ORIGINAL ARTICLE

Everolimus for Advanced Pancreatic Neuroendocrine Tumors

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ABSTRACT

BACKGROUND

Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors, in two phase 2 studies. We evaluated the agent in a prospective, randomized, phase 3 study.

METHODS

We randomly assigned 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months to receive everolimus, at a dose of 10 mg once daily (207 patients), or placebo (203 patients), both in conjunction with best supportive care. The primary end point was progression-free survival in an intention-to-treat analysis. In the case of patients in whom radiologic progression occurred during the study, the treatment assignments could be revealed, and patients who had been randomly assigned to placebo were offered open-label everolimus.

RESULTS

The median progression-free survival was 11.0 months with everolimus as compared with 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval [CI], 0.27 to 0.45; P<0.001), representing a 65% reduction in the estimated risk of progression or death. Estimates of the proportion of patients who were alive and progression-free at 18 months were 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group), rash (49% vs. 10%), diarrhea (34% vs. 10%), fatigue (31% vs. 14%), and infections (23% vs. 6%), which were primarily upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%). The median exposure to everolimus was longer than exposure to placebo by a factor of 2.3 (38 weeks vs. 16 weeks).

CONCLUSIONS

Everolimus, as compared with placebo, significantly prolonged progression-free survival among patients with progressive advanced pancreatic neuroendocrine tumors and was associated with a low rate of severe adverse events. (Funded by Novartis Oncology; RADIANT-3 ClinicalTrials.gov number, NCT00510068.)

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The incidence and prevalence of pancreatic neuroendocrine tumors are increasing[1-3]; these tumors represent approximately 1.3% of all cases of pancreatic cancer in incidence and 10% of cases in prevalence.[1-3] Pancreatic neuroendocrine tumors are frequently diagnosed at a late stage, with approximately 65% of patients presenting with unresectable or metastatic disease; as a result, these patients have a poor prognosis. The median survival time for patients with distant metastatic disease is 24 months,[2] and limited treatment options are available for this population.

Streptozocin is the only approved therapy for pancreatic neuroendocrine tumors in the United States; however, the role of chemotherapy in advanced cases continues to be debated.[3-12] The criteria that were used to determine the outcome measures in many earlier trials are considered unacceptable today, and a substantial number of adverse events were seen with regimens that showed improved response rates.[3,10,13,14] Large, prospective, randomized trials that use validated criteria are therefore required to show the value of promising new treatment regimens for advanced pancreatic neuroendocrine tumors. A recent prospective study (reported by Raymond et al. elsewhere in this issue of the *Journal*) shows that sunitinib has antitumor activity.[15]

Everolimus (Afinitor, Novartis Pharmaceuticals) has recently shown promising antitumor activity in two phase 2 studies involving patients with pancreatic neuroendocrine tumors.[3,16] Everolimus inhibits mammalian target of rapamycin (mTOR), a serine–threonine kinase that stimulates cell growth, proliferation, and angiogenesis.[3,16,17] Autocrine activation of the mTOR signaling pathway, mediated through insulin-like growth factor 1, has been implicated in the proliferation of pancreatic neuroendocrine tumor cells.[18] Consistent with this observation is the finding that inhibition of mTOR has a significant antiproliferative effect on pancreatic neuroendocrine tumor cell lines.[19,20]

The RAD001 in Advanced Neuroendocrine Tumors, third trial (RADIANT-3) study was conducted to determine whether everolimus, at a dose of 10 mg per day, as compared with placebo, would prolong progression-free survival among patients with advanced pancreatic neuroendocrine tumors.

METHODS

PATIENTS

Patients were eligible to be included in the study if they were 18 years of age or older and had low-grade or intermediate-grade advanced (unresectable or metastatic) pancreatic neuroendocrine tumors and radiologic documentation of disease progression (an unequivocal increase in the size of tumors) in the 12 months preceding randomization. Prior antineoplastic therapy was not an exclusion criterion. Other key eligibility criteria included the presence of measurable disease, as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (see the Supplementary Appendix, available with the full text of this article at NEJM.org)[21]; a World Health Organization (WHO) performance status of 2 or less (with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction; 1 indicating that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work; and 2 indicating that the patient is ambulatory and up and about more than 50% of waking hours and is capable of all self-care but unable to carry out any work activities)[22]; adequate bone marrow, renal, and hepatic function; and adequately controlled lipid and glucose concentrations. Patients were ineligible if they had undergone hepatic-artery embolization within 6 months before enrollment (within 1 month if there were other sites of measurable disease) or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrollment, had any severe or uncontrolled medical conditions, had received prior therapy with an mTOR inhibitor, or were receiving long-term treatment with glucocorticoids or other immunosuppressive agents.

STUDY OVERSIGHT

The protocol was approved by the institutional review board or ethics committee at each participating center, and the study was conducted in accordance with Good Clinical Practice principles and applicable local regulations. All patients provided written informed consent.

The study was designed by the academic investigators and by representatives of the sponsor,

Novartis Oncology. The data were collected with the use of the sponsor's data management systems and were analyzed by the sponsor's statistical team. All the authors contributed to the interpretation of data and the subsequent writing, reviewing, and amending of the manuscript; the first draft of the manuscript was prepared by the first author and by a medical writer employed by Novartis Oncology. The protocol, including the statistical analysis plan, is available at NEJM.org. All the authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan.

STUDY DESIGN AND TREATMENT

In this international, multicenter, double-blind, phase 3 study, patients were randomly assigned to treatment with oral everolimus, at a dose of 10 mg once daily, or matching placebo, both in conjunction with best supportive care. Patients were stratified according to status with respect to prior chemotherapy (receipt vs. no receipt) and according to WHO performance status (0 vs. 1 or 2) at baseline.

Treatment continued until progression of the disease, development of an unacceptable toxic effect, drug interruption for 3 weeks or longer, or withdrawal of consent. The study-group assignments were concealed from the investigators, but disclosure was permitted if an investigator determined that the criteria for disease progression according to RECIST had been met and if there was an intention to switch the patient to open-label therapy. Patients who had been assigned to placebo initially could then switch to open-label everolimus. This element of the study design was incorporated to address both ethical and recruitment considerations, given that the trial involved patients with a rare disease. We recognized the potential influence of this aspect of the study design on the analysis of the end point of overall survival.

Doses were delayed or reduced if patients had clinically significant adverse events that were considered to be related to the study treatment, according to an algorithm described in the protocol. In such cases, two reductions in the dose of the study drug were permitted: an initial reduction to 5 mg daily and a subsequent reduction to 5 mg every other day.

EFFICACY AND SAFETY ASSESSMENTS

The primary end point was progression-free survival, documented by the local investigator according to RECIST and defined as the time from randomization to the first documentation of disease progression or death from any cause. If the disease had not progressed and the patient had not died as of the cutoff date for the analysis, data for progression-free survival were censored at the time of the last adequate tumor assessment — which was defined as the last assessment of overall lesion response that showed complete response, partial response, or stable disease — before the cutoff date or the date of initiation of other anticancer therapy.[23] In the primary analysis, data for progression-free survival were censored at the time of the last adequate tumor assessment if an event occurred after two or more missing tumor assessments. Data for patients without any valid post-baseline tumor assessment were censored on day 1 (the date of randomization). Secondary end points included the confirmed objective response rate (according to RECIST, version 1.0), the duration of response, overall survival, and safety.

All randomly assigned patients were assessed for efficacy (intention-to-treat analysis). Tumor measurements (assessed by triphasic computed tomography or magnetic resonance imaging) were performed at baseline and were repeated every 12 weeks. Scans were reviewed at the local site and centrally. In cases of a discrepancy between the local investigator's assessment and the radiologic assessment at the central location with respect to the determination of progression-free survival, adjudication was performed by an independent central adjudication committee comprising a board-certified radiologist and an oncologist, both of whom had extensive experience with neuroendocrine tumors. The central adjudication committee, whose members were unaware of the patients' study-group assignments and of the source of the data (local or central), selected the assessment that in their expert opinion reflected the more accurate evaluation.

All patients who received at least one dose of the study drug and had at least one follow-up assessment were evaluated for safety. Safety assessments consisted of the monitoring and recording of all adverse events, regular monitoring of hematologic and clinical biochemical levels (lab-

oratory evaluations) and vital signs, and physical examinations every 4 weeks. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

The estimation of the sample size was based on the ability to detect a clinically meaningful improvement in the primary end point, which was defined as a 33% reduction in the risk of disease progression or death (a hazard ratio for progression or death of 0.67), corresponding to a 50% prolongation in median progression-free survival, from 6 months with placebo to 9 months with everolimus. We estimated that with a total of 282 progression-free survival events (i.e., disease progression or death), the study would have 92.6% power to detect a clinically meaningful improvement, with the use of an unstratified log-rank test, at a one-sided significance level of 2.5%. Taking into account the estimated rate of patient accrual and a 10% loss of the study population to follow-up, we estimated that we would have to enroll 392 patients to observe the required number of events.

Progression-free and overall survival were analyzed with the use of Kaplan–Meier methods; study groups were compared with the use of a log-rank test, stratified according to prior receipt or no prior receipt of chemotherapy and WHO performance status, and the hazard ratio was estimated with the use of a stratified Cox proportional-hazards model.

RESULTS

PATIENTS AND TREATMENT

Between July 2007 and May 2009, a total of 410 patients from 82 centers in 18 countries worldwide who had advanced pancreatic neuroendocrine tumors were randomly assigned to everolimus (207 patients) or placebo (203 patients) (see the figure in the Supplementary Appendix). The baseline demographic and clinical characteristics of the patients were well balanced between the two groups (Table 1). More than 80% of the patients had well-differentiated disease, more than 90% had metastases in the liver, and approximately 60% had received a diagnosis of pancreatic neuroendocrine tumor more than 2 years before entering the study. A total of 24% of the patients had gastrinoma, glucagonoma, VIPoma, insulinoma, or somatostatinoma. The two groups were similar with respect to prior receipt of radiother-

Table 1. Demographic and Baseline Clinical Characteristics of the Patients.

Characteristic	Everolimus (N=207)	Placebo (N=203)
Age — yr		
Median	58	57
Range	23–87	20–82
Sex — no. (%)		
Male	110 (53)	117 (58)
Female	97 (47)	86 (42)
WHO performance status — no. (%)		
0	139 (67)	133 (66)
1	62 (30)	64 (32)
2	6 (3)	6 (3)
Histologic status of tumor — no. (%)		
Well differentiated	170 (82)	171 (84)
Moderately differentiated	35 (17)	30 (15)
Unknown	2 (1)	2 (1)
Time from initial diagnosis — no. (%)		
≤6 mo	24 (12)	33 (16)
>6 mo to ≤2 yr	65 (31)	43 (21)
>2 yr to ≤5 yr	54 (26)	81 (40)
>5 yr	64 (31)	46 (23)
Time from disease progression to randomization — no. (%)		
≤1 mo	73 (35)	61 (30)
>1 mo to ≤2 mo	43 (21)	53 (26)
>2 mo to ≤3 mo	30 (14)	29 (14)
>3 mo to ≤12 mo	58 (28)	54 (27)
>12 mo	3 (1)	1 (<1)
No. of disease sites — no. of patients (%)		
1	51 (25)	62 (31)
2	85 (41)	64 (32)
≥3	70 (34)	77 (38)
Organ involved — no. (%)		
Liver	190 (92)	187 (92)
Pancreas	92 (44)	84 (41)
Lymph nodes	68 (33)	73 (36)
Lung	28 (14)	30 (15)
Bone	13 (6)	29 (14)

Table 2. **Progression-free Survival.**

Variable	Everolimus (N=207)	Placebo (N=203)	Difference	Hazard Ratio for Disease Progression or Death with Everolimus (95% CI)	P Value
Assessment by local investigator					
Progression-free survival events — no. (%)*	109 (53)	165 (81)			
Censored data — no. (%)	98 (47)	38 (19)			
Median progression-free survival — mo	11.0	4.6	6.4	0.35 (0.27–0.45)	<0.001
Review by central adjudication committee					
Progression-free survival events — no. (%)*	95 (46)	142 (70)			
Censored data — no. (%)	112 (54)	61 (30)			
Median progression-free survival — mo	11.4	5.4	6.0	0.34 (0.26–0.44)	<0.001

* Progression-free survival events include disease progression and death.

apy (23% of patients in the everolimus group and 20% in the placebo group), chemotherapy (50% in both groups), and somatostatin analogue therapy (49% in the everolimus group and 50% in the placebo group). Best supportive care included the use of somatostatin analogue therapy in approximately 40% of the patients.

With a median follow-up period of 17 months, the median duration of treatment with everolimus was 8.79 months (range, 0.25 to 27.47), as compared with 3.74 months (range, 0.01 to 37.79) with placebo. A total of 31% of the patients in the everolimus group, as compared with 11% in the placebo group, were administered treatment for a minimum of 12 months. The mean relative dose intensity (the ratio of administered doses to planned doses) was 0.86 in the everolimus group and 0.97 in the placebo group. Dose adjustments (reductions or temporary interruptions) were required by 59% of the patients receiving everolimus and 28% of the patients receiving placebo.

At the time the analysis was performed for this article, treatment was ongoing for 32% of the patients in the everolimus group and 13% of the patients in the placebo group; the primary reasons for discontinuation of treatment included disease progression (in 44% of patients in the everolimus group vs. 80% in the placebo group), adverse events (17% vs. 3%), withdrawal of consent (2% in both groups), and death (2% vs. 1%).

EFFICACY

The median progression-free survival (the primary end point), as assessed by the local investigators, was 11.0 months (95% confidence interval [CI], 8.4 to 13.9) in the everolimus group, as compared with 4.6 months (95% CI, 3.1 to 5.4) in the placebo group, representing a 65% reduction in the estimated risk of progression (hazard ratio for disease progression or death with everolimus, 0.35; 95% CI, 0.27 to 0.45; P<0.001) (Table 2 and Fig. 1A). The estimated proportion of patients who were alive and progression-free at 18 months was 34% (95% CI, 26 to 43) with everolimus as compared with 9% (95% CI, 4 to 16) with placebo, indicating that a sizable proportion of patients derived a prolonged benefit with everolimus.

The findings of the independent adjudicated central assessment of median progression-free survival were consistent with those of the assessment by local investigators. The median progression-free survival according to the central assessment was 11.4 months (95% CI, 10.8 to 14.8) with everolimus, as compared with 5.4 months (95% CI, 4.3 to 5.6) with placebo (hazard ratio for disease progression or death with everolimus, 0.34; 95% CI, 0.26 to 0.44; P<0.001) (Table 2 and Fig. 1B).

Prespecified subgroup analyses indicated that the benefit was maintained across subgroups. A benefit with everolimus was evident irrespective of status with respect to prior chemotherapy (receipt or no receipt), WHO performance status, age, sex, race, geographic region, status with respect to prior somatostatin analogue therapy (receipt or no receipt), and tumor grade (Fig. 1C).

Everolimus was associated with a superior response profile, as assessed according to RECIST (P<0.001 with the use of a two-sided Mann–Whit-

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