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ORIGINAL ARTICLE

Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial

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Background: There is a high unmet clinical need for treatments of advanced/metastatic biliary tract cancers after progression on first-line chemotherapy. Regorafenib has demonstrated efficacy in some gastrointestinal tumors that progress on standard therapies.

Patients and methods: REACHIN was a multicenter, double-blind, placebo-controlled, randomized phase II study designed to evaluate the safety and efficacy of regorafenib in patients with nonresectable/metastatic biliary tract cancer that progressed after gemcitabine/platinum chemotherapy. Patients were randomly assigned 1 : 1 to best supportive care plus either regorafenib 160 mg once daily 3 weeks on/1 week off or placebo until progression or unacceptable toxicity. No crossover was allowed. The primary objective was progression-free survival (PFS). Secondary objectives were response rate, overall survival, and translational analysis.

Results: Sixty-six patients with intrahepatic ($n = 42$), perihilar ($n = 6$), or extrahepatic ($n = 9$) cholangiocarcinoma, or gallbladder carcinoma ($n = 9$) were randomized, 33 to each treatment group (33 per group). At a median follow-up of 24 months, all patients had progressed and six patients were alive. Median treatment duration was 11.0 weeks [95% confidence interval (CI): 6.0—15.9] in the regorafenib group and 6.3 weeks (95% CI: 3.9—7.0) in the placebo group ($P = 0.002$). Fourteen of 33 patients (42%) in the regorafenib group had a dose reduction. Stable disease rates were 74% (95% CI: 59—90) in the regorafenib group and 34% with placebo (95% CI: 18—51; $P = 0.002$). Median PFS in the regorafenib group was 3.0 months (95% CI: 2.3—4.9) and 1.5 months (95% CI: 1.2—2.0) in the placebo group (hazard ratio 0.49; 95% CI: 0.29—0.81; $P = 0.004$) and median overall survival was 5.3 months (95% CI: 2.7—10.5) and 5.1 months (95% CI: 3.0—6.4), respectively ($P = 0.28$). There were no unexpected/new safety signals.

Conclusion: Regorafenib significantly improved PFS and tumor control in patients with previously treated metastatic/unresectable biliary tract cancer in the second- or third-line setting.

Clinical Trial Registration: The trial is registered in the European Clinical Trials Register database (EudraCT 2012-005626-30) and at ClinicalTrials.gov (NCT02162914).

Key words: advanced biliary tract cancers, progression after first-line chemotherapy, REACHIN, regorafenib

INTRODUCTION

Biliary cancers represent the second most common hepatobiliary tumors worldwide.[1] Surgical resection is the only option that can increase 5-year overall survival (OS). Evidence for the benefit of adjuvant treatment is weak, with the BILCAP randomized trial showing improved survival for chemotherapy only in the per-protocol analysis.[2,3] For patients with unresectable/metastatic disease, guidelines from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend front-line gemcitabine/cisplatin combination therapy based on level I evidence.[3–5] At the time the REACHIN trial was designed, there was no standard second-line treatment approved (although other trials were in progress using FOLFOX or FOLFIRINOX, for example).

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Regorafenib is a multikinase inhibitor approved for the treatment of metastatic colorectal cancer, locally advanced or metastatic gastrointestinal stromal tumors, and unresectable hepatocellular carcinoma.[6–8] It inhibits angiogenesis through vascular endothelial growth factor (VEGF) receptors 1—3 and TIE2, targets oncogenesis through inhibition of the downstream pathways of KIT, RET, RAF1, and BRAF, affects the tumor microenvironment by blocking the activity of the intracellular domain of the platelet-derived growth factor receptor and fibroblast growth factor receptor (FGFR), and also acts on tumor immunity (colony-stimulating factor 1 receptor).[9–11]

Biliary tract cancers have molecular alterations characterized by a disrupted mitogen-activated protein kinase (MAPK) pathway, RAS and BRAF activating mutations, and overexpression of VEGF, and are associated with macrophages and cancer-associated fibroblasts localized in a dense desmoplastic stroma.[12–14] In cholangiocarcinoma cell lines, tumor growth is inhibited by sorafenib, a tyrosine kinase inhibitor (TKI) that inhibits RAF kinase and its subsequent RAF/MEK/ERK pathway and VEGFR, in a time- and dose-dependent manner.[9,15] Unfortunately, these results were not confirmed in clinical trials in which sorafenib demonstrated low response rates and a trend towards improving progression-free survival (PFS) and OS without reaching the prespecified cut-off for efficacy.[16,17]

Based on the presence of actionable targets in biliary tract cancers, this randomized, placebo-controlled phase II study was designed to assess the activity of regorafenib in patients who progressed on first-line gemcitabine/platinum-based chemotherapy.[18]

PATIENTS AND METHODS

Design and participants

REACHIN was a randomized, double-blind, placebo-controlled, multicenter phase II trial conducted in 12 Belgian centers under the auspices of the Belgian Group of Digestive Oncology (BDGO) Cooperative Group. The trial is registered in the European Clinical Trials Register database (EudraCT 2012-005626-30) and at ClinicalTrials.gov (NCT02162914).

Patients with histologically proven locally advanced unresectable or metastatic intrahepatic (IH), perihilar (PH), or extrahepatic cholangiocarcinoma or gallbladder tumor who had progressed after gemcitabine/platinum-based chemotherapy (cisplatin or oxaliplatin, delivered in one or successive lines) were eligible. Additional inclusion criteria were age older than 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and measurable disease (RECIST 1.1). Written approval for the trial was provided by all local ethics committees and all patients signed an informed consent form before enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomization and masking

Eligible patients were randomly assigned (1 : 1) using a computer-generated randomization list (pre-allocated block design, no stratification factors). Pharmacists in each center were unblinded and managed the study drug supply. To maintain blinding, study medication was labeled with a unique preprinted label including vial and batch number.

Procedures

Sixty-six patients were randomly assigned to either regorafenib 160 mg once daily given orally as four 40 mg tablets during 3 weeks of each 4-week cycle, or matching placebo with the same schedule; all patients also received best supportive care (including biliary drainage, analgesics, antibiotics, steroids, and antiemetics). Patients were treated until disease progression, death, unacceptable toxicity, or consent withdrawal. No crossover was allowed. Dose modifications and re-escalation were prespecified in the protocol. Dose reductions leading to a daily dose below 80 mg were not permitted. Treatment was discontinued if the toxicity did not resolve after a 4-week interruption.

Before starting the study drug, all patients underwent hepatic magnetic resonance imaging (MRI) including diffusion parameters and [^{18}F]2-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT), which were repeated after 14 days. The first assessment was done locally by investigators blinded to assigned treatment, except if a progression was seen. Central evaluation was carried out at the end of the trial.

Tumor radiological assessment (RECIST 1.1) was done locally using a thoracoabdominal scan at baseline, then after 6, 12, and 18 weeks of treatment, and then every 8 weeks until progression. In case of treatment discontinuation before the first radiologic planned assessment, patients were considered as nonassessable.

Tumor samples were collected for central molecular profiling (*FGFR*2 fusion testing carried out on the Ion Torrent™, Thermo Fisher Scientific, Waltham, MA platform using the Oncomine™ Focus assay, Thermo Fisher Scientific). Laboratory abnormalities and adverse events were recorded as the worst grade experienced by the patient according to the Common Terminology Criteria for Adverse Events version 4.0.

Outcomes

The primary objective was to demonstrate an improvement in median PFS from 1.5 months in the placebo arm to 3 months in the regorafenib arm.

Secondary objectives included OS, objective response rate, disease control rate (DCR), safety, and to explore correlations between radiological response and metabolic response, between metabolic response and PFS, between radiologic response rate and dynamic tumor response, and between dynamic tumor response rate and metabolic response rate. Exploratory translational analysis of the primary tumor included *FGFR2* fusion assessment and potential efficacy correlation.

Statistical analysis

The sample size calculation was based on the log-rank test to assess PFS with regorafenib versus placebo. Assuming a

one-sided significance level of 0.1 and power of 80% with a 1 : 1 randomization, the study required 38 PFS events to demonstrate an improvement in median PFS of 100% (from 1.5 months median PFS in the placebo arm to 3 months for patients treated with regorafenib). Considering potential accrual and length of follow-up, we anticipated reaching this number of events with the randomization of 66 eligible patients.

PFS was defined as the time from randomization to progression or death in the absence of documented progression. OS was the time from randomization to death from any cause or the date of last follow-up. Distribution of time-to-event end points was estimated using the Kaplan–Meier method and compared between treatment groups using an unstratified log-rank test. PFS and OS rates at 12 months were reported with 95% confidence intervals (CIs) and calculated according to an approximate normal distribution. Hazard ratios with 95% CIs were estimated using a Cox model and the Wald method. Fisher's exact test was used to compare the proportion of patients achieving disease control or response between the two treatment groups; CIs for proportions were obtained using the asymptotic normal distribution. All analyses were done using SAS v9.4.

All patients were analyzed using the intent-to-treat principle. This means that all patients were analyzed for PFS and for OS. For disease control or response, we considered as nonassessable those patients who stopped treatment before the first radiologic planned assessment (excluding baseline assessment), but these patients were included in the primary comparisons and were considered as nonresponders.

RESULTS

Sixty-six patients were enrolled between 14 May 2014 and 27 February 2018, 33 patients in each treatment group (Figure 1). At the analysis cut-off date of 10 April 2019, the median follow-up was 24 months and all patients had progressed. Six patients (three in each arm) were alive.

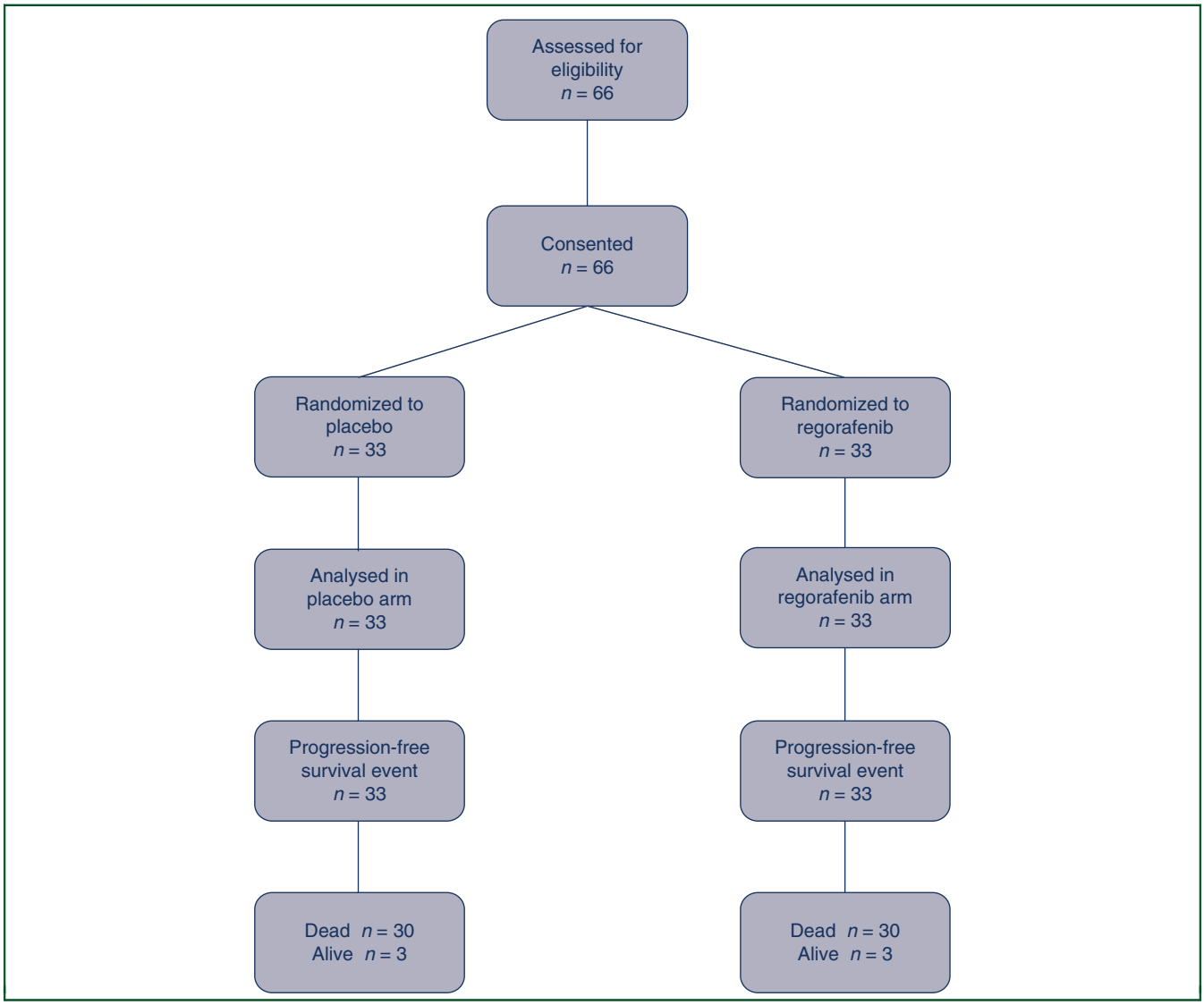

Figure 1. CONSORT diagram as of April 10, 2019.

Baseline characteristics

Baseline characteristics were well balanced between the groups and without any significant differences (Table 1). There was a predominance of male patients having a median age of 60 years. Tumor distributions were similar in both groups except for IH tumors, which were more prevalent in the regorafenib arm. Two patients in each arm had a locally-advanced unresectable tumor. Gemcitabine—cisplatin was the predominant first-line treatment. Half the patients received more than one line of treatment before inclusion and received gemcitabine monotherapy and platinum-based chemotherapy in subsequent treatment lines.

Forty-three patients had available tumor samples for biomarker analysis. There was insufficient tumor sample to test 11 patients (including eight IH tumors) in the regorafenib arm and in 12 patients (including eight IH tumors) in the placebo arm. Only one *FGFR2* fusion was found in the regorafenib arm; this patient was a 36-year-old male with an IH tumor with synchronous pulmonary and bone metastases who was previously treated with gemcitabine—cisplatin and oxaliplatin for 1 year before entering the study. No other mutation, fusion, or alteration possibly targeted by regorafenib was found in our study population, according to the Ion torrent panel (supplementary Figure S1, available at *Annals of Oncology* online).

Table 1. Baseline characteristics of the patients

	Regorafenib (n = 33)	Placebo (n = 33)
Sex		
Female, *n* (%)	12 (36)	14 (42)
Male, *n* (%)	21 (63)	19 (59)
Age (years)		
Median	59	64
Range	35—83	38—78
Primary tumor location, *n* (%)		
Intrahepatic	23 (70)	19 (58)
Extrahepatic	3 (9)	6 (18)
Gallbladder	4 (12)	5 (15)
Perihilar	3 (9)	3 (9)
ECOG performance status, *n* (%)		
0	21 (64)	15 (45)
1	12 (36)	18 (55)
Median CEA (µg/l)	2.5	2.9
Median CA19.9 (kU/l)	85.7	180
Metastatic sites		
Locally advanced tumor	2	2
Liver metastasis	24	29
Lung metastasis	11	12
Carcinomatosis	13	6
Time between diagnosis and randomization (months)		
Median	14	12
Range	3—41	3—103
Treatments before inclusion		
One line	18 (55%)	16 (48%)
GEM-CDDP	15	14
GEM-OX	2	2
GEM-carboplatin	1	0
More than one line	15 (45%)	17 (52%)
FGFR2 fusions		
Number detected	1	0
Tumor location	Intrahepatic	NA

Data are shown as number of patients (%).
CA19.9, Carbohydrate Antigen 19.9; CEA, Carcinoembryonic Antigen; ECOG, Eastern Cooperative Oncology Group; GEM-carboplatin, gemcitabine-carboplatin; GEM-CDDP, gemcitabine-cisplatin; GEM-OX, gemcitabine-oxaliplatin.

Treatment characteristics

The median treatment duration was 11.0 weeks (95% CI: 6.0—15.9) in the regorafenib group and 6.3 weeks (95% CI: 3.9—7.0) in the placebo group ($P = 0.002$). Disease progression was the major reason for stopping treatment in both arms (Table 2). In the regorafenib arm, radiological disease progression was observed in 24/33 patients (73%) and clinical progression in 1/33 patients (3%). In the placebo arm, radiological progression was observed in 30/33 patients (91%). In the regorafenib arm, 2/33 patients (6%) stopped treatment due to an adverse event (one for grade 3 fatigue and one for grade 3 general status deterioration), 3/33 patients (9%) died (while still in treatment) from causes not related to cancer (mainly infections, no angiocholitis), and 3/33 (9%) patients chose to stop treatment. Three patients discontinued placebo, 2/33 (6%) for an adverse event and another (3%) for death unrelated to cancer (infection but no angiocholitis).

Fourteen of 33 patients treated with regorafenib had dose reductions (two patients started at a reduced dose of 120 mg due to investigator decision and protocol violation; six patients had one dose reduction to 120 mg, six patients had two consecutive dose reductions to 80 mg). In the placebo group, 5/33 patients had dose reductions (four patients started at 120 mg due to investigator decision and protocol violation, and one patient had one dose reduction to 120 mg). Treatment was interrupted in 10 patients in the regorafenib group and in five patients in the placebo group.

Efficacy

The DCR was significantly higher in the regorafenib arm. In the intent-to-treat population, 23/33 patients (70%; 95% CI: 54—85) achieved stable disease in the regorafenib arm versus 11/33 patients (33%; 95% CI: 17—49) in the placebo arm ($P = 0.002$). In the population of assessable patients (two patients were not assessable in the regorafenib arm and one was not assessable in the placebo arm because treatment was stopped before first radiologic evaluation or clinical progression), rates of stable disease were 74% (95% CI: 59—90) in the regorafenib arm and 34% (95% CI: 18—51) in the placebo arm ($P = 0.002$). There were no partial or complete responses.

Primary objective

All patients had a PFS event. Median PFS (Figure 2) was 3.0 months (95% CI: 2.3—4.9) in the regorafenib arm and 1.5 months in the placebo arm (95% CI: 1.2—2.0), with an estimated hazard ratio of 0.49 (95% CI: 0.29—0.81; $P = 0.004$). Estimated PFS at 6 months was 21% (95% CI: 7—35%) in the regorafenib arm and 3% (95% CI: 0—12) in the placebo arm. After adjusting for tumor location, the hazard ratio became 0.42 (95% CI: 0.26—0.76, $P = 0.003$). We evaluated median PFS by tumor location, even though the

Table 2. Reasons for treatment discontinuation

Reasons for treatment discontinuation	Regorafenib $n = 33$	Placebo $n = 33$
Disease progression	25	30
Radiologic progression	24	30
Clinical progression	1	0
Death	3	1
Adverse event	2	2
Patient choice	3	0

trial was not designed for subgroup analysis (Figure 3). In the placebo arm, the median PFS was similar according to tumor location. Despite the exploratory nature of the analysis and the small number of patients per tumor location, regorafenib appears superior to placebo in IH, gallbladder, and PH. Data in extrahepatic tumors were inconclusive. Of note, the patient with an *FGFR2* fusion, and treated with regorafenib, had a PFS of 10.6 months.

Survival

At the time of this analysis, the median follow-up was 24 months and six patients were still alive (three in each arm). Median OS in the regorafenib group was 5.3 months (95% CI: 2.7—10.5) and 5.1 months with placebo (95% CI: 3.0—6.4; $P = 0.28$) (Figure 4). Hazards did not appear proportional over time and, therefore, a unique measure of treatment effect did not appear appropriate. The hazard ratio was estimated to be 0.77 (95% CI: 0.45—1.31) and should be interpreted with caution.

Estimated survival at 12 months was 30% (95% CI: 14—46) in the regorafenib group and 15% (95% CI: 3—27) in the placebo group.

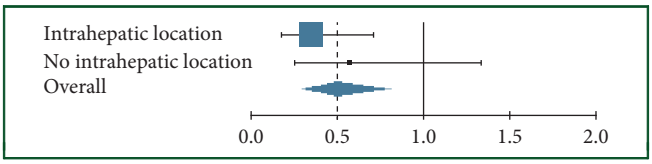

Figure 3. Progression-free survival by tumor location.
Forrest plot analysis.

The patient with an *FGFR2* fusion, treated with regorafenib, had an OS of 26.1 months (after disease progression in this trial, he was included in a clinical trial and treated with pemigatinib).

Safety

Treatment-related adverse events are reported in Table 3. There were no treatment-related grade 5 events. Thirty-six percent of patients (12/33) in the regorafenib group experienced at least one treatment-related grade ≥3 adverse event versus 24% (8/33) in the placebo group (not significant). Seventy-nine percent of patients (26/33) in the regorafenib group had at least one treatment-related adverse event of any grade versus 55% (18/33) in the placebo group (not significant). The absence of a statistically significant difference in grade ≥3 adverse event incidence between the two arms is important in the setting of this blinded study.

There were no new or unexpected safety signals and the toxicity of regorafenib was consistent with the known safety profile. The most common treatment-related grade 3 or 4 toxicities in the regorafenib arm were fatigue (18%), nausea and vomiting (9%), skin toxicity (9%), and hypophosphatemia (3%).

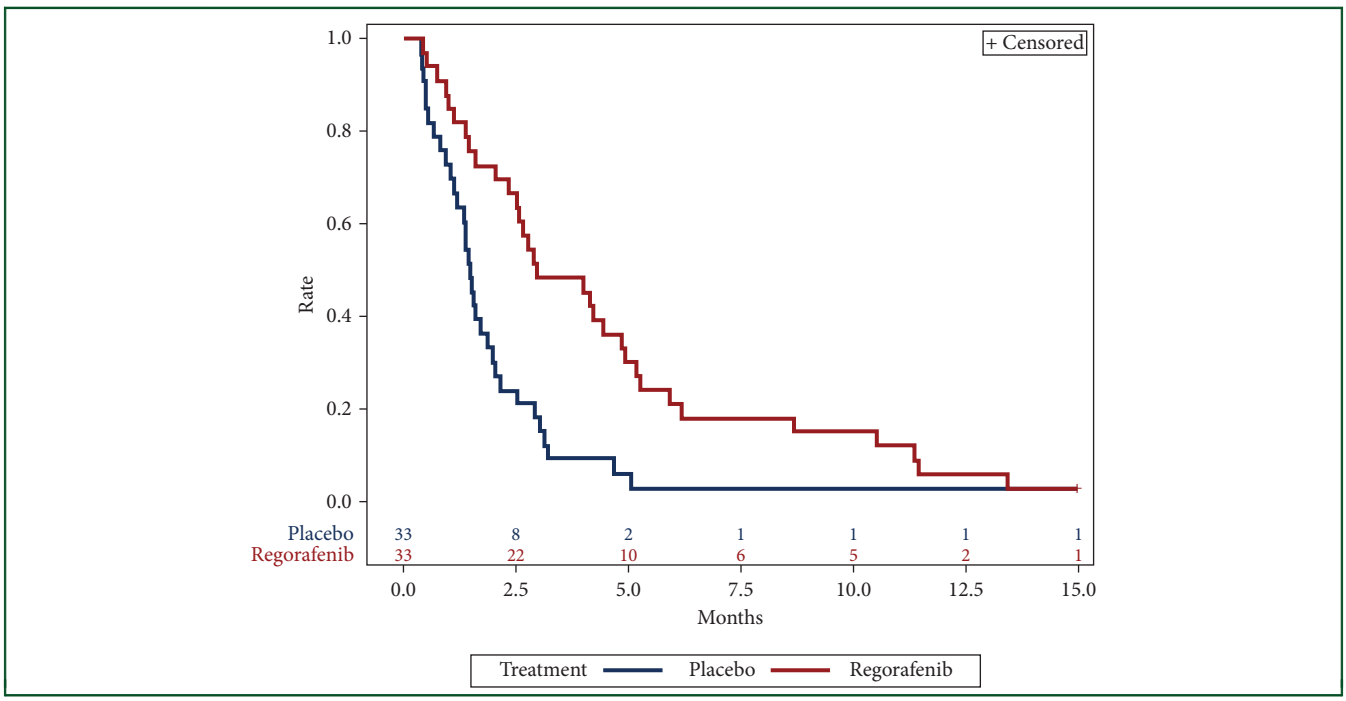

Figure 2. Progression-free survival.
Kaplan—Meier plot of median progression-free survival.

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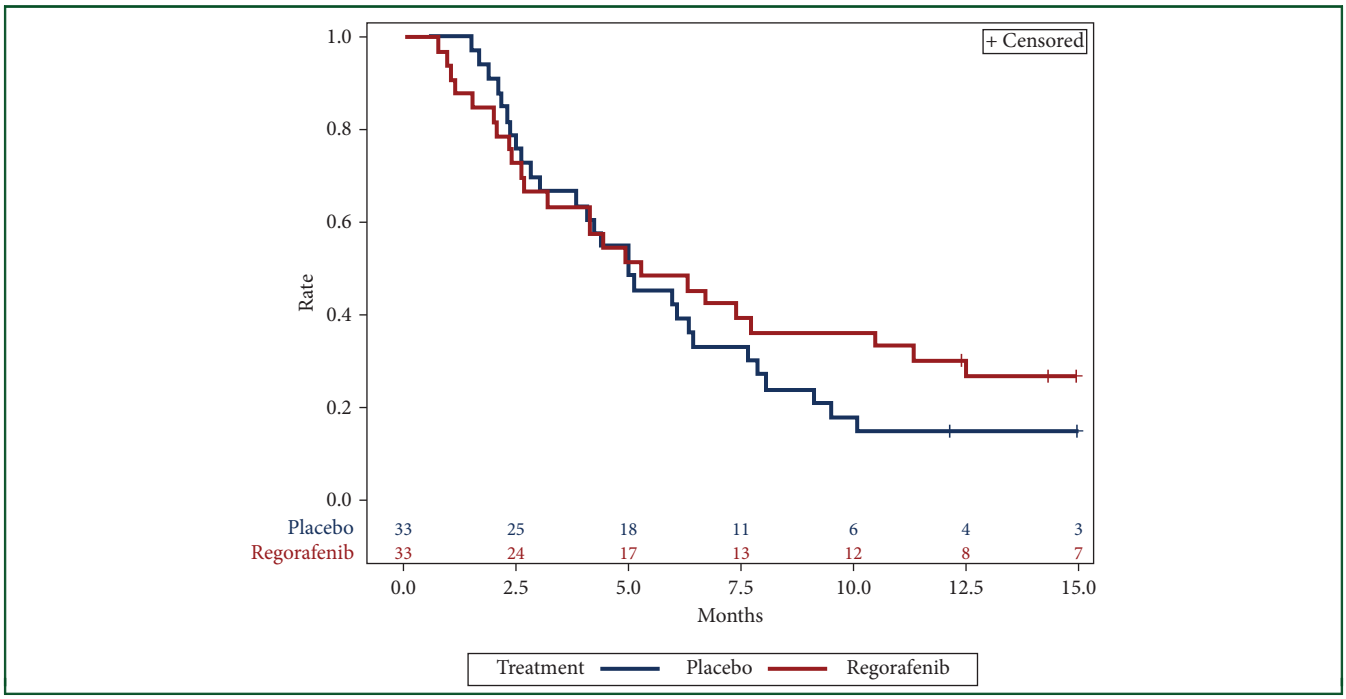

Figure 4. Overall survival.
Kaplan–Meier plot of median overall survival.

Subsequent treatments

Details of post-study treatments are reported in Table 4, and are unknown for two patients in the placebo arm. In the regorafenib group, 18/33 patients (55%) received at least one post-study treatment and three patients (9%) received two further lines. In the placebo arm, 10/31 patients (32%) received at least one additional treatment line and one patient (3%) received two lines ($P = 0.08$).

DISCUSSION

REACHIN is the first double-blind, placebo-controlled, phase II trial to demonstrate the efficacy of regorafenib in advanced biliary tract cancer. Regorafenib significantly improved median PFS (3.0 versus 1.5 months, $P = 0.004$) and disease control after failure of gemcitabine/platinum-based chemotherapy compared with placebo (whether in second or subsequent lines). Although the trial was not designed for subgroup analyses and the sample size did not allow for interaction tests, this clinical benefit was present across all tumor subgroups, and, despite having a higher proportion of IH tumors, it is not possible to conclude if this benefit is related to *FGFR2* fusions or IH location.

These results are consistent with two recently published single-arm phase II trials of regorafenib in biliary tract cancer. Sun et al.[19] reported a median PFS of 15.6 weeks in 43 patients receiving regorafenib monotherapy. In the phase II trial from Kim et al.,[20] median PFS was 2.8 months (39 patients). In both of these trials and the one reported here, the IH tumor location was predominant (70% in REACHIN, 62% Sun et al.,[19] 69% Kim et al.[20]). The dose of

Table 3. Safety: related adverse events (grade 1–2 and ≥ grade 3) in regorafenib arm and placebo arms

Related adverse events	Regorafenib ($n = 33$)		Placebo ($n = 33$)	
	Grade 1–2 *n*	Grade ≥3 *n*	Grade 1–2 *n*	Grade ≥3 *n*
Hematological				
Anemia	2	0	1	0
Thrombocytopenia	2	0	1	0
Neutropenia	0	0	0	0
Non-hematological				
Nausea/vomiting	5/1	2/1	4/6	2/0
Fatigue	11	6	11	3
Diarrhea	5	1	1	0
Constipation	4	0	0	0
Hypophosphatemia	3	1	0	0
Cutaneous rash	2	0	0	0
Hand foot skin reaction	12	3	5	0
Mucositis	6	1	2	0
Hypertension	1	0	2	0
Hypothyroidism	3	0	0	0
Anorexia	9	1	3	1
Dysphonia	7	0	1	0

Table 4. Subsequent anticancer treatments

Subsequent anticancer treatment	Regorafenib arm $n = 33$ *n* (%)	Placebo arm $n = 31$ *n* (%)
FOLFOX	4 (12)	4 (13)
FOLFIRI	8 (24)	1 (3)
FOLFIRINOX	1 (3)	0 (0)
Fluoropyrimidines	2 (6)	2 (6)
Gemcitabine + platinum salts	2 (6)	1 (3)
Paclitaxel	0 (0)	3 (9)
Paclitaxel–carboplatin	1 (3)	0 (0)
Nal-IRI	1 (3)	0 (0)
Clinical trials	2 (6)	0 (0)

Nal-IRI, Nanoliposomal irinotecan.

regorafenib was the same in both REACHIN and the Kim et al.[20] study (160 mg daily, 3 weeks on-1 week off), but the dose was decreased to 120 mg after the inclusion of the first three patients in the Sun et al.[19] trial due to early grade 3 toxicity. In REACHIN, we selected a daily dose of 160 mg before presentation of the regorafenib dose optimization study data in 2018, which showed the superiority of a weekly dose-escalation strategy from 80 to 160 mg daily in patients with metastatic colorectal cancer.[21] Although the dose was 160 mg, we did not observe a higher than expected rate of adverse events.

Other TKIs have already been tested in advanced biliary tract cancers. In the first line, cediranib added to gemcitabine/cisplatin did not significantly improve median PFS (8.0 versus 7.4 months, $P = 0.74$) in the randomized, placebo-controlled ABC-03 phase II trial.[22] Sorafenib has also been tested as first-line therapy. The SWOG 0514 trial[5,17] was stopped for futility after the first stage of accrual due to the absence of objective responses (primary end point) in 31 patients, a DCR of 39%, and a median PFS of 3 months (compared with 8 months median PFS for first-line gemcitabine/cisplatin in ABC-02[6]). In the single-arm study of Pan et al.,[23] 15 patients with IH cholangiocarcinoma who were treated with sorafenib in the first line had a DCR of 73% and median OS of 5.7 months (compared with 11.7 months for first-line gemcitabine/cisplatin in ABC-02[6]).

Sorafenib and cabozantinib have been evaluated in the second-line setting. In a single-arm study of sorafenib in 44 IH cholangiocarcinoma patients, median PFS was 3.2 months and the DCR at 12 weeks was 15.9%.[24] Patients treated with cabozantinib had a median PFS of 1.8 months in a single-arm phase II study of 19 patients.[25] These differences in activity/efficacy may be due to the inhibition of different targets by the various TKIs and related to the specific profile of regorafenib that includes inhibition of angiogenesis (VEGFR1-3, TIE2) and oncogenesis (downstream pathways of KIT, RET, RAF1, and BRAF), as well as effects on the tumor microenvironment (blocks the activity of the intracellular domain of platelet-derived growth factor receptor and FGFR) and tumor immunity (colony-stimulating factor 1 receptor).[9–12]

Due to the anti-*FGFR* activity of regorafenib, we tested tumor samples for *FGFR* fusions. *FGFR1* and *2* alterations/aberrations occur almost exclusively in IH cholangiocarcinoma and, in particular, *FGFR2* fusions occur in approximately 10% of patients with IH cholangiocarcinoma.[26–28] These patients have a better prognosis and a longer OS after surgery.[28] Pemigatinib and infigratinib have shown interesting objective response rates and PFS in cholangiocarcinoma patients with *FGFR2* translocations and fusions. In our study, only one patient with IH cholangiocarcinoma treated with regorafenib had this fusion. We were unable to test eight IH tumors in each arm due to a lack of residual material, and, therefore, we lacked the necessary data to draw a correlation between mPFS and *FGFR* fusions.

In our study, the DCR was 74% in patients treated with regorafenib. This is consistent with the DCRs reported by Sun et al.[19] (55%) and Kim et al.[20] (62.5%). Due to the activity profile and the antiangiogenic properties of regorafenib, RECIST 1.1 evaluation criteria may not be best adapted for response evaluation; that is the reason why early dynamic tumor evaluations (FDG PET/CT and dynamic MRI) were carried out as exploratory analyses. FDG PET/CT and dynamic MRI results are being analyzed and will be reported in a separate publication.

In this study, the toxicity profile of regorafenib was as expected and similar to that reported in previous phase III trials.[6–8] Dose reductions due to adverse events occurred in 36% of patients treated with regorafenib (3% in the placebo arm), and 30% of patients had dose interruptions. This is less than in the Kim et al.[20] trial, where 49% of patients had dose reductions. This toxicity had no impact on the administration of further treatments and one-half of the patients in the regorafenib arm received a further treatment as compared with one-third of the patients in the placebo arm.

Although regorafenib led to an increased median PFS and DCR, this did not lead to significantly increased OS after a median follow-up of 24 months, although OS was higher in our study than in historical controls. However, the estimated survival at 12 months was 30% in the regorafenib arm and double that of patients in the placebo arm. This lack of statistical survival benefit may be explained by the fact that the study was not designed to demonstrate OS as a main end point, but also by other factors. For example, one-half of the patients treated with regorafenib were able to receive subsequent treatments, mainly chemotherapy, compared with one-third of patients treated with placebo, but this difference was not statistically significant and probably did not translate into gains in OS. Moreover, three patients in the regorafenib arm died rapidly from infection (but no angiocholitis) and three of them decided to stop the treatment very early (not due to an adverse event), despite being stabilized under treatment. These six patients (18% of the patients in that arm) may have shortened the observed OS. This may explain the lack of a survival benefit, which was not a designed end point of our study.

In the ABC-06 phase III trial, 162 patients with biliary tract cancer who progressed after front-line gemcitabine/cisplatin were randomized to either placebo + active symptom control (including biliary drainage, antibiotics, analgesia, steroids, and antiemetics) or FOLFOX + active symptom control.[29] A significant increase in median OS from 5.3 to 6.3 months favored the FOLFOX arm. The placebo arms of ABC-06 and REACHIN were equivalent regarding the level of best supportive care. However, we must emphasize the fact that the populations of the ABC-06 trial and the REACHIN trial were different. Patients did not receive more than one treatment line before inclusion in ABC-06, as opposed to REACHIN in which patients were more likely to have been pretreated (half of the patients received more than one previous line of treatment). Moreover, in ABC-06, only 14% of the patients received a subsequent anticancer therapy (15% in the placebo arm and 12% in the FOLFOX arm) which is clearly less than in our

population (32% and 55%). A comparison between the results of the two studies is difficult, mainly due to major design differences (phase II versus phase III), and to differences in the number of pre- and post-therapies received. FOLFOX is now considered to be the new standard of care in second-line therapy but, due to the positive signal observed in three phase II trials, regorafenib deserves further interest and evaluation in later lines and could be proposed to patients with severe chemo-derived toxicities (e.g. neurotoxicity of previous platinum therapy or hematologic toxicities) or to those preferring oral therapy. Furthermore, regorafenib can be tested against FOLFOX, and is a potentially good candidate for testing in combination therapy (e.g. with checkpoint inhibitors[30]).

In conclusion, REACHIN is the first multicenter, randomized, placebo-controlled, phase II trial to show that regorafenib is active and significantly increases median PFS in patients with locally advanced/metastatic biliary tract tumors that progress after gemcitabine/platinum-based chemotherapy, whether in second or subsequent lines.

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DISCLOSURE

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