Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors

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Abstract

Pasireotide long-acting repeatable (LAR) is a novel somatostatin analog (SSA) with avid binding affinity to somatostatin receptor subtypes 1, 2, 3 ($SSTR_{1,2,3}$) and 5 ($SSTR_5$). Results from preclinical studies indicate that pasireotide can inhibit neuroendocrine tumor (NET) growth more robustly than octreotide *in vitro*. This open-label, phase II study assessed the clinical activity of pasireotide in treatment-naïve patients with metastatic grade 1 or 2 NETs. Patients with metastatic pancreatic and extra-pancreatic NETs were treated with pasireotide LAR (60 mg every 4 weeks). Previous systemic therapy, including octreotide and lanreotide, was not permitted. Tumor assessments were performed every 3 months using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), overall radiographic response rate (ORR), and safety. Twenty-nine patients were treated with pasireotide LAR (60 mg every 4 weeks) and 28 were evaluable for response. The median PFS was 11 months. The most favorable effect was observed in patients with low hepatic tumor burden, normal baseline chromogranin A, and high tumoral $SSTR_5$ expression. Median OS has not been reached; the 30-month OS rate was 70%. The best radiographic response was partial response in one patient (4%), stable disease in 17 patients (60%), and progressive disease in ten patients (36%). Although grade 3/4 toxicities were rare, pasireotide LAR treatment was associated with a 79% rate of hyperglycemia including 14% grade 3 hyperglycemia. Although pasireotide appears to be an effective antiproliferative agent in the treatment of advanced NETs, the high incidence of hyperglycemia raises concerns regarding its suitability as a first-line systemic agent in unselected patients. $SSTR_5$ expression is a potentially predictive biomarker for response.

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms characterized by a relatively indolent rate of growth and a propensity to produce and secrete a variety of hormones that give rise to diverse clinical syndromes, including carcinoid syndrome. Based on their site of origin, NETs are often subclassified as pancreatic NETs (pNETs) and carcinoid tumors which are defined as NETs originating in the enterochromaffin cells of the airways and gastrointestinal tract (Kulke *et al.* 2012). In recent years, treatment options for metastatic NETs have expanded and targeted agents, including somatostatin analogs (SSAs), everolimus, and sunitinib, have entered into clinical use (Fazio *et al.* 2014).

Among the various emerging treatments, SSAs are associated with the most favorable side effect profile. Initially developed to palliate hormonal symptoms (Kvols *et al.* 1986), SSAs such as octreotide and lanreotide have also been shown to slow tumor progression in patients with advanced NETs (Faiss *et al.* 2003, Rinke *et al.* 2009). The randomized phase III PROMID trial evaluated octreotide long-acting repeatable (LAR) versus placebo in patients with metastatic midgut NETs and demonstrated a significant improvement in time-to-progression, thus defining a new paradigm in the treatment of small-intestinal NETs (Rinke *et al.* 2009). More recently, the CLARINET trial randomized patients with hormonally nonfunctioning gastroenteropancreatic NETs to receive depot-lanreotide versus placebo, also demonstrating a statistically significant improvement in median progression-free survival (PFS) from 18 months on placebo to unreached with lanreotide (Caplin *et al.* 2014). Tumor growth suppression is thought to be mediated through direct interaction between the SSA and its receptors on the tumor surface (direct effect) and also through inhibition of various circulating growth factors and cytokines such as insulin-like growth factor (indirect effect). It is still unclear which specific somatostatin receptor (SSTR) subtypes are primarily active in the antiproliferative effect of SSAs (Villaume *et al.* 2010, Sidéris *et al.* 2012).

Pasireotide is a novel multireceptor-targeted SSA with avid binding affinity to four of the five SSTR subtypes ($SSTR_{1,2,3}$ and $SSTR_5$) (Schmid 2008). Compared with octreotide, pasireotide shows a 2.5 times lower binding affinity to $SSTR_2$, but a 30-, five-, and 40-fold higher affinity for $SSTR_1$, $SSTR_3$, and $SSTR_5$ respectively (Schmid & Schoeffter 2004). Results of preclinical studies have indicated that pasireotide reduces NET secretion and growth both *in vitro* and *in vivo* (van Hoek *et al.* 2009, Somnay *et al.* 2013), displaying an antiproliferative activity higher than octreotide, at least against the NCI-H727 bronchial carcinoid cell line (Ono *et al.* 2007). When tested in clinical trials, pasireotide has shown a favorable tolerability profile (Dietrich *et al.* 2012, Wolin *et al.* 2013*b*, Shenouda *et al.* 2014). Pasireotide has demonstrated superior efficacy over the current standard of care (octreotide LAR) in patients with acromegaly (Colao *et al.* 2014) and, based on the results of a phase III trial (Colao *et al.* 2012), has been approved in both Europe and the USA for the treatment of patients with Cushing's disease for whom surgery has failed or is not an option. Recently, in a phase II study enrolling patients with advanced NETs refractory or resistant to SSAs, s.c. pasireotide up to 1200 μg twice daily was effective in controlling the symptoms of carcinoid syndrome in 27% of the cohort (Kvols *et al.* 2012).

Given the tolerable side effect profile of pasireotide LAR, its enhanced affinity for SSTRs, and its putative antiproliferative effects in patients with NETs, we conducted an open-label, single-arm, phase II study to investigate the antitumor activity of pasireotide LAR in treatment-naïve patients with metastatic pancreatic and extra-pancreatic NETs. The study also offered an opportunity to assess the correlation between SSTR staining pattern and clinical outcomes.

Patients and methods

Patient selection

This study was an open-label, single-arm, phase II prospective clinical trial. The protocol was approved by the Ethics Committee or the Institutional Review Board at each participating center. All patients provided written informed consent. The study was registered with clinicaltrials.gov (NCT01253161).

Eligible patients were required to be 18 years of age or older and have locally unresectable or metastatic grade 1 or 2 pancreatic or extra-pancreatic NETs. Mitotic count and ki-67 thresholds for the tumor grade index were based on the World Health Organization (WHO) 2010 classification (Rindi & Arnold 2010). Patients with a tumoral ki-67 index of over 20% were excluded. Previous systemic antineoplastic treatment, including octreotide and lanreotide, was not permitted. Other key eligibility criteria were measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), minimum of 4 weeks since any major surgery, absolute neutrophil count of 1000 cells/μl or greater, platelets at a level of 75 000 cells/μl or greater, hemoglobin over 8 g/dl, total bilirubin at or below 2 times the upper limit of normal (ULN), AST and ALT at or below 2 times ULN (less than 3 times ULN if liver metastases were present), creatinine at or below 2 times ULN, fasting serum cholesterol of 300 mg/dl or lower, and fasting serum triglycerides at or below 2.5 times ULN. Patients with uncontrolled diabetes mellitus or a fasting plasma glucose above 1.5 times ULN or HbA1c exceeding 8% were excluded, as were patients with symptomatic cholelithiasis. Other key exclusion criteria included a prolonged corrected QT interval (over 470 ms at screening) and a history of clinically significant cardiac arrhythmias.

Treatment and evaluation

Pasireotide LAR (60 mg) was administered intramuscularly every 4 weeks. A dose reduction to 40 mg every 4 weeks was allowed for patients unable to tolerate the full dose. All patients who developed hyperglycemia were required to monitor their fasting blood glucose levels using finger sticks twice daily and maintain a diary. Hyperglycemia was managed according to the investigators' judgment. Toxicities were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Evaluation visits were scheduled every 4 weeks along with standard blood tests (complete blood count, comprehensive metabolic panel), while tumor markers such as chromogranin A (CgA) and other secretory hormones including 5-hydroxyindoleacetic acid (5-HIAA), gastrin, and glucagon were measured every 12 weeks, if elevated at baseline. Radiological assessment of tumor burden was performed by local radiologists who were blinded to patient clinical characteristics every 12 weeks using computed tomography (CT) or magnetic

resonance imaging (MRI) scans and RECIST version 1.0 (Therasse *et al.* 2000) was used for evaluation of tumor response. Hepatic tumor load was quantified from CT/MRI scans by a semiquantitative three-dimensional approach (Rinke *et al.* 2009). Hepatic tumor burden was categorized as 0%, between 0 and 10% and more than 10%.

Immunohistochemical analysis of archival specimens

Immunohistochemistry (IHC) was used to evaluate the expression of the SSTR subtypes $SSTR_{1-5}$. Sections of 3–4 μm in thickness were cut from archival paraffin-embedded pathology specimens of accrued patients and subjected to an IHC staining protocol using the DakoCytomation Autostainer (DakoCytomation, Carpinteria, CA, USA). Microwave antigen retrieval with IHC Select EDTA buffer, pH 7.5 (Chemicon International, Temecula, CA, USA), was utilized. Endogenous peroxidase was blocked by hydrogen peroxide and blockage of avidin-binding protein was accomplished by using the Avidin–Biotin blocking kit (Vector Laboratories, Burlingame, CA, USA). The rabbit polyclonal primary antibodies against $SSTR_{1-5}$ were provided by the University of Uppsala, Sweden. Dilutions and timing for the five SSTR antibodies were used as previously reported by Nasir *et al.* (2006). EnVision+ HRP-labeled polymer antirabbit detection was used. Rabbit IgG was used for 60 min to replace the primary antibodies in the negative control sections. Pancreatic tissue was used as a positive control. The immunostained sections were examined under a light microscope by an experienced neuroendocrine pathologist (D Coppola) who was blinded to the patient clinical outcome. Immunoreactivity was scored into four categories, according to the intensity of the staining: 0, 1+, 2+, and 3+. The percentage of positive tumor cells was also scored semiquantitatively on a four-tiered scale: 0 (0%), 1 (1–33%), 2 (34–66%), and 3 (67–100%). The product of the intensity and the percentage scores determined the final score, which was classified as negative (score 0), weak (score 1–3), moderate (score 4–6), or strong (score 7–9). The correlation between SSTR staining patterns and clinical outcomes was analyzed in a descriptive fashion.

Sample size calculation

The primary efficacy endpoint was PFS. Secondary endpoints included overall survival (OS), overall radiographic response rates (ORR), and adverse events. The sample size calculation was based on the assumption that a true 1-year PFS rate of over 40% would be necessary to consider the investigational treatment sufficiently effective to pursue in further studies, whereas a true 1-year PFS of less than 19% would not yield further interest in this agent. These PFS rates correspond to null and alternative hypothesis median PFS of 5 and 9 months respectively. The sample size was chosen based on a one-sided α level of 10% and a power of 90%.

Statistical analysis

The Kaplan–Meier method was used to estimate all time-to-event functions. PFS was calculated from the date of first study treatment until the date of first detection of progressive disease or death due to any cause. OS was defined as the time from start of treatment until death as a result of any cause, with patients censored at the date of last follow-up if still alive. Exact 95% CI were calculated for each proportion of interest. All

tests were two sided and statistical significance was declared at *P*<0.05. Statistical analysis was performed using MedCalc statistical software 12.7 (MedCalc Software bvba, Ostend, Belgium). The assumption of exponential distribution was verified using the Hollander–Proschan test.

Results

Patient population

Demographic variables and clinical characteristics of 29 patients enrolled in the study are listed in Table 1. Median age of patients at study entry was 59 (31–75) years. Primary tumor sites included small intestine (14 patients), pancreas (*n*=6), rectum (*n*=2), unknown (*n*=4), and other sites (*n*=3). Thirteen patients had grade 1 tumors and 16 patients had grade 2 tumors. Twenty-seven patients had liver metastases, and hepatic tumor load was 10% in 15 patients (52%). The two patients without liver involvement had lymph node metastases unresectable by surgery. Octreoscan was performed in 26 patients before study entry, and 73% were positive. Five patients had carcinoid syndrome.

Duration of therapy

The intended total study duration was 24 months. Enrolled patients received a median of nine 28-day treatment cycles. Reasons for discontinuation included radiographic tumor progression (18), symptomatic decline (3), toxicity (2), and death on study (1). Five patients remained on the drug at the time of data analysis. One patient required a single-dose reduction, due to QTc prolongation. Hyperglycemia was the only toxicity leading to discontinuation of treatment (two patients).

Progression-free and overall survival

At the time of data cutoff, six patients had died and 23 patients were alive, with follow-up duration ranging from 5.8 to 34.6 months. As depicted in Fig. 1A, the overall median PFS was 11 months (95% CI, 7.6–16 months). Stratified by tumor group (Fig. 1B), the median PFS of patients with midgut carcinoids and NETs of other primary sites was 14.8 months (95% CI, 8.6–25.6 months) and 7.6 months (95% CI, 4.5–12.7 months) respectively (*P*=0.14). By grade (Fig. 1C), the median PFS of patients with grade 1 and 2 tumors was 13.4 months (95% CI, 7.5–23.9 months) and 9.3 months respectively (95% CI, 5.7–15.2 months; *P*=0.43). Patients with high (10%) hepatic tumor load had a significantly shorter PFS (7 months; 95% CI, 4.4–11.3 months) compared with patients with low (<10%) hepatic tumor burdens, who showed a median PFS of 17.8 months (95% CI, 9.6–33.1 months; *P*=0.05). Among patients with elevated baseline CgA, those experiencing at least a 50% reduction or normalization of the tumor marker within 3 months from the initiation of the treatment showed a median PFS of 11.8 months (95% CI, 5.2–26.7 months), whereas among late and non-responders, the median PFS was 5.7 months (95% CI, 3.3–9.9 months). Patients with normal baseline CgA exhibited a median PFS of 18.5 months (95% CI, 9.4–36 months). There was no correlation between Octreoscan positivity and PFS (*P*=0.55).

Median OS has not been reached. The 12-, 24-, and 30-month survival rates estimated by the Kaplan–Meier method were 89, 70, and 70% respectively (data not shown).

Biochemical and radiological response

Patients were followed for biochemical and radiological responses with CgA and 5-HIAA levels and imaging studies after every 12 weeks of treatment. Among 18 patients who had baseline-elevated (above the ULN) serum CgA levels, eight patients (44%) experienced major reductions (over 50%) or normalization of the tumor marker. This biochemical response was always noted within 3 months of treatment initiation. Differences between the median baseline CgA concentration and its lowest values following initiation of treatment were statistically significant (*P*=0.02). Best biochemical responses of CgA levels compared with baseline in patients with evaluable data are depicted in Fig. 2A. An insufficient number of patients had baseline elevations of 5-HIAA to allow reliable conclusions to be drawn regarding the 5-HIAA response.

Twenty-eight patients were assessable for radiological response. One patient withdrew from the study before radiographic evaluation due to toxicity (hyperglycemia). When best response to therapy was evaluated, 4% (1/28) of patients partially responded according to RECIST criteria, 60% (17/28) had stable disease, and 36% (10/28) experienced progressive disease. The waterfall plot analysis showed some degree of tumor shrinkage in 46% (13/28) of evaluable patients, while 54% (15/28) of the cohort appeared to experience continued tumor growth. Figure 2B summarizes the maximum percentage changes from baseline in the sum of the longest diameters of target lesions. Of the five patients with carcinoid syndrome, four experienced an improvement of their symptoms.

Safety profile

All enrolled patients received treatment and were evaluated for toxicity. Pasireotide LAR was generally well tolerated with the exception of hyperglycemia. The side effects considered at least possibly related to the treatment are listed in Table 2. No drug-related grade 4 adverse events were observed on the trial, whereas grade 3 toxicities included cholecystitis (3.5%) and hyperglycemia (14%). Among the most common mild or moderate adverse events with a suspected study drug relationship were hyperglycemia (65%), diarrhea (14%), rash (7%), fatigue (7%), and myalgia (7%). Hyperglycemia required intervention in 13 out of 22 patients and was managed with oral hypoglycemic agents or insulin in seven and six patients respectively. Despite discontinuation of pasireotide, three patients have remained on long-term insulin therapy. Only one of the 22 patients who experienced hyperglycemia during treatment with pasireotide had a medical history of diabetes at baseline. Mean fasting glucose levels increased from 106 mg/dl at baseline to 150 mg/dl at the end of the study.

Tissue analysis

Archival pathology specimens were available for 23 patients. Eight specimens were obtained from the primary tumor location and 15 were from liver metastases. As summarized in Table 3, the median primary tumor size was 2 cm (0.4–3.5). Necrosis was present in 4% (1/23) of specimens and vascular invasion in 30% (7/23). When specimens were immunostained using antibodies to $SSTR_{1-5}$, the median IHC intensity score was four for $SSTR_2$ (range 0–9) and $SSTR_3$ (range 2–9), three for $SSTR_4$ (range 1–9), five for $SSTR_1$ (range 0–9), and six for $SSTR_5$ (range 2–9). No difference in terms of median intensity of

immunostaining was observed after stratification for tumor site (primary/hepatic metastasis; P=0.68), primary tumor origin (midgut/non-midgut; P=0.73), and grade (P=0.7). The pattern of immunostaining was predominantly diffuse (cytoplasmic and nuclear) for $SSTR_1$, whereas the expression of the other SSTR subtypes was mainly cytoplasmic (Fig. 3).

Univariate analyses revealed that only high $SSTR_5$ expression was associated with prolonged PFS (P=0.0068). The median PFS for patients with tumors expressing low levels of $SSTR_5$ was 2.8 months (95% CI, 2.3–12.1 months) compared with 19.9 months (95% CI, 7.7–29.1 months) among the patients expressing high levels of $SSTR_5$. There was no significant correlation between expression of $SSTR_5$ and the proliferative activity by ki-67 (P=0.52). After stratification for median expression of $SSTR_{1-5}$, the median PFS was 14.3 months (95% CI, 3.2–29.1 months) and 5.8 months (95% CI, 2.8–12.1 months) in the population showing median high or low intensity of SSTR expression respectively (P=0.13).

Discussion

SSAs have an established place in the medical treatment of patients with NETs, being the standard of care for symptom control in patients with functional, hormone-secreting neoplasms. Moreover, both the PROMID (Rinke *et al.* 2009) and CLARINET (Caplin *et al.* 2014) studies have recently provided compelling evidence that SSAs can inhibit tumor growth in patients with metastatic well-differentiated NETs of the gastroenteropancreatic tract. Whereas both octreotide and lanreotide primarily target $SSTR_2$, pasireotide targets four of the five SSTRs and theoretically represents a more potent antiproliferative agent (Schmid & Schoeffter 2004).

As a practical matter, assessing the efficacy of an antiproliferative agent in a single-arm phase II study is quite difficult, particularly in a very heterogeneous cohort of patients. Our assumption was that median PFS in the absence of treatment would be approximately 5 months (null hypothesis) whereas a median study PFS of longer than 9 months would indicate that pasireotide had significant activity. These assumptions were based on data sets from several clinical trials, including the placebo arms of the PROMID study (median PFS 6 months) (Rinke *et al.* 2009), and the RADIANT 3 trial in pNETs (median PFS 4.6 months on local review) (Yao *et al.* 2011). Also, we did not expect to achieve as long a median PFS as was seen in the treatment arm of the PROMID study (14.3 months) given the more aggressive tumor types eligible for our trial. With these previous study results in mind, the median PFS of 11 months observed in our study is encouraging and indicates that pasireotide LAR is an active antiproliferative agent capable of inhibiting tumor growth in a heterogeneous population of NETs.

Our trial patients were monitored carefully for emergence of hyperglycemia, and a high rate of elevated fasting blood glucose was observed. Although the majority of cases were mild, 45% of trial patients began medical treatment for hyperglycemia, nearly half of whom required insulin. Three patients remained on insulin for over a year after discontinuation of pasireotide. In contrast with results reported previously (Kvols *et al.* 2012), no correlation between a medical history of diabetes or impaired glucose tolerance at study entry and pasireotide-induced hyperglycemia was seen. The high rate of hyperglycemia observed in

this trial raises questions regarding the suitability of pasireotide as a first-line treatment agent in NETs, particularly compared with octreotide or lanreotide, which are lacking in significant toxicities.

A potential role for pasireotide in NETs may exist in the salvage setting where the risk:benefit ratio may be more favorable. Indeed, results of a phase III study of pasireotide versus high-dose octreotide among patients with refractory carcinoid syndrome were reported recently (Wolin *et al.* 2013*a*). Although, in this study, pasireotide treatment did not achieve the primary endpoint of improvement in carcinoid syndrome, it was associated with a statistically significant prolongation in PFS (exploratory endpoint) compared with octreotide. Future studies that preselect tumors based on SSTR profile may identify patients more likely to respond to pasireotide than to the currently available SSAs. Our results indicate that $SSTR_5$-expressing tumors may be particularly sensitive to pasireotide therapy.

Conclusion

Pasireotide LAR appears to significantly inhibit growth of NETs; however, it remains unclear whether its antiproliferative effect is superior to those of the currently available SSAs octreotide and lanreotide, and whether targeting multiple SSTRs results in improved tumor control in unselected patients. The high rate of hyperglycemia requiring intervention represents a potential impediment to the use of pasireotide as a first-line agent. Future studies should focus on the evaluation of pasireotide in patients progressing on octreotide or lanreotide. Expression of $SSTR_5$ is a potential predictive biomarker for response.

Acknowledgments

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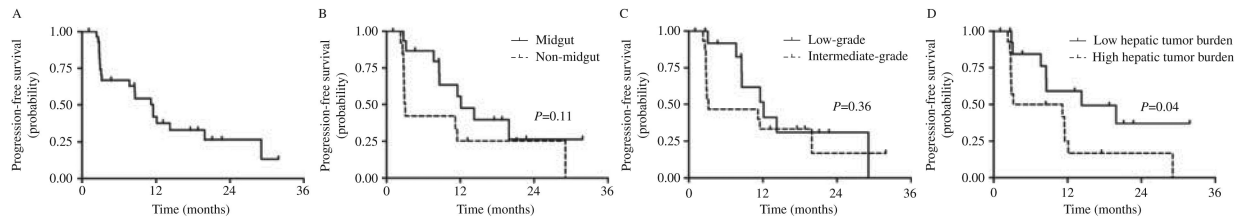
Figure 1.
Kaplan–Meier estimate of progression-free survival (PFS). (A) For all 29 patients, 6- and 12-month PFS rates were 66.9% (±9) and 41.9% (±9.9) respectively. (B) PFS by primary site, (C) PFS by tumor grade, and (D) PFS by hepatic tumor burden.
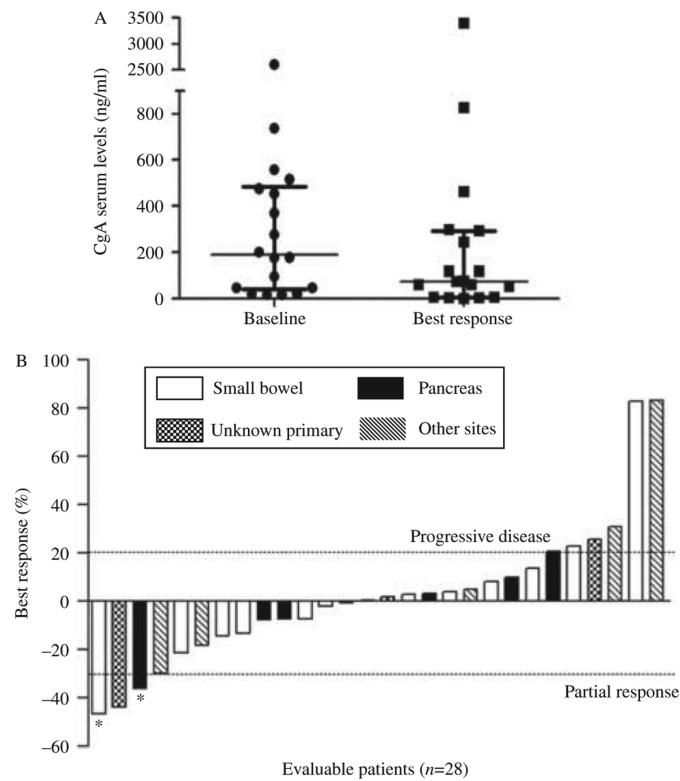
Figure 2.
Biochemical and radiological response following pasireotide treatment. (A) In patients with
elevated baseline CgA, median CgA concentrations decreased from 189 to 73.5 ng/ml. The
decrease was statistically significant (*P*=0.02) according to the Wilcoxon-matched pairs
signed rank test. Paired row values, median change, and interquartile range are represented.
(B) Waterfall plot illustrating best radiographic response (percentage change) in each
enrolled patient. *Decrease not confirmed at subsequent assessment, thus failing to match
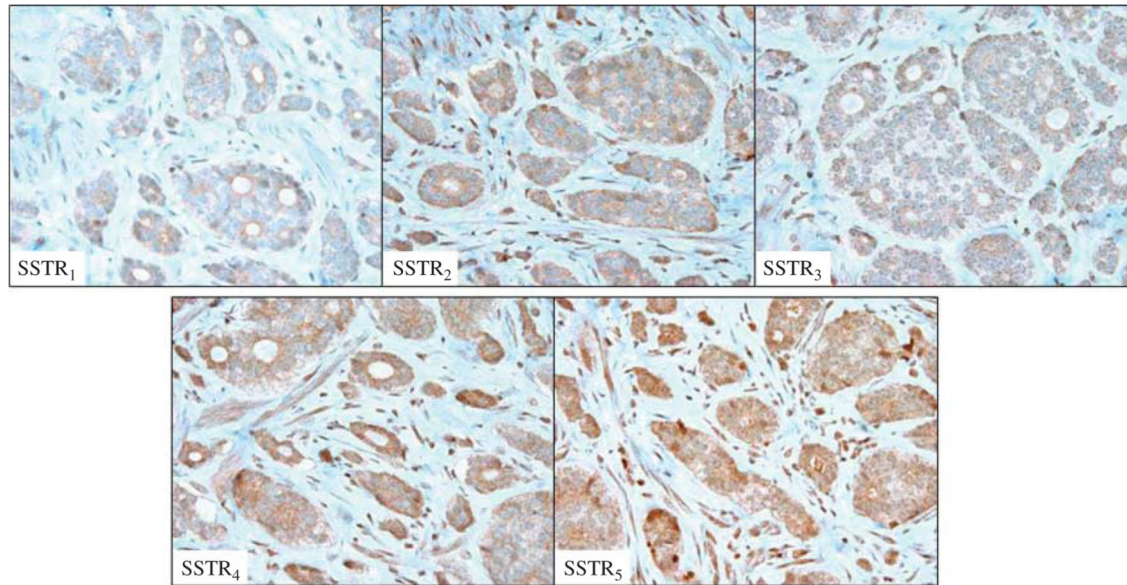RECIST criteria for partial response.

Figure 3.
Examples of positive immunohistochemical staining for SSTR$_{1-5}$ subtypes (magnification: ×40). A full colour version of this figure is available at http://dx.doi.org/10.1530/ERC-14-0360.

Table 1

Patient demographics and clinical characteristics

Characteristic	No. of patients (= 29)	%
Age (years)		
Median	59	
Range	31–75	
Gender		
Male	19	66
Female	10	34
Race		
White	22	76
Black	3	10
Hispanic	3	10
Asian	1	4
Performance status (ECOG)		
0	21	72
1	8	28
Location of primary tumor		
Small intestine	14	49
Pancreas	6	21
Rectum	2	7
Appendix	1	3
Lung	1	3
Thymus	1	3
Unknown	4	14
Tumor grade		
Low grade	13	45
Intermediate grade	16	55
Elevated baseline chromogranin A (> ULN)		
Yes	18	62
No	11	38
Baseline chromogranin A (nl < 15 ng/ml)		
Median	21	
Mean	236	
Range	1–2600	
Elevated baseline 5-HIAA		
Yes	9	31
No	13	45
Unknown	7	24
Liver involvement (%)		
0	2	7

Characteristic	No. of patients (= 29)	%
<10	12	41
10	15	52
Octreoscan positivity		
No	5	17
Yes	21	73
Unspecified	3	10

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Table 2

Treatment-related toxicity

	Grade 1	Grade 2	Grade 3	Total
Hematological toxicity, *n* (%)				
Anemia	1 (3)	0 (0)	0 (0)	1 (3)
Thrombocytopenia	1 (3)	0 (0)	0 (0)	1 (3)
Gastrointestinal toxicity (%)				
Diarrhea	4 (14)	0 (0)	0 (0)	4 (14)
Nausea	0 (0)	1 (3)	0 (0)	1 (3)
Vomiting	0 (0)	1 (3)	0 (0)	1 (3)
Bloating	1 (3)	0 (0)	0 (0)	1 (3)
Cholecystitis	0 (0)	0 (0)	1 (3)	1 (3)
Mucositis	1 (3)	0 (0)	0 (0)	0 (0)
Abdominal pain				
Cardiovascular toxicity (%)				
QT prolongation	1 (3)	0 (0)	0 (0)	1 (3)
Skin toxicity (%)				
Rash	2 (7)	0 (0)	0 (0)	2 (7)
Metabolism disorders (%)				
Hyperglycemia	9 (32)	9 (32)	4 (14)	22 (79)
Hypoglycemia[a]	1 (3)	0 (0)	0 (0)	1 (3)
Miscellaneous				
Fatigue	2 (7)	0 (0)	0 (0)	2 (7)
Myalgia	2 (7)	0 (0)	0 (0)	2 (7)
Hypertransaminasemia	1 (3)	0 (0)	0 (0)	1 (3)
Elevated alkaline phosphatase	1 (3)	0 (0)	0 (0)	1 (3)

[a]Hypoglycemia that occurred during an episode of bowel obstruction in an insulin-treated patient.

Table 3

Pathological characteristics of the patient population

Characteristic	No. of patients (= 23)	%
Primary tumor size (cm)		
Median	2	
Range	0.4–3.5	
Tumor necrosis		
Present	1	4
Absent	12	52
Unknown	10	44
Angioinvasion		
Present	7	30
Absent	16	70
Ki-67 (%)		
Median	5	
Range	1–20	
SSTR expression		
$SSTR_1$		
Low (negative/weak)	2/5	8/22
High (moderate/strong)	9/6	39/26
Unknown	1	4
$SSTR_2$		
Low (negative/weak)	1/8	4/35
High (moderate/strong)	12/1	52/4
Unknown	1	4
$SSTR_3$		
Low (negative/weak)	0/7	0/30
High (moderate/strong)	13/2	57/8
Unknown	1	4
$SSTR_4$		
Low (negative/weak)	0/16	0/69
High (moderate/strong)	5/1	22/4
Unknown	1	4.5
$SSTR_5$		
Low (negative/weak)	0/5	0/22
High (moderate/strong)	14/3	61/13
Unknown	1	4