A Phase II Study of Ziv-Aflibercept in Patients With Advanced Extrapancreatic Neuroendocrine Tumors

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Objectives: Neuroendocrine tumors (NETs) are characterized by their expression of vascular endothelial growth factor (VEGF). This trial investigated the activity of Ziv-aflibercept, a recombinant protein that binds to and inhibits the activity of VEGF, in patients with advanced NETs (NCT01782443).

Methods: A single-arm, phase II trial enrolling patients with advanced, progressive extrapancreatic NET. Patients were treated with Ziv-aflibercept 4 mg/kg intravenously on day 1 and 15 of a 28-day cycle; the starting dose was reduced to 2 mg/kg on days 1 and 15 of a 28-day cycle because of hypertension-related events. The primary end point was progression-free survival.

Results: The trial enrolled 19 patients (13 male:6 female). Patients received a median of 7 cycles (range, 1–18 cycles). The median progression free survival was 11.8 months (95% confidence interval, 3.2–16.1 months), and the median overall survival was 36.4 months (95% confidence interval, 16.1–not reached). Best responses by Response Evaluation Criteria in Solid Tumors 1.1 are as follows: 1 (5%) partial response, 13 (68%) stable disease, 2 (10%) with progressive disease, and 3 (15%) unevaluable. Hypertension occurred in 18 patients (95%), including grade 3–4 hypertension in 12 patients (63%).

Conclusions: Although the progression free survival is similar to other VEGF inhibitors in NET, toxicity may preclude further investigation.

Key Words: Ziv-flibercept, extrapancreatic neuroendocrine tumors, carcinoid tumors

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Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that are classified based on anatomical origin, pathological features, and clinical behavior. Multiple options are available for the management of patients with advanced well-differentiated NETs, including surgical resection, liver-directed therapies for patients with metastases predominantly in the liver, and systemic therapy. Systemic therapy options for patients with NETs of nonpancreatic origin include somatostatin analogs, radiolabeled somatostatin analogs, molecularly targeted agents including everolimus, and cytotoxic chemotherapy.

Neuroendocrine tumors are characterized by their hypervascularity and expression of vascular endothelial growth factor (VEGF) and its receptors (VEGFRs).[1] Phase II and III clinical trials have demonstrated activity of several multitargeted tyrosine kinase inhibitors (TKIs) targeting VEGFR.[2–6] In randomized placebo-controlled trials, both pazopanib and surufatinib have improved progression-free survival in patients with extrapancreatic NET.[2,5] In addition, bevacizumab, a monoclonal antibody targeting VEGF, demonstrated similar single agent activity as interferon in a phase III trial enrolling patients with advanced extrapulmonary NET.[7]

Ziv-aflibercept is a fully humanized recombinant fusion protein composed of the extracellular domains of a VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G1.[8] It is referred to as referred to as a "VEGF trap." Unlike other VEGF inhibitors, Ziv-aflibercept binds VEGF in the picomolar range but also binds the placental growth factor. The binding of Ziv-aflibercept to these ligands impacts vascular permeability, endothelial cell activation and proliferation, invasion, and migration.[9] In a recently published trial evaluating the role of Ziv-aflibercept in patients with advanced pancreatic NETs (pNET), 2 of 21 patients (9.5%; 95% confidence interval, 1.1%–30.4%) demonstrated a response. Treatment-related toxicities included one grade 5 gastrointestinal hemorrhage and 5 incidents of proteinuria requiring treatment discontinuation.[10]

Based on the efficacy of VEGF pathway inhibitors in NET, we conducted a clinical study to determine the clinical efficacy and safety profile of Ziv-aflibercept in patients with advanced extrapancreatic NETs.

MATERIALS AND METHODS

Study Design and Participants

We conducted a single-arm, phase II trial that enrolled patients with histologically confirmed metastatic or locally advanced well- or moderately differentiated NETs of extrapancreatic origin not amenable to curative resection. Participants were required to have evidence of disease progression within 12 months before study entry; progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was not required. Patients were further required to have measurable disease by RECIST 1.1, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or

less; adequate hepatic function (serum bilirubin ≤1.5 times upper limit of normal); aspartate transaminase less than or equal to 2.5 times upper limit of normal (≤5 times if liver metastases were present); and adequate bone marrow function (absolute neutrophil count ≥1500/mm^3; platelets ≥100,000/mm^3). There was no limit to prior treatments. Prior therapy with anti-VEGF therapy was permitted unless it was discontinued because of unacceptable toxicity.

All patients provided signed, informed consent as required by the institutional review boards of the participating centers, which included Dana-Farber Cancer Institute, Massachusetts General Hospital (both in Boston, Mass).

Study Treatment

Patients were treated with Ziv-aflibercept (Sanofi US, Bridgewater, NJ) starting at a dose of 4 mg/kg intravenously on days 1 and 15 of each 28-day cycle. Somatostatin analog therapy with octreotide was administered concurrently with aflibercept throughout the protocol. Octreotide-naive patients were allowed to initiate treatment with octreotide long-acting release (LAR) 20 mg intramuscular every 4 weeks during the screening period before the start of Ziv-aflibercept. No changes in somatostatin analog dose were made while on protocol therapy. On July 15, 2014, the protocol was amended to decrease the starting dose to 2 mg/kg intravenously on days 1 and 15 of each 28-day cycle because of hypertension (HTN) noted in the first 10 patients. Patients who were tolerating the 4-mg/kg dose were permitted to continue at this dose level. Treatment was continued until disease progression, withdrawal of consent, adverse event or intercurrent illness preventing further administration, or conditions rendering further therapy unacceptable for the patient in the judgment of the investigator. Specific adverse events mandating discontinuation of protocol therapy included any grade of gastrointestinal perforation or fistula, reversible posterior leukoencephalopathy, grade 3 or 4 hemorrhage or arterial thromboembolic event, recurrent grade 3 or 4 venous thromboembolic event, recurrent grade 3, or any occurrence of grade 4 HTN.

Pretreatment and on-study assessments included history, physical examination, and laboratory tests including complete blood count, electrolytes, and liver function tests. Disease was assessed with restaging scans after every 3 cycles of treatment. Tumor markers, serum chromogranin A and 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA), were measured at baseline and again at each radiographic restaging if elevated on baseline measurement. Biochemical response was evaluated among patients with elevated serum chromogranin or 24-hour urine 5-HIAA at baseline and defined by either a greater than 50% decrease or normalization of the biochemical marker. This measurement criteria mirrors response assessment described in other phase 2 evaluating novel therapeutics in neuroendocrine neoplasms.[11–13]

Outcomes

The primary end point was progression-free survival (PFS). Secondary objectives included toxicity, overall survival (OS), radiographic response rate, and biochemical response using serum chromogranin and 24-hour urine 5-HIAA.

Statistical Analysis

Based on the RADIANT 2 trial,[14] we assumed that an inactive agent would be associated with a median PFS of 8 months, whereas an active agent would demonstrate a median PFS of 12 months. We calculated that with 43 patients, the trial would have 80% power to detect a 4-month improvement in median PFS based on a 1-sample log-rank test with a 1-sided significance level of 5%.

Progression-free survival was defined from date of enrollment to the date of documented progression or death from any cause. Overall survival was defined as the time between study enrollment and death due to any cause. Progression-free survival and OS with 95% confidence interval (CI) were described using the Kaplan-Meier method.

Toxicity was measured using Common Terminology Criteria for Adverse Events 4.0. Radiographic response was evaluated by using RECIST 1.1. Biochemical response was defined as a decrease in chromogranin A or 24-hour urine 5-HIAA by 50% or more from baseline in patients with elevated levels at baseline.

RESULTS

Patient Characteristics

Nineteen patients with advanced extrapancreatic NET were enrolled between February 15, 2013, and July 12, 2016 (Table 1). Enrollment was closed per investigator and sponsor decision on August 15, 2018. Patients had a median age of 61 years (range, 48–74 years); 13 (68%) were male. The Eastern Cooperative Oncology Group

TABLE 1. Demographics

No. Patients	19
Age at diagnosis, median (range), y	61 (48–71)
Sex, n (%)	
Male	13 (68.4)
Female	6 (31.6)
Race, n (%)	
Black or African American	2 (10.5)
White	17 (89.5)
ECOG, n (%)	
0	5 (26.3)
1	14 (73.7)
Carcinoid syndrome	
Yes	12 (63)
No	7 (37)
Baseline hypertension, n (%)	
Yes	15 (78.9)
No	4 (21.1)
Patients with increased baseline chromogranin A (>39 ng/mL), n (%)	12 (63)
Baseline chromogranin A, median (range), ng/mL	1536 (20–6205)
Patients with increased baseline 24-hour urine 5-HIAA (>9.9 mg/24 h), n (%)	11 (63)
Baseline 24-hour urine 5-HIAA, median (range), mg/24 h	67.5 (3–2751)
Histologic grade, n (%)	
Low (grade I)	14 (73.7)
Intermediate (grade II)	5 (26.3)
Primary tumor location, n (%)	
Small Intestine	12 (57.9)
Rectum	1 (5.3)
Lung	1 (5.3)
Thymus	1 (5.3)
Unknown	4 (21.1)
Prior therapy, n (%)	
Somatostatin analog	19 (100)
Chemotherapy	6 (31.6)
Targeted therapy: everolimus	10 (52.6)
Targeted therapy: anti-VEGF	4 (21.1)
Liver-directed therapy	5 (26.3)

performance status at enrollment was 0 in 5 patients (26.3%) and 1 in 14 patients (73.7%). Sixty-three percent had carcinoid syndrome. Fifteen patients (78.9%) had HTN at baseline.

Most patients had midgut primary tumors (n = 12, 63%). Primary tumor originated in an unknown site in 4 patients and in the rectum, lung, and thymus in 1 patient each. The median number of metastatic sites was 3 (range, 1–7). The most common sites of metastatic disease were the bone, liver, lymph nodes, lungs, and peritoneum. All patients had received prior octreotide LAR. Other prior therapies included cytotoxic chemotherapy (31.6%), other VEGF pathway inhibitor therapy (21.1%), everolimus (52.5%), and liver-directed therapy (26%).

Patients completed a median of 7 cycles (28 weeks) of therapy (range, 0–47; Fig. 1). The median follow-up time was 38.7 months (range, 17.8–75.4 months). Reasons for treatment discontinuation included disease progression 9 (47.3%); unacceptable toxicity 5 (26.3%), withdrawal of consent 4 (21.1%), and death 1 (5.3%).

Toxicity

All 19 treated patients were evaluable for toxicity, as summarized in Table 2. In the first 10 patients, the incidence of high-grade HTN was notable, with 2 patients (20%) developing grade 4 HTN and 7 patients (70%) developing grade 3 HTN. Notably, HTN associated with neurologic manifestations was observed, including 1 patient (10%) who developed subarachnoid hemorrhage and 1 patient (10%) who developed cerebral vasoconstriction syndrome that was manifested by acute onset headache, left arm apraxia and numbness, and confusion. Because of the severity and nature of these events, the protocol was modified after enrollment of 10 patients to decrease the starting dose of aflibercept to 2 mg/kg every 2 weeks. At the lower starting dose of aflibercept, 4 (44%) patients developed grade 3 HTN managed with antihypertensive therapy. Other grade 3 toxicities at the 4 mg/kg starting dose included palmar-plantar erythrodesia syndrome and proteinuria in one patient for each. Other common toxicities impacting more than one-third of patients included fatigue, anorexia, transaminitis, diarrhea, hoarseness, nausea, and thrombocytopenia.

Efficacy

The median PFS duration was 11.8 months (95% CI, 3.2–16.1 months). There was no notable difference between dose groups (Figs. 2A, B). Progression-free survival at 6 and 12 months were 73.7% (95% CI, 47.9–88.1) and 47.4% (95% CI, 24.4–67.3), respectively. The median OS duration was 36.4 months (95% CI, 16.1–not reached). There was no notable difference between dose groups (Figs. 3A, B). Overall survival at both 6 and 12 months was 84.2% (95% CI, 58.7%–94.6%). Overall survival percent did not change between 6 and 12 months because no patients died or were censored during this timeframe.

Among the 14 patients who were evaluable for best response by RECIST 1.1 criteria, there was 1 (7%) partial response and 13 (93%) stable disease. The one patient meeting criteria for partial response received 4 mg/kg. As demonstrated by the waterfall plot, there was some degree of response to Ziv-aflibercept independent of the dose administered (Fig. 4). The remaining 5 patients did not undergo protocol restaging due to early withdrawal (3 unacceptable toxicity, 1 patient preference, 1 clinical decline before completion of cycle 2).

Of the 19 patients, baseline serum chromogranin A was elevated in 12 patients. Baseline 24-hour urine 5-HIAA was elevated in 11 patients, although baseline was not available for 1 patient. A biochemical response was noted in 2 patients (11%) who demonstrated a greater than 50% drop of chromogranin from baseline and 1 (1/18 = 6%) patient who demonstrated a greater than 50% drop of 24-hour urine 5-HIAA from baseline. The one patient who met criteria for a partial radiographic response had a stable chromogranin A and a drop by greater than 50% of 24-hour urine 5-HIAA while on Ziv-aflibercept.

DISCUSSION

Angiogenesis plays a key role in NET biology and progression. Vascular endothelial growth factor inhibitors, such as Bevacizumab, have demonstrated an encouraging impact on PFS,[7] whereas TKIs targeting VEGF have demonstrated activity in the treatment of NET.[5,6] In this phase II trial, we observed

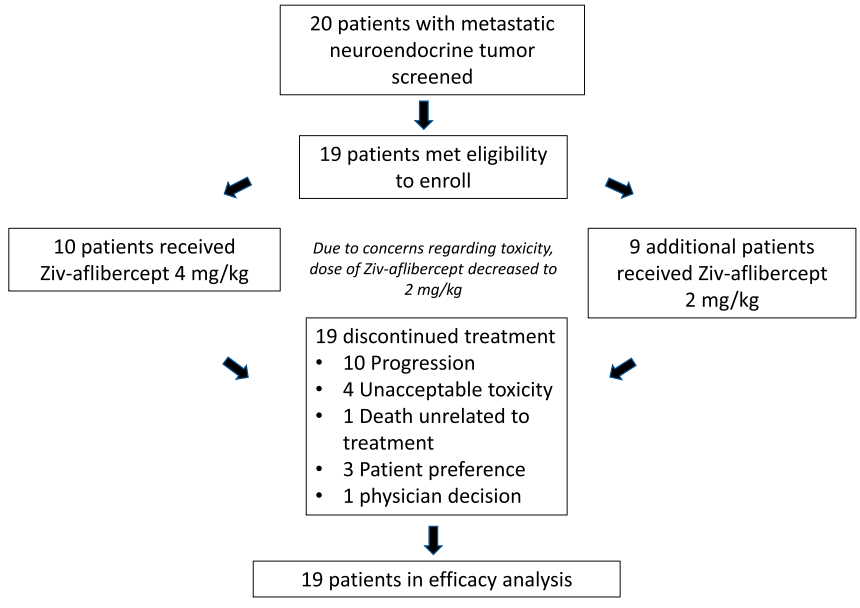

FIGURE 1. Diagram of the patients enrolled.

TABLE 2. Toxicities for Patients With a Starting Dose of 2 or 4 mg/kg of Ziv-Aflibercept

Category	Grade II, n (%)	Grade III, n (%)	Grade IV, n (%)
A. 4 mg/kg (n = 10)			
Anemia	2 (20)		
Anorexia	2 (20)		
Diarrhea	1 (10)		
Edema limbs	1 (10)		
Fatigue	5 (50)		
Headache	1 (10)		
Hypertension		7 (70)	2 (20)
Hypoalbuminemia	1 (10)		
Subarachnoid hemorrhage/intracranial hemorrhage	1 (10)		
Oral mucositis	1 (10)		
Nervous system disorders—other, specify	1 (10)		
Palmer-plantar erythrodysesthesia syndrome		1 (10)	
Proteinuria		1 (10)	
Cerebral vasoconstriction syndrome/stroke	1 (10)		
B. 2 mg/kg (n = 9)			
Alkaline phosphatase increased	1 (11)		
Anorexia	2 (22)		
Confusion	1 (11)		
Constipation	1 (11)		
Creatinine increased	1 (11)		
Diarrhea	1 (11)		
Fatigue	3 (33)		
Flushing	1 (11)		
General disorders and administration site conditions—other, specify	1 (11)		
Headache	2 (22)		
Hypertension	5 (55)	4 (44)	
Hoarseness	2 (22)		
Hypoalbuminemia	1 (11)		
Injection site extravasation	1 (11)		
Metabolism and nutrition disorders	1 (11)		
Palmer-plantar erythrodysesthesia syndrome	1 (11)		
Proteinuria	3 (33)		
Rectal pain	1 (11)		
Renal and urinary disorder—other, specify	1 (11)		

modest efficacy of Ziv-aflibercept, although also observed high rates of HTN in patients with advanced extrapancreatic NET who were treated at an initial starting dose of Ziv-aflibercept 4 mg/kg every 2 weeks. Unlike other trials, which report the incidence of HTN with Ziv-aflibercept between 16.7% and 51.4%, we observed an all-grade incidence of HTN of 95%.

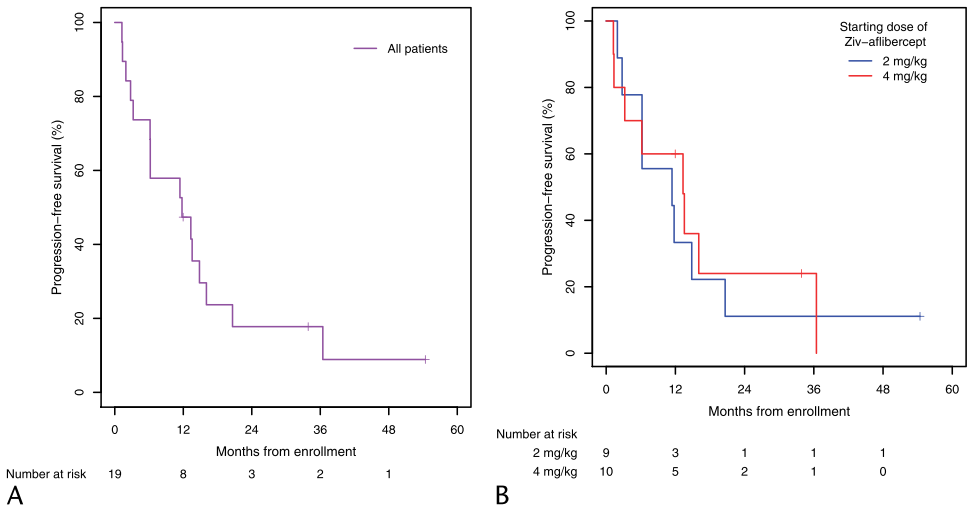

FIGURE 2. Kaplan-Meier survival distribution in extrapancreatic NET patients: PFS. A, PFS of evaluable cohort. B, PFS of evaluable cohort based on Ziv-aflibercept dose 4 or 2 mg/kg.

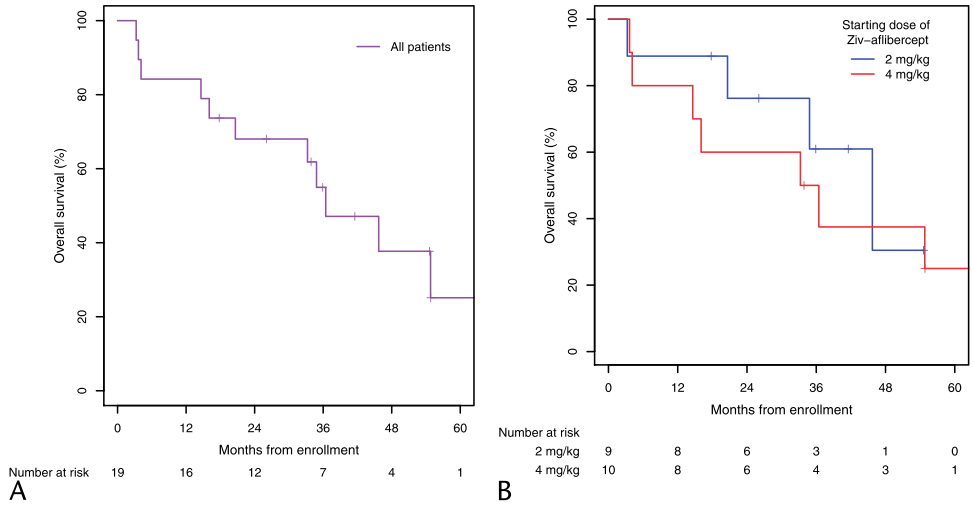

FIGURE 3. Kaplan-Meier survival distribution in extrapancreatic NET patients: OS. A, OS of evaluable cohort. B, OS of evaluable cohort based on Ziv-aflibercept dose 4 or 2 mg/kg.

When compared with other VEGF pathway inhibitors, aflibercept has been associated with a higher incidence of all-grade HTN. In a meta-analysis of 4451 patients who had participated in a total of 15 trials evaluating aflibercept therapy in various malignancies, the incidence of all-grade and high-grade HTN was 42.4% (95% CI, 35.0–50.3) and 17.4% (95% CI, 13.7–21.9), respectively. When compared with patients who received bevacizumab, a significantly higher risk of all-grade (odds ratio, 1.93; 95% CI, 1.61–2.32; $P < 0.001$) and high-grade (odds ratio, 2.06; 95% CI, 1.79–2.37; $P < 0.001$) HTN was also noted. The reason for this has been attributed to (1) the 1000-fold higher VEGF-A binding affinity when compared with bevacizumab; (2) aflibercept binds VEGF-B and placental growth factors, which have independent proangiogenic effects; and (3) Ziv-aflibercept has a longer circulating half-life

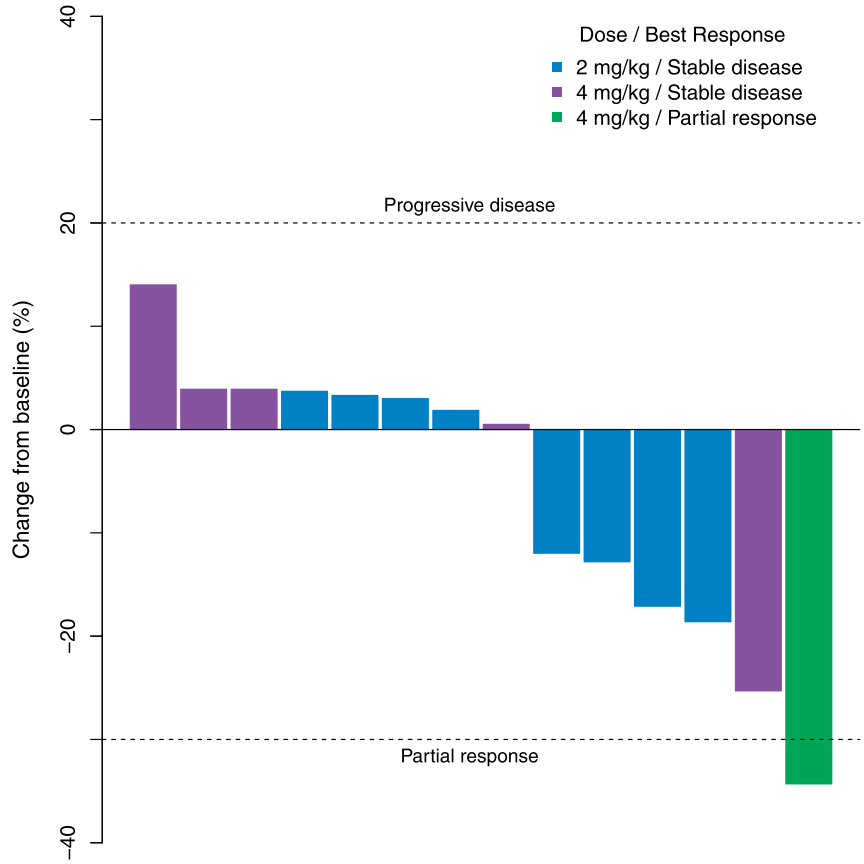

FIGURE 4. Efficacy data for Ziv-aflibercept in extrapancreatic NET patients. Waterfall plot of objective responses by RECIST 1.1.

than other soluble receptor constructs.[15] Higher rates of HTN have also been demonstrated in NET patients treated with VEGF inhibitors when compared with other tumor types. In one meta-analysis evaluating pazopanib therapy in the treatment of advanced neuroendocrine neoplasms, the incidence of grade 3 or higher HTN was 31.3%.[16] In contrast, in a meta-analysis of patients with a variety of cancers not including NET, the incidence of high-grade HTN was 6.5%.[17] The mechanism for this difference in incidence of HTN is not clear but likely involves the vascular nature of NETs when compared with other tumor types, vasoactive peptides secreted by NETs, and potentially the concurrent use of somatostatin analogs, which can also be associated with HTN.[18] Therefore, the higher incidence in this cohort likely results from the use of VEGF class and tumor type but may also be influenced by the inclusion of 15 patients (78.9%) who carried a diagnosis of HTN at baseline and the use of octreotide LAR by all participants. Neuroendocrine tumor patients with and without a baseline HTN diagnosis may need to be followed more closely for development of severe HTN when receiving antiangiogenic therapy.

Ziv-aflibercept has been evaluated as a therapeutic option for pNET. In a single-arm open-label study, patients with advanced pNET were treated with 6 mg/kg of Ziv-aflibercept. Twenty-one patients were treated, and the response rate was 9.5% (95% CI, 1.1%–30.4%) with 71% demonstrating some degree of tumor shrinkage. The median PFS was 15 months (95% CI, 12.69–17.32 months), with a median OS of 34 months (95% CI, 21.17–46.83 months). Treatment was well tolerated although all-grade HTN was demonstrated in 77% of patients. The trial was closed prematurely because of concerns regarding slow accrual. The overall best response and median PFS were slightly higher in this trial when compared with the clinical outcomes in our trial, including patients extrapancreatic NET. It is unclear whether this discrepancy is secondary to the higher dose administered in the pNET study or the small number of patients included in our trial. It is also possible that the response discrepancy is a reflection of greater sensitivity of pNET to VEGF inhibition.

Limitations of this study deserve comment. Because the study was terminated prematurely, assessment of clinical efficacy is limited. In a relatively small single-arm study including a potentially heterogeneous patient population, estimates of PFS may be dependent on tumor biology. In addition to this selection bias, the estimates of PFS from this study may be impacted by informative censoring, which also limits meaningful comparison to other studies. Although the response rate to treatment was low, radiographic response rate may not reflect an antiproliferative effect of targeted agents that can slow disease progression in diseases, such as NET.

In summary, treatment of patients with advanced extrapancreatic NET with Ziv-aflibercept is associated with an encouraging impact on clinical outcomes but high rates of HTN, particularly at a starting dose of 4 mg/kg every 2 weeks. Although the median PFS duration is consistent with what has been observed with other VEGF inhibitors in extrapancreatic NET, toxicity may preclude further investigation of Ziv-aflibercept in this patient population. Inhibition of the VEGF pathway remains an area of active investigation in extrapancreatic NET.

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