Sponsor

Novartis

Generic Drug Name

Everolimus

Trial Indication

Advanced carcinoid tumors

Protocol Number

CRAD001C2325

Protocol Title

A randomized, double-blind, placebo-controlled, multicenter Phase III study in patients with advanced carcinoid tumor receiving Sandostatin LAR® Depot and RAD001 10 mg/d or Sandostatin LAR® Depot and placebo

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

26-Dec-2006 to 13-Jun-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Randomized, double-blind, multicenter, placebo-controlled, parallel-group Phase III study designed to evaluate the safety and efficacy of everolimus 10 mg/day plus depot octreotide or matching placebo plus depot octreotide in patients with advanced carcinoid tumor. The two distinct parts to the study were: the core and the extension phase. The core phase of the study was from the start of the study up to the time of the final primary analysis (until the data cut-off of 02-Apr-2010). The data from the core phase were used for the primary statistical analyses of efficacy and safety. In the extension phase, patients who were initially randomized to placebo were offered open label treatment with everolimus following documented disease progression. Patients were also offered to switch to open-label everolimus after study unblinding at the end of the core phase. Patients who entered the open-label phase continued to have the same safety and efficacy assessments as in the core phase (with the exception of pharmacokinetic and biomarker assessments which were not collected in the open-label phase) until disease progression.

Centers

93 centers in 16 countries worldwide

Publication

Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM, Oberg K, Van Cutsem E, Yao JC. "Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study." *Lancet* 378 (2011): 2005-12.

Objectives:

Primary objective

The primary objective was to determine whether treatment with everolimus 10 mg/day plus depot octreotide prolongs progression-free survival (PFS) compared to treatment with depot octreotide alone in patients with advanced carcinoid tumor.

Secondary objective(s)

Secondary objectives were: (1) to evaluate the anti-tumor effect of everolimus on other tumor endpoints (best overall response rate – complete response [CR] and partial response [PR] – response duration); (2) to compare overall survival (OS) between the study arms; (3) to compare changes from baseline in 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A (CgA) levels; (4) to determine the safety and tolerability of the combination of everolimus (10 mg/day) plus depot octreotide; (5) to characterize the pharmacokinetics of everolimus and depot octreotide administered in combination in carcinoid indications

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

Everolimus was administered in accordance with a 10-mg oral daily dosing regimen (two 5-mg tablets) in conjunction with depot octreotide (Sandostatin LAR® Depot) 30 mg intramuscularly (i.m.) every 28 days.

Statistical Methods

The primary statistical analysis was performed using all available data from the core phase of the study (with a data cut-off date of 02-Apr-2010). Data for those placebo patients who were unblinded and crossed over to receive everolimus open-label treatment are documented separately for the open-label phase. Analysis of the open-label phase focused primarily on safety. Demographic and other baseline characteristics are summarized by means of contingency tables for each treatment group and quantitative data are summarized by appropriate descriptive statistics (mean, standard deviation, median, and range).

Efficacy: Efficacy analyses include all data from the full analysis set (FAS) irrespective of whether these are observed on-treatment or after study drug discontinuation.

Primary efficacy endpoint was PFS (as determined by adjudicated central radiology review). Progression evaluation was performed according to RECIST and was based exclusively on radiological findings obtained at tumor assessments. Progression-free survival was analyzed using Kaplan-Meier methodology. Homogeneity of the treatment effect was investigated across subgroups defined by important prognostic factors. Key prognostic factors were also included in a multivariate Cox proportional hazard model.

Further supportive PFS analyses, using the same conventions as for the primary analysis, included:

- Using the independent central adjudicated assessment on the Per-protocol Set
- Using the local investigator assessment on the FAS
- Using the independent central radiology assessment on the FAS
- Combination of both the independent central radiology and local investigator assessments on the FAS. This analysis used the worst-case scenario when combining data, i.e., the shortest time to PFS event was considered for those cases where an event was noted in both sources and ‘progressive disease (PD)’ would be selected rather than ‘censor’ if sources were divergent.

The following PFS sensitivity analyses were performed to investigate the impact of missing tumor assessments:

- The actual event date of disease progression/death was used for the PFS event date, irrespective of whether it was preceded by missing tumor assessments – ‘actual event PFS analysis’

- In case of a documented progression/death after one or more missing tumor assessments, disease progression was considered to have occurred at the next scheduled tumor assessment after the date of the last tumor assessment with overall lesion response of CR, PR, or stable disease (SD) – 'backdating PFS analysis'

Secondary variables were objective response rate, duration of response, and overall survival.

Objective response rate was defined as the proportion of patients with a best overall response of CR or PR and is summarized in terms of the percentage rate with the corresponding 95% CI for each treatment group taking the adjudicated central radiology review as the primary source. Best overall response was also summarized by category (CR, PR, SD, PD, and unknown) and treatment group.

Duration of response applied to patients with a best overall response of CR or PR. The start date was the date of first documented response while the end date was defined as the first documented progression or death from the underlying cancer. If documented progression or death were not reported, duration was censored at the date of the last adequate tumor assessment, i.e., the last tumor assessment with a response or CR, PR, or SD.

Overall survival was defined as the time from the date of randomization to the date of death from any cause. If a patient was not known to have died, survival was censored at the date of last contact. Kaplan-Meier methodology was used to estimate the median overall survival for each treatment group, together with the associated 95% CIs. Treatment arms were compared using a one-sided log-rank test and the hazard ratio and associated two-sided 95% CI were obtained from a Cox proportional hazard model.

Safety: Rate, type, severity, and causal relationship of adverse events (AEs) and serious AEs (SAEs) to treatment. Regular monitoring of hematology, blood clinical chemistry, urine, regular assessments of vital signs, and physical condition. Safety and tolerability were assessed according to the National Institute of Health/National Cancer Institute Common Terminology Criteria (NIH/NCI CTC).

Pharmacokinetics: Pharmacokinetic analyses were performed on the Safety Set and included all valid PK blood samples taken at steady-state within defined time-windows and without vomiting after the last dose. The following PK parameters were determined using non-compartmental methods. area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC0-t last), area under the concentration time curve from time zero to time τ, where τ is the end of the dosing interval (AUC0-τ), maximum (peak) drug concentration, (Cmax), time to maximum (peak) drug concentration (tmax), and minimum (trough) drug concentration (Cmin). Apparent clearance (CL/F) was also derived.

Biomarkers: Baseline levels of serum CgA were characterized relative to the upper limit of normal (ULN). CgA levels exceeding 2 x ULN was considered to be 'elevated'. Baseline levels of 5-HIAA in urine were defined as 'high' if they exceeded the median value, and 'low' if they were lower than or equal to the median.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Advanced (unresectable or metastatic) biopsy-proven carcinoid tumor
- Confirmed low-grade or intermediate-grade neuroendocrine carcinoma
- Radiological documentation of disease progression within 12 months prior to randomization. (Progression of disease was demonstrated by an unequivocal increase in tumor size on radiological study.)
- Measurable disease per RECIST determined by triphasic computer tomography (CT) scan or magnetic resonance imaging (MRI)
- A history of secretory symptoms, defined as symptoms of diarrhea or flushing or both consistent with carcinoid syndrome. Such symptoms need not have been active at the time of enrollment.
- Adequate bone marrow function as shown by:
  - absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  - platelets $\geq 100 \times 10^9$/L
  - hemoglobin (Hb) > 9 g/dL
- Adequate liver function as shown by:
  - serum bilirubin $\leq$ 1.5-times the upper limit of normal (ULN)
  - international normalized ratio (INR) < 1.3 (or < 3 if receiving anticoagulants)
  - alanine transaminase (ALT) and aspartate transaminase (AST) $\leq$ 2.5 x ULN ($\leq$ 5 x ULN in patients with liver metastases)
- Adequate renal function as shown by:
  - serum creatinine $\leq$ 1.5 x ULN
- Fasting serum cholesterol $\leq$ 300 mg/dL or $\leq$ 7.75 mmol/L and fasting triglycerides $\leq$ 2.5 x ULN. In case one or both of these thresholds were exceeded, the patient could only be included after initiation of appropriate lipid-lowering medication.
- Performance status (PS) of 0-2 on the World Health Organization (WHO) scale
- Adult male or female patients $\geq$ 18 years of age
- A negative serum or urine pregnancy test within 48 hours of administration of the first study treatment, if female and of child-bearing potential
- Provided written informed consent according to local guidelines

Exclusion criteria:

- Poorly-differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet-cell carcinoid, or small-cell carcinoma
- Cytotoxic chemotherapy, immunotherapy, or radiotherapy within 4 weeks prior to randomization

- Received treatment with Sandostatin LAR® Depot or any other long-acting somatostatin analog within 2 weeks prior to randomization
- Hepatic artery embolization within the last 6 months (1 month if there were other sites of measurable disease) or cryoablation, or radiofrequency ablation of hepatic metastasis within 2 months of randomization
- Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus)
- Known intolerance or hypersensitivity to octreotide, Sandostatin LAR® Depot, everolimus, or other rapamycins (sirolimus, temsirolimus)
- Uncontrolled diabetes mellitus (as defined by fasting serum glucose > 1.5 x ULN)
- Any severe and/or uncontrolled medical conditions, such as:
  - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, or serious uncontrolled cardiac arrhythmia
  - active or uncontrolled severe infection
  - cirrhosis, chronic active hepatitis, or chronic persistent hepatitis
  - severely impaired lung function (spirometry and diffusing capacity of the lung for carbon monoxide [DLCO] ≤ 50% of normal and O_2 saturation ≤ 88% at rest on room air)
  - active, bleeding diathesis
- Receiving chronic treatment with corticosteroids or other immunosuppressive agent
- A known history of human immunodeficiency virus (HIV) seropositivity
- A history of another primary malignancy ≤ 3 years, with the exception of non-melanoma skin cancer or carcinoma in situ of uterine cervix
- Female patients who were pregnant or nursing (lactating), or adults of reproductive potential who were not using effective birth control methods. If barrier contraceptives were being used, these were to be continued throughout the trial by both sexes.

Participant Flow Table

Patient disposition in double-blind phase (Full analysis set)

Disposition Reason	Everolimus plus depot octreotide N=216 n (%)	Placebo plus depot octreotide N=213 n (%)
Discontinued	216 (100.0)	213 (100.0)
Disease progression	101 (46.8)	154 (72.3)
Adverse event(s)	61 (28.2)	16 (7.5)
Final primary analysis	26 (12.0)	14 (6.6)
Patient withdrew consent	18 (8.3)	20 (9.4)
Death	6 (2.8)	3 (1.4)

Disposition Reason	Everolimus plus depot octreotide N=216 n (%)	Placebo plus depot octreotide N=213 n (%)
Protocol violation	3 (1.4)	4 (1.9)
New cancer therapy	1 (0.5)	1 (0.5)
Lost to follow-up	0	1 (0.5)

Patient disposition in open-label (Open-label safety set)

Disposition Reason	Open-label everolimus plus depot octreotide N=170 n (%)
Discontinued	170 (100.0)
Disease progression	86 (50.6)
Adverse event(s)	46 (27.1)
Patient withdrew consent	15 (8.8)
Administrative problems	13 (7.6)
Death	7 (4.1)
Lost to follow-up	2 (1.2)
New cancer therapy	1 (0.6)

Baseline Characteristics

Demographic characteristics (Full Analysis Set)

Demographic characteristic	Everolimus plus depot octreotide N=216	Placebo plus depot octreotide N=213	All patients N=429
Age (years)			
N	216	213	429
Mean (standard deviation)	60.1 (10.72)	59.4 (11.13)	59.8 (10.92)
Median	60.0	60.0	60.0
Range	22 to 83	27 to 81	22 to 83
Age group - n (%)			
< 65 years	143 (66.2)	143 (67.1)	286 (66.7)
≥ 65 years	73 (33.8)	70 (32.9)	143 (33.3)
Gender - n (%)			
Female	119 55.1)	89 (41.8)	208 (48.5)
Male	97 (44.9)	124 (58.2)	221 (51.5)
Race - n (%)			
Caucasian	204 (94.4)	199 (93.4)	403 (93.9)
Black	5 (2.3)	7 (3.3)	12 (2.8)

Demographic characteristic	Everolimus plus depot octreotide N=216	Placebo plus depot octreotide N=213	All patients N=429
Asian	1 (0.5)	1 (0.5)	2 (0.5)
Other	6 (2.8)	6 (2.8)	12 (2.8)

Summary of Efficacy

Primary Outcome Result(s)

Analysis of PFS as per adjudicated central radiology review using Kaplan-Meier methodology (Full Analysis Set)

	Everolimus plus depot octreotide N=216	Placebo plus depot octreotide N=213	p-value [a]	Hazard ratio [b] [95% CI]
No. of PFS events (n [%])	103 (47.7)	120 (56.3)	0.026	0.77 [0.59, 1.00]
Progression	69 (31.9)	101 (47.4)		
Death	34 (15.7)	19 (8.9)		
No. censored (n [%])	113 (52.3)	93 (43.7)		
Kaplan-Meier estimates [95% CI] at:				
4 months	89.9 [84.8, 93.4]	82.6 [76.6, 87.2]		
6 months	78.6 [71.9, 83.8]	70.2 [63.1, 76.2]		
12 months	60.6 [52.6, 67.6]	48.7 [41.0, 56.0]		
18 months	47.2 [38.9, 55.1]	37.4 [29.9, 44.9]		
24 months	39.0 [30.7, 47.3]	29.5 [22.2, 37.2]		
Median PFS [95% CI] (months)	16.43 [13.67, 21.19]	11.33 [8.44, 14.59]		

[a] p-value is obtained from the one-sided log-rank test.
[b] Hazard ratio is obtained from the unadjusted Cox model

Secondary Outcome Result(s)

Best overall response as per adjudicated central radiology review (Full Analysis Set)

Best overall response	Everolimus plus depot octreotide N=216 n (%)	Placebo plus depot octreotide N=213 n (%)
Complete response	0	0
Partial response	5 (2.3)	4 (1.9)
Disease stabilization	182 (84.3)	172 (80.8)
Progressive disease	9 (4.2)	26 (12.2)
Unknown	20 (9.3)	11 (5.2)
Response analysis		
Objective response rate	5 (2.3)	4 (1.9)
95% CI for ORR	[0.8, 5.3]	[0.5, 4.7]

Comparison of PFS as per adjudicated central review by baseline CgA level within each treatment group (Full analysis set)

	CgA ≤ 2 x ULN N=138	CgA >2 x ULN N=282
Everolimus + Octreotide		
Number of patients	60	152
Number of events	20	80
Median PFS (months)	31.31	13.93
95% CI for median PFS (months)	[19.32; NA]	[11.30; 17.08]
Placebo + Octreotide		
Number of patients	78	130
Number of events	34	84
Median PFS (months)	20.07	8.41
95% CI for median PFS (months)	[13.04; NA]	[7.72; 11.14]
Unstratified Cox's model		
Hazard ratio [1]	0.74	0.66
95% CI for hazard ratio	[0.42; 1.28]	[0.48; 0.89]
Log-rank test [2]		
p-value	0.1401	0.0034

[1] Hazard ratio <1 implies lower risk of progression for patients in everolimus + octreotide
[2] p-value obtained from an unstratified one-sided log-rank test

Comparison of PFS as per adjudicated central review by baseline 5-HIAA level within each treatment group (Full analysis set)

	5-HIAA ≤ median N=189	5-HIAA >median N=189
Everolimus + Octreotide		
Number of patients	93	94
Number of events	37	52
Median PFS (months)	21.75	13.83
95% CI for median PFS (months)	[13.93; NA]	[10.67; 18.63]
Placebo + Octreotide		
Number of patients	96	95
Number of events	49	62
Median PFS (months)	13.90	8.41
95% CI for median PFS (months)	[8.71; 22.44]	[8.08; 11.33]
Unstratified Cox's model		
Hazard ratio [1]	0.70	0.66
95% CI for hazard ratio	[0.46; 1.08]	[0.46; 0.96]
Log-rank test [2]		
p-value	0.0514	0.0147

[1] Hazard ratio <1 implies lower risk of progression for patients in everolimus + octreotide
[2] p-value obtained from an unstratified one-sided log-rank test

Analysis of overall survival using Kaplan-Meier methodology (Full Analysis Set)

	Everolimus plus depot octreotide N=216	Placebo plus depot octreotide N=213
No. of events (n [%])	143 (66.2)	128 (60.1)
No. censored (n [%])	73 (33.8)	85 (39.9)
Kaplan-Meier estimates [95% CI] at:		
12 months	80.5 [74.5, 85.3]	81.8 [75.8, 86.4]
24 months	57.0 [49.9, 63.4]	63.6 [56.6, 69.8]
36 months	42.9 [36.0, 49.6]	48.5 [41.4, 55.3]
48 months	37.4 [30.7, 44.1]	41.7 [34.7, 48.6]
25^{th} percentile OS [95% CI] (months)	15.74 [11.99; 18.43]	16.66 [12.91; 20.14]
Median OS [95% CI] (months)	29.21 [23.75, 35.94]	35.22 [30.03, 44.71]
75^{th} percentile OS [95% CI] (months)	67.84 [57.86; NA]	NA [67.22; NA]

Summary of Safety

Safety Results

Double-blind phase

Adverse events by system organ class irrespective of relationship to treatment (Safety Set)

System organ class	Everolimus plus depot octreotide N=215 n (%)	Placebo plus depot octreotide N=211 n (%)
Any system organ class	**215 (100.0)**	**203 (96.2)**
Gastrointestinal disorders	203 (94.4)	160 (75.8)
General disorders and administration site conditions	174 (80.9)	144 (68.2)
Skin and subcutaneous tissue disorders	151 (70.2)	76 (36.0)
Metabolism and nutrition disorders	145 (67.4)	77 (36.5)
Infections and infestations	140 (65.1)	96 (45.5)
Respiratory, thoracic and mediastinal disorders	136 (63.3)	85 (40.3)
Nervous system disorders	127 (59.1)	99 (46.9)
Musculoskeletal and connective tissue disorders	121 (56.3)	109 (51.7)
Investigations	110 (51.2)	66 (31.3)
Blood and lymphatic system disorders	103 (47.9)	32 (15.2)
Vascular disorders	68 (31.6)	63 (29.9)
Renal and urinary disorders	59 (27.4)	38 (18.0)
Psychiatric disorders	56 (26.0)	43 (20.4)

System organ class	Everolimus plus depot octreotide N=215 n (%)	Placebo plus depot octreotide N=211 n (%)
Cardiac disorders	47 (21.9)	32 (15.2)
Injury, poisoning and procedural complications	40 (18.6)	29 (13.7)
Eye disorders	37 (17.2)	23 (10.9)
Ear and labyrinth disorders	21 (9.8)	17 (8.1)
Reproductive system and breast disorders	21 (9.8)	25 (11.8)
Hepatobiliary disorders	20 (9.3)	13 (6.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (6.5)	15 (7.1)
Endocrine disorders	10 (4.7)	11 (5.2)
Immune system disorders	5 (2.3)	3 (1.4)
Congenital, familial and genetic disorders	2 (0.9)	1 (0.5)
Surgical and medical procedures	0	1 (0.5)

Adverse events by preferred term irrespective of relationship to treatment (reported in at least 10% of patients from either group) (Safety set)

Preferred term	Everolimus plus depot octreotide N=215 n (%)	Placebo plus depot octreotide N=211 n (%)
Any preferred term	**215 (100.0)**	**203 (96.2)**
Diarrhoea	114 (53.0)	79 (37.4)
Stomatitis	109 (50.7)	25 (11.8)
Fatigue	105 (48.8)	91 (43.1)
Nausea	94 (43.7)	64 (30.3)
Oedema peripheral	93 (43.3)	48 (22.7)
Rash	88 (40.9)	37 (17.5)
Abdominal pain	72 (33.5)	71 (33.6)
Vomiting	72 (33.5)	44 (20.9)
Headache	65 (30.2)	50 (23.7)
Decreased appetite	64 (29.8)	37 (17.5)
Dyspnoea	62 (28.8)	20 (9.5)
Anaemia	60 (27.9)	22 (10.4)
Cough	60 (27.9)	32 (15.2)
Weight decreased	59 (27.4)	32 (15.2)
Asthenia	51 (23.7)	31 (14.7)
Hypokalaemia	51 (23.7)	8 (3.8)
Pyrexia	45 (20.9)	23 (10.9)
Dysgeusia	42 (19.5)	12 (5.7)

Preferred term	Everolimus plus depot octreotide N=215 n (%)	Placebo plus depot octreotide N=211 n (%)
Hyperglycaemia	42 (19.5)	9 (4.3)
Pruritus	42 (19.5)	12 (5.7)
Arthralgia	38 (17.7)	28 (13.3)
Thrombocytopenia	35 (16.3)	1 (0.5)
Back pain	33 (15.3)	42 (19.9)
Epistaxis	33 (15.3)	5 (2.4)
Pain in extremity	32 (14.9)	24 (11.4)
Constipation	31 (14.4)	22 (10.4)
Dizziness	29 (13.5)	24 (11.4)
Aphthous stomatitis	28 (13.0)	3 (1.4)
Flatulence	27 (12.6)	28 (13.3)
Upper respiratory tract infection	27 (12.6)	12 (5.7)
Urinary tract infection	27 (12.6)	17 (8.1)
Hypertension	25 (11.6)	21 (10.0)
Abdominal pain upper	23 (10.7)	28 (13.3)
Dehydration	23 (10.7)	13 (6.2)
Dry skin	23 (10.7)	5 (2.4)
Dry mouth	22 (10.2)	6 (2.8)
Musculoskeletal pain	21 (9.8)	21 (10.0)
Nasopharyngitis	19 (8.8)	26 (12.3)

Preferred terms are sorted by descending frequency in the everolimus plus octreotide group.

A patient with multiple occurrences of an AE under one treatment is counted once in the AE category for that treatment.

AEs occurring more than 28 days after discontinuation of study treatment or after the start of the everolimus open-label phase are not summarized.

Number of patients who died, had SAE, discontinued due to AE, by treatment (Safety Set)

Category	Everolimus plus depot octreotide N=215 n (%)	Placebo plus depot octreotide N=211 n (%)
All deaths [a]	137 (63.7)	44 (20.9)
On-treatment deaths [b]	19 (8.8)	11 (5.2)
Serious adverse events	126 (58.6)	744 (35.1)
Adverse events leading to discontinuation	65 (30.2)	17 (8.1)

[a] Deaths occurring in double-blind phase are summarized.

[b] Deaths occurring after >28 days after discontinuation of study and in the everolimus open-label phase are not summarized.

Open-label phase

Adverse events by system organ class irrespective of relationship to treatment (Open-label set)

System organ class	Everolimus plus depot octreotide N=170 n (%)
Any system organ class	**167 (98.2)**
Gastrointestinal disorders	146 (85.9)
General disorders and administration site conditions	120 (70.6)
Skin and subcutaneous tissue disorders	98 (57.6)
Infections and infestations	96 (56.5)
Respiratory, thoracic and mediastinal disorders	91 (53.5)
Metabolism and nutrition disorders	89 (52.4)
Nervous system disorders	81 (47.6)
Musculoskeletal and connective tissue disorders	72 (42.4)
Blood and lymphatic system disorders	64 (37.6)
Investigations	63 (37.1)
Vascular disorders	44 (25.9)
Renal and urinary disorders	42 (24.7)
Psychiatric disorders	36 (21.2)
Injury, poisoning and procedural complications	33 (19.4)
Eye disorders	27 (15.9)
Cardiac disorders	26 (15.3)
Reproductive system and breast disorders	14 (8.2)
Endocrine disorders	12 (7.1)
Hepatobiliary disorders	12 (7.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (6.5)
Ear and labyrinth disorders	9 (5.3)
Immune system disorders	6 (3.5)
Drug hypersensitivity	3 (1.8)
Congenital, familial and genetic disorders	2 (1.2)

Primary system organ classes are presented by descending frequency

A patient with multiple occurrences of an AE under one treatment is counted once in the AE category for that treatment.

AEs occurring prior to open-label everolimus phase or more than 28 days after the end of everolimus open-label phase are not summarized.

Adverse events by preferred term irrespective of relationship to treatment (reported in at least 10% of patients) (Open-label set)

Preferred term	Everolimus (OL) plus depot octreotide N=170 n (%)
Any preferred term	**167 (98.2)**
Diarrhoea	80 (47.1)
Stomatitis	64 (37.6)
Fatigue	63 (37.1)
Oedema peripheral	63 (37.1)
Nausea	62 (36.5)
Rash	59 (34.7)
Abdominal pain	48 (28.2)
Cough	38 (22.4)
Anaemia	36 (21.2)
Decreased appetite	35 (20.6)
Vomiting	34 (20.0)
Pyrexia	33 (19.4)
Weight decreased	33 (19.4)
Headache	32 (18.8)
Asthenia	30 (17.6)
Dysgeusia	30 (17.6)
Dysponea	27 (15.9)
Hypokalaemia	27 (15.9)
Hyperglycemia	25 (14.7)
Epistaxis	24 (14.1)
Arthralgia	19 (11.2)
Nasopharyngitis	19 (11.2)
Pain in extremity	19 (11.2)
Urinary tract infection	19 (11.2)
Back pain	18 (10.6)
Constipation	18 (10.6)
Pruritus	18 (10.6)
Abdominal pain upper	17 (10.0)
Hypertension	17 (10.0)
Sinusitis	17 (10.0)

Preferred terms are sorted by descending frequency.

A patient with multiple occurrences of an AE during the open-label phase is counted once in the AE category.

AEs occurring prior to open-label everolimus phase or more than 28 days after the end of everolimus open-label phase are not summarized.

Number of patients who died, had SAE, discontinued due to AE, by treatment (Safety Set)

Category	Everolimus (OL) plus depot octreotide N=170 n (%)
All deaths [a]	89 (52.4)
On-treatment deaths [b]	22 (12.9)
Serious adverse events	93 (54.7)
Adverse events leading to discontinuation	48 (28.2)

[a] Deaths occurring in the everolimus open-label phase are summarized
[b] Deaths occurring >28 days after discontinuation of study treatment are not summarized

Other Relevant Findings

Everolimus pharmacokinetic parameters at steady-state (Safety Set)

Regimen	Cmax (ng/mL)	tmax (h)	AUC0-t last (ng.h/mL)	CL/F (L/h)	Cmin (ng/mL)
10 mg QD (n=9) [a]	74.8 ± 33.6 (49.9%)	0.50 (0.50-5.0)	578 ± 243 (42.1%)	19.5 ± 6.8 (35.0%)	9.47 ± 2.59 (27.3%)

Values are mean ± standard deviation (coefficient of variation %) with the exception of tmax where median (range) is summarized
[a] n=5 for AUC_{0-T} and CL/F

Conclusion:

Results from this study must be considered carefully in the context of other reports in this patient population. With the exception of PROMID, no randomized trial in the recent past has reported evidence of clinical benefit in patients with advanced NET with a history of carcinoid syndrome. Current treatment decisions are based on the results from small Phase-II studies. The present trial demonstrates that everolimus, in conjunction with depot octreotide, provides important benefits for this patient population.

- Results provide evidence for the clinical benefit of everolimus in this patient population despite the study narrowly failing to meet its primary PFS endpoint (as per the adjudicated central radiology review) (p=0.026 when the boundary for statistical significance was p=0.0246).
    - PFS results as per local investigator assessment attained the level of statistical significance and the magnitude of the treatment effect was consistent with the primary analysis
- The objective tumor response rate was low reflecting the cytostatic nature of everolimus in this setting.

- No significant difference was evident for overall survival, although numerically more deaths were reported in the everolimus treatment group (HR 1.17; 95% CI: 0.92, 1.49). Imbalances in key baseline prognostic factors, types of subsequent therapy offered, and total duration of exposure to somatostatin analogs, in addition to the crossover design of the study, were all likely to have contributed to this result.
- Safety is consistent with previous experience in the oncology setting.

Date of Clinical Trial Report

11-Dec-2013

Date of Initial Inclusion on Novartis Clinical Trial Results website

Interim Analysis – 18Nov2011

Date of Latest Update

Final Analysis – 13 June 2014

Reason for Update

Final analysis after interim report