Sponsor:

Novartis

Generic Drug Name

RAD001

Trial Indication

Advanced gastric cancer

Protocol Number

CRAD001R2301

Protocol Title

A randomized, double-blind, multi-center phase III study comparing everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in patients with advanced gastric cancer after progression on prior systemic chemotherapy

Clinical Trial Phase

III

Phase of Drug Development

III

Study Start/End Dates

07 Jul 2009 (first patient first visit) to 30-Jan-2014 (last patient last visit)

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was a phase III, double blind, randomized, multi-centered study comparing treatment of everolimus + BSC with matching placebo + BSC in patients with AGC who had progressed after one or two prior chemotherapy lines. Patients were randomized to receive either everolimus or placebo using an Interactive voice and web Response System (IXRS). Randomization was unbalanced, 2:1 ratio in favor of everolimus. Further, patients were stratified by number of prior chemotherapy lines for advanced disease (1 versus 2) and region (Asia versus ROW). Asia included China, Hong Kong, Japan, Korea, Taiwan and Thailand.

Rest of the world included Europe (Belgium, France, Germany, Great Britain, Italy, Netherlands, and Spain), and others (Australia, Canada, Peru, Argentina, New Zealand, Russia, Israel, Mexico, Columbia, and US). Study treatment continued until disease progression or intolerable toxicity. After treatment discontinuation, patients continued to be followed for survival every three months or until study completion. Further treatment after disease progression was at the Investigator's discretion.

Centers

China (14), Hong Kong (1), Japan (14), Korea (7), Taiwan (5), Thailand (3), Belgium (4), France (14), Germany (4), Great Britain (8), Italy (5), Netherlands (1), Spain (1), Australia (9), Canada (8), Peru (3), Argentina (4), New Zealand (1), Russia (2), Israel (5), Mexico (2), Columbia (1), and US (17).

Publication

Ohtsu A, Ajani JA, Bai YX, et al, Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J. Clin. Oncol. 2013; 31(31):3935-43.

Objectives:

Primary objective: To compare overall survival (OS) between everolimus + best supportive care (BSC) and placebo + BSC in patients with advanced gastric cancer (AGC), after progression on prior systemic chemotherapy.

Secondary objectives:

- To compare progression free survival (PFS) between everolimus + BSC and placebo + BSC.
- To compare quality of life between everolimus + BSC and placebo + BSC.
- In the everolimus + BSC arm, to evaluate the overall response rate (ORR) defined as the proportion of patients with best overall response (OR) of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST).
- To compare time to deterioration of Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) between everolimus + BSC and placebo + BSC.
- To further characterize the safety and tolerability of everolimus in this population.
- To compare C_{min} and C_{max} between patients with and without gastrectomy.
- To compare exposure levels (C_{min} and C_{max}) of Asia versus Rest of World (ROW) patients with gastric cancer.

Test Product, Dose, and Mode of Administration

Oral tablets of everolimus 10 mg once each morning.

Statistical Methods

The primary efficacy objective was to compare OS between everolimus + BSC and placebo + BSC. The primary endpoint, OS, is defined as the time from date of randomization to the date of death due to any cause. If at the analysis cut-off date a patient was not known to have died, survival was censored at the date of the last contact. The primary analysis was a comparison of OS between the treatment groups in the full analysis set (FAS) consisting of all randomized patients. The statistical hypotheses were: H_0: $S_{everolimus(t)} = S_{Placebo(t)}$ versus H_1: $S_{everolimus(t)} > S_{Placebo(t)}$, where. $S_{everolimus(t)}$ and $S_{Placebo(t)}$ are the survival functions in Everolimus + BSC and placebo + BSC groups, respectively. The null hypothesis was tested with the one-sided log-rank test using an overall type I error rate of 2.5%. The test was stratified by the randomization stratification factors: number of prior chemotherapy lines for advanced disease (one line versus two lines) and geographical region (Asia versus ROW). OS was presented descriptively for each treatment arm using a Kaplan-Meier curve. The hazard ratio (HR) with the two-sided 95% confidence interval (CI) was estimated from a Cox proportional hazard model.

The secondary efficacy objectives were analyzed using a hierarchical testing strategy:

- PFS was to be compared between the two treatment arms provided the primary endpoint, OS, was statistically significant.
- If PFS was statistically significant, then the time to definitive deterioration from baseline in the ECOG-PS scale was to be compared between the two treatment groups.
- If the time to definitive deterioration in the ECOG PS was statistically significant, then the time to definitive 5% deterioration from baseline in the global health status/quality of life scale of the QLQ-C30 questionnaire was to be statistically analyzed.
- If the time to definitive deterioration in the global health status/quality of life scale of the QLQC30 was statistically significant, then the time to definitive 5% deterioration from baseline in the three QLQ-C30 domain scores of physical functioning, social functioning, and emotional functioning were to be successively compared between the two treatment groups (using the same hierarchical approach).

Study Population: Key Inclusion/Exclusion Criteria

- Male or female patients ≥ 18 years with histologically or cytologically confirmed advanced gastric cancer who have progressed after 1 or 2 prior systemic chemotherapy.
- Patients with advanced gastro-esophageal junction adenocarcinoma, of which the majority involved the stomach, as assessed by the Investigator.

- Documented progression after 1 or 2 prior systemic chemotherapy lines for advanced disease and ECOG PS of δ 2.

Note: One line of prior systemic therapy in the advanced disease setting consisted of one or more drugs given for ≥ 21 days. Prior adjuvant/neoadjuvant therapy was allowed. If recurrence occurred during adjuvant/neoadjuvant therapy or ≤ 24 weeks after adjuvant/neoadjuvant therapy completion, the adjuvant/neoadjuvant therapy was considered as one prior line of systemic chemotherapy for advanced disease. Prior treatment with chemotherapy combined with targeted agents was permitted.

Patients with the following laboratory parameters:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500/mm^3).
- Platelets ≥ 100 x 10^9/L (≥ 100,000/mm^3).
- Hemoglobin ≥ 8 g/dL (≥ 4.9 mmol/L).
- Prothrombin International normalized ratio (INR) ≤ 2.0.
- Serum creatinine ≤ 2 x upper limit of normal (ULN).
- Adequate liver function as defined as:
- If there was no evidence of liver metastases: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN.
    - If liver metastases were documented: ALT and AST ≤ 5.0 x ULN.
- Serum bilirubin ≤ 1.5 x ULN.
- Total serum calcium (corrected for serum albumin) or ionized calcium ≥ Lower limit of normal (LLN).
- Serum potassium ≥ LLN.

Note: Serum calcium, potassium, magnesium, and phosphate levels were to be above the LLN prior to patients enrolling on the study. Supplements may have been given prior to enrollment to correct values.

Women of childbearing potential must have had a negative serum pregnancy test within 7 days of the first administration of study treatments and must have been willing to use adequate methods of contraception during the study and for 8 weeks after last study drug administration.

Participant Flow Table

Patient disposition (FAS)

Disposition reason	Everolimus 10 mg/day N = 439 n (%)	Placebo N = 217 n (%)

Disposition reason	Everolimus 10 mg/day N = 439 n (%)	Placebo N = 217 n (%)
Patients still on treatment	11 (2.5)	0
Discontinued study treatment[1]	428 (97.5)	217 (100)
Adverse event(s)	94 (21.4)	34 (15.7)
Abnormal laboratory value(s)	1 (0.2)	0
Subject withdrew consent	20 (4.6)	7 (3.2)
Lost to follow-up	2 (0.5)	1 (0.5)
Administrative problems	2 (0.5)	0
Death	16 (3.6)	5 (2.3)
Disease progression	292 (66.5)	169 (77.9)
Protocol deviation	1 (0.2)	1 (0.5)

[1] Per 'End of Treatment' page. All percentages related to discontinuation of treatment use N as the denominator. Screened patients = 872

Baseline Characteristics

Demographic characteristics by treatment group (FAS).

	Everolimus 10 mg/day N = 439	Placebo N = 217	All patients N = 656
Age (years)			
n	439	217	656
Mean (standard deviation)	60.3 (11.59)	60.8 (11.61)	60.4 (11.59)
Median	62.0	62.0	62.0
Range	(20.0 – 86.0)	(26.0 – 88.0)	(20.0 – 88.0)
Age category (years), n (%)			
< 65	260 (59.2)	129 (59.4)	389 (59.3)
≥ 65	179 (40.8)	88 (40.6)	267 (40.7)
Sex, n (%)			
Male	322 (73.3)	161 (74.2)	483 (73.6)
Female	117 (26.7)	56 (25.8)	173 (26.4)
Race, n (%)			
Caucasian	166 (37.8)	75 (34.6)	241 (36.7)
Black	3 (0.7)	1 (0.5)	4 (0.6)
Asian	251 (57.2)	126 (58.1)	377 (57.5)
Native American	0	1 (0.5)	1 (0.2)
Other	19 (4.3)	14 (6.5)	33 (5.0)

Summary of Efficacy from primary CSR

Primary Outcome Result

Analysis of overall survival using Kaplan-Meier method and Cox PH model by treatment (FAS)

	Everolimus 10 mg/day N = 439	Placebo N = 217	p-value[1]	Everolimus/Placebo[2] Hazard ratio [95% CI]
No. of deaths	352 (80.2)	180 (82.9)	0.1244	0.90 [0.75,1.08]
No. of censored	87 (19.8)	37 (17.1)		
Kaplan-Meier estimates [95% CI] at:				
3 months	70.4 [65.8;74.4]	69.3 [62.7;75.0]		
6 months	45.8 [41.1;50.5]	39.2 [32.7;45.7]		
9 months	30.5 [26.2;35.0]	26.6 [20.8;32.7]		
12 months	19.7 [15.8;23.9]	19.9 [14.6;25.8]		
Median OS [95% CI] months	5.39 [4.80;6.01]	4.34 [3.81;5.49]		

[1]p-value is obtained from the one-sided stratified log-rank test.
[2]Hazard ratio is obtained from stratified Cox regression model.

Secondary Outcome Results

Analysis of progression free survival using Kaplan-Meier method and Cox PH model (FAS)

	Everolimus 10 mg/day N = 439	Placebo N = 217	p-value[1]	Everolimus/Placebo[2] Hazard ratio [95% CI]
No. of PFS events, n (%)	386 (87.9)	206 (94.9)	< 0.0001	0.66 [0.56,0.78]
Progression	315 (71.8)	174 (80.2)		
Death	71 (16.2)	32 (14.7)		
No. of censored	53 (12.1)	11 (5.1)		
Kaplan-Meier estimates [95% CI] at :				
3 months	30.0 [25.6;34.6]	13.5 [9.3;18.5]		
6 months	12.0 [9.0;15.4]	4.3 [2.1;7.7]		
Median PFS [95% CI] months	1.68 [1.51;1.94]	1.41 [1.38;1.45]		

[1]P-value is obtained from the one-sided stratified log-rank test.
[2]Hazard ratio is obtained from stratified Cox regression model.

Analysis of time to definitive deterioration of EORTC QLQ-C30 scores using Kaplan-Meier method and Cox PH model (FAS)

	Everolimus 10 mg/day N = 439	Placebo N = 217	p-value[1]	Everolimus/Placebo[2] Hazard ratio [95% CI]
Definitive deterioration in the QL score by at least 5 % compared to baseline				
No. of events, n (%)	295 (67.2)	144 (66.4)	0.0936	0.84 [0.69, 1.03]
No. of censored, n (%)	144 (32.8)	73 (33.6)		
Median time to event [95% CI] months	1.51 [1.28;1.84]	1.45 [1.05;1.68]		
Definitive deterioration in the PF score by at least 5 % compared to baseline				
No. of events, n (%)	311 (70.8)	149 (68.7)	0.5711	0.95 [0.78, 1.15]
No. of censored, n (%)	128 (29.2)	68 (31.3)		
Median time to event [95% CI] months	1.35 [1.12;1.54]	1.15 [1.02;1.64]		
Definitive deterioration in the SF score by at least 5 % compared to baseline				
No. of events, n (%)	242 (55.1)	125 (57.6)	0.2108	0.87 [0.70, 1.09]
No. of censored, n (%)	197 (44.9)	92 (42.4)		
Median time to event [95% CI] months	1.87 [1.84;2.30]	1.87 [1.64;2.46]		
Definitive deterioration in the EF score by at least 5 % compared to baseline				
No. of events	278 (63.3)	139 (64.1)	0.0735	0.83 [0.67, 1.02]
No. of censored	161 (36.7)	78 (35.9)		
Median time to event [95% CI] months	1.84 [1.61;2.10]	1.71 [1.41;1.87]		

QL = Global health status/quality of life sub-scale; PF = Physical Functioning; SF = Social Functioning; EF = Emotional Functioning
[1]p-value derived from stratified two-sided log-rank test
[2]Hazard ratio is obtained from stratified Cox regression model.

Analysis of time to definitive deterioration of ECOG PS score using Kaplan-Meier method and Cox PH model (FAS)

	Everolimus 10 mg/day N = 439	Placebo N = 217	p-value[1]	Everolimus/Placebo[2] Hazard ratio [95% CI]
Definitive worsening in the ECOG PS by at least one category compared to baseline				
No. of events, n (%)	250 (56.9)	109 (50.2)	0.6925	0.96 [0.76, 1.20]
No. of censored, n (%)	189 (43.1)	108 (49.8)		
Median time to event [95% CI] months	2.30 [1.97;2.79]	2.23 [1.87;2.92]		

[1]p-value derived from stratified two-sided log-rank test
[2]Hazard ratio is obtained from stratified Cox regression model.

Best overall response as per investigator (FAS)

Best overall response	Everolimus 10mg/d N=439 n (%)	Placebo N=217 n (%)
Patients with measurable disease [1]	379 (86.3)	191 (88.0)
Complete Response (CR)	1 (0.3)	0 (0.0)
Partial Response (PR)	16 (4.2)	4 (2.1)
Stable Disease (SD)	147 (38.8)	38 (19.9)
Progressive Disease (PD)	157 (41.4)	119 (62.3)
Unknown	58 (15.3)	30 (15.7)
Overall response rate ORR (CR or PR)	17 (4.5)	4 (2.1)
95% CI for ORR[2]	[2.6; 7.1]	[0.6; 5.3]
Disease control rate DCR (CR or PR or SD)	164 (43.3)	42 (22.0)
95% CI for DCR[2]	[38.2; 48.4]	[16.3; 28.5]

Summary of Pharmacokinetics from primary CSR

Everolimus steady state concentrations (ng/mL) by time point and actual everolimus dose at sample time (Safety set)

	Everolimus 10 mg/day	Everolimus 5 mg/day
Pre-dose		
n	201	18
Mean	16.143	10.498
SD	10.7723	6.1432
Median	13.800	9.265
Min − Max	0.00 − 81.80	2.08 − 24.30
CV% mean	66.73	58.52
Geometric mean	13.62	8.81
CV% Geometric. mean	66.57	70.72
C1h		
n	212	16
Mean	67.538	35.558
SD	38.3040	27.8619
Median	63.350	31.600
Min − Max	6.39 − 269.00	5.50 − 98.90
CV% mean	56.71	78.36
Geometric mean	56.45	25.60
CV% Geometric. mean	71.26	109.47

	Everolimus 10 mg/day	Everolimus 5 mg/day
C2h		
n	218	16
Mean	53.562	29.469
SD	29.2049	19.4638
Median	48.250	25.650
Min − Max	12.70 − 282.00	6.30 − 81.20
CV% mean	54.53	66.05
Geometric mean	47.76	23.88
CV% Geometric. mean	49.90	78.60
C_{max}		
n	218	16
Mean	72.775	37.269
SD	36.5435	27.2086
Median	67.450	34.700
Min − Max	15.30 − 282.00	6.30 − 98.90
CV% mean	50.21	73.01
Geometric mean	64.00	28.17
CV% Geometric. mean	56.53	97.02

C_{max} = max(C1h,C2h).
Pre-dose concentrations are summarized by the leading dose administered (on the day prior to blood sampling). C1h, C2h and Cmax concentrations are summarized by the actual dose administered on the blood sampling day. Only valid samples are included.

Summary statistics of C_{min} and C_{max} in patients with and without gastrectomy by region

By region	Gastrectomy	Everolimus 10 mg/ day C_{min} (ng/mL)	Everolimus 10 mg/ day C_{max} (ng/mL)	Everolimus 5 mg/ day C_{min} (ng/mL)	Everolimus 5 mg/ day C_{max} (ng/mL)
All patients	Yes	15.5 ± 10.2 (n = 118)	79.1 ± 36.4 (n = 125)	11.2 ± 6.7 (n = 10)	41.1 ± 18.1 (n = 9)
	No	17.1 ± 11.5 (n = 83)	64.3 ± 35.1 (n = 93)	9. 7 ± 5.6 (n = 8)	32.3 ± 36.9 (n = 7)
All patients – sensitivity analysis[a]	Yes	15.5 ± 11.6 (n = 81)	77.0 ± 38.4 (n = 85)	7.9 ± 2.0 (n = 3)	32.8 ± 16.1 (n = 3)
	No	15.7 ± 9.3 (n = 52)	56.9 ± 28.3 (n = 57)	8.6 ± 7.0 (n = 4)	34.5 ±43.0 (n = 4)
Patients in Asia	Yes	15.1 ± 8.0 (n = 78)	78.7 ± 31.9 (n = 82)	11.6 ± 5.6 (n = 6)	46.1 ± 23.5 (n = 5)
	No	19.6 ± 11.3 (n = 49)	65.1 ± 36.3 (n = 50)	8.0 ± 4.3 (n = 5)	23.0 ± 27.0 (n = 5)
Patients in Rest of the World	Yes	16.3 ± 13.7 (n = 40)	79.8 ± 44.2 (n = 43)	10.6 ± 9.1 (n = 4)	34.8 ± 6.2 (n = 4)

By region	Gastrectomy	Everolimus 10 mg/ day C_{min} (ng/mL)	Everolimus 10 mg/ day C_{max} (ng/mL)	Everolimus 5 mg/ day C_{min} (ng/mL)	Everolimus 5 mg/ day C_{max} (ng/mL)
	No	13.5 ± 10.9 (n = 34)	63.3 ± 34.0 (n = 43)	12.5 ± 7.4 (n = 3)	55.6 ± 61.2 (n = 2)

[a] PK samples not associated with co-administration of CYP3A4/PgP inhibitors and/or inducers.
Summary statistics are mean ± SD.

Summary statistics of C_{min} and C_{max} with and without co-administration of CYP3A4/PgP substrate, inhibitor, or inducer

	Everolimus 10 mg/ day C_{min} (ng/mL)	Everolimus 10 mg/ day C_{max} (ng/mL)	Everolimus 5 mg/ day C_{min} (ng/mL)	Everolimus 5 mg/ day C_{max} (ng/mL)
Sensitivity analysis[a]	15.6 ± 10.7 (n = 133)	68.9 ± 36.0 (n = 142)	8.3 ± 5.1 (n = 7)	33.8 ± 31.8 (n = 7)
Substrate of CYP3A4 and/or PgP	16.4 ± 10.3 (n = 132)	74.0 ± 35.3 (n = 151)	10.6 ± 6.4 (n = 16)	36.5 ± 29.1 (n = 14)
Weak inhibitor of CYP3A4	19.7 ± 13.4 (n = 21)	79.2 ± 39.6 (n = 22)	7.3 ± 2.9 (n = 5)	21.9 ± 16.3 (n = 4)
Moderate inhibitor of CYP3A4	19.6 ± 19.8 (n = 7)	79.8 ± 54.1 (n = 8)	18.0 ± 9.0 (n = 2)	41.9 (n = 1)
Strong inhibitor of CYP3A4	28.2 ± 22.4 (n = 4)	94.7 ± 24.6 (n = 4)	--	--
Inducer of CYP3A4 and/or PgP	14.4 ± 6.8 (n = 44)	77.3 ± 35.2 (n = 50)	11.3 ± 5.3 (n = 9)	39.5 ± 28.5 (n = 7)
Inhibitor of PgP	26.2 ± 14.4 (n = 9)	92.5 ± 44.5 (n = 11)	24.3 (n = 1)	41.9 (n = 1)

[a] PK samples not associated with co-administration of CYP3A4/PgP inhibitors and/or inducers.
Summary statistics are mean ± SD.

Summary of Safety

Safety Results from primary CSR:

Adverse events regardless of study drug relationship by primary system organ class (Safety set)

System organ class	Everolimus 10 mg/day N = 437 n (%)	Placebo N = 215 n (%)
Any system organ class	**433 (99.1)**	**208 (96.7)**
Gastrointestinal disorders	378 (86.5)	164 (76.3)
General disorders and administration site conditions	298 (68.2)	118 (54.9)
Metabolism and nutrition disorders	285 (65.2)	104 (48.4)

System organ class	Everolimus 10 mg/day N = 437 n (%)	Placebo N = 215 n (%)
Blood and lymphatic system disorders	207 (47.4)	50 (23.3)
Skin and subcutaneous tissue disorders	177 (40.5)	41 (19.1)
Respiratory, thoracic and mediastinal disorders	165 (37.8)	56 (26.0)
Investigations	157 (35.9)	45 (20.9)
Infections and infestations	112 (25.6)	41 (19.1)
Musculoskeletal and connective tissue disorders	98 (22.4)	45 (20.9)
Nervous system disorders	97 (22.2)	37 (17.2)
Psychiatric disorders	68 (15.6)	41 (19.1)
Renal and urinary disorders	54 (12.4)	23 (10.7)
Vascular disorders	45 (10.3)	15 (7.0)
Hepatobiliary disorders	41 (9.4)	19 (8.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	24 (5.5)	14 (6.5)
Injury, poisoning and procedural complications	22 (5.0)	7 (3.3)
Cardiac disorders	21 (4.8)	11 (5.1)
Eye disorders	12 (2.7)	6 (2.8)
Ear and labyrinth disorders	8 (1.8)	4 (1.9)
Reproductive system and breast disorders	5 (1.1)	3 (1.4)
Immune system disorders	4 (0.9)	1 (0.5)
Congenital, familial and genetic disorders	2 (0.5)	1 (0.5)

System organ classes are sorted by descending frequency in the everolimus 10 mg/day group.
A patient with multiple adverse events within a system organ class is counted only once.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Adverse events regardless of study drug relationship (≥ 5% in everolimus arm) by preferred term (Safety set)

Preferred term	Everolimus 10 mg/day N = 437 n (%)	Placebo N = 215 n (%)
Any preferred term	**433 (99.1)**	**208 (96.7)**
Decreased appetite	208 (47.6)	78 (36.3)
Stomatitis	174 (39.8)	23 (10.7)
Fatigue	150 (34.3)	65 (30.2)
Nausea	132 (30.2)	69 (32.1)
Diarrhea	115 (26.3)	33 (15.3)
Anemia	114 (26.1)	42 (19.5)
Abdominal pain	107 (24.5)	57 (26.5)
Vomiting	107 (24.5)	62 (28.8)

Preferred term	Everolimus 10 mg/day N = 437 n (%)	Placebo N = 215 n (%)
Constipation	91 (20.8)	42 (19.5)
Rash	87 (19.9)	19 (8.8)
Weight decreased	86 (19.7)	19 (8.8)
Pyrexia	81 (18.5)	24 (11.2)
Thrombocytopenia	80 (18.3)	5 (2.3)
Asthenia	70 (16.0)	22 (10.2)
Dyspnea	61 (14.0)	23 (10.7)
Abdominal pain upper	53 (12.1)	27 (12.6)
Edema peripheral	53 (12.1)	23 (10.7)
Hypokalemia	52 (11.9)	9 (4.2)
Insomnia	51 (11.7)	22 (10.2)
Cough	50 (11.4)	17 (7.9)
Back pain	48 (11.0)	16 (7.4)
Neutropenia	47 (10.8)	6 (2.8)
Pruritus	47 (10.8)	9 (4.2)
Abdominal distension	41 (9.4)	21 (9.8)
Aspartate aminotransferase increased	34 (7.8)	8 (3.7)
Blood alkaline phosphatase increased	34 (7.8)	6 (2.8)
Headache	33 (7.6)	8 (3.7)
Hyperglycemia	32 (7.3)	6 (2.8)
Leukopenia	30 (6.9)	3 (1.4)
Epistaxis	29 (6.6)	1 (0.5)
Alanine aminotransferase increased	28 (6.4)	9 (4.2)
Dysgeusia	26 (5.9)	7 (3.3)
Dyspepsia	25 (5.7)	9 (4.2)
Hypoalbuminemia	25 (5.7)	12 (5.6)
Proteinuria	24 (5.5)	5 (2.3)
Dizziness	23 (5.3)	13 (6.0)
Dry skin	23 (5.3)	7 (3.3)
Hyperbilirubinemia	23 (5.3)	13 (6.0)
Palmar-plantar erythrodysaesthesia syndrome	22 (5.0)	2 (0.9)
Pneumonia	22 (5.0)	10 (4.7)

Adverse events are sorted by descending frequency in the everolimus 10 mg/day treatment group.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Summary of deaths and adverse events (Safety set)

	Everolimus 10 mg/day	Placebo

	N = 437 n (%)	N = 215 n (%)
All deaths[1]	352 (80.5)	179 (83.3)
On-treatment deaths[2]	88 (20.1)	49 (22.8)
Adverse events (AEs)	433 (99.1)	208 (96.7)
AEs suspected to be drug-related	365 (83.5)	108 (50.2)
Grade 3 − 4 AEs	310 (70.9)	115 (53.5)
Suspected to be drug-related	159 (36.4)	22 (10.2)
Clinically notable AEs	342 (78.3)	111 (51.6)
Suspected to be drug-related	274 (62.7)	48 (22.3)
Serious adverse events (SAEs)	207 (47.4)	89 (41.4)
Suspected to be drug-related	63 (14.4)	13 (6.0)
AEs leading to discontinuation	94 (21.5)	34 (15.8)
Suspected to be drug-related	49 (11.2)	7 (3.3)
Other significant AEs	407 (93.1)	176 (81.9)
AEs requiring dose interruption and / or reduction	242 (55.4)	46 (21.4)
AEs requiring additional therapy	395 (90.4)	174 (80.9)

[1] 532 deaths observed in the FAS; 531 deaths observed in the Safety population (patient R2301-0207-00014 died before starting the study treatment; this patient is not included in the Safety population.
[2]On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment. Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized
Additional therapy includes all non-drug therapy and concomitant medications
Clinically notable AEs are adverse events for which there is a specific clinical interest in connection with everolimus or adverse events which are similar in nature.
An additional patient death occurred before the primary analysis but was not included in the primary CSR. Three deaths were reported after primary analysis (cut-off date: 05-Sep-2011) during survival follow up.
After the primary cut-off date (05-Sep-2011), three patients reported four SAEs; intervertebral disc protrusion (grade: 3), asthenia (grade: 3), peritonitis bacterial (grade: 2), and malignant melanoma (grade: 3). Of these 4 reported SAEs, only malignant melanoma was suspected to be related to the study drug and lead to discontinuation of study treatment.

Other Relevant Findings

Clinically notable adverse events regardless of study drug relationship by grouping (Safety set)

	Everolimus 10 mg/day N = 437 n (%)		Placebo N = 215 n (%)	
Grouping	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Any clinically notable adverse event	**342 (78.3)**	**147 (33.6)**	**111 (51.6)**	**45 (20.9)**
Stomatitis/oral mucositis/ulcers	200 (45.8)	21 (4.8)	26 (12.1)	0
Cytopenia	122 (27.9)	52 (11.9)	11 (5.1)	5 (2.3)
Infections and infestations	112 (25.6)	32 (7.3)	41 (19.1)	13 (6.0)

	Everolimus 10 mg/day	Placebo

Grouping	N = 437 n (%) All grades	N = 437 n (%) Grade 3/4	N = 215 n (%) All grades	N = 215 n (%) Grade 3/4
Rash and similar events	97 (22.2)	2 (0.5)	21 (9.8)	0
Hemorrhages	80 (18.3)	29 (6.6)	22 (10.2)	10 (4.7)
Renal events	41 (9.4)	6 (1.4)	13 (6.0)	6 (2.8)
Hyperglycemia/ new onset of diabetes mellitus	38 (8.7)	12 (2.7)	6 (2.8)	1 (0.5)
Intestinal obstruction/ileus	26 (5.9)	18 (4.1)	19 (8.8)	11 (5.1)
Non-infectious pneumonitis	21 (4.8)	5 (1.1)	0	0
Thromboembolism	18 (4.1)	11 (2.5)	9 (4.2)	7 (3.3)
Hypersensitivity reactions (anaphylactic reaction)	3 (0.7)	0	1 (0.5)	0

Groupings are presented by descending frequency in the everolimus 10 mg/day group.
A patient with multiple adverse events within a grouping is counted only once.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

Conclusion from primary CSR:

This study did not meet its primary objective. However, there is a trend for reduction in risk of death with everolimus in the overall population, especially in patients from the ROW treated with two prior chemotherapy regimens. Further, an improvement in PFS was observed. The higher number of patients free of progression at 6 months in the everolimus arm suggests everolimus activity in this heavily pre-treated patient population. There were no new safety concerns identified in this study.

Conclusion from Close-out CSR:

In this close-out report the data gathered from 11 patients since the last cut-off used for the primary analysis does not affect conclusions (regarding efficacy and safety) drawn from the primary CSR [RAD001R2301 CSR (cut-off date: 05-Sep-2011)].

Date of Clinical Trial Report

22 June 2012 (Primary CSR)

20 October 2014 (Close-out CSR)

Date of Initial Inclusion on Novartis Clinical Trial Results website

26 Jan 2015

Date of Latest Update

Reason for Update