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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Everolimus in combination with BEZ235

Trial Indication

Advanced solid tumors

Protocol Number

CRAD001X2109

Protocol Title

An open-label, multi-center Phase I dose-finding study of RAD001 in combination with BEZ235 in patients with advanced solid tumors.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

12-Jan-2012 to 16-Feb-2015

Reason for Termination

The study was prematurely terminated by Novartis as the results from the dose-finding phase failed to corroborate the strong synergistic activity on tumor cell inhibition demonstrated in pre-clinical studies.

Study Design/Methodology

This was an open-label, multicenter Phase I study using a sequential dose escalation scheme and a Bayesian logistic regression model (BLRM) for the end-of-cycle-1 dose-limiting toxicity (DLT) rate that aimed to identify a feasible dose of BEZ235 in combination with RAD001. The study enrolled patients with advanced solid tumors who received standard of care previously and had documented progression of disease.

Centers

10 centers in 7 Countries: Belgium (1), France (2), Italy (1), New Zealand (1), Spain (1), United Kingdom (1), USA (3).

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Publication

None

Objectives:

Primary objective

- Dose finding phase: To determine the MTD and/or RP2D of RAD001 (given weekly or once daily) and BEZ235 (given twice daily) in combination when administered orally to adult patients with advanced solid tumors.
- Dose expansion phase: To assess the safety and tolerability of RAD001 and BEZ235 in combination at the MTD and/or RP2D as recommended in the dose-finding phase when administered to adult patients with ER+/HER2- MBC and mRCC.

Secondary objectives

- To assess RAD001 pharmacokinetics (PK) when administered alone, and in combination with BEZ235 during the initial cohorts.
- To assess the effect of co-administration of BEZ235 on the PK of RAD001 during the dose expansion phase.
- To assess preliminary anti-tumor activity of the combination using local assessments for RCC and MBC in the dose expansion phase; scans were planned to be collected in order to allow a central radiological review if needed.

The study did not proceed to the dose expansion phase and was terminated by Novartis.

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

RAD001 and BEZ235 were each considered as investigational drugs and constituted the study drug. There was no control treatment in this study.

RAD001 was formulated as tablets of 2.5 mg and 5 mg strength, blistered in units of 10 tablets each. Blisters were opened only at the time of administration as the drug is both hygroscopic and light-sensitive. RAD001 was administered immediately after a meal with a large glass of water. BEZ235 was supplied as 50 mg, 200 mg, 300 mg, and 400 mg sachets. BEZ235 was packaged in aluminum foil bags.

Statistical Methods

An adaptive BLRM for dose escalation with overdose control guided the dose escalation. The recommended dose was the one with the highest posterior probability of DLT in the target interval (16%, 33%) among the doses fulfilling the overdose criterion that there is less than 25 % chance of excessive toxicity. A clinical synthesis of the available toxicity information including adverse event that are not DLTs, PK, pharmacodynamics, efficacy as well as the recommendations from the BLRM was used to determine the dose.

Study Population: Key Inclusion/Exclusion Criteria

Main criteria for inclusion

- In the dose-finding phase, patients with histologically or cytologically confirmed advanced solid malignancies that were metastatic or unresectable, for whom all approved treatment options had been exhausted and no standard of care was available.
  In the dose expansion phase, the enrollment was planned to be limited to:
  - Patients with mRCC whose disease had progressed despite prior treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) therapy (at least one but no more than two lines of VEGFR-TKI therapy).
  - Patients with MBC which were ER+/HER2-, whose disease had progressed despite prior treatment with at least one but no more than two lines of chemotherapy and at least one prior line of endocrine therapy in the metastatic setting.
- Patients' age was ≥ 18 years and with World Health Organization (WHO) performance status <3, adequate organ function and confirmed disease progression.

Main criteria for exclusion:

- Patients who received therapy with mTOR inhibitors (e.g., sirolimus, temsirolimus, everolimus).
- Patients who had participated in clinical studies with PI3K inhibitors.
- Patients with central nervous system metastases unless previously treated with surgery, whole-brain radiation or stereotactic radiosurgery plus the disease having been stable for at least two months without steroid use for at least one month prior to the first dose of RAD001 and BEZ235. Patients were not permitted to receive enzyme-inducing anti-epileptic drugs.
- Other criteria included recent anticancer therapy and or unresolved side effects, recent corticosteroids, major surgery, radiation therapy or investigational therapy. Patient also had to be in good health without evidence of another malignancy.

Participant Flow Table

Patient disposition by dose level (FAS)

Disposition Reason	Initial cohort N=3 n (%)	RAD 2.5 mg/wk BEZ 200 mg/bid N=7 n (%)	RAD 5 mg/wk BEZ 50 mg/bid N=6 n (%)	RAD 10 mg/wk BEZ 50 mg/bid N=6 n (%)	RAD 2.5 mg/day BEZ 50 mg/bid N=8 n (%)	RAD 5 mg/day BEZ 50 mg/bid N=8 n (%)	RAD 2.5 mg/day BEZ 100 mg/bid N=8 n (%)	All patients N=46 n (%)
Patients treated								
End of treatment	3 (100)	7 (100)	6 (100)	6 (100)	8 (100)	8 (100)	8 (100)	46 (100)
Primary reason for end of treatment								
Disease progression	2 (66.7)	1 (14.3)	4 (66.7)	3 (50.0)	8 (100)	3 (37.5)	7 (87.5)	28 (60.9)

Disposition Reason	Initial cohort N=3 n (%)	RAD 2.5 mg/wk BEZ 200 mg/bid N=7 n (%)	RAD 5 mg/wk BEZ 50 mg/bid N=6 n (%)	RAD 10 mg/wk BEZ 50 mg/bid N=6 n (%)	RAD 2.5 mg/day BEZ 50 mg/bid N=8 n (%)	RAD 5 mg/day BEZ 50 mg/bid N=8 n (%)	RAD 2.5 mg/day BEZ 100 mg/bid N=8 n (%)	All patients N=46 n (%)
Adverse event(s)	1 (33.3)	4 (57.1)	1 (16.7)	0	0	3 (37.5)	0	9 (19.6)
Patient withdrew consent	0	1 (14.3)	1 (16.7)	2 (33.3)	0	1 (12.5)	1 (12.5)	6 (13.0)
Administrative problems	0	0	0	1 (16.7)	0	1 (12.5)	0	2 (4.3)
Protocol deviation	0	1 (14.3)	0	0	0	0	0	1 (2.2)

Percentage is based on N.

Baseline Characteristics

Demographic summary by dose level (FAS)

Demographic variable	Initial cohort N=3 n (%)	RAD 2.5 mg/wk BEZ 200 mg/bid N=7 n (%)	RAD 5 mg/wk BEZ 50 mg/bid N=6 n (%)	RAD 10 mg/wk BEZ 50 mg/bid N=6 n (%)	RAD 2.5 mg/day BEZ 50 mg/bid N=8 n (%)	RAD 5 mg/day BEZ 50 mg/bid N=8 n (%)	RAD 2.5 mg/day BEZ 100 mg/bid N=8 n (%)	All patients N=46 n (%)
Age at baseline (years)								
n	3	7	6	6	8	8	8	46
Mean	51.3	63.6	54.8	49.8	58.4	54.1	55.1	55.8
SD	11.68	7.98	9.37	11.79	7.46	9.17	9.36	9.62
Median	49.0	66.0	54.5	51.5	58.5	55.5	56.5	57.0
Min	41	53	43	30	48	38	40	30
Max	64	73	68	65	68	64	69	73
Age category (years) - n (%)								
<65	3 (100)	3 (42.9)	5 (83.3)	5 (83.3)	6 (75.0)	8 (100)	7 (87.5)	37 (80.4)
≥ 65	0	4 (57.1)	1 (16.7)	1 (16.7)	2 (25.0)	0	1 (12.5)	9 (19.6)
Sex - n (%)								
Male	3 (100)	2 (28.6)	2 (33.3)	3 (50.0)	4 (50.0)	1 (12.5)	2 (25.0)	17 (37.0)
Female	0	5 (71.4)	4 (66.7)	3 (50.0)	4 (50.0)	7 (87.5)	6 (75.0)	29 (63.0)
Race - n (%)								
Caucasian	3 (100)	7 (100)	6 (100)	6 (100)	8 (100)	7 (87.5)	7 (87.5)	44 (95.7)
Black	0	0	0	0	0	1 (12.5)	0	1 (2.2)
Other	0	0	0	0	0	0	1 (12.5)	1 (2.2)

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	Initial cohort N=3	RAD 2.5 mg/wk BEZ 200 mg/bid N=7	RAD 5 mg/wk BEZ 50 mg/bid N=6	RAD 10 mg/wk BEZ 50 mg/bid N=6	RAD 2.5 mg/day BEZ 50 mg/bid N=8	RAD 5 mg/day BEZ 50 mg/bid N=8	RAD 2.5 mg/day BEZ 100 mg/bid N=8	All patients N=46
Demographic variable	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Body Mass Index (kg/m2) at baseline**								
n	3	7	6	6	8	8	8	46
Mean	25.43	25.14	23.37	31.65	26.71	26.61	25.46	26.36
SD	2.663	6.361	2.702	7.583	2.410	7.193	3.654	5.416
Median	24.10	23.30	23.05	29.35	27.15	22.90	26.75	25.60
Min	23.7	19.5	19.0	25.0	22.1	20.9	18.5	18.5
Max	28.5	37.3	26.7	46.3	29.6	38.2	29.0	46.3
Performance status (World health organization) – n (%)								
0	1 (33.3)	2 (28.6)	1 (16.7)	5 (83.3)	3 (37.5)	6 (75.0)	2 (25.0)	20 (43.5)
1	2 (66.7)	4 (57.1)	5 (83.3)	1 (16.7)	5 (62.5)	2 (25.0)	4 (50.0)	23 (50.0)
2	0	1 (14.3)	0	0	0	0	2 (25.0)	3 (6.5)

Summary of Efficacy

Primary Outcome Results

Summary of posterior distribution of DLT rates (DDS)

	Posterior probabilities (%) that Pr (DLT) is in interval:			Mean	SD	____Quantiles_____		
BEZ235 Dose (mg bid)	**0-0.16**	**0.16-0.33**	**0.33-1**			**2.5%**	**50%**	**97.5%**
RAD001=2.5mg/week								
50	0.916	0.083	0.001	0.072	0.058	0.002	0.058	0.216
100	0.645	0.325	0.03	0.14	0.085	0.016	0.127	0.34
200	0.224	0.433	0.343	0.286	0.151	0.059	0.263	0.63
RAD001=5mg/week								
50	0.915	0.084	0.001	0.073	0.058	0.003	0.059	0.217
100	0.642	0.328	0.03	0.141	0.084	0.018	0.128	0.34
200	0.221	0.435	0.344	0.286	0.151	0.061	0.264	0.63
RAD001=10mg/week								
50	0.909	0.09	0.001	0.076	0.058	0.005	0.064	0.22
100	0.63	0.339	0.031	0.145	0.084	0.022	0.131	0.342
200	0.212	0.44	0.348	0.289	0.15	0.065	0.266	0.631
RAD001=2.5mg/day								

	Posterior probabilities (%) that Pr (DLT) is in interval:			Mean	SD	____Quantiles_____		
BEZ235 Dose (mg bid)	**0-0.16**	**0.16-0.33**	**0.33-1**			**2.5%**	**50%**	**97.5%**
50	0.876	0.122	0.002	0.089	0.06	0.01	0.078	0.235
100	0.578	0.385	0.037	0.156	0.083	0.032	0.143	0.351
200	0.187	0.446	0.367	0.297	0.148	0.074	0.276	0.634
RAD001=5mg/day								
50	0.289	0.533	0.179	0.232	0.111	0.068	0.215	0.493
100	0.144	0.543	0.314	0.282	0.115	0.094	0.27	0.538
200	0.051	0.333	0.617	0.388	0.151	0.13	0.377	0.7
RAD001=10mg/day								
50	0.006	0.054	0.94	0.761	0.229	0.244	0.832	1
100	0.003	0.041	0.955	0.772	0.218	0.276	0.838	1
200	0.002	0.024	0.975	0.795	0.198	0.328	0.855	1

Secondary Outcome Results

Best overall response as per Investigator (FAS)

Best overall response	**Initial cohort N=3** n (%)	**RAD 2.5 mg/wk BEZ 200 mg/bid N=7** n (%)	**RAD 5 mg/wk BEZ 50 mg/bid N=6** n (%)	**RAD 10 mg/wk BEZ 50 mg/bid N=6** n (%)	**RAD 2.5 mg/day BEZ 50 mg/bid N=8** n (%)	**RAD 5 mg/day BEZ 50 mg/bid N=8** n (%)	**RAD 2.5 mg/day BEZ 100 mg/bid N=8** n (%)	**All patients N=46** n (%)
Stable Disease (SD)	1 (33.3)	2 (28.6)	3 (50.0)	4 (66.7)	6 (75.0)	3 (37.5)	3 (37.5)	22 (47.8)
Progressive Disease (PD)	2 (66.7)	1 (14.3)	2 (33.3)	1 (16.7)	2 (25.0)	3 (37.5)	4 (50.0)	15 (32.6)
Unknown (UNK)	0	4 (57.1)	1 (16.7)	1 (16.7)	0	2 (25.0)	1 (12.5)	9 (19.6)
ORR[a] (CR + PR) 95% CI for ORR[b]	0 (0.0-70.8)	0 (0.0-41.0)	0 (0.0-45.9)	0 (0.0-45.9)	0 (0.0-36.9)	0 (0.0-36.9)	0 (0.0-36.9)	0 (0.0- 7.7)

[a] ORR=Overall Response Rate

[b] 95% CI are computed using Clopper-Pearson method.

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Summary of Safety

Adverse events, regardless of study treatment relationship, by primary system organ class and dose level (greater than 10% in All patients) (Safety set)

Primary system organ class	Initial cohort N=3	RAD 2.5 mg/wk BEZ 200 mg/bid N=7	RAD 5 mg/wk BEZ 50 mg/bid N=6	RAD 10 mg/wk BEZ 50 mg/bid N=6	RAD 2.5 mg/day BEZ 50 mg/bid N=8	RAD 5 mg/day BEZ 50 mg/bid N=8	RAD 2.5 mg/day BEZ 100 mg/bid N=8	All patients N=46
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary system organ class	3 (100)	6 (85.7)	6 (100)	6 (100)	8 (100)	8 (100)	8 (100)	45 (97.8)
Blood and lymphatic system disorders	3 (100)	4 (57.1)	0	0	2 (25.0)	4 (50.0)	3 (37.5)	16 (34.8)
Cardiac disorders	1 (33.3)	1 (14.3)	2 (33.3)	1 (16.7)	0	0	1 (12.5)	6 (13.0)
Ear and labyrinth disorders	0	1 (14.3)	1 (16.7)	1 (16.7)	1 (12.5)	0	0	4 (8.7)
Eye disorders	0	0	0	0	2 (25.0)	0	0	2 (4.3)
Gastrointestinal disorders	3 (100)	6 (85.7)	6 (100)	6 (100)	8 (100)	7 (87.5)	6 (75.0)	42 (91.3)
General disorders and administration site conditions	2 (66.7)	4 (57.1)	5 (83.3)	5 (83.3)	6 (75.0)	5 (62.5)	7 (87.5)	34 (73.9)
Hepatobiliary disorders	0	0	1 (16.7)	0	0	0	0	1 (2.2)
Infections and infestations	1 (33.3)	1 (14.3)	3 (50.0)	3 (50.0)	6 (75.0)	3 (37.5)	4 (50.0)	21 (45.7)
Injury, poisoning and procedural complications	0	0	1 (16.7)	1 (16.7)	2 (25.0)	0	0	4 (8.7)
Investigations	2 (66.7)	2 (28.6)	3 (50.0)	3 (50.0)	5 (62.5)	3 (37.5)	7 (87.5)	25 (54.3)
Metabolism and nutrition disorders	2 (66.7)	4 (57.1)	1 (16.7)	5 (83.3)	7 (87.5)	5 (62.5)	5 (62.5)	29 (63.0)
Musculoskeletal and connective tissue disorders	1 (33.3)	2 (28.6)	4 (66.7)	5 (83.3)	6 (75.0)	1 (12.5)	7 (87.5)	26 (56.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	2 (25.0)	0	2 (4.3)
Nervous system disorders	2 (66.7)	2 (28.6)	1 (16.7)	5 (83.3)	3 (37.5)	1 (12.5)	2 (25.0)	16 (34.8)
Psychiatric disorders	0	2 (28.6)	1 (16.7)	2 (33.3)	3 (37.5)	1 (12.5)	1 (12.5)	10 (21.7)
Renal and urinary disorders	0	1 (14.3)	0	1 (16.7)	1 (12.5)	2 (25.0)	2 (25.0)	7 (15.2)

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Primary system organ class	Initial cohort N=3	RAD 2.5 mg/wk BEZ 200 mg/bid N=7	RAD 5 mg/wk BEZ 50 mg/bid N=6	RAD 10 mg/wk BEZ 50 mg/bid N=6	RAD 2.5 mg/day BEZ 50 mg/bid N=8	RAD 5 mg/day BEZ 50 mg/bid N=8	RAD 2.5 mg/day BEZ 100 mg/bid N=8	All patients N=46
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Reproductive system and breast disorders	0	1 (14.3)	0	0	1 (12.5)	0	1 (12.5)	3 (6.5)
Respiratory, thoracic and mediastinal disorders	3 (100)	2 (28.6)	2 (33.3)	5 (83.3)	6 (75.0	3 (37.5)	6 (75.0)	27 (58.7)
Skin and subcutaneous tissue disorders	3 (100)	3 (42.9)	2 (33.3)	4 (66.7)	6 (75.0)	2 (25.0)	4 (50.0)	4 (52.2)
Vascular disorders	0	1 (14.3)	1 (16.7)	2 (33.3)	2 (25.0)	3 (37.5)	1 (12.5)	10 (21.7)

Primary system organ classes are presented alphabetically. Preferred terms are sorted within primary system organ class in descending frequency, as reported in the all patients column.

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 severity ratings for an AE while on a treatment, is only counted under the maximum rating.

Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized.

MedDRA version 17.1 and CTC grading version 4.03 (without CTCAE grade 5) were used for reporting.

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Adverse events, regardless of study treatment relationship, by preferred term, maximum grade and dose level (greater than 10% in All patients) (Safety set)

	Initial cohort N=3		RAD 2.5 mg/wk BEZ 200 mg/bid N=7		RAD 5 mg/wk BEZ 50 mg/bid N=6		RAD 10 mg/wk BEZ 50 mg/bid N=6		RAD 2.5 mg/day BEZ 50 mg/bid N=8		RAD 5 mg/day BEZ 50 mg/bid N=8		RAD 2.5 mg/day BEZ 100 mg/bid N=8		All patients N=46	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	3 (100)	1 (33.3)	6 (85.7)	4 (57.1)	6 (100)	3 (50.0)	6 (100)	5 (83.3)	8 (100)	7 (87.5)	8 (100)	7 (87.5)	8 (100)	5 (62.5)	45 (97.8)	32 (69.6)
Stomatitis	3 (100)	0	4 (57.1)	0	1 (16.7)	0	2 (33.3)	0	6 (75.0)	0	5 (62.5)	0	4 (50.0)	0	25 (54.3)	0
Diarrhoea	2 (66.7)	0	3 (42.9)	0	0	0	3 (50.0)	0	4 (50.0)	0	3 (37.5)	1 (12.5)	4 (50.0)	0	19 (41.3)	1 (2.2)
Nausea	2 (66.7)	0	3 (42.9)	0	3 (50.0)	0	2 (33.3)	0	2 (25.0)	0	3 (37.5)	1 (12.5)	3 (37.5)	0	18 (39.1)	1 (2.2)
Decreased appetite	0	0	2 (28.6)	1 (14.3)	1 (16.7)	0	4 (66.7)	0	3 (37.5)	0	3 (37.5)	0	4 (50.0)	0	17 (37.0)	1 (2.2)
Dyspnoea	0	0	1 (14.3)	0	2 (33.3)	2 (33.3)	2 (33.3)	0	4 (50.0)	1 (12.5)	1 (12.5)	0	3 (37.5)	0	13 (28.3)	3 (6.5)
Fatigue	1 (33.3)	0	1 (14.3)	0	3 (50.0)	0	2 (33.3)	0	2 (25.0)	0	1 (12.5)	0	3 (37.5)	0	13 (28.3)	0
Vomiting	1 (33.3)	0	2 (28.6)	0	2 (33.3)	0	3 (50.0)	0	2 (25.0)	0	2 (25.0)	1 (12.5)	1 (12.5)	0	13 (28.3)	1 (2.2)
Asthenia	0	0	3 (42.9)	1 (14.3)	0	0	3 (50.0)	0	3 (37.5)	0	1 (12.5)	0	2 (25.0)	1 (12.5)	12 (26.1)	2 (4.3)
Back pain	1 (33.3)	0	0	0	2 (33.3)	0	4 (66.7)	1 (16.7)	2 (25.0)	0	1 (12.5)	1 (12.5)	1 (12.5)	0	11 (23.9)	2 (4.3)

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	Initial cohort N=3		RAD 2.5 mg/wk BEZ 200 mg/bid N=7		RAD 5 mg/wk BEZ 50 mg/bid N=6		RAD 10 mg/wk BEZ 50 mg/bid N=6		RAD 2.5 mg/day BEZ 50 mg/bid N=8		RAD 5 mg/day BEZ 50 mg/bid N=8		RAD 2.5 mg/day BEZ 100 mg/bid N=8		All patients N=46	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hyperglycaemia	1 (33.3)	0	2 (28.6)	0	0	0	2 (33.3)	0	3 (37.5)	0	1 (12.5)	0	2 (25.0)	0	11 (23.9)	0
Pyrexia	0	0	1 (14.3)	0	2 (33.3)	0	2 (33.3)	0	1 (12.5)	1 (12.5)	4 (50.0)	0	1 (12.5)	0	11 (23.9)	1 (2.2)
Abdominal pain	1 (33.3)	0	1 (14.3)	0	1 (16.7)	0	3 (50.0)	1 (16.7)	2 (25.0)	0	1 (12.5)	0	1 (12.5)	0	10 (21.7)	1 (2.2)
Aspartate aminotransferase increased	1 (33.3)	0	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (12.5)	1 (12.5)	2 (25.0)	1 (12.5)	3 (37.5)	1 (12.5)	10 (21.7)	4 (8.7)
Blood alkaline phosphatase increased	1 (33.3)	0	1 (14.3)	0	1 (16.7)	1 (16.7)	2 (33.3)	0	2 (25.0)	1 (12.5)	1 (12.5)	0	2 (25.0)	0	10 (21.7)	2 (4.3)
Constipation	1 (33.3)	0	0	0	3 (50.0)	0	2 (33.3)	0	2 (25.0)	0	0	0	2 (25.0)	0	10 (21.7)	0
Cough	1 (33.3)	0	1 (14.3)	0	1 (16.7)	0	3 (50.0)	0	1 (12.5)	0	1 (12.5)	0	2 (25.0)	0	10 (21.7)	0
Gamma-glutamyltransferase increased	1 (33.3)	1 (33.3)	1 (14.3)	1 (14.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	0	0	1 (12.5)	1 (12.5)	3 (37.5)	0	10 (21.7)	7 (15.2)
Dry mouth	0	0	1 (14.3)	0	0	0	3 (50.0)	0	0	0	3 (37.5)	0	1 (12.5)	0	8 (17.4)	0
Alanine aminotransferase increased	1 (33.3)	0	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (12.5)	0	1 (12.5)	1 (12.5)	1 (12.5)	0	7 (15.2)	2 (4.3)
Anaemia	0	0	1 (14.3)	0	0	0	0	0	1 (12.5)	1 (12.5)	3 (37.5)	2 (25.0)	2 (25.0)	0	7 (15.2)	3 (6.5)

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	Initial cohort N=3		RAD 2.5 mg/wk BEZ 200 mg/bid N=7		RAD 5 mg/wk BEZ 50 mg/bid N=6		RAD 10 mg/wk BEZ 50 mg/bid N=6		RAD 2.5 mg/day BEZ 50 mg/bid N=8		RAD 5 mg/day BEZ 50 mg/bid N=8		RAD 2.5 mg/day BEZ 100 mg/bid N=8		All patients N=46	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Blood creatinine increased	0	0	1 (14.3)	0	1 (16.7)	0	2 (33.3)	0	2 (25.0)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	7 (15.2)	2 (4.3)
Headache	1 (33.3)	0	1 (14.3)	0	0	0	3 (50.0)	0	1 (12.5)	0	0	0	1 (12.5)	0	7 (15.2)	0
Pruritus	1 (33.3)	0	1 (14.3)	0	0	0	2 (33.3)	0	1 (12.5)	0	1 (12.5)	0	1 (12.5)	0	7 (15.2)	0
Rash	1 (33.3)	0	2 (28.6)	1 (14.3)	0	0	0	0	2 (25.0)	0	1 (12.5)	0	1 (12.5)	0	7 (15.2)	1 (2.2)
Thrombocytopenia	3 (100)	0	3 (42.9)	0	0	0	0	0	0	0	0	0	1 (12.5)	1 (12.5)	7 (15.2)	1 (2.2)
Abdominal pain upper	1 (33.3)	0	2 (28.6)	0	0	0	2 (33.3)	1 (16.7)	0	0	0	0	1 (12.5)	0	6 (13.0)	1 (2.2)
Dry skin	1 (33.3)	0	1 (14.3)	0	0	0	1 (16.7)	0	2 (25.0)	0	0	0	1 (12.5)	0	6 (13.0)	0
Abdominal distension	0	0	0	0	0	0	2 (33.3)	0	1 (12.5)	0	1 (12.5)	0	1 (12.5)	0	5 (10.9)	0
Dizziness	0	0	1 (14.3)	0	1 (16.7)	0	2 (33.3)	0	0	0	1 (12.5)	0	0	0	5 (10.9)	0
Hypertriglyceridaemia	0	0	1 (14.3)	0	0	0	2 (33.3)	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)	0	5 (10.9)	1 (2.2)
Hypokalaemia	0	0	0	0	0	0	0	0	2 (25.0)	1 (12.5)	2 (25.0)	1 (12.5)	1 (12.5)	0	5 (10.9)	2 (4.3)
Hypomagnesaemia	0	0	0	0	0	0	1 (16.7)	0	1 (12.5)	0	1 (12.5)	0	2 (25.0)	0	5 (10.9)	0

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	Initial cohort N=3		RAD 2.5 mg/wk BEZ 200 mg/bid N=7		RAD 5 mg/wk BEZ 50 mg/bid N=6		RAD 10 mg/wk BEZ 50 mg/bid N=6		RAD 2.5 mg/day BEZ 50 mg/bid N=8		RAD 5 mg/day BEZ 50 mg/bid N=8		RAD 2.5 mg/day BEZ 100 mg/bid N=8		All patients N=46	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Lipase increased	1 (33.3)	0	0	0	0	0	0	0	2 (25.0)	0	1 (12.5)	1 (12.5)	1 (12.5)	0	5 (10.9)	1 (2.2)
Musculoskeletal pain	0	0	1 (14.3)	0	1 (16.7)	0	2 (33.3)	0	1 (12.5)	0	0	0	0	0	5 (10.9)	0
Oedema peripheral	0	0	1 (14.3)	0	0	0	0	0	2 (25.0)	0	1 (12.5)	0	1 (12.5)	0	5 (10.9)	0
Pain in extremity	1 (33.3)	0	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0	0	0	0	0	1 (12.5)	0	5 (10.9)	1 (2.2)
Urinary tract infection	0	0	1 (14.3)	0	2 (33.3)	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (12.5)	0	5 (10.9)	1 (2.2)

Preferred terms are sorted in descending frequency of all grades column, as reported in the All patients column.
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 is counted only once in the total row.
MedDRA Version 17.1 has been used for reporting

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Patients who died, had grade 3/4 AEs, SAEs, AEs leading to discontinuation or other significant AEs, by dose level (Safety set)

	Initial cohort N=3		RAD 2.5 mg/wk BEZ 200 mg/bid N=7		RAD 5 mg/wk BEZ 50 mg/bid N=6		RAD 10 mg/wk BEZ 50 mg/bid N=6		RAD 2.5 mg/day BEZ 50 mg/bid N=8		RAD 5 mg/day BEZ 50 mg/bid N=8		RAD 2.5 mg/day BEZ 100 mg/bid N=8		All patients N=46	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
All deaths[1]	3 (100.0)		4 (57.1)		5 (83.3)		0 (0.0)		5 (62.5)		5 (62.5)		4 (50.0)		26 (56.5)	
On-treatment deaths[2]	0 (0.0)		0 (0.0)		1 (16.7)		0 (0.0)		2 (25.0)		2 (25.0)		0 (0.0)		5 (10.9)	
Adverse events	3 (100.0)	1 (33.3)	6 (85.7)	4 (57.1)	6 (100.0)	3 (50.0)	6 (100.0)	5 (83.3)	8 (100.0)	7 (87.5)	8 (100.0)	7 (87.5)	8 (100.0)	5 (62.5)	45 (97.8)	32 (69.6)
Suspected to be drug-related	3 (100.0)	0 (0.0)	5 (71.4)	4 (57.1)	5 (83.3)	1 (16.7)	5 (83.3)	1 (16.7)	7 (87.5)	2 (25.0)	6 (75.0)	3 (37.5)	7 (87.5)	1 (12.5)	38 (82.6)	12 (26.1)
Serious adverse events	0 (0.0)	0 (0.0)	2 (28.6)	2 (28.6)	4 (66.7)	2 (33.3)	3 (50.0)	3 (50.0)	5 (62.5)	5 (62.5)	5 (62.5)	5 (62.5)	4 (50.0)	4 (50.0)	23 (50.0)	21 (45.7)
Suspected to be drug-related	0 (0.0)	0 (0.0)	2 (28.6)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (12.5)	2 (25.0)	2 (25.0)	0 (0.0)	0 (0.0)	5 (10.9)	5 (10.9)
AEs leading to discontinuation	1 (33.3)	0 (0.0)	4 (57.1)	3 (42.9)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	2 (25.0)	0 (0.0)	0 (0.0)	9 (19.6)	5 (10.9)
Suspected to be drug-related	1 (33.3)	0 (0.0)	4 (57.1)	3 (42.9)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	2 (25.0)	0 (0.0)	0 (0.0)	9 (19.6)	5 (10.9)

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	Initial cohort N=3		RAD 2.5 mg/wk BEZ 200 mg/bid N=7		RAD 5 mg/wk BEZ 50 mg/bid N=6		RAD 10 mg/wk BEZ 50 mg/bid N=6		RAD 2.5 mg/day BEZ 50 mg/bid N=8		RAD 5 mg/day BEZ 50 mg/bid N=8		RAD 2.5 mg/day BEZ 100 mg/bid N=8		All patients N=46	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
AEs requiring dose interruption and/or change	0 (0.0)	0 (0.0)	1 (14.3)	1 (14.3)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	5 (62.5)	4 (50.0)	3 (37.5)	2 (25.0)	6 (75.0)	3 (37.5)	20 (43.5)	15 (32.6)
Suspected to be drug-related	0 (0.0)	0 (0.0)	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	4 (50.0)	1 (12.5)	9 (19.6)	4 (8.7)
AEs requiring additional therapy	3 (100.0)	0 (0.0)	5 (71.4)	3 (42.9)	6 (100.0)	2 (33.3)	6 (100.0)	3 (50.0)	8 (100.0)	7 (87.5)	8 (100.0)	6 (75.0)	8 (100.0)	3 (37.5)	44 (95.7)	24 (52.2)
Suspected to be drug-related	3 (100.0)	0 (0.0)	5 (71.4)	3 (42.9)	3 (50.0)	0 (0.0)	4 (66.7)	0 (0.0)	7 (87.5)	2 (25.0)	4 (50.0)	2 (25.0)	7 (87.5)	0 (0.0)	33 (71.7)	7 (15.2)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[1]All deaths including those >30 days after end of treatment.

[2]Deaths occurring >30 days after end of treatment are not included.

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

Other Relevant Findings

Summary of statistical analysis of PK parameters of everolimus after the 2.5 mg weekly dose (PAS)

PK parameter (unit)	Initial cohort N=3
Cycle 1 Day 1	
AUClast (h*ng/mL), n = 3	107.51 (35.98)
CL/F (L/h), n = 1	15.47
Cmax (ng/mL), n = 3	9.14 (41.98)
Tmax (h), n = 3	1.02 (1.0; 2.0)
Cycle 2 Day 1	
AUClast (h*ng/mL), n = 2	125.58 (60.17)
CL/F (L/h), n = 1	12.41
Cmax (ng/mL), n = 2	13.45 (21.18)
Tmax (h), n = 2	1.50 (1.0; 2.0)

Values are median (range) for Tmax, and geometric mean (CV%) for all other parameters.

Summary of statistical analysis of PK parameters of BEZ235, by actual dose level (PAS)

PK parameter (unit)	RAD (2.5mg/wk) + BEZ (200mg/bid) N=3 n (%)	RAD (5mg/wk) + BEZ (50mg/bid) N=4 n (%)	RAD (10mg/wk) + BEZ (50mg/bid) N=4 n (%)	RAD (2.5mg/day) + BEZ (50mg/bid) N=8 n (%)	RAD (5mg/day) + BEZ (50mg/bid) N=6 n (%)	RAD (2.5mg/day) + BEZ (100mg/bid) N=7 n (%)
AUC (h*ng/mL)	12671.25 (98.48)	160.85 (67.77)	85.78 (85.35)	238.58 (101.9)	185.19 (40.17)	392.17 (242.1)
Cmax (ng/mL)	1613.32 (61.65)	47.64 (71.13)	25.78 (49.58)	63.84 (58.26)	40.96 (45.07)	90.70 (194.7)
Tmax (h)	1.63 (1.3; 2.0)	1.03 (1.0; 2.0)	1.50 (0.9; 4.0)	1.00 (1.0; 4.0)	1.00 (1.0; 2.1)	2.00 (1.0; 4.0)

Values are median (range) for Tmax, and geometric mean (CV%) for all other parameters.

Conclusion:

The data from this study suggested that the combination of RAD001 and BEZ235 even though tolerable, failed to corroborate the strong synergistic activity on tumor cell inhibition demonstrated in pre-clinical studies.

- The study met one of its primary objectives, and RAD001 5 mg once daily in combination BEZ235 50 mg twice daily when administered orally was declared as MTD in patients with advanced solid tumors.
- The safety profile of RAD001 in combination with BEZ235 was generally consistent with that observed in earlier single agent clinical studies of RAD001 and BEZ235.

- No signs of preliminary anti-tumor activity were observed in the studied patient population.

Date of Clinical Trial Report

11-Dec-2015