RADIANT-2: A Randomized, Double-Blind, Multicenter, Phase III Trial of Everolimus + Octreotide LAR Versus Placebo + Octreotide LAR in Patients With Advanced Neuroendocrine Tumors: Progression-Free Survival by Primary Tumor Site and Updated Safety Results

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BACKGROUND

- 5-year survival rates in patients with metastatic NET vary significantly, depending on the primary tumor site. The worst prognoses are associated with primary tumors of the lung (median survival, 17 months) and colon (median survival, 7 months)[1]
- Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has demonstrated benefit to patients with advanced NET, both as a single agent and in combination with octreotide long-acting repeatable (LAR) in phase II and phase III studies[2-4]
- In the large, randomized, double-blind, placebo-controlled, phase III RADIANT-2 trial, everolimus + octreotide LAR demonstrated a clinically meaningful 5.1-month improvement in median progression-free survival (PFS) by adjudicated central radiologic review versus placebo + octreotide LAR in 429 patients with low- or intermediate-grade advanced NET and a history of secretory symptoms (flushing, diarrhea, or both)[5]

OBJECTIVE

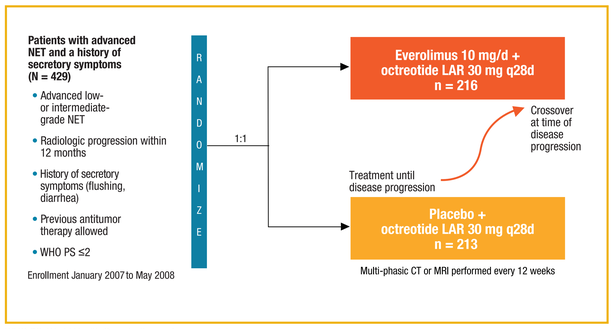
- To perform an exploratory analysis of PFS by primary tumor site and to assess the long-term safety of everolimus + octreotide LAR in patients with advanced NET who participated in the RADIANT-2 trial

METHODS

Study Design

- RADIANT-2 was an international, multicenter, randomized, double-blind, placebo-controlled, phase III study (**Figure 1**)

Figure 1. RADIANT-2 trial design.



WHO PS, World Health Organization performance status.

- Patients were randomly assigned to receive oral everolimus 10 mg/d + octreotide LAR 30 mg every 28 days or matching placebo + octreotide LAR 30 mg every 28 days
- Patients randomly assigned to placebo + octreotide LAR were permitted to cross over to open-label everolimus + octreotide LAR on progression
- Primary endpoint was PFS by central review (Response Evaluation Criteria In Solid Tumors [RECIST], version 1.0)
- At the final analysis, after 2 interim analyses, the prespecified boundary for significance was 0.0246
- In an exploratory analysis, PFS was analyzed by primary tumor site
- The cutoff date for efficacy data was April 2, 2010
- The original safety analysis was performed with the cutoff date of April 2, 2010; the updated safety analysis presented here was performed with the cutoff date of July 2, 2010

RESULTS

Demographics and Disposition

- 429 patients with advanced NET were randomly assigned to everolimus + octreotide LAR (n = 216) or placebo + octreotide LAR (n = 213) in the RADIANT-2 study
- Several prognostic baseline characteristics (including lung as the primary tumor site, World Health Organization performance status >0, and previous use of chemotherapy) showed imbalances in favor of the placebo + octreotide LAR arm (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

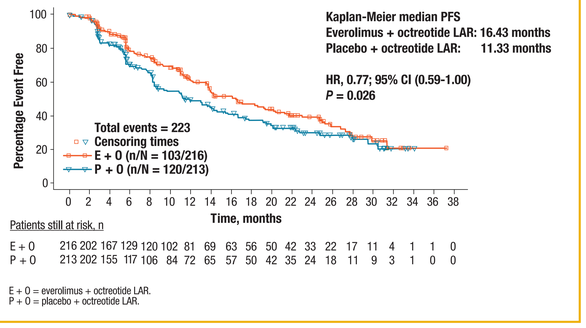
	Everolimus + Octreotide LAR n = 216	Placebo + Octreotide LAR n = 213
Median age, years (range)	60 (22-83)	59 (27-81)
Sex, %		
Male	45	58
Female	55	42
WHO PS, %		
0	55	66
1/2	39/6	29/5
Primary site of cancer, %		
Small intestine	51	53
Lung	15	5
Colon	6	7
Pancreas	5	7
Liver	3	5
Histologic grade, %		
Well differentiated	77	82
Moderately differentiated	18	14
Poorly differentiated	<1	<1
Unknown/missing	5	3
Previous long-acting somatostatin analog, %	80	78
Other previous systemic antitumor therapy, %	46	38
Chemotherapy	35	26
Immunotherapy	13	9
Targeted therapy	7	8
Other	10	13

WHO PS, World Health Organization performance status.

Progression-Free Survival

- Median PFS, as assessed by central review, was 16.43 months (95% confidence interval [CI], 13.67-21.19 months) in the everolimus + octreotide LAR group and 11.33 months (95% CI, 8.44-14.59 months) in the placebo + octreotide LAR group, representing a 23% reduction in the risk for progression (hazard ratio [HR], 0.77; 95% CI, 0.59-1.00; 1-sided log-rank test, $P = 0.026$) (**Figure 2**)

Figure 2. PFS Kaplan-Meier curves by central review (cutoff date, April 2, 2010).



HR was obtained from the unadjusted Cox model; *P* value was obtained from the 1-sided log-rank test.

Exploratory Analysis of Progression-Free Survival by Primary Tumor Site

- Primary tumor sites included the small intestine (n = 111 for everolimus + octreotide LAR and n = 113 for placebo + octreotide LAR), lung (n = 33 for everolimus + octreotide LAR and n = 11 for placebo + octreotide LAR), and colorectal (n = 19 for everolimus + octreotide LAR and n = 20 for placebo + octreotide LAR) (**Table 2**)
- Everolimus + octreotide LAR improved median PFS by 4.60 months in the small intestine subgroup, 8.04 months in the lung subgroup, and 23.33 months in the colorectal subgroup (**Table 2**)

Table 2. PFS by Primary Tumor Site

	Everolimus + Octreotide LAR Months (95% CI)	Placebo + Octreotide LAR Months (95% CI)	HR (95% CI)	*P*[a]
Overall n = 429	16.43 (13.67, 21.19) n = 216	11.33 (8.44, 14.59) n = 213	0.77 (0.59, 1.00)	0.026
Small intestine n = 224	18.63 (13.60, 25.89) n = 111	14.03 (9.40, 19.84) n = 113	0.77 (0.53, 1.13)	0.092
Lung n = 44	13.63 (5.55,14.29) n = 33	5.59 (2.79, 27.76) n = 11	0.72 (0.31, 1.68)	0.228
Colorectal n = 39	29.90 (5.59, NR) n = 19	6.57 (3.02, 13.04) n = 20	0.34 (0.13, 0.89)	0.011

HR, hazard ratio; NR, not reached.
[a]1-sided *P* values from log rank test.

Safety Update

- As of the cutoff date for this analysis (July 2, 2010), median follow-up reached 31.1 months
- Median exposure to treatment was similar between the treatment arms (37.0 weeks everolimus + octreotide LAR vs 36.6 weeks placebo + octreotide LAR); there were 227.3 patient-years of exposure in the everolimus + octreotide LAR arm and 218.2 patient-years of exposure in the placebo + octreotide LAR arm
- The most frequently reported treatment-related AEs (everolimus + octreotide LAR vs placebo + octreotide LAR) were stomatitis (61.9% vs 14.2%), rash (37.2% vs 12.3%), fatigue (31.6% vs 24.2%), diarrhea (27.4% vs 15.6%), nausea (20.0% vs 16.1%), and infection (20.0% vs 7.1%) and were consistent with previous experience (**Table 3**)

Table 4. Treatment-Related AEs (All Grades) Occurring in ≥10% of Patients (Safety Set)

Adverse Event, %	Original Study Cutoff April 2, 2010		Safety Update July 2, 2010	
	Everolimus + Octreotide LAR n = 215	Placebo + Octreotide LAR n = 211	Everolimus + Octreotide LAR n = 215	Placebo + Octreotide LAR n = 211
Stomatitis[a]	61.9	13.7	61.9	14.2
Rash	37.2	12.3	37.2	12.3
Fatigue	31.2	23.2	31.6	24.2
Diarrhea	27.4	15.6	27.4	15.6
Infections and infestations[a]	19.5	6.2	20.0	7.1
Nausea	19.5	16.1	20.0	16.1
Dysgeusia	16.7	3.3	16.7	3.3
Anemia	15.3	4.7	15.8	4.7
Decreased weight	14.9	3.3	14.9	3.8
Thrombocytopenia	14.0	0	14.4	0
Decreased appetite	13.5	6.2	13.5	6.2
Peripheral edema	13.0	3.3	13.0	3.3
Pneumonitis[a]	11.6	0	13.0	0
Hyperglycemia	12.1	1.9	12.1	1.9
Dyspnea	12.1	1.4	12.1	1.9
Vomiting	10.7	5.2	10.7	5.2
Pruritus	10.7	3.8	11.2	3.8
Asthenia	10.2	6.6	10.2	6.6

[a]Related toxicities grouped for calculations.

- The frequency of grade 3/4 treatment-related AEs remained unchanged during the extended safety follow-up of each treatment arm
  - Grade 3/4 AEs occurred in 45.1% of patients in the everolimus + octreotide LAR arm and 15.6% of patients in the placebo + octreotide LAR arm
- The most frequently reported grade 3/4 AEs related to everolimus + octreotide LAR treatment were fatigue, stomatitis, diarrhea, infections, and hyperglycemia (**Table 4**)

Table 5. Grade 3/4 Treatment-Related AEs Occurring in ≥5% of Patients (Safety Set)

Adverse Event, %	Original Study Cutoff April 2, 2010		Safety Update July 2, 2010	
	Everolimus + Octreotide LAR n = 215	Placebo + Octreotide LAR n = 211	Everolimus + Octreotide LAR n = 215	Placebo + Octreotide LAR n = 211
All	45.1	15.2	45.1	15.6
Fatigue	6.5	2.8	6.5	2.8
Stomatitis[a]	6.5	0	6.5	0
Diarrhea	6.0	2.4	6.0	2.4
Infections[a]	5.1	0.5	5.1	0.5
Hyperglycemia	5.1	0.5	5.1	0.5

[a]Related toxicities grouped for calculations.

- The most commonly reported AEs leading to discontinuation of everolimus + octreotide LAR therapy were fatigue (2.3%), dyspnea (2.3%), diarrhea (1.9%), deteriorating general physical health (1.9%), interstitial lung disease (1.9%), pneumonia (1.9%), and pneumonitis (1.9%)
- The most commonly reported AEs leading to dose interruptions in or reductions of everolimus + octreotide LAR therapy were diarrhea (9.8%), thrombocytopenia (9.8%), and stomatitis (8.8%)

CONCLUSIONS

- **In the RADIANT-2 study, the largest randomized, double-blind, placebo-controlled, phase III trial in patients with advanced NET and associated carcinoid syndrome, combination treatment with everolimus + octreotide LAR delayed disease progression by 5.1 months (adjudicated central review) compared with octreotide LAR alone**
- **Everolimus + octreotide LAR demonstrated clinically meaningful prolongation of PFS in patients with advanced NET of small intestine (by 4.6 months), lung (by 8.0 months), and colorectal (by 23.3 months) origin**
- **Updated safety results with combination everolimus + octreotide LAR were consistent with the primary analysis and the known safety profiles of everolimus + octreotide LAR in patients with cancer**
- **After 31.1 months of safety follow-up, most treatment-related AEs for everolimus + octreotide LAR were grade 1 or 2 and were manageable with proper planning, monitoring, and treatment**
- **These results support the potential utility of everolimus + octreotide LAR in patients with advanced NET, including those with primary tumor sites associated with poor prognosis, such as lung and colorectal; future studies to better understand the activity of everolimus in these subgroups are needed**

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