Published in final edited form as:

Lancet Oncol. 2014 July ; 15(8): 819–828. doi:10.1016/S1470-2045(14)70212-8.

Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial

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DM, LF, TA, MDu, J-PP, OR, and TFG contributed to study design. DM was involved with study organisation with the funder. DM, PC, TT, CdIF, EB, LF, SFa, J-FB, FV, EA, TS, TH, JG, PHam, MDo, TA, PHah, VH, MDu, OR, and TFG contributed to recruitment of patients or data collection. DM, PC, SFo, LF, VR, J-PP, DW, OR, and TFG contributed to data analysis or data interpretation. DM, SFo, VR, MDu, J-PP, and TFG contributed to report writing. The final version of the report has been approved by all authors and the study funder.

Declaration of interests

DM has consulted or advised for Roche, Amgen, Imclone, Bayer, Teva, Keocyt, Sanofi-Aventis, and Boehringer Ingelheim; has received honoraria from Merck Serono, Ipsen, Celgene, and Novartis; has received travel grants from Roche and Bayer; and has received research funding from Institut National du Cancer (INCa), Merck Serono, Amgen, Sanofi-Aventis, and Roche. TT has consulted or advised for Merck Serono, Lilly, Sanofi-Aventis, Amgen, Roche, AstraZeneca, and Ganymed; has received honoraria from Merck Serono, Lilly, Sanofi-Aventis, Amgen, Roche, AstraZeneca, and Ganymed; has received travel grants from Merck Serono, Lilly, Sanofi-Aventis, Amgen, Roche, AstraZeneca, and Ganymed; and has received research funding from Merck Serono, Amgen, Lilly, and Sanofi-Aventis. LF has received honoraria from Bayer, Bristol-Myers Squibb, Gilead, Boehringer Ingelheim, and Roche, and has received research funding from Ipsen. SFa has received honoraria from Merck Serono. TS has consulted or advised for Merck Serono, and has received travel grants from Merck Serono. TH has received honoraria from Amgen and Pfizer, and has received travel grants from Lilly, Merck Serono, Pfizer, Roche, and Sanofi-Aventis. PHam has consulted or advised for Merck Serono, and has received honoraria and research funding from Merck Serono. MDo has received research funding from Bayer. TA has received honoraria from Merck Serono. VH has consulted or advised for Merck Serono, and has received honoraria from, travel grants, and research funding from Merck Serono. MDu has consulted or advised for Roche, Merck Serono, Amgen, Lilly, Keocyt, Sanofi-Aventis, Ipsen, Celgene, Boehringer Ingelheim, and Novartis; has received honoraria from Roche, Amgen, Merck Serono, Lilly, and Novartis; has received travel grants from Roche, Amgen, Merck Serono, and Novartis; and has received research funding from Roche. J-PP has received research funding (unrestricted grant) from Roche, and has received honoraria from Merck Serono. OR has received honoraria from Bayer and Sirtex. TFG has consulted or advised for Merck Serono, and has received honoraria and research funding from Merck Serono. All other authors declare no competing interests.

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Summary

Background—Gemcitabine plus a platinum-based agent (eg, cisplatin or oxaliplatin) is the standard of care for advanced biliary cancers. We investigated the addition of cetuximab to chemotherapy in patients with advanced biliary cancers.

Methods—In this non-comparative, open-label, randomised phase 2 trial, we recruited patients with locally advanced (non-resectable) or metastatic cholangiocarcinoma, gallbladder carcinoma, or ampullary carcinoma and a WHO performance status of 0 or 1 from 18 hospitals across France and Germany. Eligible patients were randomly assigned (1:1) centrally with a minimisation procedure to first-line treatment with gemcitabine (1000 mg/m²) and oxaliplatin (100 mg/m²) with or without cetuximab (500 mg/m²), repeated every 2 weeks until disease progression or unacceptable toxicity. Randomisation was stratified by centre, primary site of disease, disease stage, and previous treatment with curative intent or adjuvant therapy. Investigators who assessed treatment response were not masked to group assignment. The primary endpoint was the proportion of patients who were progression-free at 4 months, analysed by intention to treat. This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT00552149.

Findings—Between Oct 10, 2007, and Dec 18, 2009, 76 patients were assigned to chemotherapy plus cetuximab and 74 to chemotherapy alone. 48 (63%; 95% CI 52–74) patients assigned to chemotherapy plus cetuximab and 40 (54%; 43–65) assigned to chemotherapy alone were progression-free at 4 months. Median progression-free survival was 6·1 months (95% CI 5·1–7·6) in the chemotherapy plus cetuximab group and 5·5 months (3·7–6·6) in the chemotherapy alone group. Median overall survival was 11·0 months (9·1–13·7) in the chemotherapy plus cetuximab group and 12·4 months (8·6–16·0) in the chemotherapy alone group. The most common grade 3–4 adverse events were peripheral neuropathy (in 18 [24%] of 76 patients who received chemotherapy plus cetuximab *vs* ten [15%] of 68 who received chemotherapy alone), neutropenia (17 [22%] *vs* 11 [16%]), and increased aminotransferase concentrations (17 [22%] *vs* ten [15%]). 70 serious adverse events were reported in 39 (51%) of 76 patients who received chemotherapy plus cetuximab (34 events in 19 [25%] patients were treatment-related), whereas 41 serious adverse events were reported in 25 (35%) of 71 patients who received chemotherapy alone (20 events in 12 [17%] patients were treatment-related). One patient died of atypical pneumonia related to treatment in the chemotherapy alone group.

Interpretation—The addition of cetuximab to gemcitabine and oxaliplatin did not seem to enhance the activity of chemotherapy in patients with advanced biliary cancer, although it was well tolerated. Gemcitabine and platinum-based combination should remain the standard treatment option.

Introduction

Cancers of the biliary tract are a heterogeneous group of rare tumours that include intrahepatic and extrahepatic cholangiocarcinomas, gallbladder carcinomas, and ampullary carcinomas.¹ Most patients are diagnosed with advanced-stage disease, making them ineligible for complete surgical resection, which is the only potentially curative modality available. Furthermore, recurrence is common even after complete resection, and is usually only amenable to palliative chemotherapy.

Very few randomised trials of chemotherapy have been done in patients with advanced biliary-tract cancer.² In a pooled analysis of 104 trials (including only two randomised phase 2 trials and one phase 3 trial) in 2810 patients with advanced biliary-tract cancer, the combination of gemcitabine and platinum compounds was more effective than gemcitabine alone.² The UK ABC-02 phase 3 trial³ confirmed the superiority of gemcitabine plus cisplatin over gemcitabine alone. Several single-group studies^{4–6} and one randomised trial⁷ showed that the combination of gemcitabine and oxaliplatin has antitumour activity with a favourable toxic-effect profile in advanced biliary-tract cancer, and is more efficacious than best supportive care and fluorouracil plus folinic acid.⁷ However, patients with advanced biliary-tract cancer still have a poor outlook, with median overall survival of less than 1 year.^{2,3,7}

The EGFR signalling pathway regulates biliary epithelial cell growth and proliferation, and *EGFR* is overexpressed in 67–100% of biliary cancers, making it a rational target for treatment.^{8–12} One phase 2 trial in 30 patients with advanced biliary-tract cancer showed encouraging results when cetuximab, a chimeric monoclonal antibody directed against EGFR, was added to gemcitabine and oxaliplatin.¹³

We designed the BINGO trial to assess the efficacy and tolerability of gemcitabine and oxaliplatin plus cetuximab or gemcitabine and oxaliplatin alone as first-line treatment for patients with advanced biliary-tract cancer.

Methods

Study design and participants

In this open-label, non-comparative, randomised phase 2 study, we recruited patients with biliary-tract cancer from university hospitals and cancer centres across France and Germany. Trial inclusion criteria were: age 18–75 years; histologically or cytologically confirmed adenocarcinoma of the biliary tract, including intrahepatic and extrahepatic bile ducts, gallbladder, and ampulla of Vater; and locally advanced (non-resectable) or metastatic disease. Because proper tumour staging (ie, locally advanced *vs* metastatic) was required for stratification at the time of randomisation, protocol-specified staging guidelines (appendix) had to be strictly followed by investigators, and the non-resectability confirmed by local tumour boards. Further inclusion criteria were: WHO performance status (WHO PS) of 0 or 1; expected life expectancy of more than 3 months; measurable or assessable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0;¹⁴ and adequate renal and bone marrow functions. Biliary tract obstruction (if any) had to be

adequately treated before study entry, with total bilirubin concentrations less than or equal to three times the upper limit of normal range (ULN) and aminotransferase concentrations of less than or equal to five times the ULN. Patients were excluded if they had received previous palliative chemotherapy for biliary-tract cancer, received adjuvant treatment within 6 months before study entry, previous exposure to EGFR-targeting agents, known CNS metastases, clinically significant comorbidities, active uncontrolled infection, grade 2 or worse peripheral neuropathy, or had additional malignancy within the past 5 years (except adequately treated in-situ carcinoma of the cervix or nonmelanoma skin carcinoma).

All patients gave written consent. The institutional review boards or ethics committees at each site reviewed and approved the protocol.

Randomisation and masking

Eligible patients were randomly assigned to receive gemcitabine and oxaliplatin with or without cetuximab in a 1:1 ratio. Randomisation was done centrally with a minimisation procedure using TENALEA software (Formsvision BV, Amsterdam, Netherlands), stratified by centre, disease stage (locally advanced vs metastatic disease), primary site of disease (gallbladder vs nongallbladder), and previous treatment with curative intent or adjuvant therapy (any vs none).¹⁵ Investigators or research coordinators sent the randomisation form by fax to the Institut Gustave Roussy Biostatistics Unit (Villejuif, France). After checking the inclusion criteria, the data manager sent the allocated treatment back to the investigator by fax. Neither the treating physicians nor the patients were masked to the allocated treatment. Investigators who assessed the response to the treatment were not masked to group assignment.

Procedures

In both groups, gemcitabine 1000 mg/m² was administered as a fixed dose rate, 100 min intravenous infusion (10 mg/m² per min) on day 1, and oxaliplatin 100 mg/m² was given as a 2 h infusion on day 2.⁴ Patients in the chemotherapy plus cetuximab group were also given cetuximab (Merck KGaA, Darmstadt, Germany) 500 mg/m² as a 150 min intravenous infusion on day 1 or day 2 (according to investigator's preference).¹⁶ Treatment was repeated every 2 weeks until disease progression, unacceptable toxicity, or consent withdrawal. In case of complete tumour response or a tumour response deemed sufficient for surgical resection with curative intent, treatment had to be continued for at least 3 months after complete response or tumour resection.

Assessment of patients before the start of study treatment included a complete medical history, physical examination, routine haematological and biochemical analyses, and CT or MRI scans of the thorax and abdomen to define the extent of disease. After this first assessment, complete blood-cell counts and serum biochemical analyses were obtained at least once per treatment cycle. Subjective symptoms, physical examination results, WHO PS, and all adverse events were recorded before each treatment cycle, and adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0,¹⁷ except for peripheral neuropathy, which was graded according to the modified Lévi's scale.¹⁸ Dose reductions and cycle delays were

made on the basis of the worst toxic effect recorded during the preceding cycle, as defined per protocol. All dose reductions were maintained for the remainder of the study. Oxaliplatin was stopped in case of severe (ie, grade 2 lasting >7 days or grade 3) peripheral neuropathy; gemcitabine (with or without cetuximab) was then used according to the same schedule. Guidelines for supportive treatments (eg, topical or systemic treatments for cetuximab-induced skin toxicity) were provided in the protocol. Secondary prophylaxis with a granulocyte colony-stimulating factor or a granulocyte-macrophage colony-stimulating factor was recommended in case of grade 4 or complicated neutropenia. After failure of study treatment, or consent withdrawal, further treatment was at the investigator's discretion, but crossover was not allowed.

Tumour assessments were done at baseline and every 8 weeks during therapy, at end of treatment or early termination, and every 8 weeks thereafter until disease progression, using the same imaging method as at baseline. Patients were followed up until death or study closure.

For exploratory purposes, archival tumour tissue blocks obtained at initial diagnosis or surgery, if available, were assessed centrally for *EGFR* expression and *KRAS* and *BRAF* mutational status in one laboratory (Saint-Antoine University Hospital, Paris, France). Separate written consent for optional biomarker testing was obtained. *EGFR* overexpression was scored by immunohistochemistry using the Dako *EGFR* kit (Dako, Carpinteria, CA, USA) as described previously.^{19,20} *KRAS* and *BRAF* mutation analysis is described in the appendix.

Outcomes

Because a pooled analysis of 104 trials showed that tumour response correlates poorly with overall survival in advanced biliary-tract cancers,² the primary endpoint was an intention-to-treat analysis of the crude progression-free survival rate at 4 months, defined as the proportion of patients with non-progressive disease 4 months after randomisation.

Secondary endpoints included duration of progression-free survival (defined as the time from randomisation to disease progression or death), overall survival, the proportion of patients with an objective response according to RECIST 1.0, exploratory biomarker analysis, and safety outcomes. Response and progression were assessed by the local investigator. All patients who began study treatment were assessed for safety.

Statistical analyses

We tested the null hypothesis that less than 40% of patients would be progression-free by 4 months against the alternative hypothesis that 60% or more patients would be progression-free by this timepoint using a Simon two-stage design.^{2,21} At least seven of the first 18 patients assigned to chemotherapy plus cetuximab were required to have a tumour response or stable disease at 4 months before an additional 28 patients in each treatment group were to be included for the second-stage of the trial. At the end of this stage, chemotherapy plus cetuximab would be considered effective if at least 22 of the 46 patients assigned to this treatment had a tumour response or stable disease at 4 months. We aimed to accrue 50 patients per group, allowing for a 10% loss to follow-up. The protocol was subsequently

amended to include 75 patients per group, to include at least 50 patients with non-gallbladder tumours and 50 patients with wild-type *KRAS* tumours in the chemotherapy plus cetuximab group to assess treatment effect in these subpopulations and undertake exploratory biomarker analyses.

We estimated progression-free and overall survival with the Kaplan-Meier method. Because the trial was non-comparative, no formal comparison was done between the two groups.

A Cox model was used for univariate and multivariate exploratory analyses of potential prognostic factors. The prognostic value of tumour *KRAS* and *BRAF* mutations and *EGFR* overexpression was also studied.

Data were obtained and analysed by the Institut Gustave Roussy Biostatistics Unit (Villejuif, France) using SAS (version 9.3) and R (version 2.11.1). All p values are two-sided. The study is registered with ClinicalTrials.gov, number NCT00552149.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, or data interpretation, or the writing of the report. DM, SFo, VR, and J-PP had full access to the raw data, and DM had final responsibility for the decision to submit for publication.

Results

From Oct 10, 2007, to Dec 18, 2009, 150 patients with advanced biliary-tract cancer were enrolled in the study across 11 centres in France and seven centres in Germany, with 76 patients randomly assigned to receive gemcitabine and oxaliplatin plus cetuximab and 74 assigned to gemcitabine and oxaliplatin alone (figure 1). Six (8%) patients in the chemotherapy plus cetuximab group and 11 (15%) patients in the chemotherapy alone group were not assessable for disease response for the whole duration of the study, due to disease progression in four (5%) patients in the chemotherapy plus cetuximab group and eight (11%) patients in the chemotherapy alone group (including in three untreated patients), unavailable data in two (3%) and one (1%) patients, respectively, and for other reasons in two (3%) patients in the chemotherapy alone group.

Baseline characteristics were balanced between the groups, except for WHO PS: the proportion of patients with a WHO PS of 0 was slightly higher in the chemotherapy plus cetuximab group than in the chemotherapy alone group (table 1). Most patients had cholangiocarcinoma (123 [82%] of 150) and metastatic disease (118 [79%]). The primary analysis of this trial was done on March 31, 2011, after a median follow-up of 31.1 months (IQR 19.8–35.1; 30.3 months [19.8–31.5] for the chemotherapy plus cetuximab group vs 34.9 months [25.4–35.6] for the chemotherapy alone group).

Median treatment duration was similar between the groups (23 weeks [range 4–83] for chemotherapy plus cetuximab vs 23 weeks [range 2–58] for chemotherapy alone). Patients given chemotherapy plus cetuximab completed a median of ten cycles (range 2–33) of treatment and those given chemotherapy alone also completed a median of ten cycles (1–

27). Relative dose intensity received, dose reductions, and drug non-administrations and discontinuations were similar between the groups (appendix).

All 150 patients completed the study. Main reasons for discontinuation of treatment were disease progression (in 48 [63%] of 76 patients in the chemotherapy plus cetuximab group vs 40 [54%] of 74 patients in the chemotherapy alone group), adverse events (12 [16%] vs eight [11%]), and patient's request (seven [9%] vs eight [11%]; appendix). One (1%) patient in the chemotherapy plus cetuximab group and six patients (8%) patients in the chemotherapy alone group stopped treatment because they underwent curative-intent surgery. Of these patients, four patients in the chemotherapy alone group and the patient in the chemotherapy plus cetuximab group died as a result of progressive disease.

48 (63%; 95% CI 52–74) patients assigned to chemotherapy plus cetuximab and 40 (54%; 43–65) assigned to chemotherapy alone were progression-free at 4 months. In the subgroup of patients whose primary site was not the gallbladder, 42 (65%; 95% CI 53–76) of 65 patients in the chemotherapy plus cetuximab group were progression-free at 4 months compared with 34 (54%; 42–66) of 63 in the chemotherapy alone group. In patients with gallbladder carcinoma, six (55%; 95% CI 23–83) of 11 patients in both the chemotherapy plus cetuximab and chemotherapy alone groups were progression-free at 4 months (appendix). When groups were combined, the proportion of patients who were progression-free at 4 months did not vary according to whether the primary site of disease was in the gallbladder or not (76 [60%] of 128 patients with a non-gallbladder primary site vs 12 [55%] of 22 with a gallbladder primary site; $p=0.67$).

The proportions of patients who achieved an objective response (complete or partial response) were similar between the two treatment groups: 18 (24%, 95% CI 15–35) patients in the chemotherapy plus cetuximab group had an objective response, as did 17 (23%, 14–34) in the chemotherapy alone group (table 2). 62 (82%; 71–90) of 76 patients in the chemotherapy plus cetuximab group achieved disease control (objective response or stable disease), as did 48 (65%; 53–76) of 74 in the chemotherapy alone group (table 2). Median duration of response was 5.7 months (IQR 4.1–9.1) in the chemotherapy plus cetuximab group and 8.4 months (6.1–21.9) in the chemotherapy alone group. These results were much the same in the 133 patients assessable for objective response (appendix) and in the subgroups of patients defined by primary site of disease (appendix).

At the time of this analysis, 140 (93%) patients had experienced disease progression or died (73 [96%] of 76 patients in the chemotherapy plus cetuximab group vs 67 [91%] of 74 patients in the chemotherapy alone group). In the intention-to-treat population, median progression-free survival was 6.1 months (95% CI 5.1–7.6) in the chemotherapy plus cetuximab group and 5.5 months (3.7–6.6) in the chemotherapy alone group (figure 2). Median overall survival (figure 3) was 11.0 months (9.1–13.7) in the chemotherapy plus cetuximab group and 12.4 months (8.6–16.0) in the chemotherapy alone group (figure 3). Duration of progression-free survival did not vary according to cetuximab-induced skin toxicity (appendix).

In an exploratory analysis, we studied prognostic factors and their effect on the treatment effect. In univariate and multivariate analyses, the significant predictors for duration of progression-free survival were haemoglobin and platelet count at baseline (appendix). Treatment effect was unchanged after taking into account these prognostic factors (appendix).

Overall, 32 (42%) of 76 patients in the chemotherapy plus cetuximab group and 28 (38%) of 74 patients in the chemotherapy alone group received second-line therapy after disease progression. The most frequently used agents were fluorouracil (or capecitabine) and irinotecan (in 23 [72%] and eight [25%] of 32 patients, respectively, in the chemotherapy plus cetuximab group and 12 [43%] and four [14%] of 28 patients, respectively, in the chemotherapy alone group).

From the 91 patients who consented to participate in the biomarker studies, we obtained tissue specimens with sufficient DNA for *KRAS* and *BRAF* mutation analysis from 75 patients, and samples suitable for *EGFR* overexpression analysis from 77 patients (appendix). More patients in the chemotherapy plus cetuximab group than in the chemotherapy alone group had available samples (52 [68%] of 76 vs 39 [53%] of 74; $p=0.048$). 14 (19%; 95% CI 11–29) of 75 patients' samples contained *KRAS* mutations, four (5%; 2–13) of 75 had *BRAF* mutations, and 18 (23%; 14–34) of 77 had *EGFR* overexpression (ie, *EGFR* score ≥ 200); these numbers did not significantly differ (according to CIs) between primary site of disease (appendix), and were similar between treatment groups (table 3). *KRAS* and *BRAF* mutations were mutually exclusive. Tumour *KRAS*, *BRAF*, and *EGFR* statuses were not associated with outcome either in the whole patient population or according to treatment group (table 3; appendix). However, this finding should be interpreted with caution owing to the non-comparative design of our study and the lack of statistical power (because wild-type *KRAS* tumour samples were available for only 61 patients instead of the 100 patients expected).

Both treatments were generally well tolerated, with no deaths within 30 days of randomisation in the chemotherapy plus cetuximab group and two (both untreated) deaths in the chemotherapy alone group. Peripheral neuropathy, increased aminotransferase concentrations, fatigue, and myelosuppression were the most common toxic effects in both groups (table 4). Allergic reaction or hypersensitivity, skin rash, paronychia, conjunctivitis, mucositis, alopecia, hypomagnesaemia, neutropenia, thrombocytopenia, and infection were more frequent in the chemotherapy plus cetuximab group than in the chemotherapy alone group. 70 serious adverse events were declared in 39 (51%) of the 76 patients who received treatment in the chemotherapy plus cetuximab group, whereas 41 serious adverse events were declared in 25 (35%) of the 71 patients who received treatment in the chemotherapy alone group. Of these 111 serious adverse events, 54 (49%) were deemed related to treatment (34 events in 19 [25%] patients who received chemotherapy plus cetuximab, and 20 events in 12 [17%] patients who received chemotherapy alone). One patient died after 5.7 months of atypical pneumonia possibly related to treatment in the chemotherapy alone group.

Discussion

Our data suggest that any potential antitumour activity of cetuximab does not translate into a survival advantage when combined with gemcitabine and oxaliplatin in patients with advanced biliary-tract cancer compared with chemotherapy alone. Neither tumour *KRAS* or *BRAF* mutations, nor *EGFR* overexpression (identified in nearly a quarter of patients), seemed to help to select patients able to respond to therapy.

Although gemcitabine and platinum-based chemotherapy has been established as the standard of care in the treatment of advanced biliary-tract cancer, the prognosis of these tumours is poor, underlining the need for improvement in treatment efficacy (panel).^{2,3,7,22,23} Most of recently reported or ongoing trials have assessed the tolerance and efficacy of molecularly targeted agents alone or in combination with gemcitabine and platinum-based chemotherapy.^{13,24–26} Notably, a phase 2 trial¹³ of gemcitabine and oxaliplatin plus cetuximab reported a promising objective response rate of 63%, with three patients achieving a complete response. However, in a recent Asian phase 3 trial by Lee and colleagues,²⁴ the addition of erlotinib, another *EGFR* inhibitor, to gemcitabine and oxaliplatin did not improve outcomes (table 5). To our knowledge, our study is the first to assess the activity of gemcitabine and platinum-based chemotherapy with or without an *EGFR* inhibitor in non-Asian patients with advanced biliary-tract cancer.

In line with previously reported data, both gemcitabine and oxaliplatin, and gemcitabine and oxaliplatin plus cetuximab, were well tolerated in our study, with no unexpected adverse events.^{4–7,13,24,25} Skin rash is associated with cetuximab, and was more frequent in the chemotherapy plus cetuximab group than in the chemotherapy alone group. However, no differences in peripheral neuropathy and febrile neutropenia were noted between the groups.

Almost two-thirds of patients (63%) in the chemotherapy plus cetuximab group were progression-free at 4 months, which is numerically higher than the proportion who achieved this endpoint in the chemotherapy alone group (54%), although the statistical design of our study precluded any formal statistical comparison. However, in terms of objective response, progression-free survival, and overall survival, the addition of cetuximab to gemcitabine and oxaliplatin did not show any sign of improved efficacy. Furthermore, our results did not differ in a predefined subset analysis according to the primary site of disease (ie, gallbladder vs non-gallbladder). Although we should be cautious when comparing trials, our results in both treatment groups are close to those reported with the combination of gemcitabine and cisplatin in the UKABC-02 trial³ or the combination of gemcitabine and cisplatin with erlotinib²⁴ or cetuximab²⁵ in the two Asian trials (table 5). Indeed, our results did not confirm the promising efficacy data obtained with gemcitabine and oxaliplatin plus cetuximab in a phase 2 study.¹³ However, nine (30%) of the 30 patients included in that single-group, single-centre phase 2 study¹³ underwent secondary resection with curative intent after response to therapy, suggesting that there were selection biases—eg, 97% of patients had an Eastern Cooperative Oncology Group performance status of 0–1—and even with the reported high response rate (63%), the secondary resection rate could be regarded as high. In fact, although response rate was still high (48%) in the subset of patients

ineligible for secondary surgery, median progression-free survival (6.8 months) and overall survival (11.6 months) were much closer to those in our study.¹³

Of note, response might be difficult to assess in advanced biliary-tract cancers—which often present as poorly delineated, infiltrating tumours—and was shown to be poorly correlated with overall survival ($r=0.20$; $p=0.043$) in a pooled analysis of 104 trials.² A significant progression-free and overall survival benefit of gemcitabine and cisplatin over gemcitabine alone was seen in the UK-ABC-02 trial³ despite a non-significant difference in response, whereas a significant response benefit was seen with gemcitabine and oxaliplatin plus erlotinib over gemcitabine and oxaliplatin alone in the South Korean phase 3 trial,²⁴ which did not translate into an overall survival advantage (table 5).

Our negative results could be partly explained by the results noted in the chemotherapy alone group, which were better than in those reported in the two Asian randomised trials of chemotherapy plus erlotinib²⁴ or cetuximab²⁵ (table 5). Although overall survival was not statistically different between treatment groups in any of these trials, a marginally significant progression-free survival benefit was reported with the addition of erlotinib ($p=0.087$)²⁴ or cetuximab ($p=0.064$)²⁵ to chemotherapy (table 5). Differences in sensitivity to chemotherapy between Asian and European populations might explain these discrepancies. However, again, direct comparison of these results cannot be made because of differences in chemotherapy dose (table 5) and inclusion criteria.

EGFR mutations, amplification, or overexpression, and oncogenic mutations of key effectors of the EGFR pathway (eg, *KRAS*, *BRAF*) have been consistently reported in biliary cancers.²⁷ However, the proportion of tumours with *KRAS* mutations varies widely across studies: 10% of patients in two studies^{13,24} had *KRAS* mutations, but other studies²⁵ reported higher rates, as did our study (19%), and some have attained up to 50%.^{27,28} Additionally, whether these mutations are predictive for inefficacy of EGFR inhibitors in patients with advanced biliary-tract cancers remains elusive. Of the nine patients with *KRAS* mutations included in the two studies in which 10% of patients had *KRAS* mutations,^{13,24} four had a partial response to chemotherapy plus EGFR inhibitor and three had stable disease. In the TCOG T1210 trial,²⁵ although only 14% of 44 patients with mutated *KRAS* tumours given chemotherapy alone had disease control for 16 weeks or longer compared with 48% of 78 patients with wild-type *KRAS* tumours ($p=0.025$), the presence of *KRAS* mutations did not preclude the potential benefit of adding cetuximab to chemotherapy. In our study, neither tumour *KRAS* or *BRAF* mutations nor *EGFR* overexpression were prognostic for patient outcomes. However, the small patient numbers limited the statistical power of our exploratory analyses, and along with the non-comparative design of our study, prevented the assessment of the predictive ability of these biomarkers.

Our study had several limitations. First, the design of our study precluded any formal statistical comparison. However, a phase 2 study including 150 patients with a comparative design, even with high type I (10%, one-sided) and type II (20%) errors, would have allowed detection of a difference of 17% in survival between the two groups, corresponding to a hazard ratio (HR) of 0.58, an ambitious goal considering, for instance, the survival benefit of gemcitabine and cisplatin over gemcitabine alone (HR 0.63) in the UK-ABC-02 trial.³

Second, a 4-month crude progression-free survival rate, the primary endpoint of the study, might not be an appropriate surrogate marker for progression-free survival. In fact, the survival curves graphically suggest an early treatment effect that is reversed after about 8 months, with outcome eventually becoming worse in the experimental group compared with the standard group. We have no clear explanation for this finding. However, we should be cautious because the CIs for survival are wide and overlapping. Our results vary from those of the UK-ABC-01 randomised phase 2 trial,²² in which 6-month progression-free survival (the primary endpoint) and median progression-free survival were higher in the gemcitabine and cisplatin group than in the gemcitabine alone group (57% [95% CI 41–70] vs 46% [31–59], and 8.0 months [3.9–8.8] vs 4.0 months [2.9–7.9], respectively). This result was in line with the aforementioned pooled analysis of 104 trials,² in which time to tumour progression seemed to be the best surrogate marker of activity in this disease group with the best correlation with overall survival ($r=0.73$, $p<0.0005$). We chose 4-month rather than 6-month progression-free survival because in the pooled analysis,² the median time to progression was 4.1 months. Third, both patients with locally advanced biliary-tract cancer and those with metastatic disease were eligible to participate in our study, although each population might have had different outcomes. However, the study design included disease stage as a stratification factor for randomisation. Furthermore, a randomised phase 2 trial²⁹ showed no benefit, and even suggested a deleterious effect, of concurrent radiotherapy and chemotherapy with fluorouracil and cisplatin as compared with chemotherapy alone with gemcitabine and oxaliplatin in patients with locally advanced biliary-tract cancer.

Despite national or international collaboration, three randomised trials,^{24,25} including this study, did not confirm the promising results of previous phase 2 trials^{13,30} regarding the therapeutic potential of EGFR inhibition in patients with advanced biliary-tract cancer. More preclinical and early clinical studies are needed to suggest which targeted agent to use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all participating patients and their families, the study investigators (appendix), study nurses, study monitors, data manager, and all other members of the BINGO study team. We also thank members of the independent data monitoring committee (Emmanuel Mitry, Julien Taïeb, Ludovic Trinquart), and members of the International Biliary Cancer Task Force for their helpful comments. The sponsor of the BINGO study was Institut Gustave Roussy, Villejuif, France. Audrey Mauguen, Benjamin Lacas, and Jean Mendiboure (Institut Gustave Roussy) provided statistical support. Cheryl Jenkins provided medical writing services, funded by Merck Serono, France. Merck KGaA has reviewed the manuscript; however, the views and opinions described in the publication do not necessarily reflect those of Merck KGaA.

Funding Institut National du Cancer, Merck Serono.

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Panel: Research in context

Systematic review

Combination chemotherapy regimens with gemcitabine and either cisplatin^{2,3,22,23} or oxaliplatin^{2,7} are regarded as standard first-line options for advanced cholangiocarcinomas^{2,3,22,23} and gallbladder carcinomas^{2,3,7,22,23} both in European and North American^{2,3,22} and Asian^{2,7,23} populations, after a pooled analysis of 104 trials² and several randomised phase 2^{22,23} and phase 3^{3,7} trials. However, median overall survival reported in recent randomised trials with such combination regimens are consistently shorter than 1 year,^{2,3,7,22–25} outlining the need for improvement in treatment efficacy. Preclinical data support a role for EGFR inhibitors in the treatment of advanced biliary-tract cancer.^{8–12} We searched PubMed for published studies, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) for any additional open or closed phase 2 or phase 3 trials, of gemcitabine and platinum-based chemotherapy with or without an EGFR inhibitor in advanced biliary-tract cancer with the search term “chemotherapy AND EGFR AND (advanced biliary tract cancer or cholangiocarcinoma or gallbladder carcinoma)”, published between January, 2000, and February, 2014. We retrieved four randomised trials of gemcitabine and platinum-based chemotherapy with or without an EGFR inhibitor for advanced biliary-tract cancer: one phase 3 trial of gemcitabine and oxaliplatin with or without erlotinib²⁴ and three randomised phase 2 trials of gemcitabine and oxaliplatin with or without cetuximab,²⁵ gemcitabine and oxaliplatin with or without panitumumab (NCT01389414), and gemcitabine and cisplatin with or without panitumumab in *KRAS* wild-type tumours (NCT01320254). In another randomised phase 2 trial in progress (NCT01206049), patients with *KRAS* wild-type advanced biliary-tract cancer are being assigned to gemcitabine, oxaliplatin, capecitabine, and either panitumumab or bevacizumab. Additionally, we found four non-randomised, single-group phase 2 trials of gemcitabine and platinum-based chemotherapy with an EGFR inhibitor (gemcitabine and oxaliplatin with cetuximab,¹³ gemcitabine, oxaliplatin, and capecitabine with panitumumab in *KRAS* wild-type tumours,²⁶ gemcitabine and oxaliplatin with erlotinib [NCT00832637], and hepatic arterial oxaliplatin plus systemic gemcitabine, capecitabine and cetuximab [NCT01247337]).

Interpretation

Our data suggest that the antitumour activity of cetuximab (if any) does not translate into a survival advantage when combined with gemcitabine and oxaliplatin in patients with advanced biliary-tract cancer compared with chemotherapy alone. These findings are in line with those reported for the addition of erlotinib²⁴ or cetuximab²⁵ to gemcitabine and oxaliplatin in Asian populations. Neither tumour *KRAS* or *BRAF* mutations, nor *EGFR* overexpression seem to help with the selection of responsive patients. Gemcitabine and platinum-based combination chemotherapy is the only reasonable first-line treatment option in patients with advanced biliary-tract cancer.

Figure 1:
Trial profile

Figure 2: Progression-free survival
Shaded areas show 95% CIs of the curves.

Figure 3: Overall survival
Shaded areas show 95% CIs of the curves.

Table 1:

Baseline characteristics in randomly assigned patients

	Gemcitabine and oxaliplatin plus cetuximab (n=76)	Gemcitabine and oxaliplatin (n=74)
Age (years)	61 (35–75)	62 (39–75)
Sex		
Men	43 (57%)	42 (57%)
Women	33 (43%)	32 (43%)
Primary site		
Cholangiocarcinoma	62 (82%)	61 (82%)
Intrahepatic	49 (64%)	46 (62%)
Extrahepatic	8 (11%)	14 (19%)
Missing data	5 (7%)	1 (1%)
Gallbladder	11 (14%)	11 (15%)
Ampulla of Vater	1 (1%)	0
Multifocal	1 (1%)	1 (1%)
Non-gallbladder, unspecified [*]	1 (1%)	1 (1%)
Disease stage		
Locally advanced	17 (22%)	15 (20%)
Metastatic	59 (78%)	59 (80%)
WHO performance status		
0	35 (46%)	27 (36%)
1	36 (47%)	42 (57%)
2	0	1 (1%)
Unspecified	5 (7%)	4 (5%)
Previous treatments		
Curative-intent surgery	18 (24%)	16 (22%)
Biliary stenting	15 (20%)	17 (23%)
Radiotherapy	2 (3%)	0
Adjuvant chemotherapy	1 (1%)	1 (1%)
CA19–9 concentration (U/mL) [†]	105 (1–50 701)	166(1–61 883)

Data are median (range), or number (%).

^{*} Non-gallbladder primary site of disease, according to the stratification form.[†] Missing data from 11 (14%) patients in the chemotherapy plus cetuximab group and 15 (20%) patients in the chemotherapy alone group.

Table 2:

Best tumour response by RECIST 1.0 in the intention-to-treat Population

	Gemcitabine and oxaliplatin plus cetuximab (n=76)	Gemcitabine and oxaliplatin (n=74)
Complete response	1 (1%; 0–7)	2 (3%; 0–9)
Partial response	17 (22%; 14–33)	15 (20%; 12–31)
Stable disease	44 (58%; 46–69)	31 (42%; 31–54)
Progressive disease	8 (11%; 5–20)	15 (20%; 12–31)
Not assessable	6 (8%; 3–16)	11(15%; 8–25)

Data are number (%; 95% CI). RECIST=Response Evaluation Criteria in Solid Tumors.

Table 3:
4-month progression-free survival according to *KRAS*, *BRAF*, and *EGFR* tumour status and treatment group

	All patients		Per treatment group		Odds ratio (95% CI) [‡]
	n/N (%)	p value [*]	Gemcitabine and oxaliplatin plus cetuximab	Gemcitabine and oxaliplatin	
<i>KRAS</i> (n=75)	..	0.72	..	..	..
Wild-type	38/61 (62%)	..	24/37 (65%)	14/24 (58%)	1.32 (0.46–3.79)
Mutated	8/14 (57%)	..	5/8 (63%)	3/6 (50%)	1.67 (0.20–14.27)
<i>BRAF</i> (n=75)	..	1.00	..	..	..
Wild-type	43/71 (61%)	..	27/43 (63%)	16/28 (57%)	1.27 (0.48–3.34)
Mutated	3/4 (75%)	..	2/2 (100%)	1/2 (50%)	ND
<i>KRAS</i> or <i>BRAF</i> (n=75)	..	0.98	..	..	..
Wild-type	35/57 (61%)	..	22/35 (63%)	13/22 (59%)	1.17 (0.39–3.49)
Mutated	11/18 (61%)	..	7/10 (70%)	4/8 (50%)	2.33 (0.34–16.18)
EGFR score (n=77)	..	0.42	..	..	..
<200	39/59 (66%)	..	25/37 (68%)	14/22 (64%)	1.19 (0.39–3.61)
200	10/18 (56%)	..	7/12 (58%)	3/6 (50%)	1.40 (0.20–10.03)

Data are number of patients without progression/total number of patients (%), unless otherwise specified. ND=not done (because samples were too small).

^{*} χ^2 test was used for all comparisons of percentages except for the comparison of *BRAF* type, for which the Fisher's exact test was used.

[‡] Gemcitabine and oxaliplatin plus cetuximab versus gemcitabine and oxaliplatin alone.

Table 4:

Adverse events

	Gemcitabine and oxaliplatin plus cetuximab (n=76)					Gemcitabine and oxaliplatin (n=68)*				
	Grade 1-2	Grade 3	Grade 4	Grade 5		Grade 1-2	Grade 3	Grade 4	Grade 5	
Any toxicity [†]	15 (20%)	38 (50%)	23 (30%)	0		8 (12%)	40 (59%)	17 (25%)	0	
Peripheral neuropathy [‡]	48 (63%)	18 (24%)	NA	NA		43 (63%)	10 (15%)	NA	NA	
Neutropenia	18 (24%)	12 (16%)	5 (7%)	0		11 (16%)	9 (13%)	2 (3%)	0	
Increased AST/ALT	46 (61%)	15 (20%)	2 (3%)	0		46 (68%)	10 (15%)	0	0	
Fatigue	45 (59%)	13 (17%)	0	0		44 (65%)	9 (13%)	0	0	
Thrombocytopenia	51 (67%)	7 (9%)	1 (1%)	0		41 (60%)	13 (19%)	0	0	
Anaemia	56 (74%)	6 (8%)	1 (1%)	0		54 (79%)	5 (7%)	0	0	
Diarrhoea	29 (38%)	6 (8%)	0	0		26 (38%)	3 (4%)	0	0	
Constipation	26 (34%)	0	0	0		32 (47%)	0	0	0	
Allergic reaction or hypersensitivity	25 (33%)	5 (7%)	1 (1%)	0		16 (24%)	1 (1%)	0	0	
Skin rash	59 (78%)	5 (7%)	0	0		4 (6%)	0	0	0	
Infection [§]	3 (4%)	8 (11%)	0	0		0	3 (4%)	2 (3%)	0	
Anorexia	43 (57%)	3 (4%)	0	0		40 (59%)	3 (4%)	0	0	
Vomiting	35 (46%)	3 (4%)	0	0		32 (47%)	2 (3%)	0	0	
Neutropenic fever [¶]	NA	2 (3%)	1 (1%)	0		NA	2 (3%)	0	0	
Nausea	46 (61%)	2 (3%)	0	0		45 (66%)	2 (3%)	0	0	
Mucositis	28 (37%)	1 (1%)	0	0		13 (19%)	0	0	0	
Conjunctivitis	8 (11%)	1 (1%)	0	0		3 (4%)	0	0	0	
Fever	31 (41%)	0	0	0		24 (35%)	1 (1%)	0	0	
Alopecia	27 (36%)	NA	NA	NA		16 (24%)	NA	NA	NA	
Hypomagnesaemia	25 (33%)	0	0	0		9 (13%)	0	0	0	
Paronychia	11 (14%)	0	0	0		1 (1%)	0	0	0	
Other	55 (72%)	14 (18%)**	1 (1%) ^{††}	0		48 (71%)	8 (12%) ^{‡‡}	1 (1%) ^{§§}	1 (1%) ^{¶¶}	

Data are number of patients with one or more episodes of an adverse event (% of patients); the highest toxicity grade for each type of event is recorded in this table. NA=not applicable. AST=aspartate aminotransferase. ALT=alanine aminotransferase.

* Three patients in the chemotherapy alone group did not receive any treatment, and data for toxicity were missing for three patients who received only one cycle of treatment.

[†] Includes laboratory abnormalities.

[‡] According to the modified Levi's scale, which grades peripheral neuropathy from grade 1 to grade 3.¹⁸

[§] With grade 0 or unknown neutrophil count.

[¶] Including infections with grade 1 or worse neutrophil count; neutropenic fever is not recognised below grade 3.

// Alopecia is not recognised above grade 2.

^{**} Abdominal pain (four patients); hypokalaemia (two patients); and tumour necrosis, haematemesis, shoulder calcification, deep-vein thrombosis, arterial hypertension, acute pancreatitis, hepatic encephalopathy, and dyspnoea (one patient each).

^{††} Increase in serum creatinine concentration (one patient).

^{‡‡} Abdominal pain (two patients), bile duct stenosis, dysphonia, ascites, dehydration, deep-vein thrombosis, arthralgia (one patient each).

^{§§} Hypercalcaemia (one patient).

^{¶¶} Atypical pneumonia (one patient).

Table 5:

Selected randomised trials of treatment for advanced biliary-tract cancer

	Number of patients	Objective response		Progression-free survival		Overall survival	
		%	p value	Median (months)	p value	Median (months)	p value
UK-ABC-02 ^{3*}			NS [‡]		<0.001		<0.001
Gencitabine and cisplatin	204	26%	..	8.0	..	11.7	..
Gencitabine	206	15%	..	5.0	..	8.1	..
BT-22 ²³			0.380		0.077		0.139
Gencitabine and cisplatin	42	19%	..	5.8	..	11.2	..
Gencitabine	42	12%	..	3.7	..	7.7	..
Sharma et al ⁷			<0.001		<0.001		0.039
Gencitabine and oxaliplatin [‡]	26	31%	..	8.5	..	9.5	..
Fluorouracil/folinic acid	28	14%	..	3.5	..	4.6	..
Best supportive care	27	0%	..	2.8	..	4.5	..
Lee et al ²⁴			0.005		0.087		0.611
Gencitabine and oxaliplatin [§] + erlotinib	135	30%	..	5.8	..	9.5	..
Gencitabine and oxaliplatin [§]	133	16%	..	4.2	..	9.5	..
TCOG T1210 ²⁵			0.192		0.064		0.909
Gencitabine and oxaliplatin [¶] + cetuximab	62	27%	..	6.7	..	10.6	..
Gencitabine and oxaliplatin [¶]	60	17%	..	4.1	..	9.8	..
BINGO (present study)			NA		NA		NA
Gencitabine and oxaliplatin [§] + cetuximab	76	24%	..	6.1	..	11.0	..
Gencitabine and oxaliplatin [§]	74	23%	..	5.5	..	12.4	..

NS=not significant. NA=not applicable.

^{*} Includes the 86 patients enrolled in the ABC-01 randomised phase 2 trial.²²[‡] p value not reported.[‡] Gencitabine 900 mg/m² plus oxaliplatin 80 mg/m² on day 1 and day 8, every 3 weeks.[§] Gencitabine 1000 mg/m² (10 mg/m²/min fixed-dose infusion rate) plus oxaliplatin 100 mg/m², every 2 weeks.

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Gemcitabine 800 mg/m² (10 mg/m²/min fixed-dose infusion rate) plus oxaliplatin 85 mg/m², every 2 weeks.