Impact of Prior Somatostatin Analog Use on PFS in the Phase III RADIANT-2 Trial of Everolimus + Octreotide LAR Versus Placebo + Octreotide LAR in Patients With Advanced Neuroendocrine Tumors

Lowell Anthony,[1] Neha Singh,[2] Vanessa Q. Passos,[3] Marianne Pavel,[4] Kjell Öberg,[5] James C. Yao[6]

[1]Markey Cancer Center, University of Kentucky, Lexington, Kentucky; [2]Novartis Healthcare Pvt. Ltd., Madhapur, Hyderabad, India; [3]Novartis Pharmaceuticals Corporation, Florham Park, New Jersey; [4]Department of Hepatology and Gastroenterology, Charité-Universitätsmedizin Berlin/Campus Virchow Klinikum, Berlin, Germany; [5]Department of Endocrine Oncology, University Hospital, Uppsala, Sweden; [6]The University of Texas MD Anderson Cancer Center, Houston, Texas

BACKGROUND

- Neuroendocrine tumors (NET) are a heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body[1]
- The annual incidence of NET is 5.3 per 100,000 (Surveillance, Epidemiology and End Results [SEER] database), and the incidence has increased nearly 5-fold since the 1970s[2]
- At the time of diagnosis, nearly 50% of patients with NET have advanced disease; 65% of patients with advanced disease die within the first 5 years after diagnosis[2]
- Some NET may secrete a variety of hormones or vasoactive peptides, leading to characteristic hormonal syndromes (eg, hyperinsulinemia, carcinoid syndrome)[1]
- NET have been linked to genetic alterations that activate the mammalian target of rapamycin (mTOR) pathway[3,4]
- Everolimus, an oral inhibitor of mTOR, has demonstrated promising antitumor activity in patients with advanced NET, both as a single agent and in combination with octreotide long-acting repeatable (LAR) in phase II and III studies[5-7]
- Octreotide LAR, historically used for hormone-related symptom control, has also been shown to prolong the time to tumor progression in patients with treatment-naive advanced midgut NET[8]
- In the large, randomized, double-blind, placebo-controlled, phase III RADIANT-2 trial, everolimus + octreotide LAR demonstrated a 5.1-month improvement in median progression-free survival (PFS) by adjudicated central radiologic review compared with placebo + octreotide LAR in 429 patients with low- or intermediate-grade advanced NET and a history of secretory symptoms (flushing, diarrhea, or both)[9]
  - Median PFS was 16.4 months for everolimus + octreotide LAR compared with 11.3 months for placebo + octreotide LAR (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.59-1.00; 1-sided *P* = 0.026)

OBJECTIVE

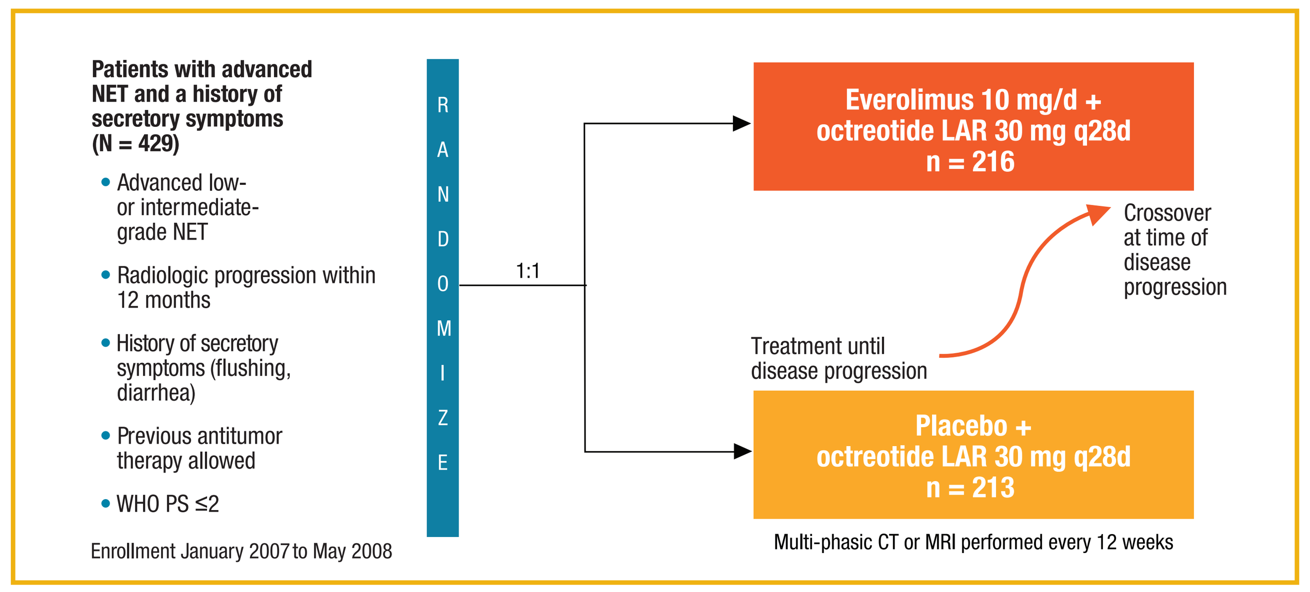
- To assess the effect of previous somatostatin analog (SSA) therapy on PFS in an exploratory analysis in patients who were enrolled in the phase III RADIANT-2 trial

METHODS

Study Design

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

Figure 1. RADIANT-2 study design.



WHO PS, World Health Organization performance status.

- Patients were randomly assigned to receive oral everolimus 10 mg/d + octreotide LAR 30 mg intramuscularly (IM) every 28 days or matching placebo + octreotide LAR 30 mg IM every 28 days
- Treatment continued until progression of disease, development of unacceptable toxicity, or withdrawal of consent
- Dose adjustments were permitted for patients unable to tolerate the protocol-specified dosing schedule
- Patients randomly assigned to placebo + octreotide LAR were permitted to cross over to open-label everolimus + octreotide LAR on investigator-assessed disease progression
- Primary endpoint was PFS by adjudicated central review (Response Evaluation Criteria In Solid Tumors [RECIST], version 1.0)
- At the final analysis, based on 2 interim analyses, the prespecified boundary for significance was 0.0246
- SSA treatment before study entry was permitted, though the previous doses used were not available

RESULTS

Demographics and Disposition

- A total of 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
- Slightly higher proportions of patients in the everolimus + octreotide LAR arm had a history of tumor-related flushing (77.8% vs 69.0%); similar proportions in both treatment arms had a history of tumor-related symptoms (95.4% vs 96.7%) and tumor-related diarrhea (79.2% vs 82.2%)
- 79% (339) of enrolled patients received SSA therapy before study entry
  - 173 patients were randomly assigned to receive everolimus + octreotide LAR
  - 166 patients were randomly assigned to receive placebo + octreotide LAR
- Higher proportions of patients who received previous SSA therapy than of patients who did not had small intestine (56% vs 38%) as the primary tumor site; higher proportions of those who did not receive previous SSA therapy than those who did had lung (17% vs 9%) or pancreas (12% vs 4%) as the primary tumor site
- Patients who received previous SSA therapy had longer duration of illness (>6 months) before study entry than those who did not (96% vs 73%) (**Table 1**)
- 68% of patients who received previous SSA therapy had elevated chromogranin A (CgA) levels at baseline compared with 59% of patients who did not receive previous SSA therapy (**Table 1**)
- Similarly, 47% of patients who received previous SSA therapy had elevated 5-hydroxyindoleacetic acid (5-HIAA) levels at baseline compared with 31% who did not receive previous SSA therapy (**Table 1**)

Table 1. Patient Characteristics by Previous SSA Therapy

	Overall, n (%)	Previous SSA, n (%)	No Previous SSA, n (%)
Patients	429	339	90
Age			
<65 years	286 (67)	221 (65)	65 (72)
≥65 years	143 (33)	118 (35)	25 (28)
Sex			
Male	221 (52)	177 (52)	44 (49)
Female	208 (48)	162 (48)	46 (51)
Region			
United States	208 (48)	171 (50)	37 (41)
Europe	190 (44)	143 (42)	47 (52)
Rest of world	31 (7)	25 (7)	6 (7)
Primary site			
Small intestine	224 (52)	190 (56)	34 (38)
Lung	44 (10)	29 (9)	15 (17)
Colon	28 (7)	22 (6)	6 (7)
Pancreas	26 (6)	15 (4)	11 (12)
Liver	18 (4)	15 (4)	3 (3)
Histologic			
Well differentiated	341 (79)	272 (80)	69 (77)
Moderately differentiated	68 (16)	50 (15)	18 (20)
Poorly differentiated	2 (<1)	2 (<1)	0
Unknown	17 (4)	15 (4)	2 (2)
Time since diagnosis			
≤6 months	37 (9)	13 (4)	24 (27)
>6 months and ≤2 years	98 (23)	80 (24)	18 (20)
>2 and ≤5 years	119 (28)	91 (27)	28 (31)
>5 and ≤10 years	121 (28)	107 (32)	14 (16)
>10 years	50 (12)	45 (13)	5 (6)
History of carcinoid symptoms			
Flushing	315 (73)	260 (77)	55 (61)
Diarrhea	346 (81)	291 (86)	55 (61)
Elevated baseline CgA	282 (66)	229 (68)	53 (59)
Elevated baseline 5-HIAA	189 (44)	161 (47)	28 (31)

- Treatment arms were balanced for the percentages of patients who previously received SSA exposure: 80% (173/216) of patients randomly assigned to everolimus + octreotide LAR compared with 78% (166/213) of patients assigned to placebo + octreotide LAR (**Table 2**)
- Patients in both treatment arms had similar durations of previous SSA exposure: 1.7 years for everolimus + octreotide LAR compared with 1.8 years for placebo + octreotide LAR (**Table 2**)

Table 2. Previous SSA Exposure by Study Treatment

	All	Everolimus + Octreotide LAR	Placebo + Octreotide LAR
Patients, N[a]	339	173	166
Median (range) duration of previous SSA exposure, years	1.8 (0-12.5)	1.7 (0-11.7)	1.8 (0-12.5)
<6 months, n (%)	62 (18.3)	35 (20.2)	27 (16.3)
6 months to <2 years, n (%)	118 (34.8)	55 (31.8)	63 (38.0)
2 to <5 years, n (%)	101 (29.8)	52 (30.1)	49 (29.5)
≥5 years, n (%)	58 (17.1)	31 (17.9)	27 (16.3)

Percentages are based on N (number of evaluable patients in each treatment arm).
[a]All patients received previous SSA therapy.

Efficacy

- For all tumor sites, PFS was prolonged (25.2 months) in patients who were treated with everolimus + octreotide LAR and had not previously received SSA therapy compared with those who had previously received SSA therapy (14.3 months) (**Table 3**)
- When small intestine as the primary site was excluded, the PFS seen in patients treated with everolimus + octreotide was similar in patients with and without previous SSA therapy (**Table 3**)
- When small intestine was the primary tumor site, patients who were treated with everolimus + octreotide LAR had longer median PFS than did those who received placebo + octreotide LAR in the overall population and regardless of previous SSA therapy (**Table 3**)
- Among patients with small intestine NET who received placebo + octreotide LAR, those who were SSA naive had a median PFS of 22.7 (**Table 3**)
- Patients in the placebo + octreotide arm who were previously treated with SSA (median exposure, 1.8 years) even after confirmation of disease progression (criteria at study entry) still experienced PFS of 11.1 months (**Table 3**); a possible effect of an increased octreotide dose to 30 mg (some patients were receiving lower doses before study entry) cannot be excluded

Table 3. PFS Analysis by Previous SSA Exposure

	Overall Population N = 429		Previous SSA Exposure n = 339		No Previous SSA Exposure n = 90	
	Everolimus + Octreotide LAR	Placebo + Octreotide LAR	Everolimus + Octreotide LAR	Placebo + Octreotide LAR	Everolimus + Octreotide LAR	Placebo + Octreotide LAR
All tumor sites						
Patients, N	216	213	173	166	43	47
Median PFS (95% CI)	16.4 (13.7-21.2)	11.3 (8.4-14.3)	14.3 (12.0-20.1)	11.1 (8.4-14.6)	25.2 (12.0-NR)	13.6 (8.2-22.7)
HR	0.77 (0.59-1.00)		0.81 (0.60-1.09)		0.63 (0.35-1.11)	
P	0.026		0.077		0.054	
All tumor sites (excluding small intestine)						
Patients, n	105	100	79	70	26	30
Median PFS (95% CI)	14.0 (11.0-20.1)	8.7 (6.6-13.9)	14.0 (11.0-20.1)	11.0 (6.6-14.3)	13.8 (8.6-27.8)	8.3 (5.6-22.2)
Small intestine NET						
Patients, n	111	113	94	96	17	17
Median PFS (95% CI)	18.6 (13.6-25.9)	14.0 (9.4-19.8)	17.1 (11.2-24.8)	11.1 (8.3-19.3)	NR (13.7-NR)	22.7 (11.1-30.4)

NR, not reached.

CONCLUSIONS

- **In the RADIANT-2 study—the largest randomized, double-blind, placebo-controlled, phase III trial in patients with advanced NET associated with carcinoid syndrome—combination treatment with everolimus + octreotide LAR compared with octreotide LAR alone delayed disease progression by 5.1 months according to central review[9]**
- **Everolimus + octreotide LAR treatment demonstrated benefit and prolonged PFS regardless of previous SSA exposure**
- **Patients with progressing advanced NET who were SSA naive had longer median PFS when treated with octreotide LAR alone than did patients who had previously received SSA; however, other confounding factors that might have contributed to the difference in PFS between treatment arms could not be ruled out**

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Presented at the 4th Annual Neuroendocrine Tumor Symposium; October 20–22, 2011; Minneapolis, Minnesota

This study was sponsored by Novartis Pharmaceuticals Corporation.