Correlation of Progression-Free Survival With Early Response of Biomarkers Chromogranin A and 5-Hydroxyindoleacetic Acid Levels in Patients With Advanced Neuroendocrine Tumors: Phase III RADIANT-2 Study Results

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BACKGROUND

- Neuroendocrine tumors (NET) are a heterogeneous group of malignancies that can arise from neuroendocrine cells throughout the body[1,2] and are defined by the presence of secretory granules within tumor cells stained by chromogranin A (CgA) antibodies[3]
- More recently, plasma measurement of CgA has become available and has demonstrated that CgA is a sensitive general biomarker of NET.[4] Additionally, in functioning tumors, 5-hydroxyindoleacetic acid (5-HIAA), a biomarker for carcinoid syndrome,[5] should be measured in 24-hour urine samples
  - Biomarkers such as 5-HIAA and CgA act as indicators of secretory symptoms and tumor burden, respectively, in patients with NET[4,5]
  - The prognostic roles of these 2 biomarkers have not been evaluated in large patient populations, and only 1 study previously analyzed their roles as surrogate markers in NET[6]
- Octreotide long-acting repeatable (LAR) reduces 5-HIAA levels by 38% to 50% in patients with NET and controls the symptoms of diarrhea and flushing associated with carcinoid syndrome[7]; octreotide LAR is also associated with reductions in CgA in patients with NET[8,9]
- Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), demonstrated antitumor activity in patients with advanced NET, both as a single agent and in combination with octreotide LAR, in phase II and phase III studies[6,10,11]
- In the large, randomized, double-blind, placebo-controlled, phase III RADIANT-2 trial, everolimus + octreotide LAR compared with placebo + octreotide LAR demonstrated a clinically meaningful 5.1-month improvement in median progression-free survival (PFS) (16.4 months vs 11.3 months) in 429 patients with low- to intermediate-grade advanced NET and a history of secretory symptoms (flushing, diarrhea, or both)[12]
  - Everolimus significantly reduced or normalized serum CgA ($P = 0.004$) and 24-hour urinary 5-HIAA levels compared with placebo + octreotide LAR ($P < 0.001$)[13]

OBJECTIVE

- To correlate baseline serum CgA and urinary 5-HIAA levels and early biomarker responses with PFS in patients with advanced NET in the phase III RADIANT-2 trial

METHODS

- RADIANT-2 was an international, multicenter, double-blind, placebo-controlled, phase III study[12]
- Biomarkers were assessed at baseline for all patients and on day 1 of each 28-day cycle for each patient whose baseline level was elevated
  - Serum was collected for CgA measurement
  - 24-hour urine output was collected for 5-HIAA measurement
  - Samples were analyzed by a central laboratory (Quest Diagnostics) using enzyme-linked immunosorbent assay for CgA and high-performance liquid chromatography for 5-HIAA
- For purposes of these analyses, elevated baseline levels were defined as >2× upper limit of normal (ULN) for CgA and >2× ULN for 5-HIAA, and only those patients with ≥1 evaluable post-baseline measurement were included
  - Early biomarker response was defined as ≥30% reduction from baseline in biomarker levels during the first cycle (4 weeks) of treatment in patients who had elevated levels at baseline

RESULTS

- Baseline assessments of serum CgA levels were available for evaluation in 212 of 216 (98%) of patients randomly assigned to everolimus + octreotide LAR and 208 of 213 (98%) of patients randomly assigned to placebo + octreotide LAR
  - 152 of 216 (70%) of patients receiving everolimus + octreotide LAR and 130 of 213 (61%) of patients receiving placebo + octreotide LAR had elevated CgA levels at baseline
  - 36% of evaluable patients had a ≥30% reduction in CgA levels on the first day of cycle 2 after 4 weeks of treatment with everolimus + octreotide LAR compared with 23% of those treated with placebo + octreotide LAR
- Baseline assessments of 24-hour urinary 5-HIAA levels were available for 187 of 216 (87%) of patients randomly assigned to everolimus + octreotide LAR and 191 of 213 (90%) of patients randomly assigned to placebo + octreotide LAR
  - 127 of 216 (59%) of patients randomly assigned to everolimus + octreotide LAR and 126 of 213 (59%) of patients randomly assigned to placebo + octreotide LAR had elevated 5-HIAA levels at baseline
  - 37% of evaluable patients had a ≥30% reduction in 5-HIAA levels on the first day of cycle 2 after 4 weeks of treatment with everolimus + octreotide LAR compared with 24% of those treated with placebo + octreotide LAR
- Patients who previously received somatostatin analog therapy were less likely to experience early CgA response (86% nonresponders vs 73% responders) or early 5-HIAA response (91% nonresponders vs 66% responders) (**Table 1**)
- Patients with ≥2 involved organs were less likely to experience early CgA response (80% nonresponders vs 70% responders) or early 5-HIAA response (82% nonresponders vs 70% responders) (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics Biomarker Response and Treatment

Patient Characteristics, n (%)	CgA Responders			CgA Nonresponders			5-HIAA Responders			5-HIAA Nonresponders		
	All Patients N = 77	Everolimus + Octreotide LAR n = 49	Placebo + Octreotide LAR n = 28	All Patients N = 179	Everolimus + Octreotide LAR n = 86	Placebo + Octreotide LAR n = 93	All Patients N = 61	Everolimus + Octreotide LAR n = 36	Placebo + Octreotide LAR n = 25	All Patients N = 139	Everolimus + Octreotide LAR n = 61	Placebo + Octreotide LAR n = 78
Age												
<65 years	50 (65)	29 (59)	21 (75)	105 (59)	51 (59)	54 (58)	35 (57)	22 (61)	13 (52)	91 (66)	36 (59)	55 (71)
≥65 years	27 (35)	20 (41)	7 (25)	74 (41)	35 (41)	39 (42)	26 (43)	14 (39)	12 (48)	48 (35)	25 (41)	23 (30)
Sex												
Male	44 (57)	24 (49)	20 (71)	96 (54)	45 (52)	51 (55)	33 (54)	19 (53)	14 (56)	80 (58)	33 (54)	47 (60)
Female	33 (43)	25 (51)	8 (29)	83 (46)	41 (48)	42 (45)	28 (46)	17 (47)	11 (44)	59 (42)	28 (46)	31 (40)
Region												
Europe	36 (47)	22 (45)	14 (50)	84 (47)	37 (43)	47 (51)	28 (46)	13 (36)	15 (60)	57 (41)	22 (36)	35 (45)
United States	33 (43)	21 (43)	12 (43)	80 (45)	43 (50)	37 (40)	26 (43)	19 (53)	7 (28)	71 (51)	35 (57)	36 (46)
Other	8 (10)	6 (12)	2 (7)	15 (8)	6 (7)	9 (10)	7 (12)	4 (11)	3 (12)	11 (8)	4 (7)	7 (9)
Time since initial diagnosis												
≤6 months	6 (8)	3 (6)	3 (11)	16 (9)	6 (7)	10 (11)	8 (13)	4 (11)	4 (16)	9 (7)	2 (3)	7 (9)
>6 months to ≤2 years	16 (21)	10 (20)	6 (21)	37 (21)	16 (19)	21 (23)	15 (25)	9 (25)	6 (24)	25 (18)	9 (15)	16 (21)
>2 to ≤5 years	21 (27)	19 (39)	2 (7)	47 (26)	25 (29)	22 (24)	14 (23)	10 (28)	4 (16)	37 (27)	17 (28)	20 (26)
>5 years	33 (43)	16 (33)	17 (61)	78 (44)	39 (45)	39 (42)	23 (38)	12 (33)	11 (44)	67 (48)	33 (54)	34 (44)
Histologic grade												
Well differentiated	62 (81)	37 (76)	25 (89)	147 (82)	67 (78)	80 (86)	51 (84)	28 (78)	23 (92)	116 (84)	50 (82)	66 (85)
Moderately differentiated	12 (16)	9 (18)	3 (11)	25 (14)	14 (16)	11 (12)	9 (15)	8 (22)	1 (4)	17 (12)	6 (10)	11 (14)
Poorly differentiated	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	3 (4)	3 (6)	0 (0)	6 (3)	5 (6)	1 (1)	1 (2)	0 (0)	1 (4)	6 (4)	5 (8)	1 (1)
WHO PS												
0	40 (52)	23 (47)	17 (61)	105 (59)	45 (53)	60 (65)	37 (61)	19 (53)	18 (72)	90 (65)	36 (59)	54 (69)
1	35 (46)	24 (49)	11 (39)	61 (34)	33 (38)	28 (30)	22 (36)	16 (44)	6 (24)	41 (30)	21 (34)	20 (26)
2	2 (3)	2 (4)	0 (0)	13 (7)	8 (9)	5 (5)	2 (3)	1 (3)	1 (4)	8 (6)	4 (7)	4 (5)
Previous long-acting somatostatin analog therapy	56 (73)	38 (78)	18 (64)	154 (86)	74 (86)	80 (86)	40 (66)	27 (75)	13 (52)	126 (91)	55 (90)	71 (91)
Organs involved												
1	23 (30)	16 (33)	7 (25)	36 (20)	17 (20)	19 (20)	18 (30)	13 (36)	5 (20)	25 (18)	10 (16)	15 (19)
2	20 (26)	11 (22)	9 (32)	64 (36)	28 (33)	36 (39)	18 (30)	10 (28)	8 (32)	44 (32)	18 (30)	26 (33)
≥3	34 (44)	22 (45)	12 (43)	79 (44)	41 (48)	38 (41)	25 (41)	13 (36)	12 (48)	70 (50)	33 (54)	37 (47)
History of tumor-related symptoms	72 (94)	45 (92)	27 (96)	177 (99)	84 (98)	93 (100)	60 (98)	36 (100)	24 (96)	137 (99)	59 (97)	78 (100)
Diarrhea	64 (83)	40 (82)	24 (86)	146 (82)	68 (79)	78 (84)	52 (85)	31 (86)	21 (84)	114 (82)	48 (79)	66 (85)
Flushing	54 (70)	36 (74)	18 (64)	148 (83)	74 (86)	74 (80)	40 (66)	27 (75)	13 (52)	114 (82)	52 (85)	62 (80)
Tumor-related symptoms at study entry	59 (77)	37 (76)	22 (79)	157 (88)	74 (86)	83 (89)	49 (80)	31 (86)	18 (72)	120 (86)	53 (87)	67 (86)
Diarrhea	48 (62)	31 (63)	17 (61)	117 (65)	55 (64)	62 (67)	39 (64)	25 (69)	14 (56)	90 (65)	38 (62)	52 (67)
Flushing	42 (55)	28 (57)	14 (50)	125 (70)	59 (69)	66 (71)	29 (48)	18 (50)	11 (44)	96 (69)	44 (72)	52 (67)

WHO PS, World Health Organization performance status.

- PFS was significantly longer for patients with nonelevated baseline CgA biomarker levels than for patients with elevated baseline CgA biomarker levels (26.8 months vs 11.3 months; $P < 0.001$) (**Table 2**)
- Biomarker analyses based on both treatment arms combined showed baseline CgA (≤2× ULN vs >2× ULN; hazard ratio [HR], 0.43; 95% CI, 0.32-0.59; $P < 0.001$) had a prognostic effect on PFS (**Table 2**)

Table 2. Median PFS per Adjudicated Central Review by Biomarker Baseline Levels

	Elevated Baseline Biomarker Levels	Nonelevated Baseline Biomarker Levels
	CgA >2× ULN n = 282	**CgA ≤2× ULN n = 138**
Median PFS (95% CI)	11.3 months (9.7-13.8)	26.8 months (17.7-NR)
HR (95% CI)	0.43 (0.32-0.59) $P < 0.001$[a]	
	5-HIAA >2× ULN n = 253	**5-HIAA ≤2× ULN n = 125**
Median PFS (95% CI)	13.6 months (11.0-16.1)	15.4 months (11.7-21.2)
HR (95% CI)	0.79 (0.58-1.06) $P = 0.119$[a]	

NR, not reached.
[a]*P* values were obtained from a 2-sided log-rank test stratified by treatment.

- Treatment with everolimus + octreotide LAR resulted in significantly longer PFS for patients with elevated baseline CgA biomarker levels (13.9 months vs 8.4 months; $P = 0.003$) or elevated baseline 5-HIAA biomarker levels (16.4 months vs 9.7 months; $P = 0.007$) than placebo + octreotide LAR treatment (**Table 3**)
- Patients with nonelevated baseline CgA or 5-HIAA biomarker levels treated with everolimus + octreotide LAR also had improved, but not statistically significantly prolonged, PFS compared with patients who received placebo + octreotide LAR (**Table 3**)

Table 3. Median PFS per Adjudicated Central Review by Biomarker Baseline Levels and Treatment

	Elevated Baseline Biomarker Levels			
	CgA > 2× ULN n = 282		**5-HIAA > 2× ULN n = 253**	
	Everolimus + Octreotide LAR n = 152	**Placebo + Octreotide LAR n = 130**	**Everolimus + Octreotide LAR n = 127**	**Placebo + Octreotide LAR n = 126**
Median PFS (95% CI)	13.9 months (11.3-17.1)	8.4 months (7.7-11.1)	16.4 months (12.2-22.9)	9.7 months (9.3-13.8)
HR (95% CI)	0.66 (0.48-0.89) $P = 0.003$[a]		0.66 (0.47-0.92) $P = 0.007$[a]	
	Nonelevated Baseline Biomarker Levels			
	CgA ≤2× ULN n = 138		**5-HIAA ≤2× ULN n = 125**	
	Everolimus + Octreotide LAR n = 60	**Placebo + Octreotide LAR n = 78**	**Everolimus + Octreotide LAR n = 60**	**Placebo + Octreotide LAR n = 65**
Median PFS (95% CI)	31.3 months (19.3-NR)	20.1 months (13.0-NR)	20.1 months (13.7-NR)	13.0 months (6.6-19.1)
HR (95% CI)	0.74 (0.42-1.28) $P = 0.140$[a]		0.73 (0.44-1.21) $P = 0.110$[a]	

NR, not reached.
[a]*P* value was obtained from a 1-sided log-rank test.

- Patients who experienced early CgA response within the first cycle of treatment had significant improvement in PFS compared with nonresponders (20.0 months vs 10.8 months; HR, 0.49; 95% CI, 0.33-0.72; $P < 0.001$) (**Table 4**)
- Patients who experienced early 5-HIAA response within the first cycle of treatment also had improvement in PFS compared with nonresponders (17.1 months vs 12.0 months; HR, 0.76; 95% CI, 0.51-1.15; $P = 0.193$) (**Table 4**)

Table 4. Median PFS per Adjudicated Central Review by Biomarker Response

	Biomarker Responders	Biomarker Nonresponders
	CgA Responders n = 77	**CgA Nonresponders n = 179**
Median PFS (95% CI)	20.0 months (13.8-27.8)	10.8 months (8.3-11.7)
HR (95% CI)	0.49 (0.33-0.72) $P < 0.001$[a]	
	5-HIAA Responders n = 61	**5-HIAA Nonresponders n = 139**
Median PFS (95% CI)	17.1 months (11.3-25.9)	12.0 months (8.4-14.3)
HR (95% CI)	0.76 (0.51-1.15) $P = 0.193$[a]	

Response analysis included only patients with elevated baseline values.
[a]*P* values were obtained from a 2-sided log-rank test stratified by treatment.

CONCLUSIONS

- **The RADIANT-2 trial included a large population of patients with advanced NET and allowed, for the first time, assessment of the effect of elevated versus nonelevated baseline CgA and 5-HIAA biomarker levels and early biomarker response on PFS within 4 weeks of treatment**
- **Baseline CgA and 5-HIAA biomarker levels have prognostic, but not predictive, effects on PFS regardless of treatment; patients with elevated levels have significantly shorter PFS than patients with nonelevated levels**
  - **Treatment effects were observed in patients with elevated and in patients with nonelevated baseline biomarker values**
  - **Patients with nonelevated baseline biomarker levels also had increased PFS when treated with everolimus + octreotide LAR, but the increased PFS did not reach statistical significance**
- **Regardless of treatment, early CgA response was associated with significantly improved PFS ($P < 0.001$) compared with CgA nonresponse in all patients, suggesting that early CgA response may serve as a surrogate for favorable PFS**
- **Greater understanding is needed of the relationship between the antisecretory and the antitumor activities of everolimus + octreotide LAR**

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