

Impact of Prior Chemotherapy Use on the Efficacy of Everolimus in Patients With Advanced Pancreatic Neuroendocrine Tumors

A Subgroup Analysis of the Phase III RADIANT-3 Trial

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Objective: The aim of this study was to evaluate efficacy and safety of everolimus in patients with pancreatic neuroendocrine tumors (pNET) by prior chemotherapy use in the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3).

Methods: Patients with advanced, progressive, low- or intermediate-grade pNET were prospectively stratified by prior chemotherapy use and World Health Organization performance status and were randomly assigned (1:1) to everolimus 10 mg/d (n = 207) or placebo (n = 203).

Results: Of the 410 patients, 204 (50%) were naive to chemotherapy (chemonaive). Baseline characteristics were similar for patients with or without prior chemotherapy. Everolimus significantly prolonged median progression-free survival regardless of prior chemotherapy use (prior chemotherapy: 11.0 vs 3.2 months; hazard ratio, 0.34; 95% confidence interval, 0.25–0.48; $P < 0.0001$) (chemonaive: 11.4 vs 5.4 months; hazard ratio, 0.42; 95% confidence interval, 0.29–0.60; $P < 0.0001$). Stable disease was the best overall response in 73% of everolimus-treated patients (151/207). The most common drug-related adverse events included stomatitis (60%–69%), rash (47%–50%), and diarrhea (34%).

Conclusions: As more treatment options become available, it is important to consider the goals of treatment and to identify patients who would potentially benefit from a specific therapy. Findings from this planned subgroup analysis suggest the potential for first-line use of everolimus in patients with advanced pNET.

Key Words: chemotherapy, everolimus, first-line therapy, mammalian target of rapamycin inhibition

Abbreviations: AE - adverse event, CI - confidence interval, HR - hazard ratio, NET - neuroendocrine tumors, PFS - progression-free survival, pNET - pancreatic neuroendocrine tumors, RADIANT - RAD001 in Advanced Neuroendocrine Tumors, RECIST - Response Evaluation Criteria in Solid Tumors, SSA - somatostatin analogue, WHO - World Health Organization

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Neuroendocrine tumors (NET) are a family of malignancies with diverse origins, including gastrointestinal tract, lung, and pancreas.¹ Pancreatic NET (pNET) arise from endocrine cells in the pancreas and may have a more aggressive course in patients with advanced disease.² A review of all cases of pNET registered in the United States–based Surveillance, Epidemiology, and End Results database from 1973 to 2000 suggested that the annual estimated incidence of pNET is 2.2 every 1,000,000.³ The incidence and prevalence of pNET is increasing.¹ These tumors represent approximately 1.3% of all cases of pancreatic cancer in incidence and 10% of cases in prevalence.⁴

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version of the manuscript. Sotirios Stergiopoulos participated in the study design, conducted statistical analysis, reviewed the manuscript drafts, and approved the final version of the manuscript. Manisha H. Shah enrolled patients, treated patients in accordance with the protocol, collected data, and approved the final version of the manuscript. Jaume Capdevila recruited patients, reviewed the manuscript, and approved the final version of the manuscript. Rodney Pommier enrolled patients in the trial, participated in the conduct of the trial, drafted and edited the manuscript, and approved the final version of the manuscript.

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With the exception of small insulinomas, pNET are usually diagnosed at an advanced stage, and most are metastatic. Approximately 65% of patients present with unresectable or metastatic disease.¹ Pancreatic NET may secrete bioactive peptide hormones. Those that secrete the compounds and cause clinical symptoms are called *functional*.⁵ The incidence of functional pNET in the Surveillance, Epidemiology, and End Results analysis was determined to be 0.2 every 1,000,000 cases, corresponding to 10% of all pNET.³ Therapeutic management of pNET depends on the degree of differentiation of the tumor (well differentiated vs poorly differentiated), stage at diagnosis, and presence of symptoms from hormone oversecretion.⁵

Until the approval of everolimus and sunitinib in 2011, streptozocin was the only approved antitumor agent for pNET in the United States. Streptozocin was approved in 1982.⁶ In a small phase III randomized trial, the combination of streptozocin and doxorubicin demonstrated improvement in overall survival compared with combination streptozocin and fluorouracil or single-agent chlorozotocin.⁷ The efficacy of streptozocin-based chemotherapy for pNET in terms of response rate is difficult to determine because of changes in response criteria from the time of its initial approval for pNET to the present.⁵ Although temozolomide also has demonstrated clinical activity in pNET, its efficacy remains unclear because of the paucity of prospective clinical trial data. Since the approval of streptozocin for pNET, an increasing number of treatment options have become available. Data are limited, however, regarding which treatment should be used as first-line therapy. Although chemotherapy is recommended as first-line treatment for patients with poorly differentiated pNET, optimal use of chemotherapy in well-differentiated pNET continues to be debated.⁸

Everolimus, an oral mammalian target of rapamycin inhibitor, was approved by the US Food and Drug Administration and the European Medicines Agency's Committee for Medicinal Products for Human Use based, in part, on the positive results from 2 phase II trials (open-label RADIANT-1 [RAD001 in Advanced Neuroendocrine Tumors, First Trial] in patients who progressed after the failure of chemotherapy)^{9,10} and the phase III, randomized, placebo-controlled RADIANT-3 trial.¹¹ In the RADIANT-3 trial, everolimus significantly prolonged median progression-free survival (PFS) compared with placebo in patients with pNET (11.0 months vs 4.6 months; hazard ratio [HR], 0.35; 95% confidence interval [CI], 0.27–0.45; $P < 0.001$).¹¹ Given that chemotherapy was the only approved therapy for advanced pNET before the approval of oral targeted therapies, the RADIANT-3 protocol prospectively stratified patients according to prior exposure to chemotherapy at study entry.¹¹ The objective of this subgroup analysis was to evaluate the efficacy and safety of everolimus in the RADIANT-3 trial in patients with and without prior chemotherapy (ie, chemo-naïve).

MATERIALS AND METHODS

Study Design

The RADIANT-3 trial was a prospective, double-blind, randomized, parallel-group, placebo-controlled, multicenter, phase III study (trial registration: ClinicalTrials.gov, number NCT00510068, <http://clinicaltrials.gov/show/NCT00510068>). The detailed study design has been reported previously.¹¹ Patients were randomly assigned to receive either everolimus 10 mg/d or placebo in conjunction with best supportive care. Treatment was continued until disease progression, development of an unacceptable adverse event (AE), drug interruption of 3 weeks or longer, or withdrawal of consent. Patients were prospectively stratified according to

status with respect to prior chemotherapy (receipt vs no receipt) and World Health Organization (WHO) performance status (0 vs 1 or 2) at baseline. Patients who experienced disease progression could have their assigned treatment unblinded, and those who received placebo could receive open-label everolimus. The primary end point was PFS, documented by the local investigator according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0)¹² and defined as the time from randomization to the first documentation of disease progression or death from any cause. For the safety analysis, AEs were assessed using the National Cancer Institute Common Terminology Criteria for AEs (version 3.0).¹³ The study was reviewed by an independent ethics committee or institutional review board at each participating site and complied with the Declaration of Helsinki. All patients provided written informed consent before participation in the study.

Patient Population

Adult patients (18 years or older) with histologically confirmed low- or intermediate-grade advanced (unresectable or metastatic) pNET and radiological documentation of disease progression in the 12 months before randomization were eligible. Additional key inclusion criteria included the presence of measurable disease according to RECIST criteria¹² 1.0 using triphase computed tomography or multiphase magnetic resonance imaging for radiological assessment; WHO performance status of 2 or lower; and adequate bone marrow, renal, and hepatic function. Key exclusion criteria included cytotoxic chemotherapy, immunotherapy, or radiotherapy within 4 weeks before randomization; prior therapy with mammalian target of rapamycin inhibitors (sirolimus, temsirolimus, or everolimus); or ongoing long-term treatment with corticosteroids or other immunosuppressive agents.

Statistical Analyses

The cutoff date for this analysis was February 28, 2010. Progression-free survival was assessed with the Kaplan-Meier methodology, and study groups were compared using log-rank tests. Hazard ratios and CIs were calculated using a Cox proportional hazards model.

RESULTS

Demographics and Disposition

In the RADIANT-3 trial, 410 patients were randomly assigned (1:1) to everolimus 10 mg/d ($n = 207$) or placebo ($n = 203$).¹¹ Of these, 206 (50%) patients (104 patients in the everolimus arm and 102 patients in the placebo arm) had received chemotherapy before study entry, and 204 (50%) patients (103 patients in the everolimus arm and 101 patients in the placebo arm) were chemo-naïve.

Baseline demographics and clinical characteristics of patients who did and did not receive prior chemotherapy were similar (Table 1). More than 80% of the patients had well-differentiated disease, more than 90% had liver involvement, and the majority (>70%) had more than 1 tumor site before study entry. For both groups (prior chemotherapy and chemo-naïve), 22% to 26% of patients had functional pNET (gastrinoma, glucagonoma, VIPoma, insulinoma, or somatostatinoma). World Health Organization performance status was very good (0) in 61% of patients in the prior chemotherapy group and in 72% of patients in the chemo-naïve group. Similar proportions of patients had undergone radiotherapy in the prior chemotherapy group (22%) and the chemo-naïve group (21%). Somatostatin analogue (SSA) therapy was used in 45% of chemo-naïve patients and 54% of patients who received

TABLE 1. Baseline Demographics by Previous Chemotherapy Use

Characteristic	Previous Chemotherapy (n = 206)	No Previous Chemotherapy (Chemonaive) (n = 204)
Age, y		
<65, n (%)	154 (75)	145 (71)
≥65, n (%)	52 (25)	59 (29)
Median (range)	58 (23–87)	58 (20–86)
Sex, n (%)		
Male	118 (57)	109 (53)
Female	88 (43)	95 (47)
Race, n (%)		
White	163 (79)	159 (78)
Asian	37 (18)	37 (18)
Black	4 (2)	7 (3)
Other	2 (1)	1 (<1)
WHO performance status, n (%)		
0	126 (61)	146 (72)
1	75 (36)	51 (25)
2	5 (2)	7 (3)
Histological status of tumor, n (%)		
Well differentiated	174 (85)	167 (82)
Moderately differentiated	31 (15)	34 (17)
Unknown	1 (<1)	3 (2)
Time since initial diagnosis, n (%)		
≤6 mo	7 (3)	50 (25)
>6 mo to ≤2 y	52 (25)	56 (28)
>2 y to ≤5 y	83 (40)	52 (26)
>5 y	64 (31)	46 (23)
Time from disease progression to randomization, n (%)		
≤1 mo	69 (34)	65 (32)
>1 mo to ≤2 mo	50 (24)	46 (23)
>2 mo to ≤3 mo	31 (15)	28 (14)
>3 mo to ≤12 mo	53 (26)	59 (29)
>12 mo	2 (1)	2 (1)
Disease sites, n (%)		
1	54 (26)	59 (29)
2	72 (35)	77 (38)
≥3	80 (39)	67 (33)
Organ involved, n (%)		
Liver	193 (94)	184 (90)
Pancreas	90 (44)	86 (42)
Lymph nodes	89 (43)	92 (45)
Lung	28 (14)	30 (15)
Bone	22 (11)	20 (10)
Time between discontinuation of previous treatment and disease progression before study start, n (%)		
≤6 mo	96 (47)	13 (6)
>6 mo to ≤2 y	48 (23)	8 (4)
>2 y to ≤5 y	24 (12)	6 (3)

(Continued)

(Continued)

Characteristic	Previous Chemotherapy (n = 206)	No Previous Chemotherapy (Chemonaive) (n = 204)
>5 y	6 (3)	1 (<1)
Missing	32 (16)	176 (86)
Prior SSA use, n (%)		
Yes	111 (54)	92 (45)
No	95 (46)	112 (55)
Concomitant SSA use, n (%)		
Yes	79 (38)	84 (41)
No	127 (62)	120 (59)
Elevated baseline CgA, n (%)	110 (53)	108 (53)
Elevated baseline NSE, n (%)	143 (69)	150 (74)

CgA, chromogranin A; NSE, neuron-specific enolase; SSA, somatostatin analogue; WHO, World Health Organization.

prior chemotherapy. A smaller proportion of chemonaive patients (49% vs 71% who received prior chemotherapy) had diagnosis of pNET more than 2 years before study entry.

The median duration of everolimus treatment for patients who received prior chemotherapy was 35.9 (range, 3.6–106.0) weeks. In those who were naive to chemotherapy, the median duration of everolimus exposure was 41.8 (range, 1.1–118.1) weeks. In the placebo arm, the median duration of treatment was 13.4 (range, 0.4–87.4) weeks for patients with a history of chemotherapy treatment and 23.9 (range, 1.7–132.4) weeks for those patients who did not receive prior chemotherapy. For the prior chemotherapy group, treatment duration of at least 52 weeks was observed among 28% of patients in the everolimus arm (vs 34% of patients in the everolimus arm who were chemonaive) and 10% of patients in the placebo arm who received prior chemotherapy (vs 12% of patients in the placebo arm who were chemonaive).

As of the cutoff date, treatment was ongoing in the everolimus arm for 32% of patients who received prior chemotherapy and for 32% of patients who had no prior exposure to chemotherapy, whereas in the placebo arm, treatment was ongoing for 9% of patients who received prior chemotherapy and 17% of those who were chemonaive. Primary reasons for discontinuation of treatment for patients who received prior chemotherapy included disease progression (41% of patients in the everolimus arm vs 87% in the placebo arm), AEs (23% vs 2%), withdrawal of consent (1% in each arm), and death (3% vs 1%). For chemonaive patients, the primary reasons for discontinuation of treatment included disease progression (48% of patients in the everolimus arm vs 73% in the placebo arm), AEs (12% vs 5%), withdrawal of consent (3% in each arm), and death (1% vs 2%).

Efficacy

Everolimus improved PFS regardless of prior chemotherapy use (Fig. 1). For patients who received prior chemotherapy, the median PFS assessed by local investigator review was 11.0 months (95% CI, 8.2–13.9) for everolimus versus 3.2 (2.8–5.1) months for placebo, representing a 3.5-fold prolongation in median PFS and a 66% reduction in the estimated risk for progression (HR, 0.34; 95% CI, 0.25–0.48; $P < 0.0001$). For patients who were chemonaive, the median PFS per local investigator review for everolimus was 11.4 months (95% CI, 8.3–15.4) versus 5.4 months (95% CI, 3.2–5.6) for placebo, representing a 2.1-fold prolongation in median PFS and a 58% reduction in the estimated

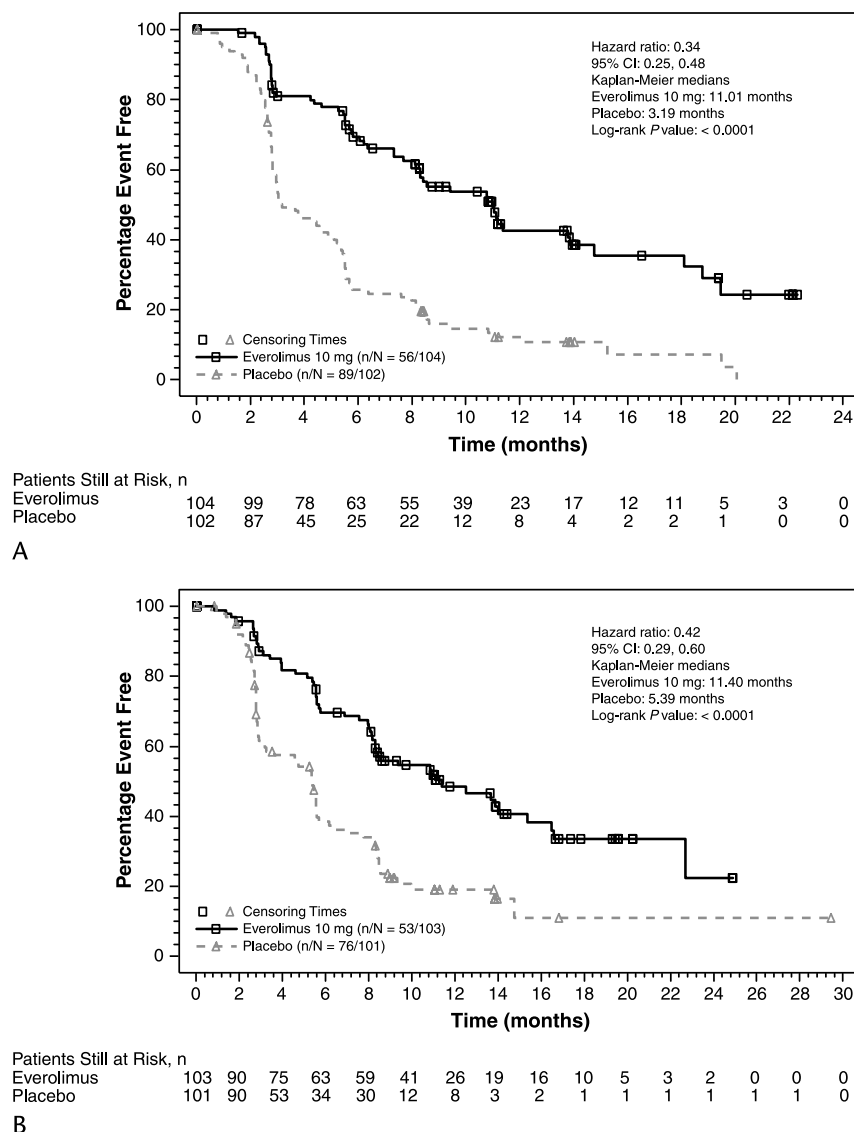


FIGURE 1. Progression-free survival assessed by local investigators for both treatment arms (everolimus and placebo) in the patients who received prior chemotherapy (A) and did not receive prior chemotherapy (B).

risk for progression (HR for disease progression or death with everolimus, 0.42; 95% CI, 0.29–0.60; $P < 0.0001$).

The median PFS assessment by independent adjudicated central review was consistent with the assessment by local investigators (Fig. 2). In the prior chemotherapy group, median PFS according to central assessment was 11.4 months (95% CI, 8.7–18.1) for everolimus versus 5.5 months (95% CI, 3.1–6.4) for placebo (HR for disease progression or death with everolimus, 0.32; 95% CI, 0.21–0.48; $P < 0.0001$). For the chemonaive group, median PFS (per central review) for everolimus was 14.0 months (95% CI, 11.2–19.8) versus 8.3 months (95% CI, 5.5–10.0) for placebo (HR for disease progression or death with everolimus, 0.45; 95% CI, 0.29–0.70; $P < 0.0001$).

The response waterfall plot for patients who did and did not receive prior chemotherapy is shown in Figure 3. No differences in objective response rate or disease control rate were observed between previously treated and chemonaive patients (Table 2).

Safety

Safety findings according to prior chemotherapy use and treatment were similar to those reported for the overall population.¹¹ Most reported AEs were grade 1 or 2. The most common drug-related AEs occurring with a frequency of 10% or greater are listed in Table 3. The most common drug-related AEs (prior chemotherapy vs chemonaive group) included stomatitis (59.6% vs 69.0%), rash (50.0% vs 47.0%), diarrhea (33.7% vs 34.0%), and fatigue (28.8% vs 34.0%). In the everolimus arm, the frequency of grade 3 or 4 drug-related stomatitis (6.7% of patients in the prior chemotherapy group vs 7.0% in the chemonaive group), anemia (4.8% vs 7.0%), and pneumonitis (1.9% vs 3.0%) was comparable in both groups. In the everolimus arm, the proportion of patients who experienced grade 3 or 4 thrombocytopenia was higher in the prior chemotherapy group (5.8% vs 2.0% for the chemonaive group), and that of grade 3 or 4 hyperglycemia was

higher in the chemonaive group (8.0% vs 2.9% for the prior chemotherapy group).

DISCUSSION

In the present subgroup analysis based on prospective stratification according to prior chemotherapy use, we analyzed whether patients who received chemotherapy before enrolling in the RADIANT-3 trial had different outcomes than chemonaive patients. We observed consistent benefit in PFS among patients receiving everolimus compared with placebo irrespective of prior chemotherapy use. Everolimus improved median PFS by 7.8 months in patients who previously received chemotherapy and by 6.0 months in patients who were chemonaive. Primary results of the RADIANT-3 trial also reported a statistically significant and clinically meaningful median PFS benefit of 6.4 months in patients who received everolimus versus placebo (HR, 0.35; 95% CI, 0.27–0.45; $P < 0.001$) and a 65% risk reduction in PFS for patients with advanced pNET, who otherwise had a poor prognosis.¹¹ In the subgroup analysis, the benefit from everolimus with respect to PFS was seen in the stabilization of disease or minor tumor shrinkage and in the lower incidence of progressive disease regardless of prior chemotherapy use. Except for a higher

proportion of patients with newly diagnosed pNET in the chemonaive group and a higher proportion of healthier patients assessed by baseline WHO performance status in the prior chemotherapy group, both groups had similar baseline characteristics.

The treatment paradigm for pNET is evolving with the approval of new therapies. Until the availability of novel targeted therapeutic agents in 2011, chemotherapy remained an established and recommended therapeutic option for advanced pNET.⁸ The response rate for streptozocin in combination with fluorouracil or doxorubicin in patients with pNET was reported to be approximately 65% based on reduction of hepatomegaly and biochemical response in these early studies.^{7,14} Subsequent retrospective studies applying more rigorous objective response criteria, such as WHO or RECIST criteria, provided conflicting results with streptozocin-based chemotherapy and reported response rates ranging from 6% to 45%.^{15–19} In addition to concerns regarding the reproducibility of chemotherapy outcomes using modern criteria, significant cumulative toxicities can occur with systemic chemotherapy that limit its long-term use. Adverse events reported in the classic study by Moertel et al⁷ include vomiting (experienced by approximately 80% of patients on streptozocin), stomatitis, diarrhea, leukopenia, thrombocytopenia, nephrotoxicity

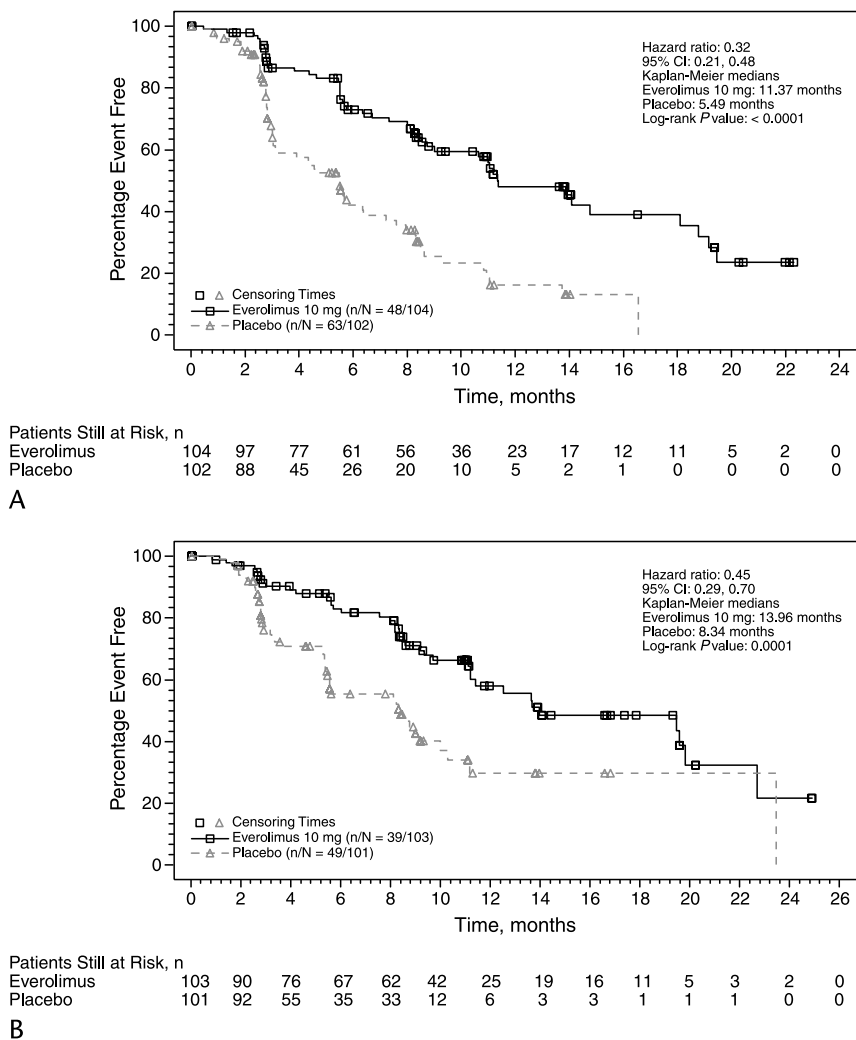


FIGURE 2. Progression-free survival review by the central adjudication committee for both treatment arms (everolimus and placebo) in the patients who received prior chemotherapy (A) and did not receive prior chemotherapy (B).

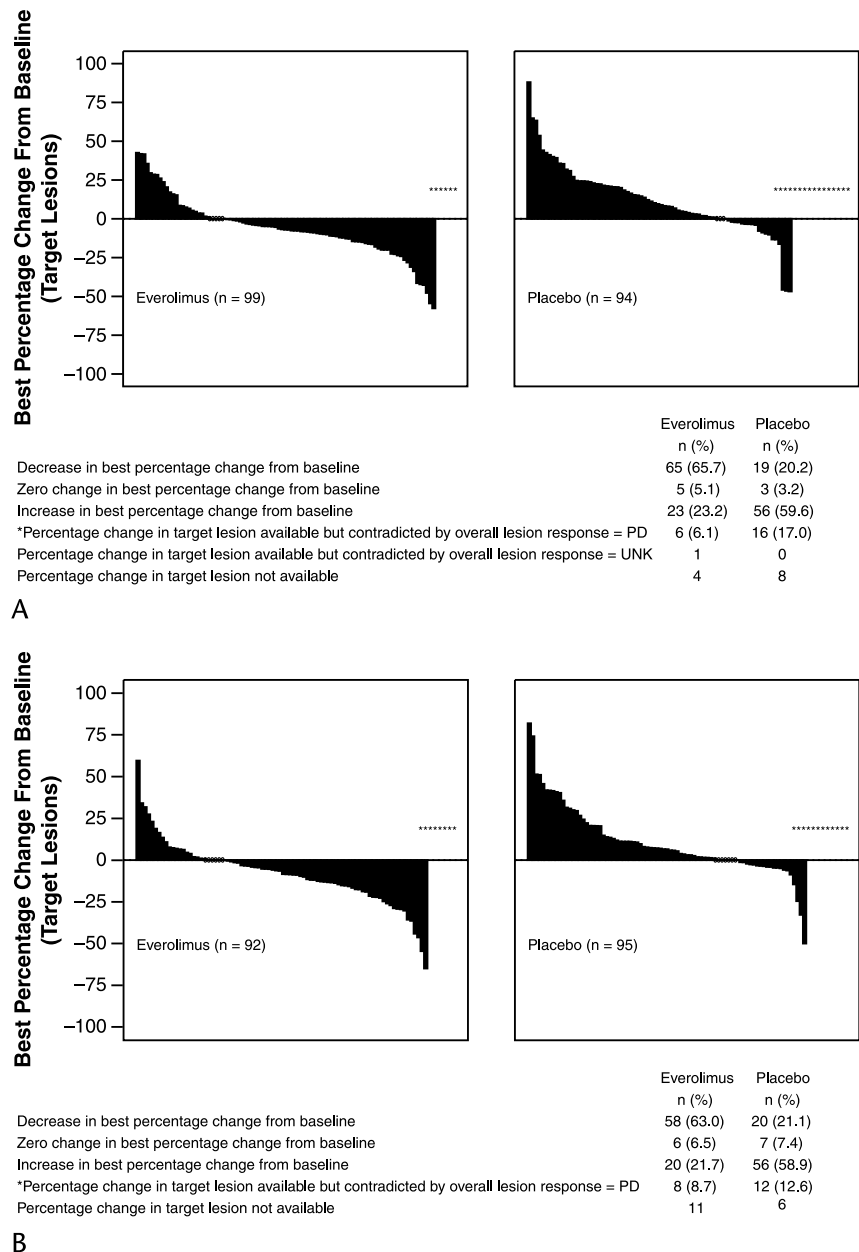


FIGURE 3. Percentage change from baseline in size of target lesion (waterfall plot) for both treatment arms (everolimus and placebo) in the patients who received prior chemotherapy (A) and did not receive prior chemotherapy (B). A, Data for 11 patients with lesions that could be evaluated in the everolimus arm and 24 in the placebo arm were not included in the analysis for the following reasons: 6 in the everolimus arm (6.1%) and 16 in the placebo arm (17.0%) showed a change in the available target lesion that contradicted the overall response of PD. One patient in the everolimus arm (1.0%) showed a change in the available target lesion, but the overall response was UNK. The change in the target lesion could not be assessed in 4 patients in the everolimus arm (4.0%) and 8 in the placebo arm (8.5%). B, For the chemo-naïve patients, data for 19 patients with lesions that could be evaluated in the everolimus arm and 18 in the placebo arm were not included in the analysis for the following reasons: 8 in the everolimus arm (8.7%) and 12 in the placebo arm (12.6%) showed a change in the available target lesion that contradicted the overall response of PD. The change in the target lesion could not be assessed in 11 patients in the everolimus arm (12.0%) and 6 in the placebo arm (6.3%). PD, progressive disease; UNK, unknown.

(using creatinine elevation criteria), and renal insufficiency (reported by 4%–7% of patients in all treatment groups). Modern supportive care can alleviate some, but not all, of these toxicities. Although they have not been approved by the US Food and Drug Administration or the European Medicines Agency, temozolomide-based chemotherapies have also been explored in patients with pNET.^{20,21} In a retrospective series evaluating temozolomide-based therapy, Kulke et al²² reported a partial

response rate of 34% (18/53 patients) for patients with pNET with the use of the RECIST criteria.²² In a recent phase II study by Chan et al,²³ temozolomide in combination with bevacizumab demonstrated a response rate of 33% for pNET patients with the use of the RECIST criteria. Because the number of pNET patients (n = 15) was small and the study did not require radiographic progression of disease before study entry,²³ it is not possible to directly compare the findings with those of RADIANT-3. The

TABLE 2. Best Overall Response by Investigator Review

	Previous Chemotherapy (N = 206)		No Previous Chemotherapy (Chemonaive) (N = 204)	
	Everolimus (n = 104)	Placebo (n = 102)	Everolimus (n = 103)	Placebo (n = 101)
Best overall response, n (%)				
CR	0	0	0	0
PR	5 (4.8)	2 (2.0)	5 (4.9)	2 (2.0)
SD	76 (73.1)	46 (45.1)	75 (72.8)	57 (56.4)
PD	16 (15.4)	47 (46.1)	13 (12.6)	38 (37.6)
UNK	7 (6.7)	7 (6.9)	10 (9.7)	4 (4.0)
Response analysis, n (%)				
ORR (CR or PR) [95% CI]	5 (4.8) [1.6–10.9]	2 (2.0) [0.2–6.9]	5 (4.9) [1.6–11.0]	2 (2.0) [0.2–7.0]
Disease control rate (CR + PR + SD)	81 (77.9)	48 (47.1)	80 (77.7)	59 (58.4)

CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.

use of temozolomide as a single agent has not been prospectively evaluated in pNET, and it is unclear whether activity with temozolomide-based regimens in pNET is attributable to temozolomide alone or to the agent used in combination. Therefore, its use in patients with advanced pNET remains undefined until evidence from multicenter, randomized trials is available.^{24–26}

To date, it is impossible to directly compare results from chemotherapy studies with results from the targeted therapies because most of the studies with chemotherapy were retrospective and most did not use modern response criteria such as RECIST to report efficacy.²⁶ The greatest advantage of recently approved targeted molecules, including everolimus and sunitinib, for the therapeutic management of advanced pNET is that they have been

TABLE 3. Drug-Related AEs Reported by 10% or More of the Patients

Preferred Term, n (%)	Prior Chemotherapy Use				No Prior Chemotherapy Use (Chemonaive)			
	Everolimus (n = 104)		Placebo (n = 102)		Everolimus (n = 100)		Placebo (n = 101)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Stomatitis*	62 (59.6)	7 (6.7)	17 (16.7)	0	69 (69.0)	7 (7.0)	17 (16.8)	0
Rash	52 (50.0)	0	10 (9.8)	0	47 (47.0)	1 (1.0)	11 (10.9)	0
Diarrhea	35 (33.7)	5 (4.8)	10 (9.8)	0	34 (34.0)	2 (2.0)	10 (9.9)	0
Fatigue	30 (28.8)	2 (1.9)	11 (10.8)	0	34 (34.0)	1 (1.0)	18 (17.8)	1 (1.0)
Infections†	23 (22.1)	3 (2.9)	6 (5.9)	1 (1.0)	23 (23.0)	2 (2.0)	6 (5.9)	0
Nausea	23 (22.1)	1 (1.0)	17 (16.7)	0	18 (18.0)	2 (2.0)	20 (19.8)	0
Peripheral edema	20 (19.2)	1 (1.0)	5 (4.9)	0	21 (21.0)	0	2 (2.0)	0
Decreased appetite	19 (18.3)	0	5 (4.9)	1 (1.0)	21 (21.0)	0	9 (8.9)	1 (1.0)
Headache	21 (20.2)	0	9 (8.8)	0	18 (18.0)	0	4 (4.0)	0
Dysgeusia	16 (15.4)	0	3 (2.9)	0	19 (19.0)	0	5 (5.0)	0
Anemia	21 (20.2)	5 (4.8)	2 (2.0)	0	14 (14.0)	7 (7.0)	4 (4.0)	0
Epistaxis	22 (21.2)	0	0	0	13 (13.0)	0	0	0
Pneumonitis‡	17 (16.3)	2 (1.9)	0	0	18 (18.0)	3 (3.0)	0	0
Weight loss	17 (16.3)	0	5 (4.9)	0	15 (15.0)	0	4 (4.0)	0
Vomiting	16 (15.4)	0	11 (10.8)	0	15 (15.0)	0	2 (2.0)	0
Pruritus	8 (7.7)	0	9 (8.8)	0	22 (22.0)	0	9 (8.9)	0
Hyperglycemia	11 (10.6)	3 (2.9)	4 (3.9)	2 (2.0)	16 (16.0)	8 (8.0)	5 (5.0)	2 (2.0)
Thrombocytopenia	15 (14.4)	6 (5.8)	1 (1.0)	0	12 (12.0)	2 (2.0)	0	0
Asthma	19 (18.3)	2 (1.9)	9 (8.8)	2 (2.0)	7 (7.0)	0	8 (7.9)	0
Nail disorder	9 (8.7)	0	2 (2.0)	0	15 (15.0)	1 (1.0)	0	0
Cough	8 (7.7)	0	2 (2.0)	0	14 (14.0)	0	1 (1.0)	0
Pyrexia	15 (14.4)	0	0	0	7 (7.0)	0	0	0
Dry skin	12 (11.5)	0	4 (3.9)	0	9 (9.0)	0	5 (5.0)	0

*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration.

†Includes all types of infection.

‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

studied in large, prospective, randomized, controlled clinical trials before being entered into the treatment paradigm. In addition, the pivotal trials evaluating the efficacy of these agents used RECIST version 1.0 criteria, facilitating objective evaluation of efficacy of the targeted agents. The phase III study that reported the efficacy of the oral tyrosine kinase inhibitor sunitinib in patients with advanced pNET did not stratify patients according to prior chemotherapy use²⁷; therefore, it is not possible to compare efficacy between the 2 targeted therapies.

Given the lack of evidence-based guidance and the heterogeneous nature of the disease, an individualized approach to the treatment of patients with NET has been recommended.⁵ The use of chemotherapy in the first-line setting is limited according to the patient's clinical and pathological characteristics. Streptozocin-based chemotherapy is an appropriate choice as first-line therapy in patients with rapidly progressive disease, or with high tumor burden (in whom further progression may be life threatening), or in symptomatic patients, whereas the combination of etoposide-cisplatin is a preferred therapeutic option for patients with poorly differentiated pNET.⁸

There is a strong need for evidence from robust, well-conducted, randomized, phase III studies to optimize the treatment paradigm of patients with well-differentiated, advanced (unresectable or metastatic) pNET. A phase III trial comparing everolimus versus streptozocin and crossover after progression or toxicity is planned (randomized, open-label study to compare the efficacy and safety of everolimus followed by chemotherapy with streptozocin–5-fluorouracil upon progression or the reverse sequence in advanced progressive pNET [SEQTOR]; NCT02246127). In addition, smaller phase II studies are exploring chemotherapy and everolimus combination therapy in pNET with the use of recent RECIST criteria and modern safety reporting. These include an ongoing randomized, phase II study using capecitabine and streptozocin with or without cisplatin in patients with pNET (NCT00602082). Phase II studies evaluating temozolomide in patients with advanced pNET (with capecitabine and bevacizumab, NCT01525082; with everolimus, NCT00576680) and in patients with well or moderately differentiated, metastatic NET (with capecitabine, NCT00869050) are also underway. To our knowledge, no trials are exploring the position of sunitinib within the treatment paradigm of combinations of chemotherapy and targeted agents.

The results presented here, together with the results from RADIANT-1,¹⁰ confirm the efficacy of everolimus in the post-chemotherapy setting and suggest that everolimus may also be efficacious as first-line therapy in patients with advanced pNET. In addition, everolimus has demonstrated long-term efficacy and tolerability. Some patients enrolled in RADIANT-3 have been treated with everolimus for more than 4 years but have stable disease and manageable AEs.²⁸ Importantly, the safety of everolimus was consistent with previous reports, regardless of patient history of chemotherapy exposure.^{10,11,29}

Prospective stratification of RADIANT-3 contributed to the statistical robustness of the present analysis. A few limitations deserve mention. First, imbalance in terms of baseline characteristics across study groups (WHO performance status, prior SSA use, and time since initial diagnosis) could have confounded the study outcomes. Second, in the prior chemotherapy group, the type of chemotherapy received by patients varied; however, previously mentioned ongoing studies, such as SEQTOR, will clarify study results in terms of individual agents. Lastly, the RADIANT-3 study enrolled patients who demonstrated disease progression before study entry but did not mandate progression while they received chemotherapy. Therefore, the patients in the prior chemotherapy group might have had tumors sensitive to

chemotherapy at the time of enrollment. Nevertheless, the efficacy of everolimus in patients who experienced disease progression while on chemotherapy has been demonstrated in the phase II RADIANT-1 study.¹⁰

In conclusion, the selection of specific subgroups of patients who would best respond to chemotherapy or everolimus in first-line treatment is an ongoing challenge for the treatment of patients with pNET. The present RADIANT-3 subgroup analysis demonstrates that patients with pNET benefit from everolimus regardless of prior chemotherapy use and suggests the potential for first-line use of everolimus in patients with advanced pNET.

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