Original Article

Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients With Neuroendocrine Tumors

An ITMO Group Study

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BACKGROUND: Preclinical and clinical studies suggest synergistic activity between somatostatin analogues and mammalian target of rapamycin inhibitors. The activity and safety of everolimus was assessed in combination with octreotide long-acting repeatable (LAR) in patients with neuroendocrine tumors (NETs) of gastroenteropancreatic and lung origin. **METHODS:** This was a phase 2, multicenter trial using a Simon's 2-stage minimax design. Treatment-naive patients with advanced well-differentiated NETs of gastroenteropancreatic tract and lung origin received everolimus 10 mg daily, in combination with octreotide LAR 30 mg every 28 days. The primary endpoint was objective response rate (ORR). **RESULTS:** A total of 50 patients (median age, 60.5 years) were enrolled. Primary tumor sites were: pancreas (14 patients), lung (11 patients), ileum (9 patients), jejunum and duodenum (2 patients), and unknown (14 patients). Thirteen patients (26%) had carcinoid syndrome. Treatment-related adverse events (AEs) were mostly grade 1 or 2; the only grade 4 AE was mucositis in 1 patient, whereas grade 3 AEs included skin rash in 1 case (2%), stomatitis in 4 cases (8%), and diarrhea in 11 cases (22%). The ORR was 18%; 2% of patients had a complete response (CR), 16% a partial response (PR) and 74% achieved stable disease (SD). All CRs and all PRs as well as 92% of SDs had a duration $\geq$6 months. The clinical benefit (CR+PR+SD) was 92%. At a median follow-up of 277 days, median time to progression and overall survival were not reached. **CONCLUSIONS:** The everolimus-octreotide LAR combination was active and well tolerated in these previously treated patients with advanced NETs, suggesting a possible role as first-line treatment in patients with NET. ***Cancer*** **2014;120:2457-63.** *© 2014 American Cancer Society.*

KEYWORDS: neuroendocrine tumor, everolimus, octreotide long-acting repeatable.

INTRODUCTION

Neuroendocrine tumors (NETs) are a group of tumors arising from various different epithelial cells with patterns of neuroendocrine differentiation. NETs can arise at any site of the gastrointestinal tract and of the bronchopulmonary system.[1] The World Health Organization (WHO) 2010 classification distinguishes this class of diseases between well-differentiated NETs and poorly differentiated neuroendocrine carcinomas (NECs).[2]

The most informative sources for NET epidemiology figures are the US National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) databases, a comprehensive cancer statistics program widely used to ascertain epidemiologic data across the range of cancer types and throughout the world. The most recently available SEER data show a significant increase over time in the annual age-adjusted incidence of NET, from 1.09 per 100,000 individuals in 1973 to 5.25 per 100,000 individuals in 2004.[3,4]

The choice of appropriate treatment for NET represents a challenge, due to the biological and morphological heterogeneity of these tumors. Treatment strategies are formulated depending on functional status and disease stage.

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For resectable carcinoma, surgery is generally recommended,[5] whereas in the case of locoregional unresectable and metastatic disease, therapeutic options include inhibitors of the mammalian target of rapamycin (mTOR),[6-8] receptor tyrosine kinase (RTK) inhibitors,[9,10] somatostatin analogs (SSAs),[11] chemotherapy,[12,13] and radiotherapy.[13,14]

In recent years, strong evidence has emerged of an antiproliferative effect of SSAs on NETs, thought to occur via direct and indirect mechanisms.[15] The direct mode of action involves interaction with somatostatin receptors on tumor cells leading to activation of phosphotyrosine phosphatases[16] and modulation of the mitogen-activated protein kinase signaling pathway.[17] The indirect antiproliferative effect occurs through the inhibition of expression of growth factors, such as insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF).[18]

The PROMID study, a randomized phase 3 trial, was designed to test the hypothesis that SSAs can inhibit tumor growth. The study evaluated octreotide long-acting repeatable (LAR) 30 mg versus placebo in 85 patients with advanced carcinoid tumors of the midgut (jejunum and ileocecum). A statistically and clinically significant improvement in median time to progression (TTP) was observed, from 6 months on the placebo arm to 14.3 months on the experimental arm (hazard ratio = 0.34; $P = .000072$). Multivariate analysis suggested that patients with resected primary tumor and low tumor burden benefited most significantly from treatment with octreotide, compared with placebo.

Based on the results of the PROMID trial, octreotide LAR therapy is considered to be an appropriate first-line systemic therapy for patients with metastatic unresectable midgut NETs.[11] However, PROMID recruited only patients with well-differentiated midgut primary or unknown primary NETs, whereas the recent CLARINET trial included patients with NETs of both gastrointestinal and pancreatic origins, as did our current study. The preliminary results of CLARINET further confirmed the antiproliferative role of SSAs (eg, lanreotide) in gastroenteropancreatic NET with a documented previous stable disease for at least 6 months.[19]

The serine-threonine kinase mTOR is involved in the regulation of a variety of cell activities (eg, growth, proliferation, motility, survival, angiogenesis, protein synthesis, and transcription). The mTOR signaling pathway is activated in gastroenteropancreatic NET cells[7,20] and its inhibition results in antiproliferative effects on these tumor types.[21,22] Everolimus is an oral mTOR inhibitor approved in the oncology setting, for treatment of advanced breast cancer, NETs of pancreatic origin (pNET), and advanced renal cell carcinoma.[23,24]

In the setting of NET, the RADIANT-3 trial was a phase 3 randomized double-blind trial of everolimus versus placebo, in patients with a diagnosis of locally advanced or metastatic well/moderately differentiated pNET. The results showed that everolimus (at a dose of 10 mg/day) was associated with a 65% reduction in the estimated risk of progression (progression-free survival of 11.0 months with everolimus versus 4.6 months with placebo, $P < .001$) and an increase by a factor of 3.7 times in estimates of the proportion of patients with progression-free survival at 18 months (34% with everolimus versus 9% with placebo). The benefit was maintained across various subgroups, including those defined according to whether patients had received previous antitumor treatments.[25]

Concurrently, the phase 3 (RADIANT-2) double-blind trial of octreotide LAR plus everolimus versus octreotide LAR plus placebo was conducted in patients with well/moderately differentiated locally advanced or metastatic NET and history of carcinoid syndrome. On central radiographic review, median progression-free survival increased from 11.3 months on the octreotide LAR plus placebo arm to 16.4 months on the octreotide LAR plus everolimus arm (hazard ratio = 0.77; $P = .026$). Although clinically significant, the P value did not meet the prespecified level of statistical significance of .024. One potential factor contributing to the lack of statistical significance was the loss of progression events, caused by discrepancies in central versus local radiographic reviews.[26]

Combination therapy with everolimus plus octreotide LAR might enhance antitumor efficacy by simultaneously targeting upstream and downstream components of the mTOR pathway.[27] The efficacy and safety of both everolimus and the SSA octreotide LAR have been demonstrated in phase 3 trials in patients with NETs.[7,11,26,28] However, this study assesses for the first time the combination of everolimus plus octreotide LAR in treatment-naive patients with NET of gastroenteropancreatic and lung origins, with and without carcinoid syndrome.[29]

MATERIALS AND METHODS

Patients were eligible for this study if they were aged 18 years or older. Thirty-six patients had histologically confirmed, well-differentiated, locally advanced or metastatic NEC of the gastroenteropancreatic tract, according to the WHO 2000 classification,[30] which was current at the

time of patient enrollment, or typical and atypical carcinoid of the lung, according to the classification of the International Agency for Research on Cancer (IARC).[31] In 14 patients, the primary tumor site was unknown.

Main exclusion criteria included any prior anticancer treatment for neuroendocrine tumors, histological diagnosis of poorly differentiated endocrine carcinoma, and presence of metastatic disease of the central nervous system. Patients with any severe and/or uncontrolled medical condition, or other conditions that could affect participation in the study or with serious neurological or psychiatric disorders, as well as immunocompromised subjects and pregnant and lactating females, were also excluded. Patients with a history of another primary malignancy were allowed to participate if they had been disease-free for at least 5 years. Patients with reproductive potential were required to use adequate contraceptive methods.

Other key eligibility criteria included the presence of measurable disease, as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; a 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); adequate bone marrow, renal, and hepatic function; and adequately controlled lipid and glucose concentrations. All patients provided written informed consent. The trial protocol was approved by the ethics committees at each participating center. The study was conducted in accordance with Good Clinical Practice guidelines and with the Declaration of Helsinki.

In this national, multicenter, phase 2 study, patients were treated with octreotide LAR 30 mg every 28 days in combination with everolimus (RAD001) 10 mg once daily continuously. Treatment was continued until progression of the disease, development of unacceptable toxicity, drug interruption for 3 weeks or longer, or withdrawal of consent. Patients were followed-up for 48 months. Patients could be treated with additional treatments after progression, at the discretion of their physician.

The primary endpoint was objective response rate (ORR); secondary endpoints were time to progression (TTP) and overall survival (OS). Tumor response was assessed by computed tomography measurements of all target lesions at baseline and every 3 months. RECIST, version 1.1, was used to assess the type of response. Adverse events were graded by means of the NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE).

Statistical Analysis

Continuous variables were summarized by descriptive statistics. Categorical variables were summarized using counts of patients and percentages. A frequency analysis of the ORR was performed including also the 95% confidence interval (CI). Survival curves for OS and TTP, medians, and their 95% CIs were estimated applying the Kaplan-Meier method. The statistical testing was conducted at the 2-sided $\alpha = 0.05$ and 95% CI was employed.

Analyses of efficacy parameters were performed on the intent-to-treat (ITT) population, which consisted of all patients who received at least one dose of study drug. Analysis of ORR was also repeated on the per-protocol (PP) analysis consisted of all patients from the ITT population who were evaluable for efficacy without any major protocol violation and who either had completed a minimum exposure requirement or discontinued for early disease progression (ie, within the first 12 weeks of treatment).

An ORR of 5% was set as the lowest probability of interest in patients with advanced NETs. According to Simon's 2-stage minimax design, 29 patients had to be enrolled in the first stage. In case of at least 2 responders, the trial could continue to the second stage with a further 15 patients. If at least 5 responders were detected among all 44 patients, the hypothesis of response rate greater than 15% was accepted. Statistical analysis was carried out using the SAS System software, version 9.2.

The safety analysis was performed on the safety population, which consisted of all patients who received at least one dose of study drug and had at least one postbaseline safety assessment. All AEs were assigned to a patient and were classified by primary System Organ Class according to the MedDRA Thesaurus, version 12.

RESULTS

Patient Population

Between March 2009 and June 2010, 50 patients were enrolled in 5 Italian hospitals. Primary tumor site was pancreas in 14 patients, lung in 11 patients, ileum in 9 patients, and jejunum/duodenum in 2 patients. In 14 patients, the primary tumor site was unknown. From

TABLE 1. Demographics and disease characteristics of the study population at baseline

Characteristic		Patients, no. (%)
Sex	Female	21 (42)
	Male	29 (58)
Ethnic group	Caucasian	50 (100)
	Other	–
Age (years)	Median	58.4
	Range	25-76
ECOG performance status	0	50 (100)
	1	–
	2	–
Primary tumor site	Pancreas	14 (28)
	Lung	11 (22)
	Ileum	9 (18)
	Duodenum/jejunum	2 (4)
	Unknown	14 (28)
Octreoscan	Positive	42 (84)
	Negative	8 (16)
Serum CgA concentration	Above ULN	38 (76)
	Normal	12 (24)
Prior surgery	Yes	25 (50)
	No	25 (50)
Carcinoid syndrome	Yes	13 (26)
	No	37 (74)

Abbreviations: CgA, chromogranin A; ECOG, Eastern Cooperative Oncology Group; ULN, upper limit of normal.

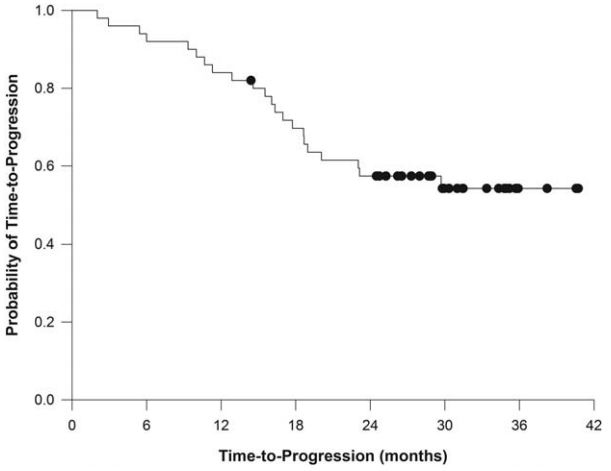

Figure 1. Kaplan-Meier plot for time to progression, defined as the time from cycle 1, day 1 until objective tumor progression or death from underlying cancer, whichever came first.

the total number of patients, 4 were excluded: 3 because they did not receive a minimum dose intensity corresponding to 50% of the planned dose of everolimus over the first 8 weeks and 1 because of a major violation of the protocol (treatment was interrupted because the patient was first defined as early disease progression; however, the progression was not confirmed by computed tomography scan). Therefore, 46 patients were assessable for response PP. However, the analysis of efficacy parameters was performed on the ITT population (n=50), consisting of all patients who received at least one dose of everolimus. Analysis of ORR, TTP, and OS was also repeated on the PP population.

At the time the manuscript was written, 17 patients, 6 with pancreatic NET (pNET), were still in treatment. At study entry, all participants had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Thirteen patients had carcinoid syndrome, and 38 had a serum chromogranin A (CgA) concentration above the upper limit of normal. Median time of treatment was 519.5 days (range, 49-1158 days), median time from diagnosis to treatment was 10 weeks, and median drug compliance was 94%. Baseline demographics and disease characteristics of the study population are shown in Table 1.

Tumor and Biochemical Response

The ORR was 18.0% (95% CI = 9.5%-31.0%) in the ITT population and 19.6% in the PP population (95% CI = 10.4%-33.4%). One patient (2%) achieved a complete response (CR) as best response. The patient had ileum NET and no carcinoid syndrome. Sites of metastases were liver and peritoneal nodes. Duration of CR was 37 weeks. Eight patients (16%, 2 pancreatic, 1 lung, 1 ileum, 1 duodenum, and 3 unknown NET) had a partial response (PR). Stable disease (SD) was observed in 38 patients (74%) and progressive disease (PD) in 3 patients (6%). The CR and all PRs as well as 91.7% of SDs had a duration $\geq$ 6 months. The clinical benefit rate, calculated as CR+PR+SD, was 92%. Among 14 patients with pNET (28% of the ITT population), 2 PR (14%) and no (0%) CR were reported. The percentage of responses did not differ between pNET and non-pNET. Thirty-eight patients had elevated serum CgA concentrations at study entry. Of these patients, 58% achieved a biochemical response, with a reduction of $\geq$ 25% of CgA levels.

Subgroup analyses by tumor primary site did not show any significant difference in ORR. No significant differences were observed in the ORR between patients with versus those without carcinoid syndrome.

Time to Progression and Overall Survival

After a median follow-up of 277 days, median TTP was not reached (Fig. 1), as in the case of median OS (Fig. 2). There were no significant differences in TTP and OS with respect to the primary tumor site.

Treatment-Related Toxicity

The majority of the AEs were related to everolimus. All the AEs associated with octreotide LAR were grade 1 or 2

and were consistent with the known safety profile of the drug.

Most AEs associated with everolimus were grade 1 or 2 and included mucositis (52%), diarrhea (38%), skin rash (46%), hypercholesterolemia (26%), and hyperglycemia (18%). Three patients (6%) experienced interstitial pneumonitis and all recovered after discontinuation of everolimus and steroid therapy administration. Grade 3 AEs were skin rash (1 patient, 2%), stomatitis (4 patients, 8%) and diarrhea (11 patients, 22%). The only grade 4 AE was mucositis in 1 patient. Hematologic AEs attributed to everolimus included grade 1 and 2 thrombocytopenia (6 patients, 12%), anemia (3 patients, 6%), and neutropenia (2 patients, 4%). Grade 3 anemia and grade 3 neutropenia occurred each in 1 patient (2%) (Table 2). One case of sepsis and one myocardial infarction were reported during treatment. There were no treatment-related deaths. The dosage was reduced from 10 to 5 mg/day in 13 patients (26%) due to toxicity. Eight patients (16%) discontinued treatment because of AE, but only 3 were considered by investigators to be drug-related (ischemic stroke, grade 4 mucositis, and hypocalcemia).

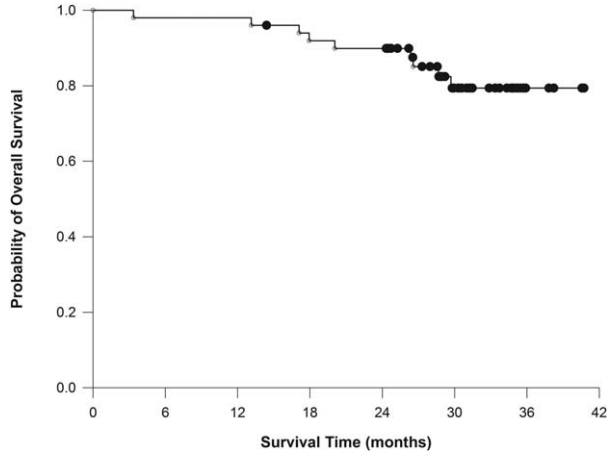

Figure 2. Kaplan-Meier plot of overall survival, defined as the time from cycle 1, day 1 until death due to any cause.

DISCUSSION

A variety of options exists for the management of advanced NETs, including surgical, medical, and nuclear medicine strategies.[10,26,32] The long-acting analogs of somatostatin have an established place in the medical treatment of patients with NETs, and the availability of molecularly targeted agents such as everolimus and sunitinib has expanded the treatment options for patients with advanced NETs.[9,10,33,34] Both everolimus and SSAs have been associated with antitumor activity in advanced NETs.[6,8,11,22] Everolimus is approved for progressive NET of pancreatic origin; however, the results reported here show that this drug also has activity in NET arising from a broader spectrum of sites.

We conducted a multicenter phase 2 trial, to our knowledge, the first ever to assess the efficacy and safety of first-line therapy with everolimus plus octreotide LAR in advanced NET with different histotypes with and without carcinoid syndrome, the results of which showed an ORR of 20%. Our study is in agreement with previous data on the efficacy of everolimus in pNET[6,35] and, most importantly, demonstrates the potential activity of the combination to achieve tumor shrinkage in NETs of all primary sites, independently from presence or absence of carcinoid syndrome. In this respect, our findings complement those reported in the RADIANT-2 trial, showing an improvement of progression-free survival with everolimus plus octreotide LAR, compared with placebo plus octreotide LAR, in patients with advanced NETs of various primary sites associated with carcinoid syndrome.[6] Notably, the combination of everolimus with octreotide LAR was generally well tolerated, and treatment-related AEs were mostly of grade 1 or 2, consistent with the known safety profile of these drugs.

TABLE 2. Everolimus-related adverse events, assessed by the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0

Adverse Event	Grade 1-2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Mucositis/stomatitis	26 (52%)	4 (8%)	1 (2%)
Rash	23 (46%)	1 (2%)	–
Diarrhea	19 (38%)	11 (22%)	–
Hypercholesterolemia	13 (26%)	–	–
Hyperglycemia	9 (18%)	–	–
Thrombocytopenia	6 (12%)	–	–
Anemia	3 (6%)	1 (2%)	–
Interstitial pneumonitis	3 (6%)	–	–
Neutropenia	2 (4%)	1 (2%)	–

The exceptional clinical benefit rate obtained in our study (CR+PR+SD = 92%) should be considered with caution, given the size of the patient population studied; nevertheless, our evidence is encouraging and holds promise in the evolving landscape of NET treatments. Therapeutic strategy for patients with NET may aim to reach a long-term disease stabilization or an objective response. In our study, 17 patients were still receiving the combination treatment at the time of the data cutoff. This provides evidence of a possible role of the combination in long-term disease control. Previous studies have reported everolimus efficacy in achieving stable disease. However, this is the first study to set ORR as the primary endpoint in treatment-naive NET patients treated with everolimus plus octreotide LAR. In view of the variable clinical course of neuroendocrine malignancies, the results of this study can be seen as encouraging.

In patients with NETs, where pursuing stable disease is the main achievable target, a sequential treatment may be suitable. In general, the main goal of clinical trials is to improve patient survival or quality of life. However, in specific cases, where the goal is to reduce the size of a tumor to allow a patient to undergo surgery or to achieve symptomatic relief, based on the results of our study, we propose that everolimus in combination with octreotide LAR is more effective than monotherapy in increasing the response rate. Further randomized controlled trials with a larger sample size will be required to establish everolimus in combination with octreotide LAR as an effective first-line therapeutic option in patients with NET of any histological type, in the presence or absence of carcinoid syndrome.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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