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First Line Gemcitabine/Pazopanib in Locally Advanced and/or Metastatic Biliary Tract Carcinoma. A Hellenic Cooperative Oncology Group Phase II Study

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Abstract. *Background/Aim: The efficacy of gemcitabine-based chemotherapy in locally advanced/metastatic biliary tract carcinoma is limited. The aim of this trial was to assess the activity of a novel gemcitabine-pazopanib combination in such patients. Patients and Methods: In this phase II, multicenter trial, patients with histologically/cytologically confirmed biliary tract carcinoma, previously untreated for advanced disease, received 1000 mg/m^2 of gemcitabine on days 1 and 8 every 21 days and 800 mg of pazopanib once daily continuously for 8 cycles, followed by pazopanib maintenance. The primary endpoint was objective response rate (ORR). Results: A total of 29 patients (median age; 69 years) were enrolled between June 2013 and March 2018. The ORR was 13.8% in the intent-to-treat and 19.1% in the per protocol population. The median progression-free and overall survival were 6.3 and 10.4 months, respectively. Conclusion: The low response rate precludes further testing of the combination in patients with biliary tract carcinoma.*

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Malignant biliary tract (or biliary tree) carcinomas are rare neoplasms. They constitute approximately 3% of all gastrointestinal malignancies (1). They represented fewer than 3% of all cancer cases diagnosed in Europe in 2018, however, precise percentage is not possible as intrahepatic cholangiocarcinoma was grouped together with hepatocellular carcinoma (2). The carcinomas of intra-hepatic and extra-hepatic bile ducts (also called cholangiocarcinomas) and gallbladder cancer are the two most common types of this group of neoplasms. From a therapeutic point of view, patients with biliary tree cancer may be divided in patients with resectable disease and patients with unresectable disease (locally advanced and/or metastatic). In the first group of patients, resection of the tumor is the treatment of choice (3). In the latter group of patients, prognosis is very poor. The

median survival of patients with advanced biliary tract cancer in best supportive care alone is only 2.5 to 7.5 months (4, 5). It has been proven, although the level of evidence is low, that in these patients chemotherapy is better than best supportive care only (6, 7). Probably the most commonly used drug in biliary tract cancer is gemcitabine (8, 9). Gemcitabine administration as monotherapy, in combination with other drugs or as a radiosensitizer in first line setting, offers in such patients a response rate ranging from 12 to 26% and a median survival from 8 to 12 months (10-14).

Due to the very poor prognosis of patients with advanced biliary tree carcinoma, a lot of research is taking place in the laboratory for these patients. One of the areas of interest in such patients is angiogenesis, which is included among the factors that seem to contribute to the development and metastasis of such malignancies (15). Several phase I and II studies have been completed or are underway with anti-angiogenic drugs alone or in combination with chemotherapy (15). Among the various drugs targeting angiogenesis and which has not been tested so far in biliary tree carcinoma is pazopanib. Pazopanib is an orally administered inhibitor of multiple-proteins acting as tyrosine kinases such as vascular endothelial growth factor receptor (VEGFR) 1-3, platelet derived growth factor receptor (PDGFR) a/b and fibroblast growth factor receptor (FGFR) 1 and 3, all of which are associated with angiogenesis (16). Based on the afore-mentioned data, a multicenter phase II study was designed and conducted with the combination of gemcitabine and pazopanib in the first line setting of patients with biliary tree carcinomas.

Patients and Methods

The target group for our phase II study was patients with non-operable locally advanced and/or metastatic biliary tree carcinoma (adenocarcinoma of the intrahepatic, proximal extrahepatic and distal extrahepatic bile duct, gallbladder adenocarcinoma and periampullar biliary duct adenocarcinoma) who had not received chemotherapy before. A subsequent amendment of the protocol allowed patients to be included even if they had received adjuvant chemotherapy, providing that this was completed more than 12 months prior to the inclusion in the current study. Histologic or cytologic confirmation of the diagnosis was necessary for each patient prior to the participation in the study. Other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 indicating that the patient was in good general condition, measurable disease per response evaluation criteria in solid tumors (RECIST) v1.1, and adequate bone marrow, renal and hepatic function. Due to the potential side-effects of pazopanib regarding thyroid dysfunction, proteinuria and prolongation of QT interval, the participating patients were required to have normal thyroid tests, urine protein to urine creatinine ratio <1 and corrected QT interval calculated with the Bazett's formula ≤480 ms (assessed at the electronic address: https://www.mdcalc.com/corrected-qt-interval-qtc in October 2019).

Once the informed consent form was signed, the treatment given was the combination of 1,000 mg/m^2 gemcitabine intravenously on days 1 and 8 with 800 mg pazopanib orally once per day on days 1-21 every 21 days for 8 cycles. Following 8 cycles of combination therapy, patients with controlled disease continued with 800 mg pazopanib monotherapy daily on days 1-21 every 21 days. Re-evaluation of each patient's disease with imaging, was done every 2 months, while quality of life was assessed with the use of the EUROQOL 5D questionnaire again every 8 weeks. Treatment continued until disease progression, significant toxicity development or consent withdrawal.

The primary objective of the study was to evaluate the efficacy of the combination of gemcitabine with pazopanib followed by pazopanib monotherapy in these patients in terms of objective response rate (ORR), *i.e.* the percentage of patients with a confirmed complete or partial response as the best response. Secondary objectives of the study were progression-free survival (PFS), the percentage of patients that were progression-free at 6 months (6-month PFS rate), overall survival (OS), the safety of the combination as well as the quality of life (QoL).

The study (HE37/12) was approved by local and central Greek regulatory authorities and registered in international databases [in European clinical trial database (EudraCT) with the number 2012-001705-24 and in ClinicalTrials.gov with the number NCT01855724].

Statistical analysis. The two-stage Simon's optimal design was used for the design of the current study based on the primary endpoint (17). Assuming that the expected ORR would be at least 35% and the minimum acceptable response rate was 20%, with a type I and II error of 10% and 20% respectively, 13 patients were required to be enrolled in the first stage of the study. If a minimum of 3 responses were observed in the 13 patients of the first stage, the study would proceed to the second stage recruiting 33 more patients leading to a total sample size of 46 patients. The study treatment would be considered worth developing further if 13 or more responses were observed.

PFS was calculated from the date of study entry to the date of first documented disease progression, death (from any cause) without prior documented progression or last contact (whichever occurred first). OS was calculated from the date of study entry to the date of patient's death or last contact. Alive patients were censored at the date of last contact. Time to event data were analyzed using the Kaplan-Meier product limit method.

The study was conducted on an intent-to-treat (ITT) basis and therefore, all enrolled patients were included in the analysis. PFS, OS, QoL and ORR were assessed in the ITT population, while ORR was additionally assessed in the per protocol (PP) population consisting of all patients that received at least one cycle of the study treatment, had an initial tumor assessment and had tumors of the right histological type of cancer. The safety profile was evaluated in the safety population comprising all patients that received at least one dose of the study drugs.

All tests were two-sided and the significance level was set at 5%. The data cut-off date for the analysis was July 23, 2019. The SAS version 9.3 (SAS Institute) was used for statistical analysis and the R studio version 3.5.0 for generation of survival plots.

Results

The first patient entered the trial in June 2013. Due to safety issues, raised from a fatal hepatic event that happened in a patient at another clinical trial using the same combination

of drugs in soft tissue sarcoma patients, the study in July 2013, had to be temporarily stopped for almost a year. In December 2014, the second patient of the study was enrolled. Even though 13 patients were planned to be enrolled in the first stage of the trial according to the statistical design, a total of 17 patients were finally included in the first stage since 4 of them were non-evaluable for response [due to treatment discontinuation prior to evaluation attributed to: non-fatal adverse event (2 patients), informed consent withdrawal (1 patient) and temporary suspension of the trial (1 patient)]. Given the number of responses [3 objective (partial) responses] observed in the first stage, the continuation of the study to the second stage was decided. In March 2018, the 29th patient of the study was enrolled. However, because all these years the annual accrual rate had always been low and it was evident that the target sample size of 46 patients for the protocol would have not been reached at the prespecified date, in June 2018 the trial was prematurely terminated.

Overall, 29 patients from 10 Greek Oncology Departments affiliated with HeCOG were included in the study and their characteristics are shown in Table I. The majority of patients had cholangiocarcinoma (86%), 79% of them had been recently diagnosed with cancer and most of them had metastatic disease (82.8%). Three patients were ineligible (one due to previous breast cancer, one due to adenocarcinoma of the ampulla Vater, but of intestinal histology, and one patient due to violation of the inclusion criterion concerning simultaneous increase in both bilirubin and hepatic enzymes, but received at least one cycle of treatment.

Table I. *Patient and tumor characteristics*.

Characteristic	N (%)
Number of patients	29 (100)
Age at study entry (years)	
Median	68.6
Range	46.5-85
Gender	
Male	15 (51.7)
Female	14 (48.3)
PS (ECOG)	
0	18 (62.1)
1	11 (37.9)
Primary site	
Intrahepatic bile ducts	19 (65.5)
Perihilar bile ducts	3 (10.3)
Distal bile ducts	3 (10.3)
Gallbladder	4 (13.8)
Initial presentation or recurrence?	
Initial presentation	23 (79.3)
Recurrence	6 (20.7)
Stage	
Not metastatic	5 (17.2)
Metastatic +/–localized	24 (82.8)
CEA	
N	18 (62.1)
N with normal levels (<5 ng/ml)	9 (50.0)
Median (range) (ng/ml)	5.4 (0.5-13,201)
CA 19-9	
N	19 (65.5)
N with normal levels (<37 U/ml)	6 (31.6)
Median (range) (U/ml)	133 (5-63,984)

N: Number of patients; PS: performance status, CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9.

Treatment exposure. Twenty-six patients (89.7% of the patients) received at least one cycle of gemcitabine and pazopanib according to the protocol's treatment schedule. One patient, who received two cycles of treatment, had gemcitabine only on the first day of each cycle due to toxicity on day 8 of each cycle. The second patient received pazopanib only for a week as he discontinued the treatment due to jejunal hemorrhage and for the third, we did not have available information whether pazopanib was administered since the patient withdrew his consent for the study on day 15 of the first cycle and never returned the pazopanib bottles for accountability. In total, 10 patients (34.5%) completed the 8 cycles of gemcitabine/pazopanib combination and proceeded with pazopanib maintenance therapy, while the rest (65.5%) discontinued treatment prior to the completion of the 8 cycles of the combination or the commencement of pazopanib monotherapy. The most common reasons for discontinuation were progressive disease (in 7 patients, 36.8% of the patients who discontinued treatment) and non-fatal adverse event, which leaded to permanent discontinuation of the study drugs (6 patients; 31.6%).

Treatment efficacy. Of the 29 enrolled patients (ITT population), objective (partial) response according to the investigator's assessment of the imaging, was observed in 4 patients (13.8% of the study cohort), while 12 patients (41.4%) had stable disease leading to a disease control rate (*i.e*. percentage of patients with a confirmed complete, partial or stable disease as the best response) of 55.2%. Eight patients were not evaluated for response due to early tumor death (1 patient; 3.5%) and treatment discontinuation prior to evaluation (7 patients; 24.1%). In 5 of them, the cause of discontinuation was directly or indirectly related to side-effects of the study medications (hepatotoxicity, epigastric pain, severe fatigue, gastrointestinal bleeding and stroke were the causes leading to termination of the treatment) (Table II). In the PP population (N=21), as shown in Table II, 4 patients achieved an objective response (partial response) (19.1%) and the disease control rate was 76.2%. Neither any of the baseline tumor markers (CEA and CA 19-9) nor disease presentation (initial diagnosis or recurrence of disease) was significantly associated with disease control with the study drugs (p=0.77, p=0.60 and p=0.24, respectively).

Table II. *Best response in the ITT (N=29) and PP (N=21) population.*

	N	%
ITT population (N=29)		
PR	4	13.8
SD	12	41.4
PD	5	17.2
Early tumor death	1	3.5
Treatment discontinuation prior to evaluation	7	24.1
Due to side-effects	5	17.2
Other reasons	2	6.9
PP population (N=21)		
PR	4	19.1
SD	12	57.1
PD	5	23.8

PR: Partial response; SD: stable disease; PD: progressive disease.

By the data cut-off date for the analysis (July 23, 2019), no patients were still on treatment with the study medications. A total of 28 events of progression or death had occurred (PFS events) and 25 deaths had been reported. One patient was lost-to- follow-up. Within a median follow-up of 25.8 months (95%CI=13.5-25.8), the median PFS was 6.3 months (95%CI=2.3-8.0), while the 6-month PFS rate was 51.7%. The median OS was 10.4 months (95%CI=7.3-13.4) (Figure 1).

Safety. All patients received at least one dose of gemcitabine, as previously described, and were therefore assessed for safety. A total of 331 events were recorded in 29 patients. No toxic death was reported throughout the trial. One patient presented with hepatic failure during treatment. Even though this was a fatal event and was recorded as a serious adverse event for regulatory purposes, no causal relationship with the study medications was reported and it was considered only disease (and not treatment) related.

The adverse events observed in the study were consistent with the previously reported safety profile of gemcitabine and pazopanib as well as the disease under study. Most of them were mild, however 13 patients (44.8%) experienced 26 serious adverse events and 2 of them were unexpected. As shown in Table III, the most common, not related with a blood test, side effects were fatigue and hypertension. There was also one case each of ischemic stroke, lung abscess, jejunal hemorrhage and acute renal failure. These severe events were possibly related to the study drugs.

Quality of life. In total, 28 patients (96.6%) completed the EUROQOL 5D questionnaire at baseline and 23 (79.3%) at their last cycle of treatment. As shown in Table IV, no statistically significant difference existed in the measurement of patients' health status (EQ VAS) between baseline and end of treatment (Wilcoxon signed-rank p=0.55). The median number of EQ VAS at baseline and at the end of treatment were 67.5 *versus* 70, respectively. Most of the patients reported no mobility or self-care problems both at baseline (75% and 89.3%, respectively) and at the last cycle of treatment (69.6% and 73.9%), while the majority of patients who completed the questionnaire stated moderate anxiety/depression problems.

Discussion

We performed a hypothesis-generating phase II study with gemcitabine and pazopanib in advanced biliary tract carcinoma. The study closed prematurely due to slow accrual rate, however, based on the results on the limited number of patients included, the ORR in the ITT was around 14% and the percentage of patients who succeeded stabilization of their disease was 41%. It is highly unlikely that with the addition of the missed 17 patients from the initial statistical design of the study, the response would have risen to 28%.; this was set as the lower limit where the combination would be tested further. The 14% ORR is similar to the one succeeded with gemcitabine monotherapy. As an example, in the randomized phase II study from Japan where gemcitabine was compared to gemcitabine and cisplatin combination in 84 patients with locally advanced and/or metastatic biliary tree carcinoma, in patients who received monotherapy, the response rate was 12% and the stabilization of the disease was 38% (11). Thus, at a first glance, it seems that pazopanib and gemcitabine have no additive effect in the treatment of biliary tract carcinoma.

However, by looking the figures of PFS, the figure in our study seems to be longer (6.3 months) compared to the relevant figure in groups of patients who had been treated with gemcitabine monotherapy in other studies (4.3 months in the study of Okusaka *et al*., 3.7 in the study of Sasaki *et al*. and 5 months in the study of Valle *et al*.) (10, 11, 17). That means that maybe pazopanib confers some small benefit in these patients once control of the disease with chemotherapy has been succeeded, however, something like that is difficult to be proven from the data in our study. Perhaps, pazopanib in patients with biliary tract carcinoma is best only in patients who had at least stabilization of their disease with chemotherapy, and then continued treatment either only with pazopanib or with the combination of pazopanib and chemotherapy. Just like in the international study for patients with ovarian cancer who had been treated initially with debulking therapy and at least 5 cycles of taxane-platinum based chemotherapy, pazopanib was tested alone as maintenance therapy (18). Or in another study of patients with small-cell lung cancer (extensive disease) where pazopanib was given as maintenance therapy in patients who had received already 4 cycles of etoposide-

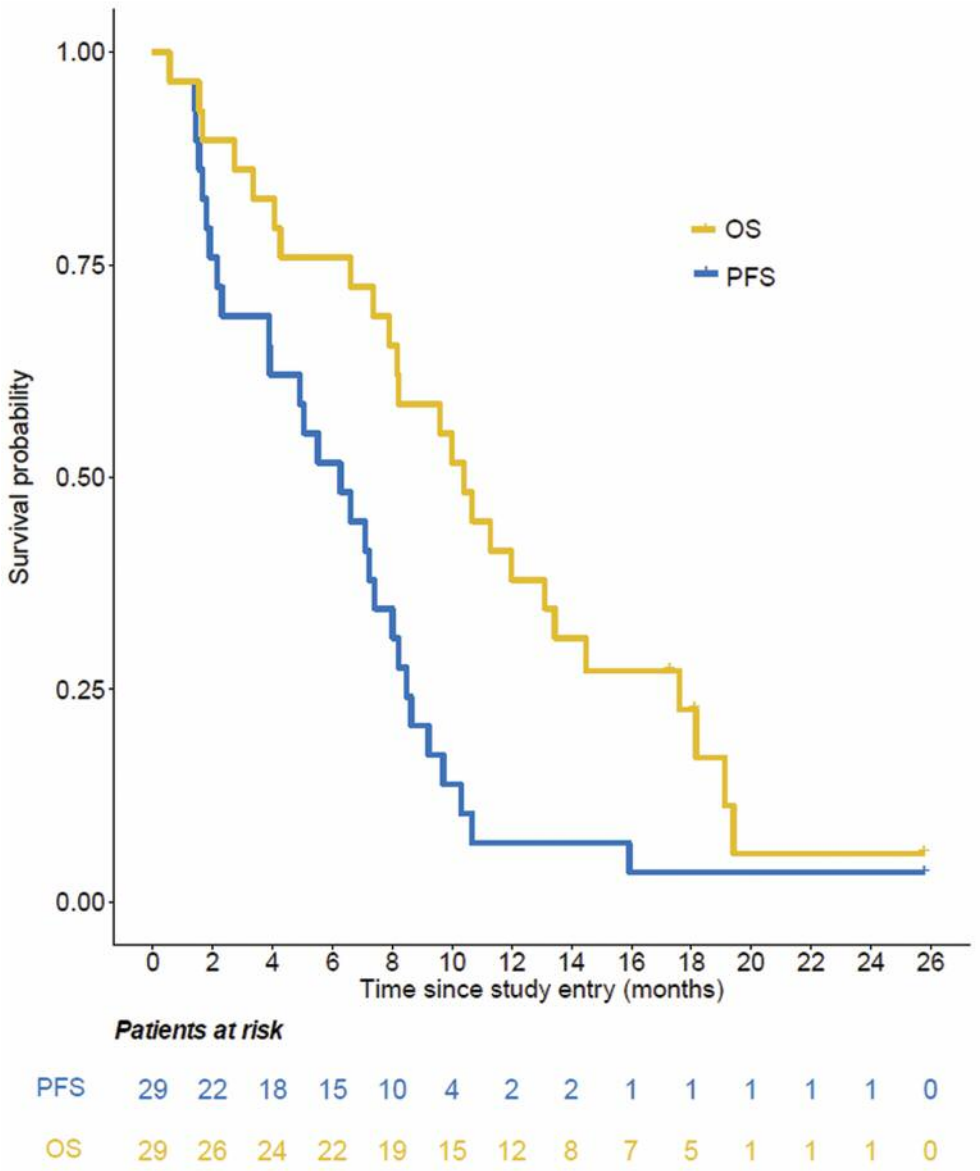

Figure 1. *Kaplan-Meier curves with respect to disease-free survival (DFS) (blue curve) and overall survival (OS) (yellow curve) in the ITT population.*

platinum chemotherapy and had not progressed (19). In both studies, pazopanib administration as maintenance therapy in patients with controlled disease who had initially been given chemotherapy, resulted in prolongation of PFS compared to placebo.

It is possible, that pazopanib in biliary tree carcinoma patients offers some prolongation of the period of control of disease in some patients in a similar manner to other anti-angiogenetic agents in various types of cancer. Also, it is certain that angiogenesis is involved in the pathogenesis and growth of biliary tree carcinoma and factors promoting angiogenesis have been found overexpressed in tumor samples, therefore agents blocking angiogenesis are expected to be active (15). For example, in a previous study of our group, we showed that the angiogenesis factors VEGFA and VEGFC were expressed in 81% and 42% of the tumor samples examined (20). Of interest, in that study, a correlation between angiogenesis factors and their receptors was found. However, so far most of the studies with anti-angiogenetic agents in biliary tract malignancy tested either alone or in combination with chemotherapy or epidermal growth factor receptor (EGFR) inhibitors were negative (15).

Table III. *Incidence of adverse events by grade*.

System organ class Preferred term	Grade 1 N evts	N pts	% pts	Grade 2 N evts	N pts	% pts	Grade 3 N evts	N pts	% pts	Grade 4 N evts	N pts	% pts	Grade 5 N evts	N pts	% pts
Overall	153	27	93.10	99	25	86.21	69	26	89.66	8	6	20.69	1	1	3.45
Blood and lymphatic system disorders	3	3	10.34	7	7	24.14	2	2	6.90	0	0	0.00	0	0	0.00
Anemia	3	3	10.34	6	6	20.69	2	2	6.90	0	0	0.00	0	0	0.00
Blood and lymphatic system disorders - Other, specify[a]	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Cardiac disorders	2	2	6.90	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Cardiac disorders - Other, specify[b]	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Sinus bradycardia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Sinus tachycardia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Endocrine disorders	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypothyroidism	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Eye disorders	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Eye disorders - Other, specify[c]	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Watering eyes	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Gastrointestinal disorders	25	15	51.72	16	11	37.93	4	4	13.79	1	1	3.45	0	0	0.00
Abdominal pain	4	4	13.79	2	2	6.90	1	1	3.45	0	0	0.00	0	0	0.00
Ascites	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Constipation	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Diarrhea	4	4	13.79	3	3	10.34	1	1	3.45	0	0	0.00	0	0	0.00
Dyspepsia	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Esophageal hemorrhage	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Gastroesophageal reflux disease	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Gastrointestinal disorders - Other, specify[d]	3	3	10.34	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Ileus	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Jejunal hemorrhage	0	0	0.00	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00
Mucositis oral	2	2	6.90	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Nausea	4	4	13.79	3	3	10.34	1	1	3.45	0	0	0.00	0	0	0.00
Periodontal disease	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Vomiting	3	3	10.34	4	4	13.79	0	0	0.00	0	0	0.00	0	0	0.00
General disorders and administration site conditions	15	14	48.28	6	5	17.24	7	7	24.14	0	0	0.00	0	0	0.00
Edema face	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Edema limbs	3	3	10.34	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Fatigue	8	8	27.59	2	2	6.90	6	6	20.69	0	0	0.00	0	0	0.00
Fever	2	2	6.90	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
General disorders and administration site conditions - Other, specify[e]	0	0	0.00	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00
Pain	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Hepatobiliary disorders	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	1	1	3.45
Cholecystitis	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Hepatobiliary disorders - Other, specify[f]	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00	1	1	3.45
Infections and infestations	1	1	3.45	6	5	17.24	5	3	10.34	0	0	0.00	0	0	0.00
Hepatic infection	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Infections and infestations - Other, specify[g]	0	0	0.00	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00
Lung infection	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Papulopustular rash	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Skin infection	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Tooth infection	0	0	0.00	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00
Upper respiratory infection	0	0	0.00	2	2	6.90	1	1	3.45	0	0	0.00	0	0	0.00

Table III. *Continued*

Table III. *Continued*

	Grade 1			Grade 2			Grade 3			Grade 4			Grade 5		
System organ class Preferred term	N evts	N pts	% pts	N evts	N pts	% pts	N evts	N pts	% pts	N evts	N pts	% pts	N evts	N pts	% pts
Urinary tract infection	0	0	0.00	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00
Investigations	43	22	75.86	38	18	62.07	44	17	58.62	7	6	20.69	0	0	0.00
Alanine aminotransferase increased	8	8	27.59	6	6	20.69	3	3	10.34	0	0	0.00	0	0	0.00
Alkaline phosphatase increased	1	1	3.45	5	5	17.24	4	4	13.79	0	0	0.00	0	0	0.00
Aspartate aminotransferase increased	7	7	24.14	4	4	13.79	4	4	13.79	0	0	0.00	0	0	0.00
Blood bilirubin increased	6	6	20.69	0	0	0.00	2	2	6.90	2	2	6.90	0	0	0.00
Cholesterol high	2	2	6.90	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Creatinine increased	3	3	10.34	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
GGT increased	0	0	0.00	0	0	0.00	8	8	27.59	2	2	6.90	0	0	0.00
Investigations - Other, specify[h]	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Lymphocyte count decreased	1	1	3.45	2	2	6.90	1	1	3.45	0	0	0.00	0	0	0.00
Neutrophil count decreased	1	1	3.45	7	7	24.14	12	12	41.38	3	3	10.34	0	0	0.00
Platelet count decreased	8	8	27.59	3	3	10.34	1	1	3.45	0	0	0.00	0	0	0.00
Serum amylase increased	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
White blood cell decreased	4	4	13.79	10	10	34.48	9	9	31.03	0	0	0.00	0	0	0.00
Metabolism and nutrition disorders	30	14	48.28	11	8	27.59	0	0	0.00	0	0	0.00	0	0	0.00
Anorexia	1	1	3.45	3	3	10.34	0	0	0.00	0	0	0.00	0	0	0.00
Hyperglycemia	3	3	10.34	3	3	10.34	0	0	0.00	0	0	0.00	0	0	0.00
Hyperkalemia	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypermagnesemia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypernatremia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypertriglyceridemia	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypoalbuminemia	4	4	13.79	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Hypocalcemia	1	1	3.45	3	3	10.34	0	0	0.00	0	0	0.00	0	0	0.00
Hypoglycemia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypokalemia	4	4	13.79	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hypomagnesemia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hyponatremia	5	5	17.24	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Hypophosphatemia	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Metabolism and nutrition disorders - Other, specify[i]	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Musculoskeletal and connective tissue disorders	3	3	10.34	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Arthralgia	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Back pain	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Chest wall pain	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Pain in extremity	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Nervous system disorders	5	3	10.34	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Dizziness	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Dysgeusia	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Nervous system disorders - Other, specify[j]	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Paresthesia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Psychiatric disorders	2	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Anxiety	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Psychiatric disorders - Other, specify[k]	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Renal and urinary disorders	6	6	20.69	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00
Acute kidney injury	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Hematuria	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Proteinuria	4	4	13.79	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00
Respiratory, thoracic and mediastinal disorders	4	4	13.79	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00

Table III. *Continued*

Table III. *Continued*

System organ class Preferred term	Grade 1 N evts	N pts	% pts	Grade 2 N evts	N pts	% pts	Grade 3 N evts	N pts	% pts	Grade 4 N evts	N pts	% pts	Grade 5 N evts	N pts	% pts
Allergic rhinitis	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Cough	0	0	0.00	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Dyspnea	1	1	3.45	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00
Epistaxis	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Pharyngolaryngeal pain	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Skin and subcutaneous tissue disorders	8	4	13.79	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Alopecia	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Dry skin	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Rash acneiform	2	2	6.90	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Skin and subcutaneous tissue disorders - Other, specify[l]	3	3	10.34	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Skin hyperpigmentation	1	1	3.45	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
Vascular disorders	3	3	10.34	8	8	27.59	4	4	13.79	0	0	0.00	0	0	0.00
Hypertension	3	3	10.34	8	8	27.59	4	4	13.79	0	0	0.00	0	0	0.00

evts: Events; pts: patients. [a]One grade 2 event of leucopenia. [b]One grade 3 event of ischemic stroke. [c]One grade 1 event of eyelash edema. [d]One (grade 1) event of hematochesia, one (grade 1) event of epigastric pain and one (grade 1) event of mucosal defecations. [e]One (grade 2) event of voice disorder and one (grade 3) event of neutropenia. [f]One grade 5 event of hepatic failure. [g]One (grade 2) event of cholangitis and one (grade 3) event of lung abscess. [h]One grade 1 event of LDH increase. [i]One grade 1 event of hyperphosphatemia and one grade 1 event of hyperbilirubinemia. [j]One grade 1 event of sleeping disorder. [k]One grade 1 event of distress. [l]One event of hand and foot syndrome, one of hair depigmentation and one event of hair hypopigmentation.

In the randomized phase II study from the German group AIO, the combination of gemcitabine with sorafenib was tested in advanced carcinoma of gallbladder and intrahepatic biliary ducts (21). The two drugs were given concurrently from the beginning, as in our study. The combination of the drugs produced a response rate of 8.1% in the modified ITT population of the study.

In addition to the studies with the anti-angiogenesis drugs, various other targeted agents have been tested or are currently under evaluation for patients with gallbladder cancer or cholangiocarcinoma. Clinical studies using agents such as those who target the epidermal growth factor receptor (EGFR), the isocitrate dehydrogenase 1 mutation (*IDH 1*) or the poly ADP ribose polymerase (PARP) are underway, however no definite evidence of their activity in these patients has been proven so far (22-24). Also, immunotherapy is being tested in these patients. There are some data in the literature regarding the activity of these drugs such as nivolumab, however these data come from studies at an early stage and large trials are needed for reaching definite conclusions (25). Until then, chemotherapy remains the treatment of choice in patients with locally advanced and/or metastatic biliary tract cancer with the combination of cisplatin and gemcitabine being the regimen with the best evidence in first line setting (26). In conclusion, despite the fact that our study closed prematurely due to low accrual rate, it seems that the combination of gemcitabine and pazopanib followed by pazopanib maintenance in patients with biliary tract carcinoma produces a similar rate of control of disease compared to gemcitabine monotherapy. The specific treatment tested in our study, should not be tested further in a larger clinical study.

Conflicts of Interest

Gerasimos Aravantinos: Advisory Boards: Novartis, BMS, Roche Hellas, Astra Zeneca, Sanofi, Amgen, Genesis Pharma, Merck, Pfizer; George Pentheroudakis: Advisory Role: Roche, Amgen, Merck, Astra-Zeneca, BMS, MSD, Lilly. Research Funding: Boehringer, Merck, Amgen, Astra-Zeneca, Roche, Enorasis, BMS, Lilly. Institutional financial support for clinical trials or contracted research: Boehringer, Merck, Amgen, Astra-Zeneca; Amanda Psyrri: Consultation Fees: Amgen, Merck Serono, Roche, BMS. AstraZeneca, MSD. Honoraria: Amgen, Merck Serono, Roche, BMS, AstraZeneca, MSD. Research funds BMS Kura; Dimitrios Pectasides: Advisory Role: Roche, MSD, Astellas. Honoraria: Roche, MSD, Astellas; Evangelia Razis: Consulting or Advisory Role: AstraZeneca, Bristol-Myers Squibb, Pfizer; Research Funding: Novartis, Demo Pharmaceutical, EORTC, Radius Pharmaceuticals, Tesaro, Parexel, Anabiosis Pharmaceuticals. Travel: Sanofi, Ipsen, Genesis Pharmaceuticals, LEO Pharma, Merck, Roche, Genekor; George Fountzilas: Advisory Board of Pfizer, Sanofi and Roche. Honoraria from Astra-Zeneca; Epaminontas Samantas: Advisory Board of Merck, MSD, Asta-Zeneca, Roche, Amgen and Genesis.

Table IV. *Quality of life results*.

	Baseline Total (N=28)	Last cycle Total (N=23)	*p*-Value
EQ-VAS			0.55[a]
Mean±SD	55±31.3	54.1±30.2	
Median	67.5	70.0	
Min-Max	4.0-100.0	6.5-96.0	
25th percentile	20.0	20.0	
75th percentile	80.0	80.0	
Mobility			
No problems	21 (75.0)	16 (69.6)	-
Moderate problems	7 (25.0)	4 (17.4)	
Inability/severe problems	0 (0.0)	3 (13.0)	
Self-care			
No problems	25 (89.3)	17 (73.9)	-
Moderate problems	3 (10.7)	5 (21.7)	
Inability/severe problems	0 (0.0)	1 (4.3)	
Usual Activities			
No problems	16 (57.1)	10 (43.5)	-
Moderate problems	10 (35.7)	10 (43.5)	
Inability/severe problems	2 (7.1)	2 (8.7)	
Unknown	0 (0.0)	1 (4.3)	
Pain/Discomfort			
No problems	11 (39.3)	10 (43.5)	-
Moderate problems	17 (60.7)	11 (47.8)	
Inability/severe problems	0 (0.0)	2 (8.7)	
Anxiety/Depression			
No problems	6 (21.4)	7 (30.4)	-
Moderate problems	20 (71.4)	15 (65.2)	
Inability/severe problems	2 (7.1)	1 (4.3)	

[a]Wilcoxon signed-rank test.

Authors' Contributions

Conceptualization: JS, GP, ES; Formal analysis: GAK; Resources: JS, GA, GP, FZ, AP, DL, MD, DP, ER, GF, ES; Writing – original draft preparation: JS, GAK, GF, ES; Writing – review and editing: All Authors.

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