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ORIGINAL REPORT

Daily Oral Everolimus Activity in Patients With Metastatic Pancreatic Neuroendocrine Tumors After Failure of Cytotoxic Chemotherapy: A Phase II Trial

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ABSTRACT

Purpose
No established treatment exists for pancreatic neuroendocrine tumor (NET) progression after failure of chemotherapy. Everolimus (RAD001), an oral inhibitor of mammalian target of rapamycin, in combination with octreotide has demonstrated encouraging antitumor activity in patients with NETs.

Patients and Methods
This open-label, phase II study assessed the clinical activity of everolimus in patients with metastatic pancreatic NETs who experienced progression on or after chemotherapy. Patients were stratified by prior octreotide therapy (stratum 1: everolimus 10 mg/d, n = 115; stratum 2: everolimus 10 mg/d plus octreotide long-acting release [LAR], n = 45). Tumor assessments (using Response Evaluation Criteria in Solid Tumors) were performed every 3 months. Chromogranin A (CgA) and neuron-specific enolase (NSE) were assessed monthly if elevated at baseline. Trough concentrations of everolimus and octreotide were assessed.

Results
By central radiology review, in stratum 1, there were 11 partial responses (9.6%), 78 patients (67.8%) with stable disease (SD), and 16 patients (13.9%) with progressive disease; median progression-free survival (PFS) was 9.7 months. In stratum 2, there were two partial responses (4.4%), 36 patients (80%) with SD, and no patients with progressive disease; median PFS was 16.7 months. Patients with an early CgA or NSE response had a longer PFS compared with patients without an early response. Coadministration of octreotide LAR and everolimus did not impact exposure to either drug. Most adverse events were mild to moderate and were consistent with those previously seen with everolimus.

Conclusion
Daily everolimus, with or without concomitant octreotide LAR, demonstrates antitumor activity as measured by objective response rate and PFS and is well tolerated in patients with advanced pancreatic NETs after failure of prior systemic chemotherapy.

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INTRODUCTION

Pancreatic neuroendocrine tumors (NETs), also known as pancreatic endocrine tumors or islet cell carcinomas, are thought to be rare and have a reported annual incidence of 0.32 cases per 100,000 in the Surveillance, Epidemiology, and End Results (SEER) Program registries.[1] They account for approximately 1% of pancreatic neoplasms by incidence and 10% by prevalence.[2] However, the reported incidence of NETs has increased over time.[1] The true incidence and prevalence may be significantly higher because many small tumors initially are thought to be benign and not reported to SEER.[3]

Advanced pancreatic NETs have a reputation for being more indolent than other pancreatic malignancies. However, they can be aggressive and are likely to be diagnosed at an advanced stage (14% localized, 22% regional, and 64% distant).[1] Analyses from the SEER data from 2000 to 2004 showed a median survival time of only 27 months among patients with advanced disease. Similar results were obtained from a large single-institution series.[4]

Pancreatic NETs are sometimes divided into functioning and nonfunctioning tumors based on

whether they cause clinical hormonal symptoms. However, the functional status of these tumors may change over time or with treatment. The introduction of somatostatin analogs has brought major advances in the management of hormonal syndromes from NETs[5,6] and has recently been shown to prolong time to tumor progression in patients with advanced midgut NETs.[7] Nevertheless, treatment options for progressive pancreatic NETs remain limited.

Despite the approval of streptozocin in 1976 by the US Food and Drug Administration, the role of chemotherapy continues to be debated. Earlier trials often used criteria to measure outcomes that are not accepted today. For example, cross-sectional imaging was not uniformly used to measure tumor size. Instead, physical examinations were sometimes used to document response to therapy. Two retrospective studies of 84 and 45 patients with advanced NETs treated with streptozocin-based chemotherapy demonstrated response rates by Response Evaluation Criteria in Solid Tumors (RECIST) or WHO criteria of 39% and 36%, respectively; however, treatment was associated with significant toxicity.[8,9] Finally, no published data have documented improvements in progression-free survival (PFS) or overall survival (OS) compared with best supportive care.[10-13] Other regimens using temozolomide-based chemotherapy have also been examined in prospective studies that included small numbers of pancreatic NETs but need confirmation in larger studies.[14-16]

Mammalian target of rapamycin (mTOR), an intracellular protein kinase, regulates cellular response to nutrients and energy and mediates signaling through growth factors (eg, insulin-like growth factor 1 [IGF-1]) downstream of their cognate receptors. Several genetic syndromes associated with NETs (tuberous sclerosis complex, neurofibromatosis, von Hippel-Lindau syndrome, and multiple endocrine neoplasia type 1) involve signaling through the mTOR pathway.[17] Sporadic NETs are known to coexpress both IGF-1 and its receptor (IGF-1R).[18,19] In pancreatic NET cell lines, IGF-1 has been shown to stimulate mTOR and increase cell proliferation.[18,19] In preclinical models, inhibition of mTOR activity suppresses NET growth.[19-21] Everolimus (RAD001) is an orally active mTOR inhibitor that blocks the mTOR pathway by binding to its intracellular receptor FKBP-12. In preclinical studies, everolimus inhibited tumor growth in a variety of human solid tumors, both in vitro and in vivo.[20,22-24]

A recent single-institution clinical trial evaluating everolimus in combination with octreotide long-acting release (LAR) found promising antitumor activity, as assessed by response rate and PFS, in patients with advanced NETs.[25] RADIANT-1 (RAD001 in Advanced Neuroendocrine Tumors) is a multinational phase II trial conducted to assess the antitumor activity of oral everolimus 10 mg daily in patients with advanced pancreatic NETs experiencing progression during or after cytotoxic chemotherapy. Patients were enrolled in one of two strata based on prior treatment with octreotide LAR to assess the clinical benefits of everolimus alone and in combination with octreotide LAR.

PATIENTS AND METHODS

Eligible patients had a histologically confirmed, well to moderately differentiated, advanced (unresectable or metastatic) pancreatic NET with progressive disease documented by RECIST during or after cytotoxic chemotherapy. Eligible patients were $\geq$ 18 years of age, with WHO performance status $\leq$ 2 and adequate bone marrow, hepatic, and renal function. Exclusion criteria included anticancer therapy within 3 weeks of enrollment, hepatic arterial embolization within 6 months, cryoablation within 2 months, concurrent or prior malignancy within 5 years, history of being immunocompromised, uncontrolled medical conditions, or any medical condition whose control might be jeopardized by the complications of therapy.

All patients provided written informed consent. The study and amendments were approved by the independent ethics committee or institutional review board for each participating center, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered with the US National Library of Medicine (ClinicalTrials.gov) as NCT00363051.

Study Design

This was an open-label, phase II, nonrandomized study stratified by ongoing octreotide therapy at study entry. Patients who were not being treated with octreotide at study entry were assigned to stratum 1 (everolimus 10 mg daily orally), and patients who were on octreotide LAR for at least 3 consecutive months at study entry were assigned to stratum 2 (everolimus 10 mg daily orally and octreotide LAR intramuscularly every 28 days at prestudy dose [$\leq$ 30 mg]). Patients enrolled onto stratum 2 were also required to have documented disease progression while receiving octreotide LAR. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. The primary end point of the study was objective response rate (ORR) in stratum 1. Secondary end points included ORR in stratum 2 and PFS, duration of response, OS, safety, and pharmacokinetics in both strata. Exploratory objectives included evaluation of biomarkers.

Efficacy and Safety Assessments

Efficacy was assessed according to RECIST (computed tomography or magnetic resonance imaging) at baseline and every 3 months; all radiographic images were reviewed locally at the investigative site and centrally (two independent reviewers). Patients were observed for survival every 3 months.

Safety evaluations (standard laboratory tests and physical examinations) were performed at baseline; at days 1, 15, and 29; and every 4 weeks thereafter. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Two everolimus dose reductions were permitted (5 mg daily and 5 mg every other day). Everolimus was discontinued if a patient could not tolerate everolimus 5 mg every other day or if toxicity required treatment interruption for more than 21 days. Everolimus was interrupted for CTCAE grade 3 hematologic or nonhematologic toxicity and resumed at one dose level lower after recovery to grade $\leq$ 1 (except hyperlipidemia). Everolimus was permanently discontinued for CTCAE grade 4 toxicity, except grade 4 neutropenia, which was managed with treatment interruption and dose reduction. In addition, dose reduction was required for grade 2 pneumonitis. Octreotide dose modifications were permitted at the investigator's discretion according to prescribing information.

Blood samples for biomarkers, including serum chromogranin A (CgA) and neuron-specific enolase (NSE), were collected and analyzed by a central laboratory (CgA: chemiluminescence enzyme linked immunosorbent assay, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA; NSE: enzyme immunoassay, CanAg Diagnostics, Gothenburg, Sweden) at baseline and monthly if elevated at baseline. Predose everolimus (trough) concentrations in whole blood were determined at day 15, day 29, and every month thereafter by liquid chromatography-mass spectrometry. Plasma octreotide concentrations in stratum 2 were determined at baseline, day 15, day 29, and every month thereafter by immunoassay.

Statistical Analyses

A two-stage Simon design allowing for early stopping was used independently in each stratum. In stratum 1, one or more responses were required in the initial 20 patients to continue accrual to 62 patients; four or more responses in the initial 62 patients were required to reject a null hypothesis of an ORR less than 3% versus an alternative hypothesis of $\geq$ 10% ORR (80% power). If the null hypothesis was rejected, accrual would continue to 100 patients. In stratum 2, two or more responses were required in the initial 29 patients to continue accrual to 44 patients; five or more responses were required in the 44 patients to reject the null hypothesis of an ORR less than 5% versus the

Table 1. Baseline Demographics and Clinical Characteristics of the Study Population

Demographic or Clinical Characteristic	Stratum 1 (n = 115) No. of Patients	%	Stratum 2 (n = 45) No. of Patients	%
Sex				
Female	49	42.6	21	46.7
Male	66	57.4	24	53.3
Race				
African American	4	3.5	2	4.4
Asian	2	1.7	0	0
White	106	92.2	43	95.6
Other	3	2.6	0	0
Age, years				
Median	55		55	
Range	23-79		21-77	
WHO PS				
0	67	58.3	32	71.1
1	38	33	9	20.0
2	9	7.8	3	6.7
Missing	1	0.9	1	2.2
Disease progression by RECIST				
Yes	114	99.1	45	100.0
No	1	0.9	0	0
Histologic grade				
Well differentiated	88	76.5	35	77.8
Moderately differentiated	23	20	6	13.3
Poorly differentiated	0	0	0	0
Undifferentiated	0	0	1	2.2
Unknown	4	3.5	3	6.7
Time since initial diagnosis				
≤ 6 months	6	5.2	0	0
> 6 months to ≤ 2 years	31	27.0	6	13.3
> 2 years to ≤ 5 years	38	33.0	21	46.7
> 5 years	40	34.8	18	40.0
Tumor type				
Insulinoma	2	1.7	5	11.1
VIPoma	3	2.6	4	8.9
Gastrinoma	9	7.8	6	13.3
Glucagonoma	3	2.6	2	4.4
Somatostinoma	2	1.7	0	0
Pancreatic polypeptidoma	3	2.6	0	0
Other	93	80.9	24	53.3
No. of organs involved				
0	0	0	1	2.2
1	19	16.5	12	26.7
2	45	39.1	19	42.2
> 2	51	44.3	13	28.9
Organ type involved				
Liver	109	94.8	42	93.3
Lung	20	17.4	8	17.8
Lymph nodes	55	47.8	17	37.8
Bone	17	14.8	6	13.3
Pancreas	53	46.1	13	28.9
Adrenals	5	4.3	2	4.4
Other	22	19.1	6	13.3
No. of prior antineoplastic medications				
1	56	48.7	21	46.7
2	26	22.6	8	17.8
3	14	12.2	7	15.6
> 3	19	16.5	9	20.0
No. of prior chemotherapy regimens				
1	62	53.9	22	48.9
2	28	24.3	13	28.9
3	12	10.4	2	4.4
> 3	13	11.3	7	15.6

Abbreviations: PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors.

alternative hypothesis of ≥ 15% ORR. Responses were summarized as percentage rates and exact two-sided 95% CIs. PFS and OS distributions were estimated using the Kaplan-Meier method. Median PFS and OS in each stratum were calculated with 95% CIs.

RESULTS

Study Population

The trial enrolled 160 patients, 115 in stratum 1 (everolimus) and 45 in stratum 2 (everolimus plus octreotide LAR), from 36 centers in 11 countries between June 2006 and June 2007. At the time of data cutoff (November 1, 2008), ongoing patients had been observed for at least 16 months; 24 patients (20.9%) in stratum 1 and 11 patients (24.4%) in stratum 2 remained on study treatment. Patient demographics and disease history are listed in Table 1. All but one patient in stratum 1 had documented disease progression by RECIST assessed locally, before study entry. Median age was 55 years, and the majority of patients had disease diagnosed more than 2 years before study entry. More than 90% of patients had metastatic disease in the liver. Analyses were performed on the intent-to-treat population and the safety population, which consisted of all patients who received at least one dose of everolimus.

Response Rate

In stratum 1, ORR by central radiology review was 9.6% (11 of 115 patients; 95% CI, 4.9% to 16.5%; Fig 1). The median duration of response was 10.6 months (95% CI, 9.8 months to not available

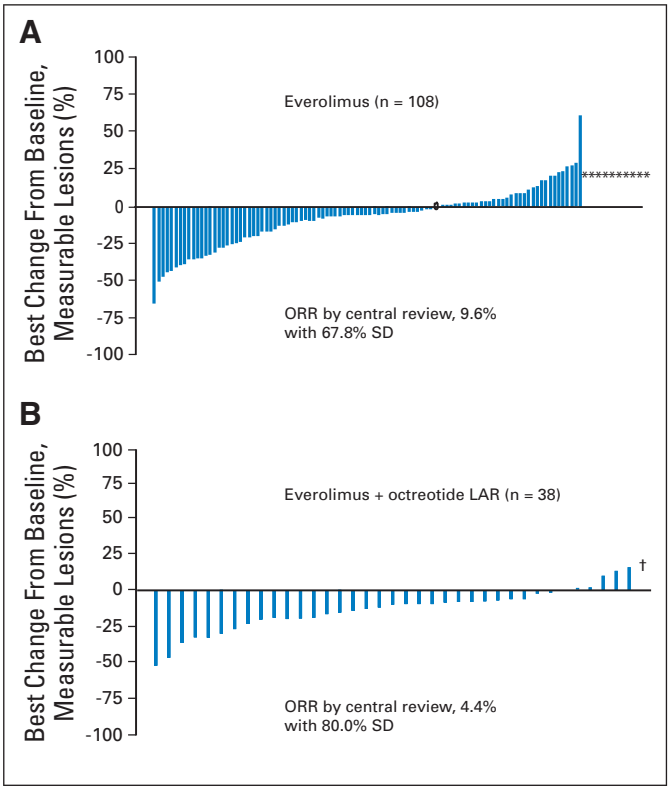

Fig 1. (A) Percent change (best response in each patient) in stratum 1. (*) Results are contraindicated by overall lesion response. (B) Percent change (best response in each patient) in stratum 2. (†) Best overall response is unknown. ORR, objective response rate; SD, stable disease; LAR, long-acting release.

Table 2. Efficacy Data

Parameter	Stratum 1 (n = 115)	Stratum 2 (n = 45)
Overall response (central review)		
PR		
No.	11	2
%	9.6	4.4
95% CI	4.9 to 16.5	0.5 to 15.1
SD		
No.	78	36
%	67.8	80.0
PD		
No.	16	0
%	13.9	0
Unknown		
No.	10	7
%	8.7	15.6
Response duration, months		
Median	10.6	ND
95% CI	9.8 to NA	—
Clinical benefit (PR + SD)		
No.	89	38
%	77.4	84.4
Overall response (investigator review)		
PR		
No.	12	5
%	10.4	11.1
95% CI	5.5 to 17.5	3.7 to 24.1
SD		
No.	71	31
%	61.7	68.9
PD		
No.	21	5
%	18.3	11.1
Unknown		
No.	11	4
%	9.6	8.9
Response duration, months		
Median	19.2	19.3
95% CI	5.3 to NA	10.6 to 19.3
Clinical benefit (PR + SD)		
No.	83	36
%	72.2	80.0
Progression-free survival (central review)		
Median, months	9.7	16.7
95% CI	8.3 to 13.3	11.1 to NA
6-month rate, %	66.2	76.3
95% CI	57.1 to 75.2	61.8 to 90.8
12-month rate, %	41.7	57.0
95% CI	31.1 to 52.2	38.7 to 75.2
18-month rate, %	30.5	46.0
95% CI	19.5 to 41.6	25.6 to 66.4
Overall survival		
Median, months	24.9	NR
95% CI	20.2 to 27.1	23.0 to NA
12-month rate, %	74.5	86.1
95% CI	66.4 to 82.5	75.7 to 96.4
24-month rate, %	51.1	54.7
95% CI	37.9 to 64.3	21.7 to 87.8

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; ND, not determined; NR, not reached.

[NA]). Stable disease (SD) was noted in an additional 78 patients (67.8%). Sixteen patients (13.9%) had disease progression as best overall response (Table 2). By investigator assessment, ORR was 10.4% (95% CI, 5.5% to 17.5%). SD was noted in an additional 71 patients (61.7%), and median duration of response was 19.2 months. Median dose-intensity of everolimus was 9.9 mg/d.

In stratum 2, ORR by central radiology review was 4.4% (two of 45 patients; 95% CI, 0.5% to 15.1%), and SD was noted in an additional 36 patients (80.0%; Fig 1). Median duration of response was not calculated by central radiology review because of the small number of patients (Table 2). By investigator assessment, ORR was 11.1% (95% CI, 3.7% to 24.1%), SD was noted in an additional 31 patients (68.9%), and median duration of response was 19.3 months. Median dose-intensity of everolimus was 9.4 mg/d.

PFS and OS

Median PFS by central radiology review (Fig 2) in stratum 1 was 9.7 months (95% CI, 8.3 to 13.3 months); in stratum 2, the median PFS was 16.7 months (95% CI, 11.1 months to NA). By investigator review, median PFS was 8.5 months (95% CI, 7.8 to 11.8 months) in stratum 1 and 15.2 months (95% CI, 9.3 months to NA) in stratum 2. Median OS in stratum 1 was 24.9 months (95% CI, 20.2 to 27.1 months). Median OS had not been reached for stratum 2 at the time of data cutoff (Fig 2); the 24-month survival rate for stratum 2 was 54.7% (95% CI, 21.7% to 87.8%; Table 2).

Biomarker Evaluation

Baseline CgA levels were elevated in 80 (70.2%) of 114 patients in stratum 1 and in 26 (59.1%) of 44 patients in stratum 2. CgA and NSE responses were defined as normalization or $\geq$ 50% decrease at any time point on treatment. In evaluable patients (CgA levels at two time points), 50.7% of patients (38 of 75 patients) in stratum 1 and 60.0% of patients (15 of 25 patients) in stratum 2 had a CgA response. An early CgA or NSE response was defined as normalization or $\geq$ 30% decrease at week 4. This threshold for CgA early response has been previously correlated with NET response to chemotherapy.[8] There was an early CgA response in 46.5% of patients (33 of 71 patients) in stratum 1 and 59.1% of patients (13 of 22 patients) in stratum 2. Median PFS in early CgA responders was 13.3 months compared with 7.5 months in patients who did not demonstrate an early CgA response (P = .00004; hazard ratio = 0.25; 95% CI, 0.13 to 0.51) in stratum 1 (Fig 3A). Baseline NSE levels were elevated in 50 (44.2%) of 113 patients in stratum 1 and in 13 (30.2%) of 43 patients in stratum 2. In evaluable patients, there was an NSE response in 68.2% of patients (30 of 44 patients) in stratum 1 and 72.7% of patients (eight of 11 patients) in stratum 2. There was an early NSE response in 71.8% of patients (28 of 39 patients) in stratum 1 and 50.0% of patients (five of 10 patients) in stratum 2. Median PFS was 8.6 months in early NSE responders compared with 2.9 months in patients who did not demonstrate an early NSE response in stratum 1 (P = .00062; hazard ratio = 0.25; 95% CI, 0.10 to 0.58; Fig 3B). PFS data by CgA or NSE in stratum 2 were not evaluable because of small patient numbers.

Adverse Events

Treatment with everolimus, with or without concomitant octreotide LAR, was generally well tolerated. Most adverse events (AEs) were mild to moderate in severity. The most common AEs suspected to be related to study drug in strata 1 and 2 were stomatitis, rash,

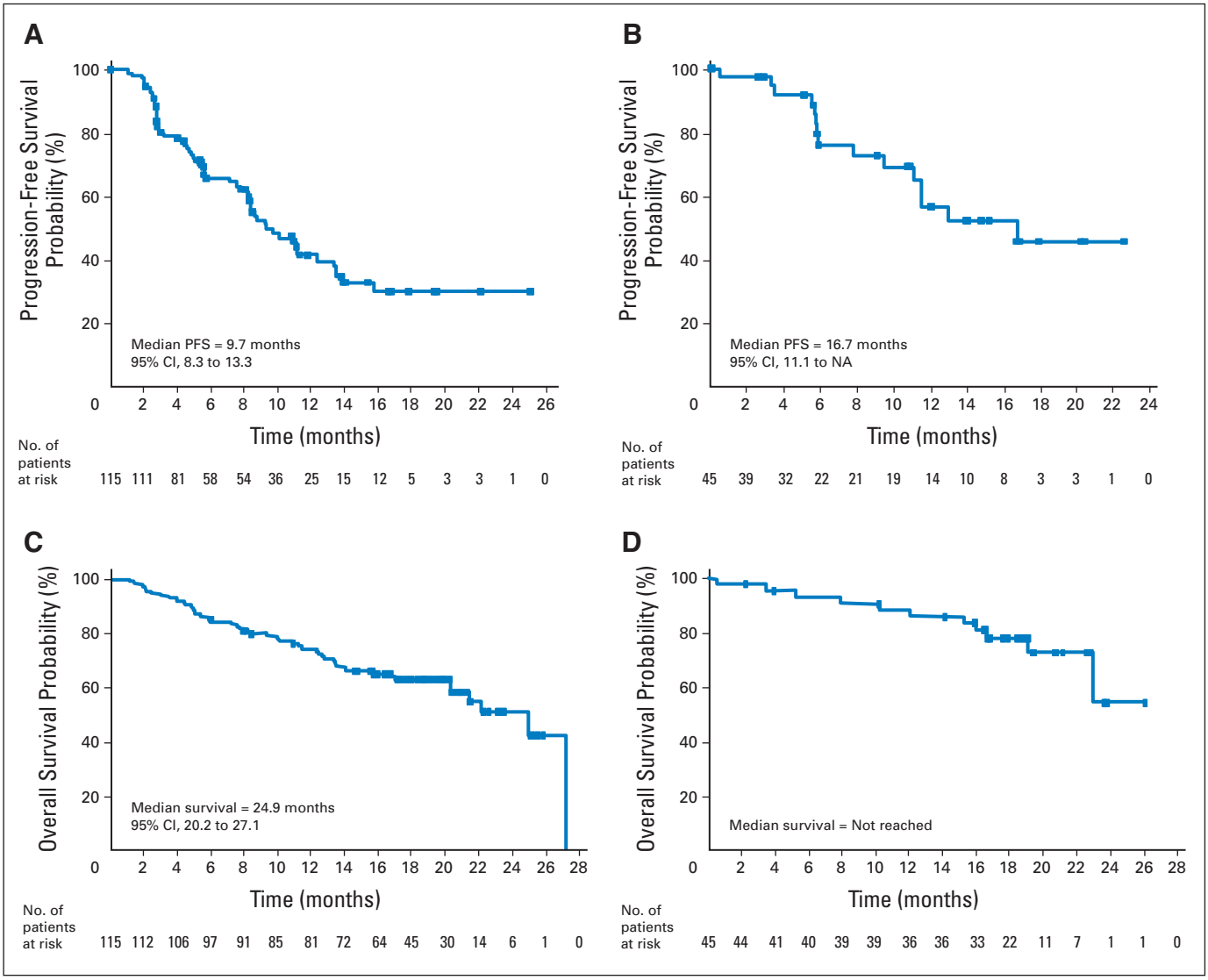

Fig 2. (A) Progression-free survival (PFS) by central radiology review in stratum 1 (Kaplan-Meier method). (B) PFS by central radiology review in stratum 2 (Kaplan-Meier method). (C) Overall survival (OS) in stratum 1 (Kaplan-Meier method). (D) OS in stratum 2 (Kaplan-Meier method). NA, not available.

diarrhea, fatigue, and nausea (Table 3). The most frequent grade 3 or 4 AEs suspected to be related to study drug were asthenia in stratum 1 and thrombocytopenia in stratum 2. AEs most commonly requiring dosage adjustment or interruption were hyperglycemia (7.8%), diarrhea (5.2%), stomatitis (7.0%), and pyrexia (4.3%) in stratum 1, and thrombocytopenia (11.1%), stomatitis (8.9%), and pyrexia (11.1%) in stratum 2. Pneumonitis or interstitial lung disease characterized by patchy ground-glass opacities was reported in seven patients in stratum 1 and six patients in stratum 2; all were grade 1 or 2. Most events were asymptomatic; no grade 3 or 4 events were observed. Pneumonitis was reversible. Symptomatic grade 2 pneumonitis was managed by dose interruption and reduction.

Pharmacokinetics

The pharmacokinetic effect of coadministration of octreotide LAR and everolimus was evaluated (Appendix Table A1, online only). The ratio of geometric means of everolimus minimum concentration in stratum 1 and stratum 2 was close to 1, suggesting that coadministration of octreotide LAR did not have a clinically significant effect on the exposure of everolimus. Similarly, coadministration of everolimus did not have clinically significant effects on the exposure of octreotide LAR.

DISCUSSION

Patients with progressive pancreatic NETs who have experienced treatment failure with prior chemotherapy have limited treatment options, and currently no drugs are approved in this setting. Moreover, data on PFS and OS after progression on chemotherapy are not readily available. The majority of recent phase II studies in patients with pancreatic NETs, using RECIST to evaluate efficacy, enrolled patients with and without prior chemotherapy. Thus, comparisons of data from these studies with data from the current study, where more than 99% of patients had disease progression by RECIST during or

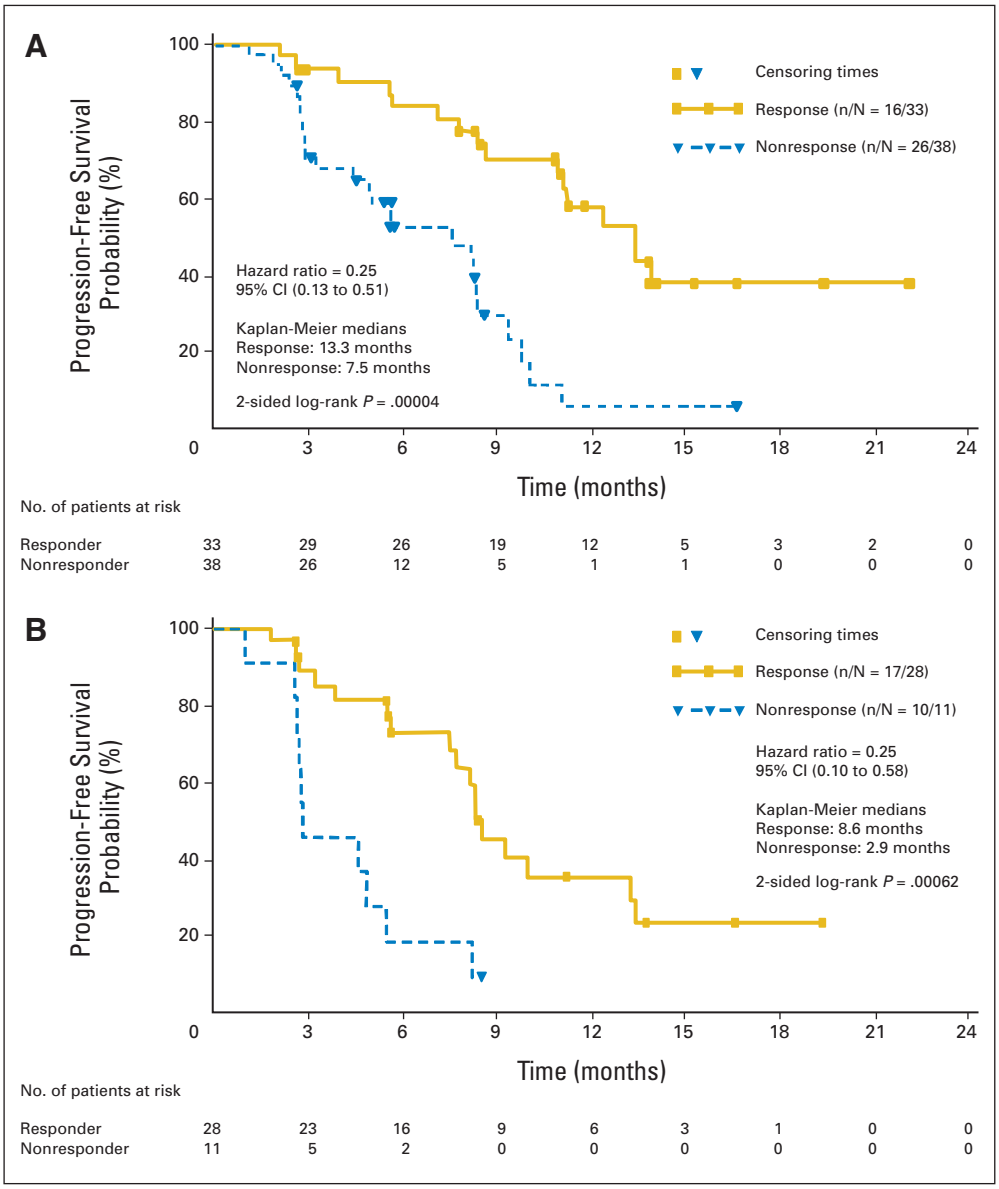

Fig 3. (A) Progression-free survival (PFS) by chromogranin A early responders (Kaplan-Meier method) in stratum 1. (B) PFS by neuron-specific enolase early responders (Kaplan-Meier method) in stratum 1.

after chemotherapy, are difficult. However, in patients with progressive NETs, therapy leading to disease stabilization also leads to improved survival.[26,27] In stratum 1 of our study, 9.6% of patients had an ORR by central radiology review, and an additional 78 (67.8%) of 115 patients had SD. In stratum 2, ORR was 4.4% by central review, and an additional 36 (80%) of 45 patients had SD. Tumor shrinkage was observed in 64 patients (59.3%) in stratum 1 and 32 patients (84.2%) in stratum 2 (Figs 1A and 1B).

The notable disease-stabilizing effect of everolimus added to concurrent octreotide LAR in stratum 2 is supported by a long median PFS of 16.7 months and the fact that in this refractory population with progressive disease, no patients had progressive disease as the best overall response by central radiology review. Additionally, the 6-month PFS rates in our study (66% in stratum 1, 76% in stratum 2) compared favorably with studies of somatostatin analogs (28%)[26] or gefitinib (31%)[28] among patients with progressive pancreatic NETs. The importance of disease stabilization as a predictor of clinical benefit is evident from recent approvals of agents in renal cell carcinoma with relatively low response rates (everolimus, temsirolimus, and sorafenib). In all instances, PFS was significantly better than the control arm.[29-32] In our study, the OS in stratum 1 of 24.9 months and the 24-month survival rate of 54.7% in stratum 2 also compare favorably with large institutional series[4] and data from large registries.[2]

This study was not designed to evaluate whether combination therapy is superior to monotherapy. Nonetheless, the combination of everolimus and octreotide is well tolerated and seems to result in a longer PFS in stratum 2. The rationale for combining everolimus and octreotide is that the upregulation of the IGF-1 pathway has been proposed as a potential resistance mechanism for everolimus,[33] and octreotide has been shown to reduce IGF-1 levels in cancer patients.[34] However, the study cannot exclude differences in biology and prior treatments between the two cohorts. A randomized study comparing everolimus versus the combination of everolimus and octreotide would be needed to address this question.

Table 3. Adverse Events Reported in ≥ 10% of Patients

Adverse Event	Stratum 1 (n = 115)				Stratum 2 (n = 45)			
	All Grades		Grade 3 or 4		All Grades		Grade 3 or 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Stomatitis	52	45.2	5	4.3	22	48.9	1	2.2
Rash	46	40.0	1	0.9	20	44.4	0	0
Diarrhea	45	39.1	4	3.5	14	31.1	0	0
Fatigue	36	31.3	5	4.3	16	35.6	1	2.2
Nausea	34	29.6	1	0.9	15	33.3	0	0
Headache	25	21.7	0	0	3	6.7	0	0
Aphthous stomatitis	20	17.4	0	0	6	13.3	0	0
Vomiting	20	17.4	0	0	6	13.3	0	0
Asthenia	17	14.8	6	5.2	5	11.1	1	2.2
Edema peripheral	17	14.8	0	0	6	13.3	1	2.2
Weight decreased	17	14.8	0	0	7	15.6	0	0
Anemia	15	13.0	5	4.3	7	15.6	2	4.4
Anorexia	15	13.0	1	0.9	7	15.6	2	4.4
Hyperglycemia	15	13.0	5	4.3	6	13.3	2	4.4
Pruritus	14	12.2	0	0	3	6.7	0	0
Dysgeusia	12	10.4	0	0	6	13.3	0	0
Dry skin	11	9.6	0	0	6	13.3	0	0
Thrombocytopenia	9	7.8	3	2.6	6	13.3	4	8.9
Neutropenia	8	7.0	5	4.3	6	13.3	0	0
Dyspnea	8	7.0	2	1.7	5	11.1	1	2.2

Together, these findings confirm the antitumor activity of everolimus in pancreatic NETs reported in a recent phase II trial of 60 patients with NETs treated with octreotide LAR 30 mg monthly and everolimus 5 or 10 mg daily.[25] In the prior trial, ORR was higher in a per-protocol analysis of 30 patients with pancreatic NETs, and median PFS was 11.5 months. In addition to the earlier trial being smaller and at a single institution, the difference in response rates between these studies could be attributed to the earlier study not requiring disease progression or prior chemotherapy. The current study also confirmed that everolimus was well tolerated in patients with advanced pancreatic NETs, either alone or in combination with octreotide LAR.

Patients with an early CgA or NSE response had a longer PFS compared with patients without an early response in stratum 1, suggesting that emergent changes in these markers show promise for selecting patients likely to benefit from everolimus. However, these biomarkers need to be evaluated further in ongoing phase III clinical trials to determine their predictive and prognostic value. There was no evidence that either everolimus or octreotide affected exposure (minimum concentration) to the other. AEs were consistent with those previously reported for everolimus.[25,35,36]

On the basis of the results of this trial, everolimus, both alone and in combination with octreotide LAR, is a promising therapeutic approach among patients with advanced pancreatic NETs who experienced progression during or after chemotherapy. An ongoing, randomized, placebo-controlled phase III trial (RADIANT-3) is currently evaluating everolimus as a first-line option for patients with advanced pancreatic NETs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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