1	79.754
	8	2	132.147 ± 57.0271	9	115.165 ± 59.6543
	22	2	70.52 ± 5.1241	8	80.441 ± 95.3131
CL/F ($L/h/m^2$)	5	0		1	48.502
	8	2	79.765 ± 43.6644	9	60.835 ± 25.7806
	22	2	36.069 ± 4.8188	8	41.505 ± 45.5781
C_{max} (ng/mL)	5	5	52.48 ± 28.221	8	72.99 ± 53.882
	8	5	45.62 ± 17.058	10	78.42 ± 50.365
	22	2	92 ± 4.95	10	143.2 ± 59.157
C_{min} (ng/mL)	5	2	16.25 ± 22.981	7	29.143 ± 14.2651
	6	4	24.725 ± 11.1455	4	57.55 ± 72.9061
	8	6	40.033 ± 53.7085	10	44.22 ± 45.6081
	22	2	39.925 ± 13.6825	10	81.535 ± 63.1627

Day 5 (D5): Erlotinib alone
Day 6 (D6): Erlotinib alone
Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for RAD001 PK profile parameters, post-amendment 1, by profile day for daily dose schedules - phase 1 (Safety population)

		RAD 5/o.d + ERL 100 N=9		RAD 2.5/o.d + ERL 100 N=13		RAD 2.5/o.d + ERL 150 N=13		RAD 5/o.d + ERL 75 N=13		RAD 5/o.d + ERL 150 N=8	
PK Parameter (units)	**Pro-file Day**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**
$AUC_{0\text{-}inf}$ (ng.h/mL)	8	8	419.35 ± 98.798	11	117.3 ± 33.932	12	231.72 ± 121.535	13	344.03 ± 155.415	6	416.7 ± 263.223
	22	7	795.24 ± 254.434	9	340.46 ± 172.668	9	368.35 ± 199.141	8	642.55 ± 409.365	4	603.64 ± 299.7
$AUC_{0\text{-}tlast}$ (ng.h/mL)	8	8	296.63 ± 62.195	11	88.28 ± 28.75	12	172.62 ± 82.722	13	250.46 ± 113.127	7	304.66 ± 177.872
	22	7	500.74 ± 157.909	8	210.26 ± 63.307	9	230.27 ± 140.992	8	405.18 ± 203.634	3	421.75 ± 227.028
CL/F (L/h)	8	8	17.59 ± 3.9939	11	30.548 ± 7.9709	12	17.672 ± 8.2658	13	24.983 ± 13.8301	7	23.298 ± 15.2059
	22	7	10.985 ± 3.9063	8	11.403 ± 6.0684	9	15.591 ± 11.5147	8	14.401 ± 5.3083	3	14.608 ± 8.0571
CL/F ($L/h/m^2$)	8	7	9.849 ± 2.783	11	16.965 ± 3.8228	12	10.081 ± 4.3187	13	13.331 ± 7.014	7	12.63 ± 8.1118
	22	6	6.404 ± 3.0644	8	6.059 ± 3.3337	9	8.603 ± 5.6266	8	7.898 ± 2.8754	3	8.937 ± 6.1094
C_{max} (ng/mL)	8	8	52.8 ± 13.329	12	14.05 ± 5.666	13	25.3 ± 14.546	13	33.61 ± 18.06	7	36.01 ± 22.739
	22	7	59.1 ± 26.988	9	23.96 ± 9.911	9	30.73 ± 21.123	8	49.29 ± 19.102	4	51.58 ± 16.88
	8	8	5.353 ± 1.4705	12	2.233 ± 2.6308	12	3.558 ± 1.7167	13	4.915 ± 2.2438	7	8.907 ± 9.0655
C_{min} (ng/mL)	15	0		0		0		0		0	
	22	7	11.461 ± 4.3159	9	6.459 ± 6.2276	9	5.344 ± 3.0403	8	11.529 ± 8.7406	4	14.528 ± 11.1415

Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for erlotinib PK profile parameters, post-amendment 1, by profile day for daily dose schedules - phase 1 (Safety population)

	RAD 5/o.d + ERL 100 N=9	RAD 2.5/o.d + ERL 100 N=13	RAD 2.5/o.d + ERL 150 N=13	RAD 5/o.d + ERL 75 N=13	RAD 5/o.d + ERL 150 N=8

PK Parameter (units)	Pro-file Day	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
$AUC_{0\text{-}inf}$ (ng.h/mL)	1	4	23679.63 ± 10060.856	10	16542.43 ± 7333.3	9	54819.2 ± 48242.872	9	19258.93 ± 8636.697	5	45940.53 ± 26908.251
	8	5	23293.97 ± 10775.531	10	16601.89 ± 7998.282	9	111005.8 ± 165108.576	9	29352.64 ± 23249.748	5	56748.55 ± 43604.731
	22	7	139753.21 ± 95364.877	9	54559.96 ± 42315.74	8	414688.8 ± 754651.694	4	57092.8 ± 35339.374	5	269031.2 ± 444144.97
$AUC_{0\text{-}tlast}$ (ng.h/mL)	1	4	12537.06 ± 4842.53	9	11250.87 ± 3131.383	9	17704.91 ± 7041.67	9	9486.2 ± 3868.543	5	18655.64 ± 9368.878
	8	5	9024.97 ± 2952.099	10	10382.24 ± 3937.666	9	20738.35 ± 12364.881	9	12786.29 ± 10528.242	5	22466.89 ± 10738.988
	22	7	30335.07 ± 8427.611	8	20544.16 ± 7989.684	8	39501.49 ± 21438.86	6	25458.78 ± 11512.204	4	44918.55 ± 17167.582
CL/F (L/h)	1	4	9.071 ± 3.9805	9	9.784 ± 3.6295	9	9.83 ± 3.7625	9	9.252 ± 4.0551	5	10.577 ± 7.4923
	8	5	12.462 ± 5.3954	10	11.075 ± 4.459	9	9.574 ± 5.5951	9	8.254 ± 3.6443	5	8.281 ± 4.5242
	22	7	3.525 ± 1.0254	8	5.915 ± 3.2584	8	4.584 ± 1.8035	5	3.861 ± 1.4529	4	3.745 ± 1.4399
CL/F ($L/h/m^2$)	1	3	4.736 ± 2.3912	9	5.507 ± 2.3282	9	5.68 ± 2.0762	9	5.06 ± 2.4306	5	6.044 ± 4.1101
	8	4	7.667 ± 4.2342	10	6.312 ± 2.823	9	5.528 ± 2.9866	9	4.526 ± 2.1047	5	4.578 ± 2.4911
	22	7	1.875 ± 0.5168	8	3.229 ± 1.9781	8	2.64 ± 1.0397	5	2.114 ± 0.8973	4	2.166 ± 1.197
C_{max} (ng/mL)	1	8	716 ± 393.682	11	749.82 ± 243.294	11	1286.55 ± 553.325	12	592.5 ± 234.183	6	1262.33 ± 738.121
	8	7	585.86 ± 234.289	12	740.83 ± 285.016	10	1381.4 ± 678.699	12	768.7 ± 571.038	7	1547.29 ± 531.13
	22	8	1698.75 ± 495.939	10	1262.4 ± 430.22	8	2118.75 ± 1218.728	8	1353.75 ± 402.951	6	2106.67 ± 652.86
C_{min} (ng/mL)	1	9	346.222 ± 155.1828	11	310.591 ± 179.4225	12	560.417 ± 161.6891	12	276.367 ± 118.4012	8	587.65 ± 325.0267
	8	7	341.143 ± 131.8502	13	295.138 ± 151.4401	11	758.273 ± 475.587	13	386.562 ± 295.5325	7	870.171 ± 588.0283
	22	8	1102 ± 392.1493	10	708.9 ± 307.97	8	1456.688 ± 674.4293	8	1072.75 ± 540.0931	6	1217.667 ± 851.2932

Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for OSI-420 PK profile parameters, post-amendment 1, by profile day for daily dose schedules - phase 1 (Safety population)

PK Parameter (units)	Pro-file Day	RAD 5/o.d + ERL 100 N=9 n	RAD 5/o.d + ERL 100 N=9 Mean ± SD	RAD 2.5/o.d + ERL 100 N=13 n	RAD 2.5/o.d + ERL 100 N=13 Mean ± SD	RAD 2.5/o.d + ERL 150 N=13 n	RAD 2.5/o.d + ERL 150 N=13 Mean ± SD	RAD 5/o.d + ERL 75 N=13 n	RAD 5/o.d + ERL 75 N=13 Mean ± SD	RAD 5/o.d + ERL 150 N=8 n	RAD 5/o.d + ERL 150 N=8 Mean ± SD
AUC_{0-inf} (ng.h/mL)	1	6	2012.4 ± 1112.858	9	1015.61 ± 515.246	9	3366.65 ± 2094.461	8	1119.49 ± 474.193	4	8731.63 ± 9420.333
	8	5	2021.94 ± 395.332	10	1237.99 ± 820.569	10	5399.67 ± 4045.906	9	4310.15 ± 6335.988	4	8568.16 ± 9774.388
	22	7	30667.84 ± 29170.372	8	8397.89 ± 16409.197	7	22382.1 ± 21782.819	4	6927.98 ± 7828.044	3	7643.69 ± 3144.949
$AUC_{0-tlast}$ (ng.h/mL)	1	6	951.28 ± 604.048	8	712.27 ± 250.55	9	1480.23 ± 693.837	9	742.3 ± 360.195	4	2186.12 ± 1530.383
	8	5	916.84 ± 243.464	10	629.47 ± 265.685	9	1956.2 ± 1632.03	9	1388.75 ± 1977.269	4	2354.42 ± 1670.382
	22	7	4242.91 ± 1991.968	7	1587.44 ± 1002.522	7	3477.98 ± 1286.1	4	2252.88 ± 1666.794	2	5450.48 ± 2775.571
CL/F (L/h)	1	6	161.189 ± 120.7307	8	160.817 ± 71.7697	9	123.96 ± 54.1052	9	128.34 ± 74.6159	4	112.783 ± 95.5631
	8	5	117.252 ± 39.1366	10	185.076 ± 70.4687	9	120.121 ± 85.157	9	108.129 ± 56.1922	4	100.186 ± 73.808
	22	7	29.082 ± 14.7316	7	95.475 ± 72.2933	7	47.849 ± 15.3982	4	47.59 ± 27.7804	2	31.583 ± 16.1553
CL/F ($L/h/m^2$)	1	5	93.797 ± 67.866	8	91.221 ± 45.7119	9	71.179 ± 29.4977	9	70.681 ± 44.3883	4	62.031 ± 52.9996
	8	4	72.329 ± 33.5235	10	102.873 ± 41.3553	9	68.754 ± 45.2424	9	59.39 ± 31.9503	4	55.084 ± 39.7566
	22	7	15.364 ± 7.1377	7	52.78 ± 44.2402	7	27.185 ± 9.1045	4	26.259 ± 16.4588	2	19.952 ± 12.8485
C_{max} (ng/mL)	1	8	69.2 ± 46.582	10	56.61 ± 18.236	11	113.94 ± 51.158	10	54.56 ± 14.377	8	102.6 ± 60.022
	8	7	59.76 ± 27.913	11	51.75 ± 21.688	10	124.33 ± 85.885	11	80.43 ± 86.876	6	159.07 ± 75.395
	22	8	233 ± 97.166	10	103.04 ± 49.133	8	242 ± 174.234	7	173.87 ± 89.37	6	278.67 ± 178.064
C_{min} (ng/mL)	1	9	35.316 ± 25.9628	11	22.024 ± 17.2819	12	50.608 ± 27.423	12	22.783 ± 14.2404	8	73.72 ± 54.3474
	8	7	35.457 ± 23.0157	13	23.235 ± 20.0102	11	69.373 ± 51.7401	13	42.324 ± 54.463	7	118.049 ± 96.1909
	22	8	164.281 ± 87.5716	10	57.66 ± 34.1193	8	158.506 ± 106.059	8	133.088 ± 98.8421	6	179.058 ± 192.7982

Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for RAD001 PK profile parameters, post-amendment 1, by profile day for weekly dose schedules - phase 1 (Safety population)

		RAD 30/wk + ERL 150 N=6			RAD 50/wk + ERL 150 N=14		
PK Parameter (units)	**Profile Day**	**n**	**Median**	**SD**	**n**	**Median**	**SD**
$AUC_{0\text{-}inf}$ (ng.h/mL)	8	5	953.61	452.808	6	2434.47	1170.576
	22	0			0		
$AUC_{0\text{-}tlast}$ (ng.h/mL)	8	5	738.03	319.418	5	1439.39	693.801
	22	0			0		
CL/F (L/h)	8	5	40.218	23.2737	5	28.953	15.7016
	22	0			0		
CL/F ($L/h/m^2$)	8	5	19.431	10.8545	5	15.912	9.1032
	22	0			0		
C_{max} (ng/mL)	8	5	134.32	55.845	7	148.11	57.128
	22	0			0		
C_{min} (ng/mL)	8	0			0		
	15	2	1.306	0.8266	0		
	22	0			0		

Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for erlotinib PK profile parameters, post-amendment 1, by profile day for weekly dose schedules - phase 1 (Safety population)

		RAD 30/wk + ERL 150 N=6			RAD 50/wk + ERL 150 N=14		
PK Parameter (units)	**Profile Day**	**n**	**Median**	**SD**	**n**	**Median**	**SD**
$AUC_{0\text{-}inf}$ (ng.h/mL)	1	5	61616.17	72062.61	8	32227.04	10834.272
	8	5	43050.46	28153.67	7	55210.49	24106.861
	22	5	125833	106845.4	5	113103.4	119751.27
$AUC_{0\text{-}tlast}$ (ng.h/mL)	1	5	15864.28	10357.26	8	15796.78	5489.678
	8	5	14420.72	8749.116	7	19829.75	6059.983
	22	5	36950.91	20145.65	5	39684.28	15094.425
CL/F (L/h)	1	5	13.079	7.5381	8	11.117	5.5427

	8	5	14.06	7.8399	7	8.19	2.0642
	22	5	7.156	8.0117	5	4.231	1.5143
CL/F (L/h/m^2)	1	5	5.944	2.8119	8	6.089	1.8664
	8	5	6.282	2.8496	7	4.668	0.833
	22	5	3.152	3.1724	5	2.375	0.6305
C_{max} (ng/mL)	1	6	944.83	642.888	11	1161	439.155
	8	5	991	659.143	10	1271.3	403.016
	22	6	2114	982.515	7	2890	1067.583
C_{min} (ng/mL)	1	6	561.5	308.9464	12	443.75	171.797
	8	6	448.333	259.4731	11	701.636	408.0888
	22	6	1373.1	757.6253	9	1671.222	901.5805

Day 1 (D1): Erlotinib alone
Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Descriptive statistics for OSI-420 PK profile parameters, post-amendment 1, by profile day for weekly dose schedules - phase 1 (Safety population)

		RAD 30/wk + ERL 150 N=6			RAD 50/wk + ERL 150 N=14		
PK Parameter (units)	**Profile Day**	**n**	**Median**	**SD**	**n**	**Median**	**SD**
AUC0-inf (ng.h/mL)	1	3	2312.15	1487.291	8	2089.25	830.587
	8	5	2240.22	1298.987	7	3527.5	2070.125
	22	5	53997.6	104944.91	4	5829.04	1430.136
AUC0-tlast (ng.h/mL)	1	3	1087.98	828.796	8	1192.42	441.393
	8	5	937.59	545.129	7	1528.01	579.412
	22	5	3269.09	2133.777	4	3622.29	680.721
CL/F (L/h)	1	3	216.267	171.4925	8	146.17	64.8636
	8	5	209.941	114.3554	7	114.49	49.6318
	22	5	103.319	132.9378	4	42.798	9.1244
CL/F (L/h/m2)	1	3	94.685	63.5467	8	80.456	23.5987
	8	5	93.802	40.4251	7	65.357	25.5577
	22	5	45.172	53.1826	4	23.884	5.2924
Cmax (ng/mL)	1	5	57.5	38.605	11	108.27	73.804
	8	5	60.02	29.414	10	97.92	38.634
	22	6	199.13	108.313	7	335.57	184.707
Cmin (ng/mL)	1	6	39.833	24.7636	12	37.85	19.7414

8	6	27.967	16.8362	11	57.8	42.8893
22	6	130.223	86.9369	9	214.306	175.7328

Day 1 (D1): Everolimus alone
Day 8 (D8): Everolimus + Erlotinib
Day 22 (D22): Everolimus + Erlotinib (At steady-state)
PK profile parameters from profiles not eligible for the PK analysis are excluded.

Analysis of DCR at 3 months, by the investigator - phase 2

	RAD001 5mg/o.d. + erlotinib 150mg N=66 n (%)	**Erlotinib 150mg N=67 n (%)**
Disease control rate at 3 months	26 (39.4)	19 (28.4)
Observed difference in DCR (everolimus 5mg/o.d. + erlotinib 150mg minus Erlotinib 150mg) - %	11.0	
Posterior distribution for the difference in DCR (everolimus 5mg/o.d. + erlotinib 150mg minus Erlotinib 150mg) - %		
10th percentile	0.40	
25th percentile	5.33	
50th percentile	10.76	
75th percentile	16.16	
90th percentile	20.99	
Pr[Difference>=efficacy threshold]*	29.80	

Disease control rate at 3 months is defined as the proportion of patients with stable disease or better at 3 months.
Posterior distribution for the difference based on a Bayesian conjugated Beta-Binomial model.
Efficacy threshold taken as 15%.
* If this probability is greater or equal to 40%, the efficacy level of proof, everolimus 5mg/o.d. + erlotinib 150mg should be declared efficacious.

Secondary Outcome Result(s)

Calculated best overall response and early progression by schedule and dose – phase 1 (FAS)

Best overall response	RAD 5/o.d + ERL 100 N=15 n (%)	RAD 5/q.o.d + ERL 100 N=12 n (%)	RAD 2.5/o.d + ERL 100 N=13 n (%)	RAD 2.5/o.d + ERL 150 N=13 n (%)	RAD 5/o.d + ERL 75 N=13 n (%)	RAD 5/o.d + ERL 150 N=8 n (%)	RAD 30/wk + ERL 150 N=6 n (%)	RAD 50/wk + ERL 150 N=14 n (%)
Overall Response (CR or PR)	1 (6.7)	2 (16.7)	2 (15.4)	3 (23.1)	1 (7.7)	0	0	0
95% CI of response rate	[0.2, 31.9]	[2.1, 48.4]	[1.9, 45.4]	[5.0, 53.8]	[0.2, 36.0]			
Complete Response (CR)	0	0	1 (7.7)	0	0	0	0	0
Partial Response (PR)	1 (6.7)	2 (16.7)	1 (7.7)	3 (23.1)	1 (7.7)	0	0	0
Stable Disease (SD)	9 (60.0)	4 (33.3)	6 (46.2)	4 (30.8)	2 (15.4)	3 (37.5)	3 (50.0)	4 (28.6)
Progressive Disease (PD)	3 (20.0)	3 (25.0)	5 (38.5)	4 (30.8)	8 (61.5)	4 (50.0)	3 (50.0)	5 (35.7)
Unknown (UNK)	2 (13.3)	3 (25.0)	0	2 (15.4)	2 (15.4)	1 (12.5)	0	5 (35.7)
Early progression	3 (20.0)	1 (8.3)	5 (38.5)	4 (30.8)	7 (53.8)	3 (37.5)	2 (33.3)	5 (35.7)
95% CI of early progression	[4.3, 48.1]	[0.2, 38.5]	[13.9, 68.4]	[9.1, 61.4]	[25.1, 80.8]	[8.5, 75.5]	[4.3, 77.7]	[12.8, 64.9]
Disease control rate (CR or PR or SD)	10 (66.7)	6 (50.0)	8 (61.5)	7 (53.8)	3 (23.1)	3 (37.5)	3 (50.0)	4 (28.6)

Tumor assessments are carried out every four weeks (+/- one week) for the first sixteen weeks and thereafter every eight weeks (+/- one week).
The calculated best overall response is based on recalculated overall lesion responses at each tumor assessment.
Early progression is demonstrated if patients record documented progressive disease within 8 weeks of treatment start.

Investigator best overall response and early progression by treatment – phase 2 (FAS)

	RAD001 5mg/o.d. + erlotinib 150mg N=66 n (%)	Erlotinib 150mg N=67 n (%)
Best Overall Response (CR or PR)	8 (12.1)	7 (10.4)
95% CI of response rate	[5.4, 22.5]	[4.3, 20.3]
Complete Response (CR)	0	0
Partial Response (PR)	8 (12.1)	7 (10.4)
Stable Disease (SD)	30 (45.5)	19 (28.4)
Progressive Disease (PD)	17 (25.8)	36 (53.7)
Unknown (UNK)	11 (16.7)	5 (7.5)
Early progression	18 (27.3)	31 (46.3)
Disease control rate (CR or PR or SD)	38 (57.6)	26 (38.8)
Disease control rate at 3 months	26 (39.4)	19 (28.4)
95% CI of disease control rate at 3 months	[27.6, 52.2]	[18.0, 40.7]

Confidence intervals are calculated using the Clopper-Pearson method.
Tumor assessments are carried out every 4 weeks (+/- 1 week) for the first sixteen weeks and thereafter every 8 weeks (+/- 1 week).
The investigator best overall response is determined based on investigator assessments of overall lesion response as recorded in the CRF.
Early progression is demonstrated if patients have progressive disease within 8 weeks of the randomization date.

Analysis of progression-free survival (PFS) as per investigator using Kaplan-Meier method by treatment – phase 2 (FAS)

	RAD001 5mg/o.d. + erlotinib 150mg N=66	Erlotinib 150mg N=67	p-value [1]
Number of PFS events - n (%)	42 (63.6)	48 (71.6)	0.228
Progression	35 (53.0)	48 (71.6)	
Death	7 (10.6)	0	
Number of censored events - n (%)	24 (36.4)	19 (28.4)	
Kaplan-Meier estimates [95% CI] at:			
2 months	64.9 [52.7, 77.0]	51.4 [39.1, 63.7]	
3 months	44.4 [31.3, 57.4]	35.6 [23.5, 47.7]	
4 months	35.4 [22.3, 48.5]	27.3 [15.5, 39.0]	
6 months	24.5 [11.7, 37.2]	19.1 [7.7, 30.5]	
8 months	18.4 [4.2, 32.5]	19.1 [7.7, 30.5]	
10 months	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	
25th percentile for PFS (months) [95% CI]	1.2 [1.0, 2.4]	1.0 [0.9, 1.0]	
Median PFS (months) [95% CI]	2.9 [2.4, 3.9]	2.0 [1.1, 2.8]	
75th percentile for PFS (months) [95% CI]	5.8 [3.8, 8.7]	5.4 [2.9, 9.2]	

[1] P-value is obtained from an unstratified Log-Rank test.
NC = Non calculable.
One month is considered to be 365.25 days divided by 12 = 30.4375 days.

Analysis of overall survival (OS) as per investigator using Kaplan-Meier method by treatment – phase 2 (FAS)

	RAD001 5mg/o.d. + erlotinib 150mg N=66	Erlotinib 150mg N=67	p-value [1]
Number of events - n (%)	23 (34.8)	18 (26.9)	0.433
Number of censored events - n (%)	43 (65.2)	49 (73.1)	
Kaplan-Meier estimates [95% CI] at:			
4 months	77.0 [66.3, 87.6]	84.4 [75.0, 93.9]	
6 months	65.6 [52.7, 78.6]	73.0 [60.6, 85.4]	
8 months	59.0 [44.3, 73.6]	60.3 [45.0, 75.6]	
10 months		60.3 [45.0, 75.6]	
25th percentile for OS (months) [95% CI]	4.5 [3.3, 7.5]	4.8 [3.8, NC]	
Median OS (months) [95% CI]	8.7 [6.8, NC]	NC [6.9, NC]	
75th percentile for OS (months) [95% CI]	NC [8.7, NC]	NC [NC, NC]	

[1] P-value is obtained from an unstratified Log-Rank test.
NC = Non calculable.
One month is considered to be 365.25 days divided by 12 = 30.4375 days.

Descriptive statistics for Everolimus trough concentrations (ng/ml), by time point and treatment - phase 2 (Safety population)

	RAD001 5mg/o.d. + erlotinib 150mg N=66			Erlotinib 150mg N=65		
Time point	n	Median	Range	n	Median	Range
Week 8	12	5.71	2.5 - 11.9	0		
Month 3	11	7.06	3.3 - 14.7	0		
Month 4	7	7.09	3.0 - 16.5	0		
All eligible trough PK samples available for the safety population are included.						

Descriptive statistics for Erlotinib trough concentrations (ng/ml), by time point and treatment - phase 2 (Safety population)

	RAD001 5mg/o.d. + erlotinib 150mg N=66			Erlotinib 150mg N=65		
Time point	n	Median	Range	n	Median	Range
Week 8	16	1165.50	287.0 - 2830.0	0		
Month 3	15	1320.00	410.0 - 2600.0	0		
Month 4	7	882.00	491.0 - 1930.0	0		
All eligible trough PK samples available for the safety population are included.						

Descriptive statistics for OSI-420 trough concentrations (ng/ml), by time point and treatment - phase 2 (Safety population)

	RAD001 5mg/o.d. + erlotinib 150mg N=66			Erlotinib 150mg N=65		
Time point	n	Median	Range	n	Median	Range
Week 8	16	157.00	24.1 - 404.0	0		
Month 3	15	140.00	21.9 - 665.0	0		
Month 4	7	62.00	38.2 - 269.0	0		
All eligible trough PK samples available for the safety population are included.						

Potential Molecular markers – phase 2

Somatic mutation analysis for KRAS, EGFR and PI3KCA was performed on available archival tumor tissues collected from consenting patients. The sample size was too limited for statistical analysis and correlation with outcome.

Tumor metabolic response with FDG-PET imaging - phase 2

No analysis was performed on the small number of images provided by the sites.

Safety Results

Adverse Events by System Organ Class (Safety Population)

Adverse events regardless of study drug relationship, by system organ class, schedule and dose – Phase 1 (Safety population)

System organ class	RAD 5/o.d + ERL 100 N=15	RAD 5/q.o.d + ERL 100 N=12	RAD 2.5/o.d + ERL 100 N=13	RAD 2.5/o.d + ERL 150 N=13	RAD 5/o.d + ERL 75 N=13	RAD 5/o.d + ERL 150 N=8	RAD 30/wk + ERL 150 N=6	RAD 50/wk + ERL 150 N=14	Total Daily N=74	Total Weekly N=20	Total N=94
Any primary system organ class	15 (100)	12 (100)	13 (100)	13 (100)	13 (100)	8 (100)	6 (100)	14 (100)	74 (100)	20 (100)	94 (100)
Gastrointestinal disorders	14 (93.3)	10 (83.3)	12 (92.3)	13 (100)	13 (100)	8 (100)	6 (100)	13 (92.9)	70 (94.6)	19 (95.0)	89 (94.7)
Skin and subcutaneous tissue disorders	14 (93.3)	11 (91.7)	8 (61.5)	12 (92.3)	10 (76.9)	6 (75.0)	5 (83.3)	10 (71.4)	61 (82.4)	15 (75.0)	76 (80.9)
General disorders and administration site conditions	11 (73.3)	10 (83.3)	10 (76.9)	10 (76.9)	8 (61.5)	8 (100)	2 (33.3)	12 (85.7)	57 (77.0)	14 (70.0)	71 (75.5)
Metabolism and nutrition disorders	13 (86.7)	6 (50.0)	6 (46.2)	11 (84.6)	9 (69.2)	4 (50.0)	2 (33.3)	10 (71.4)	49 (66.2)	12 (60.0)	61 (64.9)
Respiratory, thoracic and mediastinal disorders	7 (46.7)	9 (75.0)	9 (69.2)	10 (76.9)	6 (46.2)	7 (87.5)	3 (50.0)	8 (57.1)	48 (64.9)	11 (55.0)	59 (62.8)
Infections and infestations	8 (53.3)	4 (33.3)	8 (61.5)	9 (69.2)	8 (61.5)	5 (62.5)	3 (50.0)	6 (42.9)	42 (56.8)	9 (45.0)	51 (54.3)
Musculoskeletal and connective tissue disorders	6 (40.0)	4 (33.3)	8 (61.5)	6 (46.2)	4 (30.8)	4 (50.0)	3 (50.0)	8 (57.1)	32 (43.2)	11 (55.0)	43 (45.7)
Nervous system disorders	8 (53.3)	4 (33.3)	4 (30.8)	6 (46.2)	4 (30.8)	4 (50.0)	2 (33.3)	8 (57.1)	30 (40.5)	10 (50.0)	40 (42.6)
Investigations	4 (26.7)	3 (25.0)	1 (7.7)	7 (53.8)	7 (53.8)	4 (50.0)	2 (33.3)	9 (64.3)	26 (35.1)	11 (55.0)	37 (39.4)
Blood and lymphatic system disorders	4 (26.7)	3 (25.0)	1 (7.7)	4 (30.8)	5 (38.5)	3 (37.5)	1 (16.7)	5 (35.7)	20 (27.0)	6 (30.0)	26 (27.7)
Psychiatric disorders	6 (40.0)	5 (41.7)	2 (15.4)	2 (15.4)	2 (15.4)	4 (50.0)	1 (16.7)	3 (21.4)	21 (28.4)	4 (20.0)	25 (26.6)
Eye disorders	2 (13.3)	0	2 (15.4)	2 (15.4)	3 (23.1)	2 (25.0)	0	4 (28.6)	11 (14.9)	4 (20.0)	15 (16.0)
Vascular disorders	3 (20.0)	2 (16.7)	1 (7.7)	3 (23.1)	2 (15.4)	2 (25.0)	1 (16.7)	1 (7.1)	13 (17.6)	2 (10.0)	15 (16.0)
Injury, poisoning and procedural complications	3 (20.0)	2 (16.7)	2 (15.4)	0	3 (23.1)	1 (12.5)	0	1 (7.1)	11 (14.9)	1 (5.0)	12 (12.8)
Renal and urinary disorders	2 (13.3)	1 (8.3)	1 (7.7)	1 (7.7)	1 (7.7)	3 (37.5)	2 (33.3)	1 (7.1)	9 (12.2)	3 (15.0)	12 (12.8)
Cardiac disorders	1 (6.7)	1 (8.3)	1 (7.7)	1 (7.7)	1 (7.7)	2 (25.0)	1 (16.7)	2 (14.3)	7 (9.5)	3 (15.0)	10 (10.6)

Ear and labyrinth disorders	0	0	0	3 (23.1)	1 (7.7)	1 (12.5)	0	1 (7.1)	5 (6.8)	1 (5.0)	6 (6.4)
Reproductive system and breast disorders	2 (13.3)	1 (8.3)	0	0	0	0	0	2 (14.3)	3 (4.1)	2 (10.0)	5 (5.3)
Immune system disorders	1 (6.7)	1 (8.3)	0	1 (7.7)	0	0	0	0	3 (4.1)	0	3 (3.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (8.3)	0	1 (7.7)	0	0	0	0	2 (2.7)	0	2 (2.1)
Congenital, familial and genetic disorders	0	0	0	0	0	0	0	1 (7.1)	0	1 (5.0)	1 (1.1)
Endocrine disorders	0	0	1 (7.7)	0	0	0	0	0	1 (1.4)	0	1 (1.1)
Hepatobiliary disorders	0	0	0	0	0	0	0	1 (7.1)	0	1 (5.0)	1 (1.1)

System organ classes are sorted by descending frequency across the doses.
A patient with multiple adverse events within a primary system organ class is counted only once within that class.
A patient with multiple adverse events may be counted in more than one system organ class.

AEs regardless of study drug relationship by primary SOC – phase 2 (Safety population)

System organ class	RAD001 5mg/o.d. + erlotinib 150mg N=66 n (%)	Erlotinib 150mg N=65 n (%)
Any primary system organ class (total)	66 (100)	64 (98.5)
Skin and subcutaneous tissue disorders	62 (93.9)	60 (92.3)
Gastrointestinal disorders	61 (92.4)	51 (78.5)
General disorders and administration site conditions	40 (60.6)	37 (56.9)
Metabolism and nutrition disorders	45 (68.2)	32 (49.2)
Respiratory, thoracic and mediastinal disorders	33 (50.0)	33 (50.8)
Infections and infestations	39 (59.1)	24 (36.9)
Investigations	31 (47.0)	22 (33.8)
Nervous system disorders	28 (42.4)	16 (24.6)
Musculoskeletal and connective tissue disorders	16 (24.2)	27 (41.5)
Blood and lymphatic system disorders	28 (42.4)	9 (13.8)
Psychiatric disorders	18 (27.3)	13 (20.0)
Eye disorders	14 (21.2)	11 (16.9)
Vascular disorders	8 (12.1)	6 (9.2)
Renal and urinary disorders	8 (12.1)	2 (3.1)
Reproductive system and breast disorders	4 (6.1)	3 (4.6)
Cardiac disorders	3 (4.5)	2 (3.1)
Hepatobiliary disorders	3 (4.5)	2 (3.1)
Ear and labyrinth disorders	3 (4.5)	1 (1.5)
Immune system disorders	0	4 (6.2)
Injury, poisoning and procedural complications	3 (4.5)	1 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (6.2)

Endocrine disorders	1 (1.5)	0
Social circumstances	1 (1.5)	0

System organ classes are sorted by descending frequency across the treatments.
A patient with multiple adverse events within a primary system organ class is counted only once within that class.
A patient with multiple adverse events may be counted in more than one system organ class.

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

Frequent adverse events regardless of study drug relationship by preferred term, schedule and dose – phase 1 (Safety population)

Preferred term	RAD 5/o.d + ERL 100 N=15	RAD 5/q.o.d + ERL 100 N=12	RAD 2.5/o.d + ERL 100 N=13	RAD 2.5/o.d + ERL 150 N=13	RAD 5/o.d + ERL 75 N=13	RAD 5/o.d + ERL 150 N=8	RAD 30/wk + ERL 150 N=6	RAD 50/wk + ERL 150 N=14	Total Daily N=74	Total Weekly N=20	Total N=94
Stomatitis	8 (53.3)	5 (41.7)	10 (76.9)	9 (69.2)	10 (76.9)	5 (62.5)	5 (83.3)	10 (71.4)	47 (63.5)	15 (75.0)	62 (66.0)
Diarrhoea	5 (33.3)	5 (41.7)	8 (61.5)	8 (61.5)	10 (76.9)	4 (50.0)	6 (100)	9 (64.3)	40 (54.1)	15 (75.0)	55 (58.5)
Rash	8 (53.3)	9 (75.0)	6 (46.2)	5 (38.5)	7 (53.8)	2 (25.0)	3 (50.0)	6 (42.9)	37 (50.0)	9 (45.0)	46 (48.9)
Decreased appetite	7 (46.7)	4 (33.3)	5 (38.5)	7 (53.8)	6 (46.2)	3 (37.5)	1 (16.7)	8 (57.1)	32 (43.2)	9 (45.0)	41 (43.6)
Fatigue	7 (46.7)	8 (66.7)	8 (61.5)	4 (30.8)	4 (30.8)	2 (25.0)	1 (16.7)	3 (21.4)	33 (44.6)	4 (20.0)	37 (39.4)
Nausea	9 (60.0)	5 (41.7)	2 (15.4)	6 (46.2)	5 (38.5)	3 (37.5)	4 (66.7)	2 (14.3)	30 (40.5)	6 (30.0)	36 (38.3)
Dry skin	6 (40.0)	5 (41.7)	3 (23.1)	5 (38.5)	2 (15.4)	4 (50.0)	3 (50.0)	4 (28.6)	25 (33.8)	7 (35.0)	32 (34.0)
Dermatitis acneiform	5 (33.3)	2 (16.7)	2 (15.4)	4 (30.8)	3 (23.1)	4 (50.0)	0	6 (42.9)	20 (27.0)	6 (30.0)	26 (27.7)
Vomiting	3 (20.0)	2 (16.7)	1 (7.7)	5 (38.5)	7 (53.8)	2 (25.0)	0	4 (28.6)	20 (27.0)	4 (20.0)	24 (25.5)
Anaemia	3 (20.0)	3 (25.0)	0	3 (23.1)	5 (38.5)	3 (37.5)	1 (16.7)	5 (35.7)	17 (23.0)	6 (30.0)	23 (24.5)

Preferred terms are sorted by descending frequency by the total AEs.
A patient with multiple adverse events within a preferred term is counted only once.
A patient with multiple adverse events may be counted in more than one preferred term

Frequent AEs regardless of study drug relationship by preferred term – phase 2 (Safety population)

Preferred term	RAD001 5mg/o.d. + erlotinib 150mg N=66 n (%)	Erlotinib 150mg N=65 n (%)
Diarrhea	48 (72.7)	36 (55.4)
Stomatitis	48 (72.7)	15 (23.1)
Rash	35 (53.0)	30 (46.2)
Weight decreased	26 (39.4)	11 (16.9)
Anorexia	24 (36.4)	23 (35.4)
Nausea	20 (30.3)	22 (33.8)
Dermatitis acneiform	19 (28.8)	13 (20.0)
Anaemia	18 (27.3)	3 (4.6)
Dry skin	16 (24.2)	23 (35.4)
Fatigue	15 (22.7)	13 (20.0)

Preferred terms are sorted by descending frequency in the RAD + erlotinib group.
A patient with multiple adverse events within a preferred term is counted only once.
A patient with multiple adverse events may be counted in more than 1 preferred term.

Serious Adverse Events and Deaths

Deaths, serious adverse events, other grade 3 or 4 adverse events, or adverse events resulting in discontinuation or dose adjustment/interruption, regardless of study drug relationship, by schedule and dose – phase 1 (Safety population)

	RAD 5/o.d + ERL 100 N=15 n (%)	RAD 5/q.o.d + ERL 100 N=12 n (%)	RAD 2.5/o.d + ERL 100 N=13 n (%)	RAD 2.5/o.d + ERL 150 N=13 n (%)	RAD 5/o.d + ERL 75 N=13 n (%)	RAD 5/o.d + ERL 150 N=8 n (%)	RAD 30/wk + ERL 150 N=6 n (%)	RAD 50/wk + ERL 150 N=14 n (%)	Total Daily N=74 n (%)	Total Weekly N=20 n (%)	Total N=94 n (%)
Patients with AEs	15 (100)	12 (100)	13 (100)	13 (100)	13 (100)	8 (100)	6 (100)	14 (100)	74 (100)	20 (100)	94 (100)
Patients with any significant event [1]	11 (73.3)	8 (66.7)	10 (76.9)	10 (76.9)	13 (100)	6 (75.0)	3 (50.0)	12 (85.7)	58 (78.4)	15 (75.0)	73 (77.7)
Significant events [1]											
Death during study											
Primary reason for discontinuation	0	0	1 (7.7)	0	0	0	0	0	1 (1.4)	0	1 (1.1)
Not primary reason for discontinuation	0	0	0	0	0	0	0	0	0	0	0
SAEs	9 (60.0)	5 (41.7)	6 (46.2)	8 (61.5)	9 (69.2)	4 (50.0)	3 (50.0)	7 (50.0)	41 (55.4)	10 (50.0)	51 (54.3)
Grade 3 or 4 AEs	10 (66.7)	7 (58.3)	8 (61.5)	9 (69.2)	12 (92.3)	6 (75.0)	3 (50.0)	12 (85.7)	52 (70.3)	15 (75.0)	67 (71.3)
Discontinuation due to AEs	3 (20.0)	4 (33.3)	2 (15.4)	5 (38.5)	3 (23.1)	1 (12.5)	3 (50.0)	4 (28.6)	18 (24.3)	7 (35.0)	25 (26.6)
AEs causing dose adjusment/ interruption	7 (46.7)	3 (25.0)	6 (46.2)	9 (69.2)	7 (53.8)	4 (50.0)	2 (33.3)	6 (42.9)	36 (48.6)	8 (40.0)	44 (46.8)

[1] A significant event is defined as any of the events presented in the table.
Death on study was recorded up to and including 28 days following treatment discontinuation

Deaths, SAEs, other grade 3 or 4 AEs, or AEs resulting in discontinuation or dose adjustment/interruption regardless of study drug relationship – phase 2 (Safety population)

	RAD001 5mg/o.d. + erlotinib 150mg N=66 n (%)	Erlotinib 150mg N=65 n (%)
Total no. of patients with AEs	66 (100)	64 (98.5)
Total no. of patients with any significant event [1]	57 (86.4)	26 (40.0)
Significant events [1]		
Death during study		
Primary reason for discontinuation	1 (1.5)	0

Not primary reason for discontinuation	9 (13.6)	4 (6.2)
SAEs	27 (40.9)	12 (18.5)
Grade 3 or 4 AEs	48 (72.7)	21 (32.3)
Discontinuation due to AEs	7 (10.6)	3 (4.6)
AEs causing dose adjustment/interruption	34 (51.5)	12 (18.5)

[1] A significant event is defined as any of the events presented in the table.
Death on study was recorded up to and including 28 days following treatment discontinuation.

Other Relevant Findings

None

Date of Clinical Trial Report

07-Mar-2012

Date Inclusion on Novartis Clinical Trial Results Database

28-Mar-2012

Date of Latest Update