Capecitabine, Oxaliplatin, Irinotecan, and Bevacizumab Combination Followed by Pazopanib Plus Capecitabine Maintenance for High-Grade Gastrointestinal Neuroendocrine Carcinomas

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Objectives: Gastrointestinal neuroendocrine carcinoma (NEC) is a lethal, uncommon, and understudied neoplasm. We present the efficacy and safety of first-line capecitabine (CP), oxaliplatin, irinotecan, and bevacizumab (CAPOXIRI-BEV) combination followed by pazopanib plus CP maintenance therapy in patients with advanced high-grade poorly differentiated gastrointestinal NEC.

Methods: This was a two-stage phase II study conducted at multiple institutions. Patients were consecutively enrolled and had advanced NEC of the colon or small bowel. Patients received irinotecan 125 mg/m^2, oxaliplatin 80 mg/m^2 on day 1, CP 1000 mg/m^2 twice daily on days 1 to 14, plus bevacizumab 8 mg/kg on day 1 for six 21-day cycles. Maintenance therapy was given to those who responded (complete response/partial response) or had stable disease after 6 cycles with CAPOXIRI-BEV with pazopanib 800 mg daily plus CP 1600 mg/m^2 daily on days 1 to 14 every 3 weeks until disease progression or unacceptable toxicity. Patients who progressed on CAPOXIRI-BEV received standard etoposide-carboplatin. The primary endpoint was overall response rate.

Results: Twenty-two patients were enrolled of whom 19 were evaluable. The median age was 60 years. The overall response rate (3 complete response/6 partial response) was 47.4% (95% confidence interval: 29.5-76.1), the overall disease control rate was 78.9% (95% confidence interval: 62.6-99.6), and, at median 30 (11 to 41 mo) months' follow-up, 5 patients (26.3%) were still alive. Median progression-free survival was 13 months, and the 1-year progression-free survival rate was 52.6%. The median overall survival was 29 months. The median overall survival of the 9 patients who responded versus those with stable disease/progressive disease was 30.5 versus 14 months, respectively. The median duration of response was 16 months. Predictable toxicity was observed.

Conclusions: First-line CAPOXIRI-BEV followed by pazopanib plus CP maintenance therapy for advanced NEC demonstrates promising efficacy and predictable toxicity. Further investigation is warranted.

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Gastrointestinal tract neuroendocrine tumors (GI-NETs) are a group of rare cancers, which, due to their indolent nature, usually present at an advanced stage where treatment is challenging. Although rare, their incidence has increased to 2.5 to 5.25/100,000 probably due to improved diagnostic methods.[1,2] GI-NETs are classified according to the anatomic site of origin (pancreatic/intestinal), TNM stage, and histologic/molecular characteristics. Poorly differentiated NETs with high-grade histology (grade 3/G3), a mitotic count >20/hpf, or a Ki-67 proliferation index of >20% represent highly aggressive malignancies with increased metastatic potential, also called neuroendocrine carcinomas (NEC) as per the World Health Organization (WHO) classification.[3,4] They are associated with poor survival with a median survival of 34 months for local, 14 months for regional, and 5 months for the distal disease.[1] Some NECs are histologically similar to small cell lung cancer (SCLC). Thus, treatment directions are usually dictated by the guidelines of SCLC. GI-NETs are also highly vascular tumors that express high levels of vascular endothelial growth factor and its receptors. Such expression has an important role in tumor angiogenesis and growth in neuroendocrine tumors, especially in midgut carcinoids.[5,6] Consequently, the usage of angiogenesis inhibitors is a potentially effective treatment.[7,8] For the last 25 years, first-line chemotherapy for high-grade NET is considered cisplatin plus etoposide with an objective response rate (ORR) of 41.5% to 67%, median duration of response (DoR) 8 to 9.2 months, median overall survival (OS) 15 to 19 months, and median progression-free survival (PFS) of 8.9 to 11 months.[9,10] Interchange is also effective as cisplatin or carboplatin with etoposide or irinotecan on the basis of SCLC experience.[11] The combination of oxaliplatin, capecitabine (CP), and bevacizumab in metastatic NET, including high-grade patients, demonstrated an ORR of 23%, stable disease (SD) of 71%, and a median PFS of 13.7 months.[12] Somatostatin analogs such as octreotide and interferon do not have a clear role in high-grade NETs, but they can be used for symptomatic relief of the carcinoid syndrome.[13,14]

CP, oxaliplatin, and irinotecan (CAPOXIRI/XELOXIRI) combination with bevacizumab has been used effectively as first-line and second-line treatment in metastatic colorectal cancer.[15,16] In a phase II study, (1) FOLFOX-bevacizumab combination and (2) CP, oxaliplatin plus bevacizumab combination followed by maintenance with bevacizumab with or

without CP in advanced carcinoids were used.[17] Although the results did not reach any of the studies' primary endpoints of efficacy, oxaliplatin–fluoropyrimidine–based chemotherapy plus bevacizumab may benefit select patients such as those with high-grade NEC.

Pazopanib is a multitargeted tyrosine kinase inhibitor (MTKI) with an array of targets such as the vascular endothelial growth factor receptors-1, 2, and 3, platelet-derived growth factor receptor (PDGFR-α and β), c-kit, and fibroblast growth factor receptor (FGFR-1 and 3), and it thus displays critical antiangiogenic properties. It has been extensively used in metastatic renal cell carcinoma.[18] Sunitinib, an MTKI with similar inhibition pattern has been approved for the treatment of pancreatic NETs after the results of a phase III study that included high-grade patients.[19] In a phase II study, pazopanib monotherapy demonstrated comparable efficacy to historical control with PFS of 9.1 months, ORR of 23%, and disease control rate (DCR) of 73%. In the subgroup of high-grade nonpancreatic GI-NETs, ORR was 23%, median PFS was 5.8 months, but no durable response was noted.[20] Lately, pazopanib monotherapy was found to be effective in a mixed population of pretreated NETs with MTKIs or mTOR inhibitors with a median PFS of 9.5 months, and, in the subgroup analysis of GI-NETs, it achieved a median PFS of 10 months.[21]

High-grade GI-NETs, although very aggressive, respond to cytotoxic chemotherapy, and it seems that antiangiogenic treatment also can confer benefit. In this study, on the basis of previous experience in colorectal and neuroendocrine cancer, we incorporate the combination of CAPOXIRI in combination with bevacizumab followed by maintenance therapy with pazopanib plus CP in patients with high-grade GI-NETs.

METHODS

Patients

Eligibility criteria included (1) patients older than 18 years of age who had (2) a histologically confirmed diagnosis of high-grade, poorly differentiated (G3) GI NEC originating from the abdominal luminal tract, which was (3) advanced/metastatic and (4) was not amenable to locoregional palliative therapies including radiofrequency ablation (RFA) or transarterial hepatic embolization. (5) Patients had not received chemotherapy, (6) had adequate end-organ function, (7) disease status measurable by Response Evaluation Criteria in Solid Tumor (RECIST) v1.1, (8) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, (9) life expectancy >8 weeks, and (10) had no absolute contraindications for the protocol. The withdrawal was considered with noncompliance, severe toxicities/adverse effects (AEs), or disease progression. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study, and local institutional review boards approved the protocol.

Treatment Schedule

Patients received intravenous irinotecan 125 mg/m^2 over 90 minutes on day 1, plus oxaliplatin 80 mg/m^2 intravenously on day 1, plus per os CP 1000 mg/m^2 twice daily on days 1 to 14, plus bevacizumab 8 mg/kg on day 1 (CAPOXIRI-BEV) every 21 days for 6 cycles. Maintenance therapy was given to those who responded or had SD after 6 cycles with CAPOXIRI-BEV as pazopanib 800 mg per os once daily in addition to CP at 1600 mg/m^2 per os daily on days 1 to 14 every 3 weeks until disease progression or unacceptable toxicity. Patients who had progressed with CAPOXIRI-BEV would receive carboplatin with a target dose 5 times the area under the plasma drug concentration-time curve on day 1 plus etoposide at 80 mg/m^2 on days 1 to 3 every 21 days until progression or unacceptable toxicity. All patients received oral prednisone 16 mg along with an H_2 antagonist orally 12 and 6 hours before treatment, which was followed by intravenous premedication with dexamethasone 10 mg, diphenhydramine 50 mg, and an H_2 antagonist 30 minutes before chemotherapy. 5-HT_3 antagonists and dexamethasone were given as antiemetics if indicated. Administration of granulocyte colony–stimulating factors was allowed in cases of leucopenia/neutropenia but not prophylactically. Treatment would be delayed if patients presented with a grade ≥ 2 hematologic toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Effects (NCI-CTCAE version 4.0).[22] Subsequent doses would be reduced by 25% for grade 2 and 50% for grade 3 toxicity. Treatment would continue until the progression of the disease or until unacceptable toxicities causing a delay in the next cycle of >2 weeks.

Tumor Assessment

All patients before study enrollment were screened with a history and physical examination, PS categorization, and laboratory testing including complete blood count, electrolytes, and liver/renal function tests. This was followed by the staging of the malignancy with chest x-ray, chest and abdominal computed tomography, and, if indicated, brain or abdominal magnetic resonance imaging. During the study, patients were being evaluated with clinical examination and a complete blood count on days 1, 8, and 14 of each cycle, whereas biochemistry and urinalysis were performed on days 1 and 14 of each cycle unless otherwise indicated. Tumor assessment was made with the help of an independent board-certified radiologist using the RECIST criteria v1.1[23] and was performed with clinical examination and chest radiograph on day 1 of each cycle while complete staging scans were carried out with the completion of 3 consecutive cycles (every 8 wk). Nonmeasurable lesions either remained stable or regressed, and all responses had to be confirmed at the end of the cycle or 28 days later.

Study Design—Endpoints—Statistical Analysis

This was a nonrandomized, open-labeled, single-institution, single-arm phase II study. The primary endpoint was the ORR of the CAPOXIRI-BEV combination. Secondary endpoints were the evaluation of PFS (measured from study entry until the day with evidence of disease progression), DoR, DCR (objective response plus SD), OS (time from study entry to death including after maintenance therapy), and safety and toxicity of the combination therapy. Response evidence was classified as complete response (CR), partial response (PR), SD, and progressive disease (PD). Response assessment was made with RECIST v1.1 and AEs with NCT-CTCAE v4.0. PFS and OS were calculated using the Kaplan-Meier method.

Simon two-stage design was used.[24] The null hypothesis that the true response rate with CAPOXIRI-BEV is 15% was tested against a 1-sided alternative. In the first stage, 6 patients were accrued. If there were one or none response in these 6 patients, the study would be stopped. Otherwise, 13 additional patients would be accrued for a total of 19. The null hypothesis would be rejected if 6 or more responses were observed in those 19 patients. This design yields a type I error rate of 0.05 and a power of 0.80 when the true response rate is 45%. On the basis of these acceptable results, the patient accrual would carry on. Statistical analysis was performed using GraphPad Prism v7.00 (La Jolla, CA) and MedCalc Statistical Software version 14.8.1 (Ostend, Belgium).

RESULTS

Patients and Treatment Outcome

Between December 2012 and December 2015, a total of 22 consecutive patients were enrolled in the study and had presented at the Department of Oncology, "Henry Dunant" Hospital Center, at the Department of Surgery, "Agia Olga" Hospital, and at the Department of Surgery, Laiko Hospital, Athens, Greece. Three patients withdrew their consent to the study before the first tumor assessment. In 2 of them, the reason for withdrawal was the distant area of permanent residence and, in the third patient, personal choice. Nineteen of them were evaluable for response and toxicity assessment, able to comply with treatment, and none was lost to follow-up. Patient baseline characteristics are summarized in Table 1. All of the patients had high-grade (G3) GI-NEC, poorly differentiated and with Ki-67 index >20% originating from the luminal GI tract. The colorectal site was most common (n = 13) followed by the small intestine site (n = 6). None of those patients had ever received chemotherapy, liver RFA, liver chemoembolization, or radiation before enrollment. All of the patients had undergone surgery that was either with curative intent or in the form of gross abdominal tumor debulking to prevent bowel obstruction or to treat acute symptoms. Patients with the metastatic liver disease found intraoperatively had resection of grossly apparent lesions or intraoperative RFA when feasible. Surgery was performed at least 4 weeks before study enrollment. Radiotherapy was given in 3 patients with bone and in 1 patient with brain metastases.

TABLE 1. Baseline Patient Characteristics in the Intention-to-treat Population

Characteristics	Patients (N = 19)
Age (y)	
Median (range)	60 (49-73)
Sex, n (%)	
Male	12 (63.2)
Female	7 (36.8)
Eastern Cooperative Oncology Group performance status, n (%)	
0	3 (15.8)
1	12 (63.2)
≥2	4 (21.1)
Grade-morphology, n (%)	
High-grade (grade 3) neuroendocrine carcinoma	19 (100)
Site of origin, n (%)	
Small intestine	6 (31.6)
Cecum	4 (21.1)
Appendix	6 (31.6)
Right colon	2 (10.5)
Left colon	1 (5.2)
Tumor functionality, n (%)	
Nonfunctional	19 (100)
Time from diagnosis (mo)	
Median	10
Prior treatment, n (%)	
Chemotherapy	0
Somatostatin analogs	0
Surgery of the primary site	19 (100)
Radiotherapy	3 (15.8, bone) 1 (5.2, head)
Transhepatic arterial embolization	0
The extent of disease at enrollment, n (%)	
Metastatic	19 (100)
Metastatic sites, n (%)	
Liver	16 (84.2)
Distant lymph nodes	19 (100)
Lung	2 (10.5)
Bone	4 (21.1)
Peritoneum	6 (31.6)
Brain	1 (5.3)

Treatment Adherence and Toxicity

A total of 114 cycles of CAPOXIRI-BEV and a total of 270 cycles of maintenance CP or carboplatin plus etoposide were administered without any significant delays. Overall, all patients experienced at least 1 grade 1 to 3 AE, but, given the well-known toxicity profiles of medications, all AEs were anticipated, well-tolerated, and manageable. There were 8 hematologic and 34 nonhematologic serious grades 3 to 4 AEs (Table 2). The most

TABLE 2. Grades 1 to 4 Adverse Effects Attributed at Least to the Treatment Combination

	n (%)		
	Grade 1/2	Grade 3	Grade 4
Hematologic toxicities			
Leukopenia	5 (26.3)	3 (15.8)	—
Neutropenia	4 (21.1)	3 (15.8)	—
Anemia	3 (15.8)	1 (5.2)	1 (5.2)
Thrombocytopenia	2 (10.5)	—	—
Infections			
Febrile neutropenia	—	1 (5.2)	—
Lung infection	2 (10.5)	—	—
Constitutional toxicities			
Fatigue/asthenia	7 (36.8)	2 (10.5)	—
Weight loss	6 (31.6)	2 (10.5)	—
Pain			
Headache	7 (36.8)	1 (5.2)	—
Abdominal pain	8 (42.1)	1 (5.2)	—
Gastrointestinal			
Nausea	10 (52.6)	2 (10.5)	—
Vomiting	7 (36.8)	1 (5.2)	—
Diarrhea	11 (57.9)	3 (15.8)	—
Constipation	5 (26.3)	—	--
Mucositis (oral)	8 (42.1)	1 (5.2)	—
Anorexia	10 (52.6)	1 (5.2)	—
Pancreatitis	1 (5.2)	—	—
Laboratory			
Alkaline phosphatase elevation	4 (21.1)	1 (5.2)	—
Amylase	1 (5.2)	—	—
Hyperbilirubinemia	2 (10.5)	1 (5.2)	—
Hypokalemia	3 (15.8)	—	—
Proteinuria	6 (31.6)	1 (5.2)	—
Neurological			
Peripheral sensory neuropathy	5 (26.3)	2 (10.5)	—
Ear/auditory			
Tinnitus	2 (10.5)	—	—
Vertigo	2 (10.5)	—	—
Cardiologic			
Hypertension	—	2 (10.5)	—
Edema	5 (26.3)	—	—
Vascular/bleeding			
Pulmonary hemorrhage	—	—	—
Bleeding*	1(5.2)	1 (5.2)	—
Deep-vein thrombosis/ thromboembolic event	2 (10.5)	1 (5.2)	1 (5.2)
Dermatologic			
Hand-foot-mouth syndrome	4 (21.1)	3 (15.8)	—
Total	133	34	2

*Includes bleeding other than pulmonary hemorrhage, such as epistaxis, gingival bleeding, gastrointestinal upper or lower hemorrhage, and hematuria.

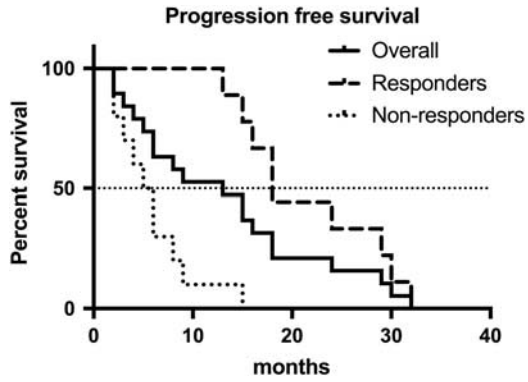

FIGURE 1. Kaplan-Meier curve of progression free survival. Responders include patients with CR+PR, Non-responders include SD+PD.

common reasons for minor treatment delay (< 2 wk) were neutropenia, diarrhea, and mucositis, but none interrupted treatment due to toxicities.

Treatment Efficacy

Primary Endpoint

There were 3 CRs (15.8%), 6 PRs (31.6%) leading to an ORR of 47.4% (95% confidence interval [CI]: 29.5-76.1); thus, the primary objective was reached.

Secondary Endpoints

Six additional patients experienced SD resulting in an overall DCR of 78.9% (95% CI: 62.6-99.6). At the time of data analysis, the median duration of follow-up was 30 months (range: 11 to 41 mo), 14 patients had died, and 5 (26.3%) were alive with progression. The Kaplan-Meier estimate for median PFS was 13 months (mean PFS: 13.4 mo, 95% CI: 9-17.8) (Fig. 1). The median PFS for patients who initially responded to CAPOXIRI-BEV (CR+PR) was 18 months (mean 14.8 mo, 95% CI: 14.3-15.2), for nonresponders (SD+PD), it was 5 months (mean 6 mo, 95% CI: 3.6-8.3), and, specifically, for SD, it was 6 months. Comparison of PFS survival curves (log-rank test) between responders and nonresponders yielded a χ^2 of 15.5, $P < 0.001$. The 1-year PFS rate was 52.6%. The median OS for the total cohort was 29 months (mean OS: 25.8 mo, 95% CI: 20.9-30.8) (Fig. 2). The median OS of the 9 patients who responded versus those with SD or PD was 30.5 months (mean 30.7 mo, 95% CI: 30.2-31.2) and 14 months (mean 16.8 mo, 95% CI: 12.8-20.8), respectively (log-rank test χ^2 15.01, $P < 0.001$). Specifically, SD and PD had a median OS of 16 and 11 months, respectively. Median DoR was 16 months (mean 19.1 mo, 95% CI: 13.5-24.7).

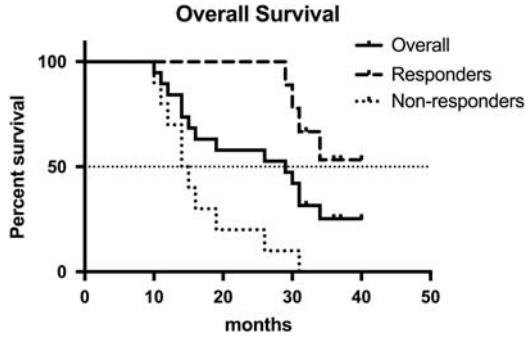

FIGURE 2. Kaplan-Meier curve of overall survival. Responders include patients with CR+PR, Non-responders include SD+PD.

DISCUSSION

In the present study, the combination of CAPOXIRI-bevacizumab followed by maintenance with CP as a treatment for advanced high-grade GI-NET was an efficient, well-tolerated, and safe treatment option in a population of patients with poor prognosis and no established treatment. Most current data on NETs involves pancreatic well or intermediate-differentiated tumors. Although this was a small cohort of patients in a single-arm, multi-institutional study, the results presented suggest that future investigations should be carried on in this subpopulation of patients. Unfortunately, there has not been a sufficient number of studies aiming at this high-grade subpopulation of GI-NETs; hence, a direct comparison cannot be made with mixed populations unless extrapolations from subpopulations of cohorts of previous studies are detailed. Moreover, treatment in mixed populations with pancreatic NETs and/or favorable histology affects survival rates, as these tumors are more chemosensitive. Furthermore, another important parameter is the PS of the patients, as toxic chemotherapy may not always be of benefit for them. Nevertheless, the results hereby presented are superior or comparable to other studies in these patients.

There is no established first-line or second-line treatment for high-grade GI-NECs. As stated earlier, cisplatin plus etoposide interchanged with carboplatin and irinotecan, on the basis of SCLC experience, are common options.[11] In the NORDIC NEC study, retreatment with platinum-etoposide resulted in SD of 42%, whereas when second-line treatment with either temozolomide (TMZ)-based or taxoter-based chemotherapy was administered, median PFS was 3 months, median OS was 19 months from diagnosis of metastatic disease, ORR was 18%, and DCR was 51%.[25] Poor results were demonstrated in small cohorts of advanced carcinoids when treated with TMZ alone (ORR 3%)[26] or in combination with thalidomide (ORR 7%).[27] TMZ in combination with bevacizumab resulted in an ORR of 0% but DCR of 92%.[28] O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation appears to be associated with better response and survival in patients given TMZ treatment.[26,29] A recent retrospective study in second-line treatment of high-grade NETs demonstrated the efficacy of TMZ alone or in combination with CP and—in a subset of patients—with the addition of bevacizumab. As a result, ORR was 33% while 38% had SD, the median DoR was 18 months, the median PFS was 6 months, and the median OS was 22 months. Only 1 patient had MGMT methylation justifying the high activity of TMZ.[30] TMZ monotherapy as second-line or third-line treatment in NEC also resulted in a median OS of 2.9 months and a median PFS of 1.9 months in extrapancreatic tumors.[31] In another phase II study with patients suffering from NEC, after the failure of etoposide-platinum combination, irinotecan with 5-fluorouracil and leucovorin (FOLFIRI) demonstrated an ORR of 31%, SD in 31% of patients, median PFS of 4 months, and median OS of 18 months.[32]

As stated earlier, CAPOXIRI/XELOXIRI combination with bevacizumab has be used effectively as first-line and second-line treatment in metastatic colorectal cancer patients.[15,16] On the basis of that experience, in a phase II study, 36 patients with advanced carcinoids who previously progressed with platinum or taxane-based treatment, received the FOLFOX-bevacizumab combination for 12 cycles (mFOLFOX-6). Treatment holidays were allowed after 6 months of treatment. This resulted in an ORR of 13.6% (primary objective not reached),

PFS of 19.3 months, median OS of 31 months, and a response in 1 of 2 patients with NEC with predictable toxicity. Similarly, 40 patients with advanced carcinoids, without necessarily PD at enrollment, received CAPOX plus bevacizumab combination (oxaliplatin 130 mg/m^2 IV over 2 h on day 1 plus CP 850 mg/m^2 twice daily on days 1 to 14 of a 21-day cycle plus bevacizumab 7.5 mg/kg IV on day 1). After 4 cycles, oxaliplatin was stopped and patients received maintenance with bevacizumab with/without CP (at the discretion of the investigator). Treatment holidays were not allowed. This resulted in an ORR of 5%, PFS of 19.1 months, and median OS of 38 months in advanced carcinoids, and there were 3 responses in 4 patients with NEC, again with predictable toxicities.[17] Although these results did not reach any of the studies' primary endpoints of efficacy, oxaliplatin/fluoropyrimidine-based chemotherapy plus bevacizumab may benefit select patients such as those with high-grade NEC.

The current trend would be to treat high-grade NECs of the colon and small intestine with regimens analogous to those of colorectal cancer, with emphasis on the antiangiogenetic treatment, which seems to be effective. It is worth mentioning that the Food and Drug Administration (FDA) approved agents for PNETs, everolimus, and sunitinib, the criteria were lower than those presented in our study or in previous studies of platinum-fluoropyrimidine-taxane–based chemotherapy in combination with bevacizumab. For everolimus, in the RADIANT-4 study of patients with GI/lung NETs, the PFS was 11 months, and the ORR was 2%, ORR median was not reached, and the 1-year PFS rate was estimated to be ~45% from the PFS curves.[33] For sunitinib, in patients with advanced pancreatic well-differentiated NET, median PFS was 10.2 months, ORR 9.3%, median OS was not reached, and the 1-year PFS rate was estimated by extrapolation from the PFS curve to be around 45%.[34]

The AE profile of this regimen was anticipated and did not affect the completion of the protocol. Cases of venous thromboembolism that could otherwise be attributed to the use of pazopanib or bevacizumab may have been confounded by the effects of epoetin analogs received by those patients.[35] The most important hematologic side-effect noted was neutropenia, and the most common nonhematologic side-effect was diarrhea, most likely due to the use of oral CP. Compared with historic data, bevacizumab-related bowel perforations were not seen.

CONCLUSIONS

In this study, we demonstrated that, in a population of patients with a dismal prognosis and difficult-to-treat carcinoma, an intense regimen of CAPOXIRI-BEV followed by pazopanib-CP in those patients who already responded to initial treatment may lead to the prolonged OS. Furthermore, as seen from the Kaplan-Meier curves of PFS and OS, it seems that a subset of patients that initially respond well to the CAPOXIRI-BEV (either CR or PR) enjoy a longer PFS and OS compared with nonresponders (SD or PD) and that pazopanib seems to provide additional benefit in those patients. Thus, it remains important to identify the responders to CAPOXIRI-BEV by searching for biomarkers signifying the response. The bulky disease tends to respond more strikingly. Finally, delayed responses were seen, and thus maintenance therapy is likely to contribute.

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