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Clinical Trial

Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: A double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme ☆

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Abstract ***Background:*** Since sorafenib has shown activity in different tumour types and gemcitabine regimens improved the outcome for biliary tract cancer (BTC) patients, we evaluated first-line gemcitabine plus sorafenib in a double-blind phase II study.

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BTC
Sorafenib
Hand-foot syndrome
VEGFR-2
VEGFR-3
c-kit
PDGFRβ
Hif1α

Patients and methods: 102 unresectable or metastatic BTC patients with histologically proven adenocarcinoma of gallbladder or intrahepatic bile ducts, Eastern Cooperative Oncology Group (ECOG) 0–2 were randomised to gemcitabine (1000 mg/m^2 once weekly, first 7-weeks + 1-week rest followed by once 3-weeks + 1-week rest) plus sorafenib (400 mg twice daily) or placebo. Treatment continued until progression or unacceptable toxicity. Tumour samples were prospectively stained for sorafenib targets and potential biomarkers. Serum samples (first two cycles) were measured for vascular endothelial growth factors (VEGFs), vascular endothelial growth factor receptor 2 (VEGFR-2) and stromal cell-derived factor 1 (SDF1)α by enzyme-linked immunosorbent assay (ELISA).

Results: Gemcitabine plus sorafenib was generally well tolerated. Four and three patients achieved partial responses in the sorafenib and placebo groups, respectively. There was no difference in the primary end-point, median progression-free survival (PFS) for gemcitabine plus sorafenib versus gemcitabine plus placebo (3.0 versus 4.9 months, $P = 0.859$), and no difference for median overall survival (OS) (8.4 versus 11.2 months, $P = 0.775$). Patients with liver metastasis after resection of primary BTC survived longer with sorafenib ($P = 0.019$) compared to placebo. Patients who developed hand-foot syndrome (HFS) showed longer PFS and OS than patients without HFS. Two sorafenib targets, VEGFR-2 and c-kit, were not expressed in BTC samples. VEGFR-3 and Hif1α were associated with lymph node metastases and T stage. Absence of PDGFRβ expression correlated with longer PFS.

Conclusion: The addition of sorafenib to gemcitabine did not demonstrate improved efficacy in advanced BTC patients. Biomarker subgroup analysis suggested that some patients might benefit from combined treatment.

1. Introduction

Most patients with biliary tract cancer (BTC) present with unresectable disease [1] and their prognosis remains bleak, with median overall survival (OS) times of approximately 6 months and 5-year survival rates of <5% for patients with advanced or metastatic disease. Chemotherapy has been used to control disease, improve survival and quality of life (QoL) in unresectable, recurrent or metastatic BTC, but OS rates of ⩾10 months remain difficult to achieve, even with triple combinations [2]. Phase II studies have reported that gemcitabine alone is active and well tolerated, with response rates of 8–60% [3]. In the ABC-02 phase III trial, gemcitabine combined with cisplatin prolonged progression-free survival (PFS) and OS compared with gemcitabine alone [4]. Similar findings were also reported for the Japanese BT22 study [5].

Understanding the molecular pathways in BTC has provided the basis for the use of targeted therapies to improve clinical outcome [6–9]. Bile acids have complex effects on the development of cholangiocarcinoma, with activation of the epidermal growth factor receptor (EGFR) leading to enhancement of the mitogen-activated protein kinase (MAPK) cascade [10]. Additionally, several molecular and genetic alterations have been reported [8]. The most frequent is disruption of the MAPK pathway as a result of *RAS* or *BRAF* mutations [11]. Proinflammatory and angiogenic molecules, such as vascular endothelial growth factor (VEGF), are also overexpressed in BTC tissue, stimulated by both paracrine and autocrine mechanisms [12,13].

Sorafenib is an oral multi-tyrosine kinase inhibitor with reported activity in a variety of tumour types and is approved for the treatment of advanced human hepatocellular carcinoma (HCC) [14]. In a preclinical model, growth of human BTC cells was suppressed by sorafenib alone or in combination [15,16].

The activity of sorafenib alone or in combination with gemcitabine in HCC has been demonstrated [14,17–19], but, at the time the trial was planned, a randomised phase III study of gemcitabine combinations in the treatment of advanced BTC was lacking. Given this concern, gemcitabine alone was chosen as the standard treatment comparator [4,20] in a double-blind placebo-controlled setting.

2. Patients and methods

2.1. Patients

Patients were aged >18 years with histologically proven adenocarcinoma of the gallbladder or intrahepatic bile ducts, not amenable to curative resection or with hepatic BTC metastases. Patients had at least one measurable lesion in a non-irradiated, non-photodynamic therapy-treated area, an ECOG performance status score of 0–2, life expectancy of >12 weeks, and adequate bone marrow, liver and renal function. Patients were not allowed to receive a prior (palliative) radio-/chemotherapy. Concomitant treatment with any other anticancer therapy and prior use of RAF-kinase, VEGF, MEK or farnesyl transferase inhibitors was not permitted. All patients provided written, informed consent.

2.2. Study design

This randomised, double-blind phase II study aimed to demonstrate a clinically meaningful outcome from addition of sorafenib to gemcitabine. The primary end-point was PFS. Patients were randomised (1:1) to receive gemcitabine plus sorafenib (sorafenib group) or gemcitabine plus placebo (placebo group). Further details of study design are presented as Supplementary Information. The primary efficacy population was the modified intention-to-treat (mITT) population comprising all patients who received at least one dose of study medication. Secondary analyses were conducted in the per-protocol (PP) population comprising all evaluable patients without major protocol violations. If patients received subsequent anticancer therapy after study discontinuation but before occurrence of progressive disease (PD) or death, PFS was censored (see Supplementary Information).

Secondary end-points included safety, OS, best overall response (OR), stable disease duration, 1-year PFS and OS rates and QoL (European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0)). Safety variables comprised treatment-emergent adverse events (AEs; coded according to MedDRA 14.0 and 14.1; severity graded by NCI-CTC v3.0), laboratory data, concomitant medications and vital signs.

The study was approved by 11 German independent ethics committees, met all regulatory requirements (ClinicalTrials.gov: NCT00661830), and was conducted in accordance with the Declaration of Helsinki.

2.3. Treatment and tumour assessments

Gemcitabine (1000 mg/m^2) was administered days 1, 8, 15, 22, 29, 36, 43 of the first cycle (8 weeks' duration) and days 1, 8 and 15 of all subsequent cycles (4 weeks' duration). Sorafenib (400 mg) or placebo tablets were administered twice daily. Dose adjustments based on patient tolerance were permitted. Evaluation of tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 was conducted every 8 weeks and 30 days after end of treatment and compared with baseline. Confirmation by a repeat computed tomography scan was required for complete or partial responses. QoL was assessed on day 29 of the first cycle and day 1 of each subsequent cycle and results compared by Wilcoxon rank-sum tests.

2.4. Protein and serum analyses

Immunohistochemical (IHC) staining of paraffin-embedded tumour samples was carried out in part to assess the expression levels of VEGF-C and -D, VEGFR-2 and -3, CXCR4, Hif1α, c-kit, PDGFRβ and PTEN (Supplementary Table 1) [21]. Overall, 51 patient samples were obtained for assessment of VEGF-C and PTEN, 52 for PDGFRβ, 53 for VEGF-D, VEGFR-3, Hif1α, 56 for c-kit, 58 for CXCR4 and 59 for VEGFR-2 by two independent, blinded investigators. Staining was evaluated (no staining 0, weak 1, moderate 2 and strong 3) and divided into two groups: negative (0) and positive (weak–moderate–strong) for statistical analysis. These biomarkers comply with the REMARK guidelines. Serum samples were tested in duplicate for SDF1α, VEGF-A, VEGF-D and soluble (s) VEGFR-2 concentrations by quantitative Duo-ELISA (R&D, Minneapolis). To explore associations between IHC results and clinical parameters, univariate analyses were performed using Pearson's Chi-2 test, Cox regression and Fisher's exact test.

2.5. Statistical considerations

Assuming a median PFS of 3 months for the placebo group and exponentially distributed time to event, 86 events were required to show a 50% improvement for sorafenib, with 80% power and one-sided significance level of 15%. With 18 months recruitment 12 months follow-up and allowing a 5% drop-out rate, 96 patients were required to be randomised. The primary population for efficacy analysis was the modified intention-to treat (mITT) population. The primary efficacy end-point was also analysed in per-protocol population.

To investigate associations between results of immunohistochemistry for all markers and clinical-pathological parameters, univariate statistical analyses were performed using Pearson's Chi-2 test, cox regression and Fisher's exact test. Duration of overall response and duration of stable disease, PFS and OS were estimated by Kaplan–Meier. Differences between treatment groups for PFS and OS were tested by the one-sided log-rank test. Post hoc Kaplan-Meier analyses for PFS and OS were done according to tumour location and HFS. Hazard ratios were estimated by Cox proportional hazard model. Rates of PFS and OS 1 year after treatment start and median length of PFS and OS were determined. For quality of life, scores of QLQ-C30 functional scales, multi-item scales and single-item scales on day 29 of first treatment cycle in each treatment group were compared by Wilcoxon rank-sum tests.

3. Results

3.1. Patient characteristics

Overall 102 patients were randomised (Fig. 1). The mITT and safety populations were identical (sorafenib, $N = 49$; placebo, $N = 48$). The PP population comprised 35 and 34 patients treated with sorafenib and placebo, respectively (Supplementary Information). Demographic and baseline characteristics were well balanced between the two arms (Table 1). Comparably, 50% of patients

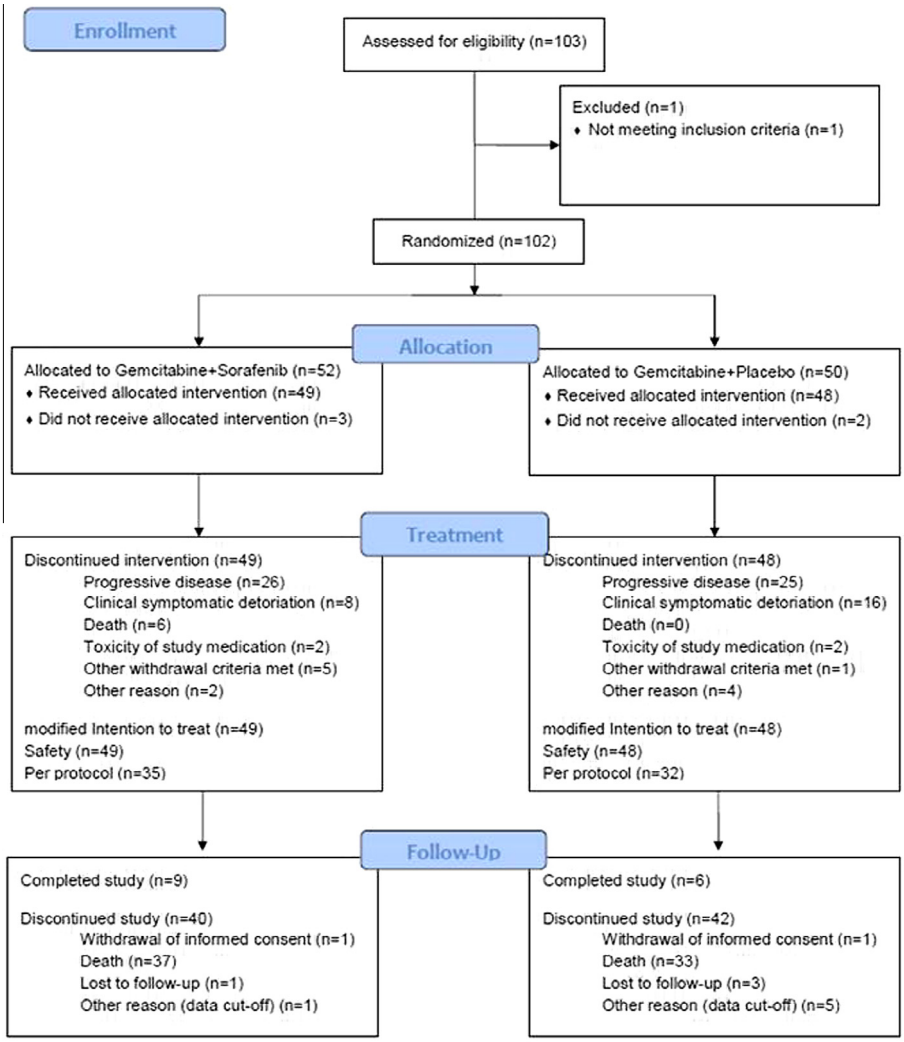

Fig. 1. CONSORT chart.

had undergone prior surgery. The proportion of patients dying from progression without further treatment was 51% for sorafenib and 54% for placebo. At the end of the observation period, 84% patients treated with sorafenib and 75% with placebo had died or progressed.

An average of 4.2 cycles of sorafenib and 5.0 cycles of placebo treatment were completed. Median treatment duration was 2.3 months (range 0–19.1) for sorafenib and 4.2 months (range 0.3–21.4) for placebo. There were fewer dose adjustments and treatment interruptions in the placebo group.

3.2. Efficacy

In the mITT population, patients receiving sorafenib plus gemcitabine had a shorter median PFS than those receiving gemcitabine alone (3.0 versus 4.9 months). The corresponding log rank test was not statistically significant ($P = 0.859$). A Cox regression model with treatment as a covariate yielded a hazard ratio (HR) of 1.28 (95% confidence interval (CI): 0.811–2.023) indicating a 28% increase in the risk of progression or death for sorafenib (Table 2). A post-hoc analysis without censoring of subsequent anticancer therapy showed similar results (2.7 and 4.2 months, respectively, HR: 1.15; 95% CI: 0.741–1.770). The PP population confirmed the mITT analysis, with median PFS for sorafenib versus placebo of 3.2 versus 4.9 months (HR: 1.18, 95% CI: 0.678–2.053). One-year PFS for sorafenib versus placebo was 16% versus 18% (mITT population) and 25% versus 18% (PP population). The median OS times in the mITT and PP populations were 8.4 and 10.8 months for sorafenib versus 11.2 and 10.6 months for placebo (mITT $P = 0.775$, HR: 1.20; 95% CI: 0.747–1.927; PP $P = 0.561$, HR: 0.96, 95% CI: 0.538–1.699). Age proved an independent negative prognostic factor for OS ($P = 0.014$, HR: 1.044, 95%CI: 1.009–1.080) in a post-hoc analysis.

Table 1
Demographic and baseline characteristics (modified intention-to-treat (mITT) population).

Parameter	Gemcitabine + sorafenib($N = 49$)	Gemcitabine + placebo($N = 48$)
Age, y, median (range)	64.0 (44–83)	64.5 (36–84)
Female, *N* (%)	20 (41)	23 (48)
Age, y, median (range)	64.0 (44–83)	64.5 (36–84)
Race, *N* (%)		
European	49 (100)	48 (100)
Type of carcinoma, *N* (%)		
Adenocarcinoma of gall bladder	6 (12)	7 (15)
Adenocarcinoma of intrahepatic bile ducts	33 (67)	29 (60)
Hepatic metastases[a]	10 (20)	12 (25)
Grade, *N* (%)		
1 (well differentiated)	2 (4)	0
2 (moderately differentiated)	23 (50)	30 (70)
3 (poorly differentiated)	20 (43)	13 (30)
4 (undifferentiated)	1 (2)	0
ECOG performance status, *N* (%)		
0	30 (64)	35 (80)
1	17 (36)	8 (18)
2	0	1 (2)
Target lesions		
Unresected primary tumour, *N*	10	9
Size, mm, mean (SD)	82.3 (28.93)	95.7 (18.97)
Liver[b], *N*	38	32
Liver hilus and/or lymph nodes[b], *N*	21	13
Lung and/or soft tissue[b], *N*	3	6
Patients with more than 1 lesion	31	31
Previous treatment		
Surgery		
Yes	25 (51)	26 (54)
No	24 (49)	22 (46)
Radiotherapy		
Yes	47 (96)	46 (96)
No	2 (4)	2 (4)
Chemotherapy		
Yes	1 (100)	1 (100)
Missing	48	47

Abbreviations: ECOG PS; Eastern Cooperative Oncology Group performance status; SD, standard deviation.
[a] Referring to study design: 'hepatic metastases of a primary resected and histological proofed biliary tract cancer'.
[b] Target lesions of a BTC tumour.

Table 2
Progression-free survival (mITT population).

	Gemcitabine + sorafenib ($N = 49$)	Gemcitabine + placebo ($N = 48$)
Patients with death/progression, *n* (%)	41 (84)	36 (75)
Patients censored, *N* (%)	8 (16)	12 (25)
PFS, months, median (95% confidence interval (CI))	3 (1.8–7.2)	4.9 (3.5–7.7)
PFS at 1 year,%	16.4	17.6
HR (95% CI) for sorafenib versus placebo[a]	1.281 (0.811–2.023)	
P-value (log-rank test)	0.8593	

[a] Estimated by Cox proportional hazards model; PFS, progression-free survival; HR, hazard ratio; mITT, modified intention-to-treat.

Best overall response was assessable in 28 and 30 patients for sorafenib and placebo, respectively. Confirmation of response turned out as challenging. Due to the short treatment period of most patients, best response data were missing and could not be confirmed in these data settings. With no complete responses, partial response was achieved in four (14%) patients receiving sorafenib and three (10%) receiving placebo. In all evaluable patients, 86% of sorafenib and 90% of placebo group reached at least stable disease. Kaplan–Meier estimates of stable disease duration were 9.2 months (sorafenib) and 7.7 months (placebo).

As BTC is a tumour with heterogeneous locations, subgroup analyses showed on the one hand a better PFS for patients with intrahepatic bile duct cancers in the placebo group ($P = 0{,}027$, Fig. 2 A) and on the other

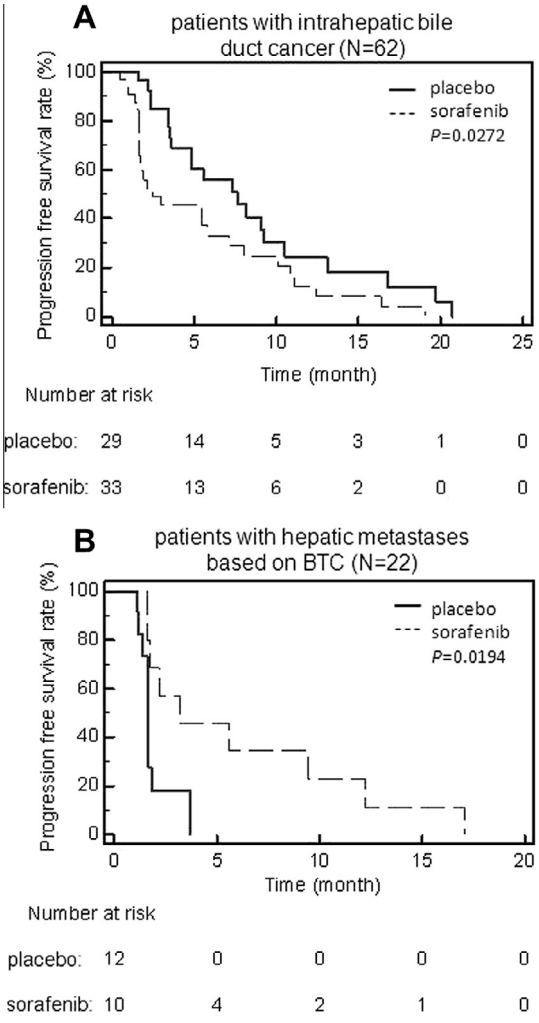

Fig. 2. Kaplan–Meier-curves for progression-free survival in relation to the BTC localisation, with patients (A) with adenocarcinomata of intrahepatic bile ducts and (B) with primarily hepatic metastases based on BTC. BTC, biliary tract cancer; PFS, progression-free survival.

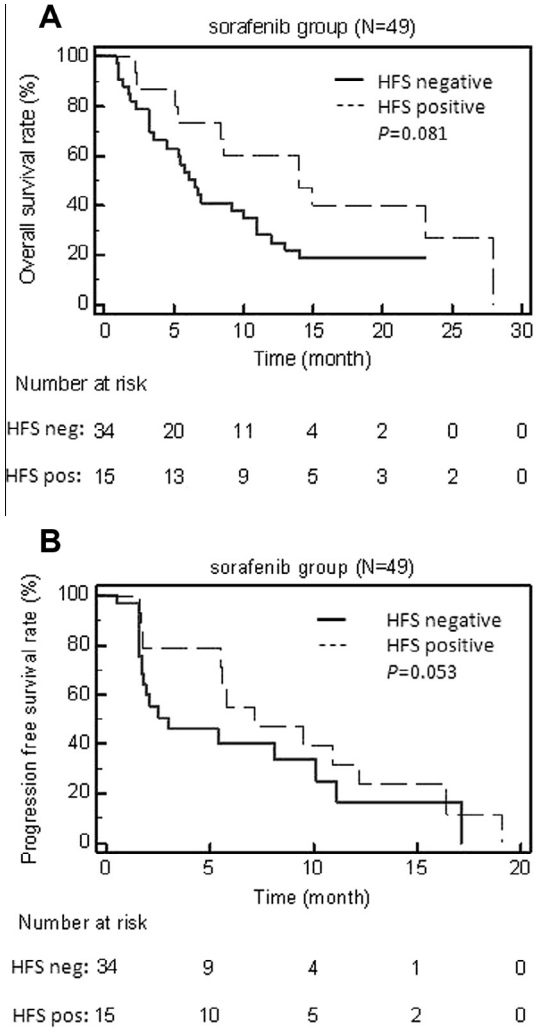

Fig. 3. Kaplan–Meier-curves for (A) OS and (B) progression-free survival in relations to hand-foot syndrome in the sorafenib group. OS, overall survival; PFS, progression-free survival.

hand a significant benefit from sorafenib in patients with hepatic metastases of BTC ($P = 0{,}019$, Fig. 2 B). For OS no differences could be detected.

Patients with hand-foot syndrome (HFS) were longer under treatment as patients without HFS ($P = 0.014$). In total, 17 (17%) patients developed hand-foot syndrome (HFS) of which 15 (88%) were in the sorafenib group ($P = 0.001$). The median PFS was 7.2 months (95% CI: 2.2–12.1) for HFS-positive versus 3.5 months (95% CI: 2.4–4.5) for HFS-negative patients ($P = 0.096$), and median OS was 14.4 months (95% CI: 5.6–23.1) versus 10.2 months (95% CI: 6.6–13.8) ($P = 0.288$), respectively. In the sorafenib group, 31% of patients developed HFS with a median PFS of 7.2 months (95% CI: 4.3–10.1) versus 1.9 months (95% CI: 1–2.8) for HFS-negative patients ($P = 0.053$) (Fig. 3).

3.3. Safety and quality of life

All patients reported at least one AE during the study. AEs possibly related to study treatment are shown in Table 3. Serious AEs (SAE) occurred in 33 (67%) patients with sorafenib and 35 (73%) patients with placebo. Seven SAEs in each group were judged to be possibly related to study treatment. The most frequent SAEs were cholangitis, fever and general health deterioration. Fatigue, occurred in >50% of patients in both groups, followed by thrombocytopenia. Major AE differences between groups were nausea (sorafenib 29%, placebo 56%), HFS (31% versus. 4%), weight loss (24% versus. 10%), epistaxis (20% versus. 0%) and oral disorder (20% versus. 2%). Eleven patients with s (22%) and four patients with placebo (8%) died due to

Table 3
Adverse events possibly related to study treatments and occurring in ⩾10% of patients in either treatment group (safety population).

Preferred term, patients	Gemcitabine/placebo (% of $N = 48$)		Gemcitabine/sorafenib (% of $N = 49$)	
Grade (%)[a]	1–2	3–4	1–2	3–4
Fatigue	35.4	2.1	22.5	4.1
Thrombocytopenia	37.5	8.3	28.6	12.2
Hand-foot syndrome	4.2	0	16.3	14.3
Diarrhoea	8.3	0	30.6	2.0
Leukopenia	27.1	4.2	20.4	8.2
Rash	14.6	0	28.6	0
Oral disorder	0	0	20.4	0
Nausea	37.5	8.3	18.4	4.1
Alopecia	20.8	0	22.5	2.0
Anaemia	8.3	2.1	6.1	4.1
Stomatitis	0	0	12.2	0
Vomiting	12.5	2.1	12.2	4.1
Pruritus	2.1	0	10.2	2.0
Epistaxis	0	0	10.2	0
Fever	10.4	2.1	10.2	4.1
Neutropenia	8.3	8.3	4.1	4.1
Obstipation	10.4	0.0	4.1	0.0

[a] Grade 5 was only reached by one patient.

Table 4
Association between tumour biomarker expression and patient characteristics.

	Biomarker population	Staining		T				N			
	N		%	1/2 %	3/4 %	Missing %	*p*	0 %	1/2 %	Missing %	*p*
VEFD-C	51	Positive	8	25	50	25		25	50	25	
		Negative	92	11	72	17	*0.378*	38	49	13	*>0.99*
VEFD-D	53	Positive	57	13	67	20		43	40	17	
		Negative	43	9	70	22	*0.685*	26	61	13	*0.224*
VEGFR-2	59	Positive	2		No analyses						
		Negative	98								
VEGFR-3	53	Positive	53	4	68	29		21	64	14	
		Negative	47	20	68	12	*0.187*	52	36	12	***0.035***
CXCR4	58	Positive	40	4	78	17		39	43	17	
		Negative	60	14	63	23	*0.377*	29	60	11	*0.372*
c-kit	56	Positive	0		No analyses						
		Negative	100								
PDGFRβ	52	Positive	27	0	93	7		36	64	0	
		Negative	73	16	61	24	*0.153*	37	45	18	*0.746*
Hif1α	53	Positive	9	60	40	0		80	20	0	
		Negative	91	8	71	21	***0.024***	31	54	15	*0.144*
PTEN	51	Positive	63	9	69	22		44	47	9	
		Negative	37	16	68	16	*0.662*	26	58	16	*0.351*

SAEs. None of these cases were directly related to sorafenib. One SAE (cause of death: toxic lung disorder), possibly related to gemcitabine, was reported for placebo. Supplementary Table 2 shows QLQ-C30 scores at baseline and day 29 and their changes in the groups. Comparison between both groups on day 29 disclosed that many items were in favour of placebo. However, for cognitive function, dyspnoea and constipation, scores between groups were quite similar; and nausea/vomiting scores were even more favourable for sorafenib.

3.4. Biomarker analysis

Fifty-nine patient tumour samples were available for analysis of the sorafenib target structures VEGFR-2 and -3, PDGFRβ and c-kit (Table 4). To depict the angiogenic microenvironment, the ligands VEGF-C and -D, Hif1α, CXCR4 and PTEN were analysed by IHC (Table 4, Supplementary Fig. 1). For c-kit, VEGFR-2, CXCR-4 and PTEN, no correlation was found with any clinical or pathological parameters. The target c-kit could not be detected in any BTC tumour tissue.

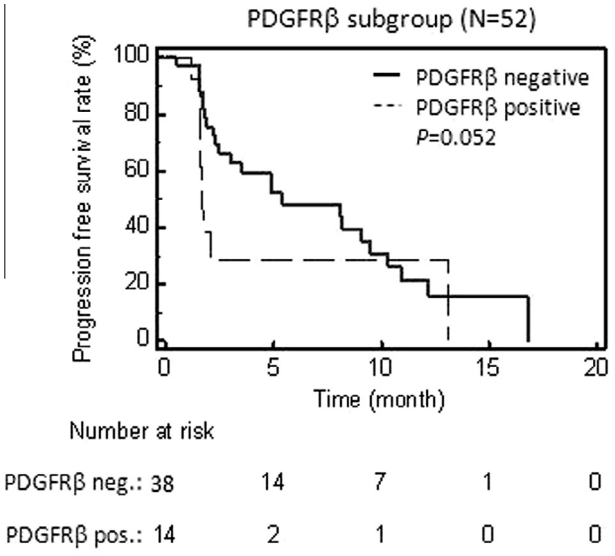

Fig. 4. Progression-free survival for PDGFRβ subgroup ($N = 52$) PFS, progression-free survival.

VEGFR-2 expression was found in 32% of vessels in close proximity to the tumour; however, only one tumour was clearly positive for VEGFR-2. Hif1α was expressed in 9% of all tumours. Higher T-stages (T3/4) were associated with negative Hif1α ($P = 0.024$). VEGFR-3 was highly expressed in 53% (28/53) and particularly in LN-positive patients ($P = 0.035$), and was co-expressed together with VEGF-D in 57% of patients ($P = 0.011$). PDGFR-β was detected in the tumour stroma in 27% of patients. Independent of treatment, PDGFR-β negative patients showed improved PFS ($P = 0.052$, Fig. 4).

Serum analyses for biomarkers were performed in 49 patients during follow-up of at least two cycles (Fig. 5A–D). Patients with a PFS of >90 days displayed a higher sVEGFR-2 increase than those who progressed before <90 days. ΔsVEGFR-2 increase was higher in the HFS-subgroup ($P < 0.008$) with late progression. Furthermore, in patients who received sorafenib and developed HFS, the ΔsVEGFR-2 increase was higher in late progressive patients ($P < 0.009$). During the first 8 weeks, patients presented no changes in SDF1α, VEGF-A and -D levels.

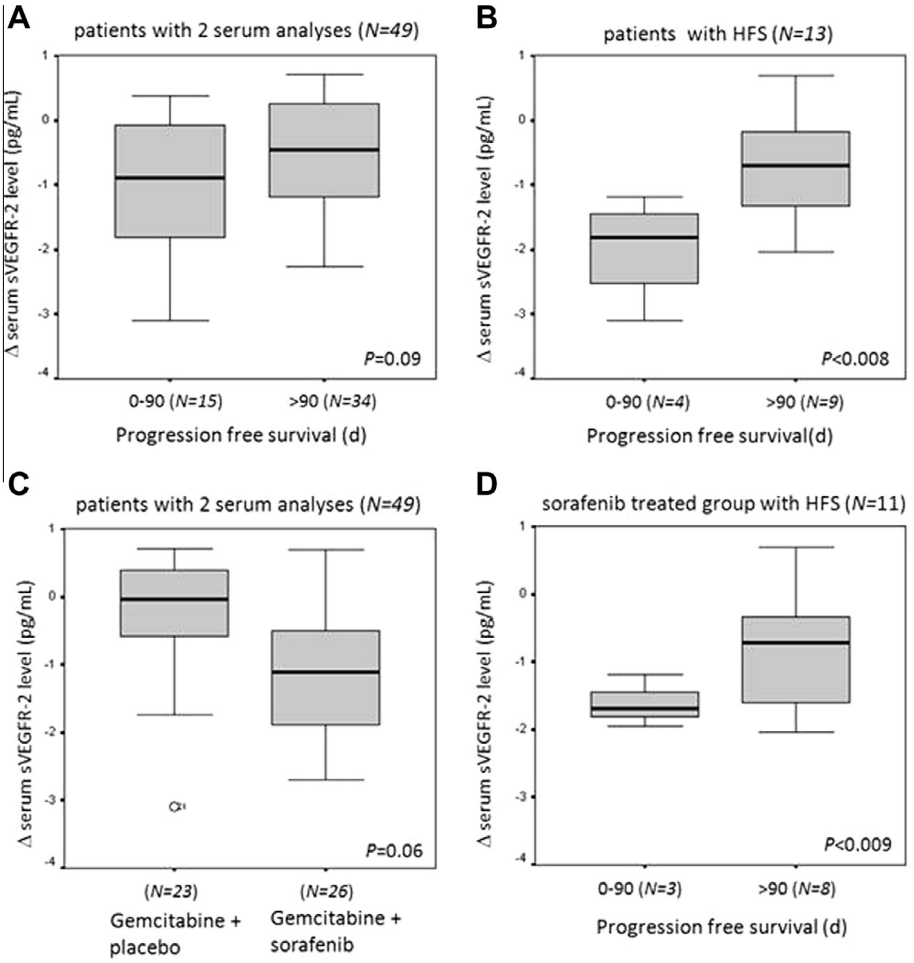

Fig. 5. Serum analysis of patients during the first 8 weeks (A) ΔsVEGFR-2 levels of all patients ($N = 49$) compared to their PFS (0–90 days and >90 days), (B) PFS (0–90 days and >90 days) of patients with hand-foot syndrome ($N = 13$), (C) ΔsVEGFR-2 levels of all patients ($N = 49$) in relation to their treatment arm and (D) PFS of the sorafenib treated group with hand-foot syndrome ($N = 11$).

4. Discussion

Even if this trial did not meet its primary efficacy end-point and PFS in mITT and PP population were not significantly different in patients receiving gemcitabine plus or minus sorafenib, our study revealed important results to be further discussed. Analysis of PFS in the PP population supported the primary analysis. Treatment duration was not only shorter for sorafenib, but also fewer dose adjustments and treatment interruptions occurred in the placebo group. However, overall mean gemcitabine doses were similar, suggesting that more patients had early discontinuation of sorafenib, even without evidence of higher grade toxicities. Consistent with this, a recent survey of HCC patients showed that those receiving half-dose sorafenib (200 mg twice daily) received longer treatment than those receiving full-dose sorafenib [22]. Furthermore, a post-hoc analysis showed that the half-dose sorafenib patients achieved longer survival times.

For any secondary efficacy end-point, again no benefit favouring sorafenib plus gemcitabine over gemcitabine alone was observed. Best response was mostly stable disease, with more than 85% of evaluable patients in both groups. Thus, tumour control rates for both groups were in the range of those reported for cisplatin-gemcitabine in the ABC-02 trial, with a tumour control rate of 81.4%, but higher than the gemcitabine alone arm (71.8%) [4].

Safety results did not raise any concerns, with no major differences in AEs or serious AEs, possibly related to treatment. Overall, most AEs were consistent with those previously identified as being associated with gemcitabine or sorafenib administration [20]. Our QoL data did not generally favour any treatment group. As HFS is one of the most common AEs associated with sorafenib, over 88% of all patients suffering HFS were in the sorafenib group. We did an exploratory and hypothesis-generating analysis on its correlation with survival data. HFS occurred more frequently when patients were treated longer with sorafenib, HFS-positive patients had a PFS advantage of ~3 months and an OS benefit of ~4 months. This positive trend was also found in the sorafenib group with a benefit for PFS and OS of ~5 and ~7 months. These results are similar to those observed for PFS in metastatic renal cancer patients [23] and compared well with other studies analysing the presence of HFS as being predictive for better OS and prolonged PFS in sorafenib-treated patients with advanced HCC [17–19].

Clinical responses to targeted therapies such as sorafenib have been shown to depend on the expression levels of their target proteins in the tumour tissue [24]. The absence of sorafenib target proteins like c-kit and VEGFR-2 in this study population as well as minor expression levels of some biomarkers (27% PDGFRβ) in BTC may explain at least in part the low efficacy of this combination treatment. Additionally, serum analyses during the first 8 treatment weeks indicated higher ΔsVEGFR-2 levels in patients with longer PFS. Since this soluble marker demonstrated some positive predictive value, not only for sorafenib and HFS, but also gemcitabine, sVEGFR-2 should be addressed in larger studies as a potentially predictive marker for small molecules [25–27].

In the recent years, treatment options expanded for BTC. Today, gemcitabine combined with platinum-based agents are somewhat standard regimens [28]. Combinations with targeted therapies are still under investigation. So far, addition of cetuximab did not enhance activity of Gemcitabine/Oxaliplatin but was well tolerated [28]. The BINGO phase 2 trial confirmed its good agreeability and led to encouraging antitumour activity and secondary resections in a third of patients [29]. Despite preclinical and clinical results reporting the activity of sorafenib alone or in combinations in HCC [14,17,22], in advanced BTC patients recent first-line and second-line phase II studies of sorafenib alone failed to display objective responses and were associated with low activity, respectively [30,31]. Studies involving small molecules offered mixed results. Sunitinib has shown marginal second-line activity [32] and a phase II trial of gemcitabine, oxaliplatin and bevacizumab reported some antitumour activity and tolerable safety in advanced BTC patients [33]. Recently, in a randomised phase III study, the addition of erlotinib to gemcitabine and oxaliplatin failed to show PFS benefit compared with chemotherapy alone [34]. Only the subgroup of cholangiocarcinoma patients had a significantly prolonged PFS with erlotinib. It has been suggested that a subset of BTC patients might benefit from dual target tyrosine kinase inhibitors, based on *KRAS* mutation status, EGFR and HER2 signalling [8,35]. In fact, localisation of metastases to the liver seemed to be beneficial in our trial, as these patients benefited from sorafenib compared to patients with adenocarcinoma of intrahepatic ducts.

In conclusion, this randomised, placebo-controlled study did not provide evidence that adding sorafenib to gemcitabine as first-line chemotherapy improves outcomes in unselected patients with advanced BTC. Further prospective double-blind biomarker-driven phase II trials are required to characterise targeted agents added to standard chemotherapy to further improve outcome in these patients with high medical need.

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Conflict of interest statement

M. Moehler, M. Dollinger, C. Schimanski and M. Woerns have honoraria to disclose (Entity: Bayer). P.R. Galle, F. Kolligs, J. Trojan, M. Woerns and S. Zeuzem have compensated consultant or advisory relationships to Bayer to disclose. Educational and research funding was provided by Bayer Vital GmbH, Leverkusen.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2014.09.013.

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