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## A phase II study of axitinib in advanced neuroendocrine tumors

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### Abstract

Neuroendocrine tumors (NETs) are highly vascular neoplasms overexpressing vascular endothelial growth factor (VEGF) as well as VEGF receptors (VEGFR). Axitinib is a potent, selective inhibitor of VEGFR-1, -2 and -3, currently approved for the treatment of advanced renal cell carcinoma. We performed an open-label, two-stage design, phase II trial of axitinib 5 mg twice daily in patients with progressive unresectable/metastatic low-to-intermediate grade carcinoid tumors. The primary end points were progression-free survival (PFS) and 12-month PFS rate. The secondary end points included time to treatment failure (TTF), overall survival (OS), overall radiographic response rate (ORR), biochemical response rate and safety. A total of 30 patients were enrolled and assessable for toxicity; 22 patients were assessable for response. After a median follow-up of 29 months, we observed a median PFS of 26.7 months (95% CI, 11.4–35.1), with a 12-month PFS rate of 74.5% ( $\pm 10.2$ ). The median OS was 45.3 months (95% CI, 24.4–45.3), and the median TTF was 9.6 months (95% CI, 5.5–12). The best radiographic response was partial response (PR) in 1/30 (3%) and stable disease (SD) in 21/30 patients (70%); 8/30 patients (27%) were unevaluable due to early withdrawal due to toxicity. Hypertension was the most common toxicity that developed in 27 patients (90%). Grade 3/4 hypertension was recorded in 19 patients (63%), leading to treatment discontinuation in six patients (20%). Although axitinib appears to have an inhibitory effect on tumor growth in patients with advanced, progressive carcinoid tumors, the high rate of grade 3/4 hypertension may represent a potential impediment to its use in unselected patients.

### Keywords

carcinoid tumor; antiangiogenesis; tyrosine kinase inhibitor; VEGF; VEGFR

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#### Declaration of interest

Dr Strosberg has performed consultation for Novartis, Ipsen and Lexicon within institutional conflict of interest payment guidelines. Dr Bergsland has served as a consultant for Ipsen (payment to institution), Novartis (uncompensated) and Lexicon (uncompensated). All the remaining authors have declared no conflicts of interest.

## Introduction

Neuroendocrine tumors (NETs) comprise a heterogeneous spectrum of malignancies characterized by a relatively indolent rate of growth and the ability to secrete a variety of hormones resulting in characteristic clinical syndromes, including carcinoid syndrome (Cives & Strosberg 2014). NETs deriving from the enterochromaffin cells of the digestive tract and airways are often referred to as carcinoid tumors and are substantially different from pancreatic NETs (pNETs) in terms of biology and clinical behavior (Kulke *et al.* 2012).

Treatment options for metastatic carcinoid tumors have improved in recent years. Based on the results of the phase III PROMID and CLARINET trials (Rinke *et al.* 2009, Caplin *et al.* 2014), somatostatin analogs (SSAs) including octreotide and lanreotide have been formally incorporated into the clinical practice for patients with gastroenteropancreatic NETs. More recently, the randomized phase III NETTER-1 trial evaluated peptide receptor radionuclide therapy (PRRT) vs octreotide 60 mg long-acting repeatable (LAR) in patients with metastatic, progressive midgut NETs and demonstrated a 79% reduction in the risk for progression (HR = 0.209,  $P < 0.0001$ ) (Strosberg *et al.* 2015). Similarly, the RADIANT-4 trial randomized patients with advanced, progressive, nonfunctioning NETs of lung or gastrointestinal origin and showed a significant improvement in progression-free survival (PFS) from 3.9 months on placebo to 11 months with everolimus (Yao *et al.* 2016). However, even if everolimus and/or PRRT are approved for the treatment of carcinoid tumors, there will still be a clear need for additional systemic agents with antitumor activity.

NETs are highly vascularized neoplasms, and overexpression of vascular endothelial growth factor (VEGF) as well as VEGF receptor (VEGFR) subtypes has been reported, suggesting that autocrine activation of the VEGF pathway may play a critical role in tumor growth (La Rosa *et al.* 2003, Zhang *et al.* 2007, Besig *et al.* 2009). Thus far, trials on VEGF pathway inhibitors have demonstrated activity primarily in pNETs. A phase III trial of sunitinib in pNETs demonstrated significant improvement in PFS from 5.5 months on the control arm to 11.4 months in the experimental arm (Raymond *et al.* 2011), leading to its approval for this indication. The activity of VEGF pathway inhibitors such as the anti-VEGF monoclonal antibody bevacizumab (Chan *et al.* 2012) and the VEGFR-targeted tyrosine kinase inhibitors (TKIs) – sunitinib (Kulke *et al.* 2008), sorafenib (Hobday *et al.* 2007) and pazopanib (Phan *et al.* 2015) – have been less convincing in carcinoid tumors, largely because phase II trials have been terminated on interim analysis due to lack of objective radiographic response. However, while the likelihood of radiographic response is low with angiogenesis inhibitors, improvement of survival durations appear to be very possible. As such, many believe that progression-free survival is a preferable end point for clinical trials with angiogenic inhibitors.

Axitinib is a TKI with picomolar potency against VEGFR-1, -2 and -3 (Hu-Lowe *et al.* 2008) and is approved for the second-line treatment of advanced renal cell carcinoma (RCC). When compared with sorafenib in patients with progressive RCC, axitinib resulted in significantly longer PFS (HR = 0.665;  $P < 0.0001$ ), higher objective response rates (19% vs 9%;  $P = 0.0001$ ) and a favorable side effect profile (Rini *et al.* 2011).

We performed an open-label, single-arm, phase II study to assess the safety and efficacy of axitinib in patients with progressive, advanced, low-to-intermediate grade extra-pancreatic NETs. To test the hypothesis that potent and selective inhibition of VEGF pathway might result in prolonged disease stability, PFS and 1-year PFS rate were chosen as primary end points.

## Patients and methods

### Patient selection

This study was an open-label, single-arm, Simon two-stage design, phase II prospective clinical trial funded by the National Comprehensive Cancer Network (NCCN). The protocol was approved by the Institutional Review Boards at each participating center. All patients provided written informed consent. The study was registered with clinicaltrials.gov (NCT01435122).

Subjects were adults (age  $\geq 18$  s) with locally unresectable or metastatic grade 1 or 2 carcinoid tumors. Mitotic count and Ki-67 thresholds of  $\leq 20$  for the tumor grade index were based on the World Health Organization (WHO) 2010 classification (Rindi & Arnold 2010). Patients with poorly differentiated or high-grade tumors were excluded. Patients were required to have evidence of progressive disease within 12 months of study entry. Any number of prior systemic or locoregional treatments was allowed, and concurrent therapy with SSAs was permitted as long as patients remained on a stable dose. For patients with midgut NETs, prior SSA therapy was required for eligibility. Other key inclusion criteria were measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer *et al.* 2009), Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ , absolute neutrophil count  $\geq 1500$  cells/ $\mu$ L, platelets  $\geq 75,000$  cells/ $\mu$ L, total bilirubin  $\leq 1.5$  times the upper limit of normal (ULN), AST and ALT  $\leq 2.5$  times ULN ( $\leq 5$  times ULN if liver metastases were present), creatinine  $\leq 1.5$  times ULN, PT and aPTT levels  $\leq 1.5$  times ULN, and proteinuria  $< 2$  g/day. Patients who had prior treatment with a dedicated VEGF pathway inhibitor, known brain metastases, a history of myocardial infarction, uncontrolled angina, congestive heart failure and cerebrovascular accident within 12 months from study entry, deep venous thrombosis, pulmonary embolism or hemorrhage within 6 months, as well as evidence of serious non-healing wound or ulcer, gastrointestinal perforation or bleeding, abdominal abscess or fistula, or uncontrolled thyroid dysfunction were excluded. Other key exclusion criteria included uncontrolled hypertension ( $> 140/90$  mmHg) and use of CYP3A4 inhibitors and CYP3A4 or CYP1A2 inducers.

### Treatment and evaluation

Axitinib was given orally with food at a dose of 5 mg twice daily on a continuous 28-day cycle, until progressive disease (PD), unacceptable toxicity or withdrawal of consent. Patients were evaluated on day 1 of every cycle with physical examinations, vital signs including blood pressure, and routine blood tests. Patients experiencing hypertension (either systolic BP  $> 140$  or diastolic BP  $> 90$ ) were managed according to the investigator's judgment. Two dose reductions (3 mg twice daily and then 2 mg twice daily) were allowed for severe hypertension ( $> 170/105$  mmHg) resistant to antihypertensive medications and

other grade 3 or 4 drug-related toxicities. Patients who experienced recurrent severe hypertension or grade 3 or 4 toxicities after two dose reductions were excluded from the study. 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 and urine tests (complete blood count, comprehensive metabolic panel and urinalysis), whereas tumor markers such as chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) were measured every 12 weeks, if elevated at baseline. Radiological assessment was performed by local radiologists who were blinded to patient clinical characteristics every 12 weeks using CT or MRI scans. The RECIST version 1.1 (Eisenhauer *et al.* 2009) was used for the evaluation of tumor response.

### Sample size calculation

The primary efficacy end points were progression-free survival (PFS) and 12-month PFS rate. Secondary end points included time to treatment failure (TTF), overall survival (OS), overall radiographic response rate (ORR), biochemical response rate and adverse events. The sample size calculation was based on the assumption that a true 12-month PFS rate of >56.5% would be necessary to consider the investigational treatment sufficiently active to pursue in further studies, whereas a true 12-month PFS rate of <36% would not yield further interest in this agent. These PFS rates correspond to null and alternative hypothesis – median PFS 8.1 and 14.6 months, respectively. The sample size was chosen based on a one-sided  $\alpha$  level of 10% and a power of 80%, assuming an exponential PFS distribution.

According to a Simon two-stage design (Simon 1989), the trial was monitored for early stopping. The interim analysis for futility was conducted when 18 patients were enrolled and followed up for 6 months. If 8 PD were observed, the trial was to be terminated. When 15 patients completed two cycles of therapy, the trial was also monitored for safety. If there were 3 grade 3 or higher toxicities (with the exception of hypertension), an additional 15 patients could be enrolled for the second stage.

### 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 progressive disease or death due to any cause. OS was defined as the time from the initiation of treatment until death due to any cause, with patients censored at the date of last follow-up if still alive. TTF was defined as the time from administration of the initial dose of axitinib until study discontinuation for any reason. Exact 95% confidence intervals (CIs) 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).

## Results

### Patient population

Demographic variables and clinical characteristics of 30 patients enrolled in the study are listed in Table 1. The median age of the patient population was 64 (35–77) s. The majority (29/30) of them had a performance status of 0 or 1, and more than two thirds (21/30) had grade 1 tumors. Primary tumor sites included small intestine (19 patients), lung ( $n = 3$ ), colon and rectum ( $n = 4$ ), thymus ( $n = 1$ ), and unknown ( $n = 3$ ). Of the total patients, 18 had hormonally functioning tumors, including 16 patients with carcinoid syndrome, one patient with gastrin-producing tumor and one patient with ectopic ACTH secretion. The primary tumor had been resected in 22/30 patients before enrollment on the trial. Most patients (21/30) had received only one prior line of systemic therapy; 27 received prior octreotide LAR, four received prior cytotoxic chemotherapy (including etoposide/cisplatin and capecitabine/temozolomide), three had prior everolimus, three had prior interferon- $\alpha$ , one had prior PRRT, and five had prior investigational agents (including pasireotide, erlotinib and ganitumab). At study entry, 25/30 patients remained on octreotide LAR.

### Duration of therapy

At the interim analysis, we recorded two PD and two grade 3/4 toxicities. Thus, the null hypothesis that treatment was futile and toxic was rejected, and we continued accrual to 30 patients in total as per protocol. Patients received a median of nine 28-day treatment cycles. Of the 30 patients, 12 (40%) had at least one dosing interruption and eight patients (27%) required at least a single-dose reduction. Of the 30 patients who began treatment, 22 received more than three cycles. The median TTF was 9.6 months (95% CI, 5.5–12 months). Reasons for discontinuation included radiographic tumor progression ( $n = 10$ ), unacceptable toxicity ( $n = 13$ ), symptomatic decline ( $n = 5$ ) and physician decision ( $n = 1$ ). One patient remained on drug at the time of data analysis. Toxicities leading to treatment discontinuation included uncontrolled hypertension ( $n = 6$ ), fatigue ( $n = 3$ ), abdominal pain ( $n = 2$ ), hand–foot syndrome ( $n = 1$ ) and hyperbilirubinemia ( $n = 1$ ).

### Progression-free and overall survival

All enrolled patients were evaluable for PFS, OS and TTF. At the time of data cutoff, nine patients had died and 21 were alive, with median follow-up of 29 months (range 1–45.3 months). As depicted in Fig. 1A, the median overall PFS was 26.7 months (95% CI, 11.4–35.1), and the 12-month PFS rate was 74.5% ( $\pm 10.2$ ). Stratified by tumor group, the median PFS of patients with small bowel carcinoids and NETs of other primary sites was 28 months (95% CI, 11.4–35.1 months) and 25.1 months (95% CI, 14.4–26.7 months), respectively ( $P = 0.99$ ). By grade, the median PFS of patients with grade 1 and 2 tumors was 28 months (95% CI, 25.1–35.1 months) and 14.4 months (95% CI, 8.5–26.7 months;  $P = 0.26$ ), respectively. There was no difference in PFS between patients with high ( $\geq 10\%$ ) and low ( $<10\%$ ) hepatic tumor burden ( $P = 0.64$ ).

The median OS was 45.3 months (95% CI, 24.4–45.3 months; Fig. 1B). The 12- and 24-month OS rates were 93% ( $\pm 4.9\%$ ) and 74.3% ( $\pm 8.4\%$ ), respectively.

## Radiological and biochemical response

Among 30 enrolled patients, 22 were evaluable for response. The remaining eight patients (27%) withdrew from the study before radiographic evaluation due to toxicity (hypertension,  $n = 6$ ; fatigue  $n = 2$ ). When the best response to therapy was evaluated, 3% (1/30) patients partially responded according to RECIST criteria, whereas 70% (21/30) had stable disease, including an unconfirmed partial response. The waterfall plot analysis showed some degree of tumor shrinkage in 68% (15/22) of evaluable patients and no change or continued tumor growth in 32% (7/22) of the cohort. Figure 2 summarizes the maximum percent change from baseline in the sum of the longest diameters of target lesions.

Among 18 patients with baseline elevated ( $>ULN$ ) serum CgA levels and at least one repeat measurement, four patients (22%) experienced major reduction ( $>50\%$ ) or normalization of the tumor marker. Eighteen patients had baseline elevations ( $>ULN$ ) of 5-HIAA, and repeat measurements were available in 11 patients. Major 5-HIAA responses were recorded in 5/11 evaluable patients (45%). Differences between the median baseline CgA and 5-HIAA concentration and their lowest value following initiation of treatment were statistically significant ( $P = 0.04$  and  $P = 0.01$ , respectively; Fig. 3A and B). As we identified only one objective response in our cohort, no reliable associations between biochemical response and likelihood of radiographic response could be made. Exploratory analysis of PFS and OS did not reveal an association with either CgA or 5-HIAA response.

## Safety

All the study patients were evaluated for toxicity. The side effects considered at least possibly related to the treatment are listed in Table 2. Hypertension was the most common toxicity and developed in 27 patients (90%), requiring intervention in 21 individuals (70%). In 19 patients (63%), hypertension was of grade 3/4. No carcinoid crisis episodes were observed. Other common adverse events included fatigue (60%), headache (47%), diarrhea (33%), nausea (30%), vomiting (20%), weight loss (23%), anorexia (20%), hoarseness (30%) and thrombocytopenia (23%). The only observed grade 4 toxicity was hypertensive emergency associated with radiographic evidence of mild intracranial hemorrhage (3%). The patient recovered fully from this event. No treatment-related death was reported.

## Discussion

This study suggests that axitinib has antitumor activity in patients with advanced, progressive carcinoid tumors, but is associated with a high rate (90%) of hypertension and other toxicities leading to study discontinuation for reasons other than disease progression in a significant number of subjects.

Antiangiogenic agents have an established place in the medical treatment of patients with NETs, and sunitinib is approved for pNETs based on the results of a phase III trial (Raymond *et al.* 2011). In carcinoid tumors, TKIs including sunitinib (Kulke *et al.* 2008), sorafenib (Hobday *et al.* 2007) and pazopanib (Phan *et al.* 2015) have shown thus far only marginal activity in terms of tumor shrinkage. However, objective response might not be the optimum end point for nonrandomized carcinoid trials, and delay in progression in the

absence of radiographically defined tumor response can be expected during treatment with cytostatic agents (Kulke *et al.* 2011).

In this trial, we assumed that median PFS in the absence of treatment would be 8.1 months, whereas a median study PFS of at least 14.6 months would indicate that axitinib had antitumor activity. These assumptions were generated according to previous clinical trials conducted in a similar population of patients with advanced, progressive extra-pancreatic NETs, including the placebo plus octreotide LAR arm of the RADIANT-2 trial (Pavel *et al.* 2011) (median PFS 8.6 months by local investigator assessment; 71% of these patients had received prior SSA therapy). Comparison with local rather than central review was justified by the lack of central adjudication in our study. We observed a median PFS of 26.7 months (95% CI, 11.4–35.1), with a 12-month PFS rate of 74.5% ( $\pm 10.2$ ). Although cross-trial comparisons should be drawn with caution, these results compare favorably with reported results for other antiangiogenic TKIs. In fact, in a phase II study of sunitinib, the median time to progression (TTP) was 10.2 months (95% CI, 9.2–17.5) in the carcinoid tumor cohort, although progressive disease was not necessary for enrollment (Kulke *et al.* 2008). Similarly, 6-month PFS rate was 40% in patients with carcinoids who received sorafenib (Hobday *et al.* 2007), and pazopanib was associated with a median PFS of 8.4 months (95% CI, 0–16.9) in carcinoid patients with progressive disease at enrollment (Phan *et al.* 2015). The median PFS recorded in this study also compares favorably with a median investigator-assessed PFS of 14 months (95% CI, 11.2–17.7) recently reported for everolimus, an agent deemed active in progressive, extra-pancreatic NETs (Yao *et al.* 2016).

However, our results are limited by a relatively high rate of patient withdrawal before progression due to toxicity. This explains the wide CIs surrounding the median PFS and the discrepancy with the observed median TTF of 9.6 months (95% CI, 5.5–12 months). The relatively high rates of hypertension and fatigue raise concerns about the tolerability of axitinib in a certain subset of carcinoid patients. Toxicities associated with axitinib were largely consistent with the known side effect profile of TKIs targeting the VEGF/VEGFR axis. However, we observed an unexpectedly high rate (90%) of elevated blood pressure, with grade 3/4 hypertension arising in 64% of the patients. These rates were substantially higher than those reported with the same agent for other cancers, including renal cell carcinoma and pancreatic adenocarcinoma (Kindler *et al.* 2011, Rini *et al.* 2011, Qi *et al.* 2013). The expected rate of grade 3/4 hypertension is approximately 15% in patients with renal cell carcinoma (Rini *et al.* 2011, Hutson *et al.* 2013). The significance of the high rate of hypertension in this study is unclear, but may reflect confounding factors unique to carcinoid. Concurrent secretion of vasoactive neuropeptides has been hypothesized as possibly related to the increased risk of hypertension in patients with carcinoid tumors following treatment with antiangiogenic TKIs (Kulke *et al.* 2008). In our study, all patients ( $n = 6$ ) who discontinued axitinib because of uncontrolled hypertension had carcinoid syndrome. Importantly, in this study the frequency and severity of hypertension were also higher than in carcinoid patients treated with bevacizumab (Yao *et al.* 2015), sunitinib (Kulke *et al.* 2008) or pazopanib (Phan *et al.* 2015). A deeper understanding of the underlying pathogenesis and potential risk factors contributing to hypertension development in NET patients treated with axitinib is needed, in order to maximize the risk:benefit ratio associated with the drug. It is conceivable that the dose, schedule and/or dose modification



scheme could be further optimized so as to limit toxicity while preserving efficacy. The predictive value of hypertension in patients treated with antiangiogenic agents is uncertain and may depend on the relative role of angiogenesis and the specific disease type (Dienstmann *et al.* 2011).

## Conclusion

Axitinib appears to have an inhibitory effect on tumor growth in patients with advanced, progressive carcinoid tumors. However, the high rate of grade 3/4 hypertension may represent a potential impediment to the use of standard dose axitinib in unselected patients. If future studies of axitinib are initiated in this disease, monitoring and earlier and more aggressive management of blood pressure upon initiation of treatment need to be incorporated into the study design. Examination of additional dose levels and/or schedules may also be fruitful, recognizing that patients with carcinoid syndrome appear to be at particularly high risk for hypertension.

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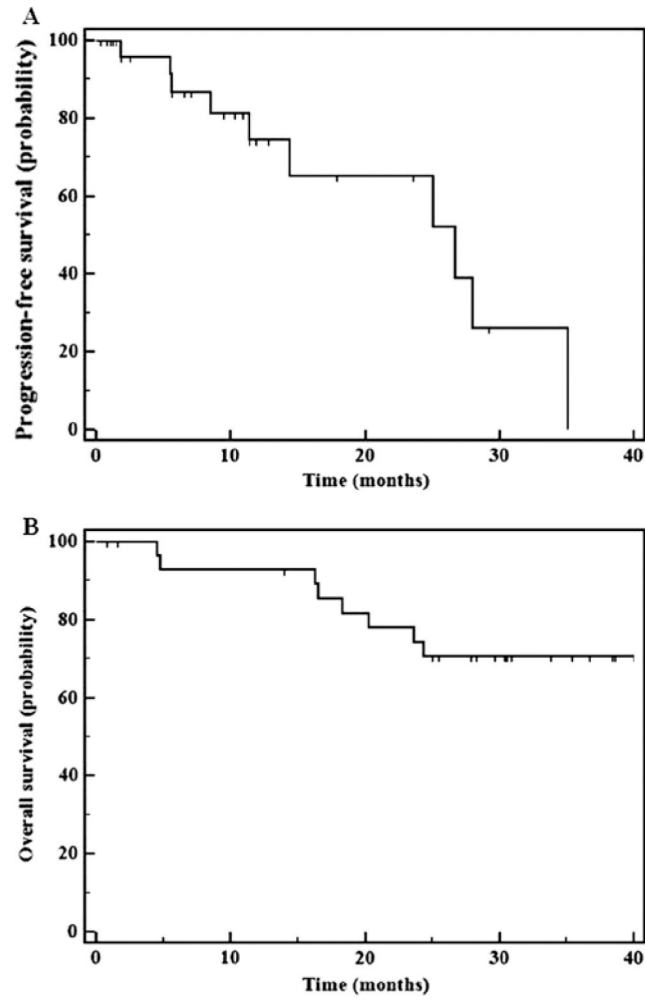
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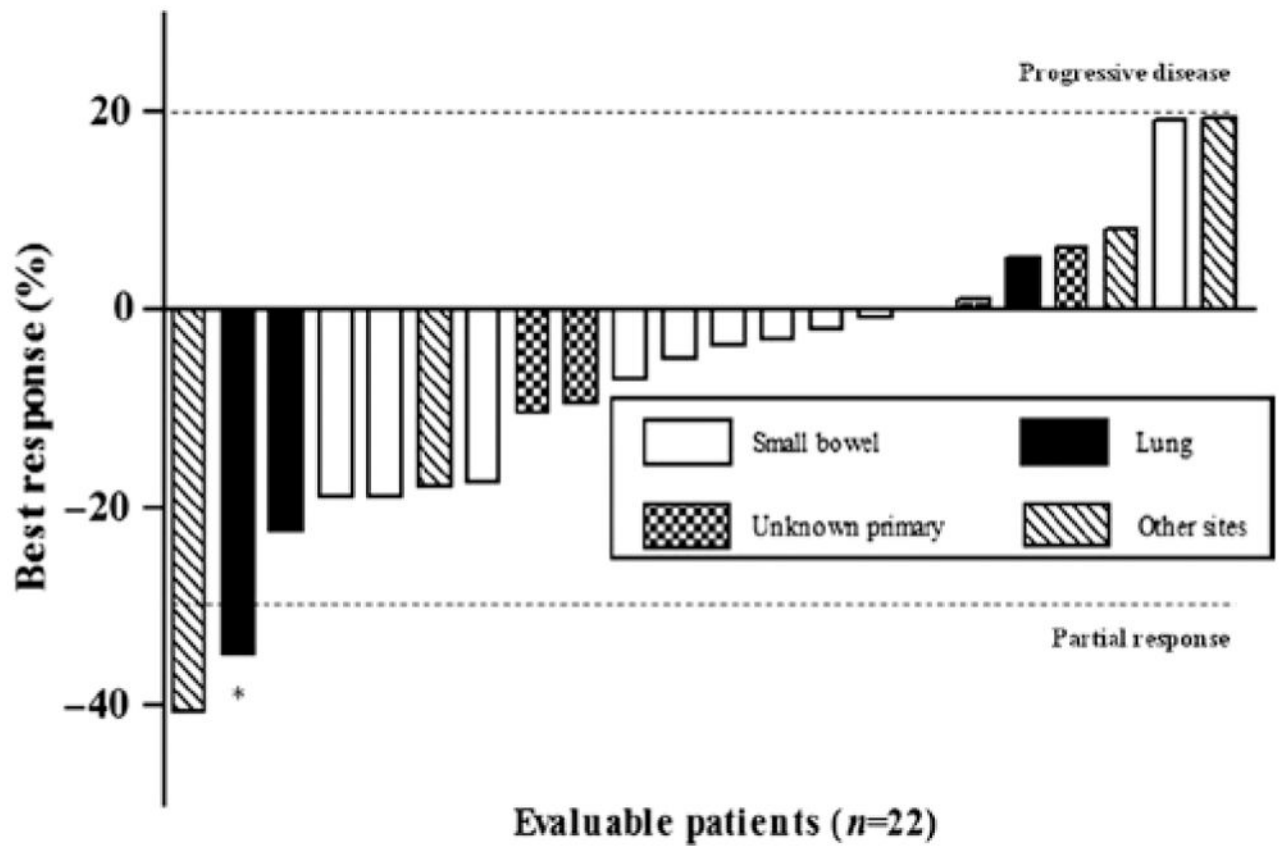
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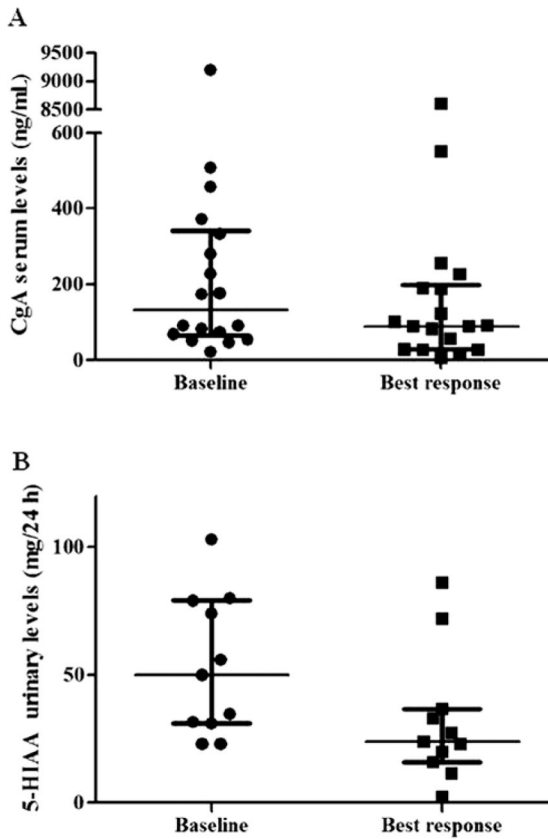
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**Figure 1.**  
Kaplan–Meier estimates of progression-free survival (A) and overall survival (B).



**Figure 2.** Waterfall plot illustrating best radiographic response (% change) in each enrolled patient. \*Decrease not confirmed at subsequent radiographic assessment, thus failing to match RECIST criteria for partial response.



**Figure 3.** Biochemical response following axitinib treatment. (A) In patients with elevated baseline CgA and repeat measurements, median CgA concentrations decreased from 132 to 89 ng/mL. The decrease was statistically significant ( $P = 0.04$ ) by Wilcoxon matched pairs signed-rank test. (B) Median urinary levels of 5-HIAA decreased from 50 mg/24 h at baseline to 24 mg/24 h when best response was evaluated ( $P = 0.01$ ). Paired row values, median change and interquartile range are represented.

**Table 1**

Baseline characteristics of the study population.

<u>Characteristics</u>	<u>Patients (n = 30)</u>	<u>%</u>
Age (years)		
Median	64	
Range	35–77	
Gender		
Male	13	43
Female	17	57
Race		
White	27	91
Black	1	3
Asian	1	3
Unknown	1	3
Performance status (ECOG)		
0	20	67
1	9	30
2	1	3
Time from diagnosis (months)		
Median	38	
Range	2–171	
Tumor grade		
Grade 1	21	70
Grade 2	9	30
Location of primary tumor		
Small intestine	19	63
Lung	3	10
Colon	2	7
Rectum	2	7
Thymus	1	3
Unknown	3	10
History of carcinoid syndrome		
Yes	16	53
No	14	47
Elevated baseline chromogranin A (>ULN)		
Yes	25	84
No	4	13
Unknown	1	3
Baseline chromogranin A (nL <15 ng/mL)		
Median	90	
Mean	597	
Range	2–9200	

<b>Characteristics</b>	<b>Patients (n = 30)</b>	<b>%</b>
Elevated baseline 5-HIAA		
Yes	18	60
No	8	27
Unknown	4	13
Primary tumor resected		
Yes	22	73
No	8	27
Liver involvement		
0	2	6
<10	11	37
10	17	57
Previous liver-directed therapy		
Yes	11	37
No	19	63
Concurrent octreotide LAR		
Yes	25	83
No	5	17
Prior lines of systemic therapy		
Median	1	
Range	1–3	
Previous systemic therapy		
Octreotide LAR	27	90
Chemotherapy	4	13
Everolimus	3	10
Interferon- $\alpha$	3	10
PRRT	1	3
Investigational agents	5	17



**Table 2**

Grade 2 and higher toxicities considered at least possibly related to treatment.

	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Total</b>
Hypertension (%)	7 (23)	17 (57)	2 (7)	26 (87)
Gastrointestinal toxicity (%)				
Abdominal pain	4 (14)	1 (3)	0 (0)	5 (17)
Diarrhea	4 (14)	1 (3)	0 (0)	5 (17)
Nausea	3 (10)	1 (3)	0 (0)	4 (13)
Vomiting	2 (7)	0 (0)	0 (0)	2 (7)
Mucositis	1 (3)	0 (0)	0 (0)	1 (3)
Oral pain	1 (3)	0 (0)	0 (0)	1 (3)
Neurologic toxicity (%)				
Headache	4 (13)	2 (7)	0 (0)	6 (20)
Confusion	0 (0)	1 (3)	0 (0)	1 (3)
Insomnia	0 (0)	1 (3)	0 (0)	1 (3)
Syncope	0 (0)	1 (3)	0 (0)	1 (3)
Anxiety	1 (3)	0 (0)	0 (0)	1 (3)
Intracranial hemorrhage	0 (0)	0 (0)	1 (3)	1 (3)
Miscellaneous (%)				
Fatigue	6 (20)	2 (7)	0 (0)	8 (27)
Weight loss	1 (3)	1 (3)	0 (0)	2 (6)
Anorexia	1 (3)	0 (0)	0 (0)	1 (3)
Myalgia	0 (0)	1 (3)	0 (0)	1 (3)
Dehydration	2 (7)	1 (3)	0 (0)	3 (10)
Hypothyroidism	1 (3)	0 (0)	0 (0)	1 (3)
Increased transaminases	1 (3)	0 (0)	0 (0)	1 (3)
Increased alkaline phosphatase	3 (10)	0 (0)	0 (0)	3 (10)
Increased gamma-glutamyl transferase	0 (0)	1 (3)	0 (0)	1 (3)
Urinary tract infection	1 (3)	0 (0)	0 (0)	1 (3)
Right ventricular dysfunction	0 (0)	1 (3)	0 (0)	1 (3)
Pain in extremity	1 (3)	0 (0)	0 (0)	1 (3)
Hand-foot syndrome	0 (0)	1 (3)	0 (0)	1 (3)