A \textit{KRAS} mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer

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\textbf{Background:} Previous clinical trials have not proved that adding epidermal growth factor inhibitor to chemotherapy confers a survival benefit for patients with advanced biliary tract cancer (ABTC). Whether the \textit{KRAS} mutation status of tumor cells confounded the results of past studies is unknown.

\textbf{Patients and methods:} ABTC patients stratified by \textit{KRAS} status, Eastern Cooperative Oncology Group performance status, and primary tumor location were randomized 1:1 to receive GEMOX (800 mg/m\textsuperscript{2} gemcitabine and 85 mg/m\textsuperscript{2} oxaliplatin) or C-GEMOX (500 mg/m\textsuperscript{2} cetuximab plus GEMOX) every 2 weeks. The primary end point was objective response rate (ORR).

\textbf{Results:} The study enrolled 122 patients between December 2010 and May 2012 (62 treated with C-GEMOX and 60 with GEMOX). Compared with GEMOX alone, C-GEMOX was associated with trend to better ORR (27% versus 15%; \textit{P} = 0.12) and progression-free survival (PFS, 6.7 versus 4.1 months; \textit{P} = 0.05), but not overall survival (OS, 10.6 versus 9.8 months; \textit{P} = 0.91). \textit{KRAS} mutations, which were detected in 36% of tumor samples, did not affect the trends of difference in ORR and PFS between C-GEMOX and GEMOX. The two treatment arms had similar adverse events, except that more patients had skin rashes, allergic reactions, and neutropenia in the C-GEMOX arm.

\textbf{Conclusions:} Addition of cetuximab did not significantly improve the ORR of GEMOX chemotherapy in ABTC, although a trend of PFS improvement was observed. The trend of improvement did not correlate with \textit{KRAS} mutation status.

\textbf{Clinical Trials number:} This study is registered at ClinicalTrials.gov (NCT01267344). All patients gave written informed consent.

\textbf{Key words:} \textit{KRAS} mutation, cetuximab, chemotherapy, biliary tract cancer

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**introduction**

Biliary tract cancer (BTC), which includes intrahepatic cholangiocarcinoma (IHCC), extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer (GBC), exhibits significant variations in incidence ethnically and geographically [1]. The current standard of care for patients with advanced BTC (ABTC) is gemcitabine plus platinum combination chemotherapy. However, the primary endpoint of this study was ORR according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Secondary end points included disease control rate (DCR, objective response plus stable disease) ≥16 weeks, PFS, OS, safety profile, and treatment efficacy across KRAS mutation status subgroups. Tumor responses were determined by radiologists at each participating center who were blinded to treatment assignments.

**study design and randomization**

This was an open-label randomized phase II trial conducted at 12 Taiwan Cooperative Oncology Group (TOOG)-affiliated medical centers. Eligible patients were stratified by KRAS mutation status (WT versus mutated) of tumors, ECOG PS (0 versus 1), and primary tumor location (IHCC versus EHCC/GBC) then randomly assigned in a 1 : 1 ratio to receive either GEMOX or C-GEMOX. Randomization was carried out centrally at the Statistical Center of TOOG, Taiwan, with a permuted block randomization.

**procedures**

GEMOX treatment was consisted of a fixed-dose rate (FDR, 10 mg/m²/min) i.v. infusion of 800 mg/m² gemcitabine followed by a 2-h infusion of 85 mg/m² oxaliplatin every 2 weeks. Patients in the C-GEMOX arm received an i.v. infusion of 500 mg/m² cetuximab on day 1 before each GEMOX cycle. Treatment courses were continued until disease progression, unacceptable toxicity, or withdrawal of consent. Adverse reactions were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0. Dose modifications were made based on the most serious adverse events encountered during the preceding cycle (see supplementary Material, available at *Annals of Oncology* online for dose modification plan details). A new treatment cycle would be given when absolute neutrophil and platelet counts were no less than 1500/µl and 75 × 10³/µl, respectively, and any treatment-related nonhematologic toxicities had resolved to grade 1 or less.

At study entry and before each cycle of treatment, patients underwent a complete medical history review, physical examination, routine hematologic and biochemical analyses. Computed tomography or magnetic resonance imaging to define the tumor extent and tumor response was carried out at study entry and every 8 weeks during treatment. Patients with first radiographic objective tumor response had confirmatory imaging examination 4 weeks later, according to RECIST 1.1. Archived tumor tissue sections and peripheral blood mononuclear cells were prospectively collected from all patients for biomarkers and pharmacogenomics studies at study entry.

**biomarker analysis**

Genomic DNA was extracted from tumor tissues using TaKaRa DEXPAT™ (TaKaRa Bio, Inc., Japan). KRAS mutation status was then determined using direct sequencing of the coding sequences of exons 2 and 3, as well as the TaqMan® assay for KRAS codon 12/13 mutations using the LightMix® Kit (TIB MOLBIOL GmbH, Germany). Tumors were considered to be KRAS mutation if any test was positive. The methodology of BRAF/NRAS mutation and EGFR protein expression is described in the supplementary Material, available at *Annals of Oncology* online.

**patients and methods**

**eligibility criteria**

Key eligibility criteria included: histologically proven advanced or metastatic BTC; at least 20 years old; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; systemic therapy-naïve; at least 1 measurable lesion; adequate organ function (supplementary Material, available at *Annals of Oncology* online). Key exclusion criteria included: major surgery or radiotherapy within 4 weeks before study entry; brain metastases; active infections; pre-existing peripheral neuropathy ≥grade 2; and other clinically significant co-morbidities. The ethics committees of each participating center approved this study. This study is registered at ClinicalTrials.gov (NCT01267344). All patients gave written informed consent.

**statistical analysis**

We assumed uninterested and interested ORRs of 20% and 30%, respectively, for the C-GEMOX arm; the GEMOX arm served as a control. Given 60 assessable patients per treatment arm, the probability of correctly ranking the two arms according to the observed ORR would be 90% [13]. Chi-squared or Fisher’s exact tests were applied to compare discrete variables. PFS and OS were estimated using the Kaplan–Meier method and compared by two-sided log-rank tests. Exploratory univariate and multivariate logistic regression for ORR and Cox regression for survival were used. All clinical data were gathered and analyzed at the Statistical Center, TOOG using SAS.
software, version 9.1. Two-sided $P$ value <0.05 were considered statistically significant.

**results**

**patient enrollment**

Between December 2010 and May 2012, 122 of 266 prescreened patients were enrolled (Figure 1). Baseline demographics were well balanced between the two treatment arms (Table 1). As of 30 April 2013, four patients (1 in C-GEMOX arm and 3 in GEMOX arm) remained on the study treatment and the median follow-up time of the intent-to-treat (ITT) population was 10.1 months (range, 0.9–24.4 months).

**treatment efficacy**

Compared with GEMOX alone, C-GEMOX-treated patients had a significantly longer treatment duration (median: 4.9 versus 3.0 months; $P = 0.01$) and received more treatment cycles (median: 10 versus 6.5 cycles; $P = 0.03$). Tumor response was assessed in 118 patients (Figure 1). In ITT analysis, C-GEMOX was associated with a trend of improvement in ORR [27% [95% confidence interval (CI) 17% to 40%] versus 15% (95% CI 7% to 27%); $P = 0.12$] and median PFS [6.7 months (95% CI 5.0–8.1 months) versus 4.1 months (95% CI 2.3–6.1 months); $P = 0.05$], and significant better long-term DCR (58% versus 37%; $P = 0.02$) compared with GEMOX (supplementary Table S1, available at *Annals of Oncology* online). However, the median OS was similar [10.6 months (95% CI 8.8–13.1 months) versus 9.8 months (95% CI 6.7–12.8 months); $P = 0.91$] (Figure 2). The ORR and DCR in IHCC, EHCC, and GBC, respectively, were shown in supplementary Table S2, available at *Annals of Oncology* online.

After withdrawal from study treatment, 48% of C-GEMOX-treated patients and 63% of GEMOX-treated patients received second-line chemotherapy ($P = 0.10$). The most commonly used second-line chemotherapy agents were cisplatin plus i.v. fluorouracil (>90%) followed by oral capecitabine or S-1 monotherapy.

**safety and dose intensity**

Incidence of significant adverse events were similar between two study arms, except significantly more grade 3–4 neutropenia and grade 2–3 skin rash in C-GEMOX arm (Table 2). No

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**Figure 1.** Study flow diagram. IHCC, intrahepatic cholangiocarcinoma; EHCC, extrahepatic cholangiocarcinoma; GB, gallbladder; ECOG, Eastern Cooperative Oncology Group; PS, performance status. *The cause of ineligibility (number of patients): previous chemotherapy (5), patient refusal (18), physician judgment (co-morbid conditions/compliance) (10), other concomitant cancer (4), no measurable lesions (5), age/performance status (9), central nervous system metastasis (1), no adequate tissue/K-RAS failure (10), liver enzyme/bilirubin (30), renal function (3), hemoglobin/platelet (9).
patients discontinued cetuximab treatment because of skin toxicity, and only one patient required a cetuximab dose reduction. Chemotherapy dose reduction due to adverse events was required in 60% and 48% of patients in the C-GEMOX and GEMOX arms, respectively. Treatment-related mortality occurred in one GEMOX-treated patient. The dose intensities of gemcitabine and oxaliplatin were similar between two arms (supplementary Table S3, available at Annals of Oncology online).

Factors correlated with treatment efficacy

Patients with WT KRAS tumors had a significantly better long-term DCR and trends toward longer median PFS and OS than patients with KRAS-mutated tumors. However, EGFR positivity did not affect clinical outcomes (supplementary Table S4, available at Annals of Oncology online).

Post hoc biomarker analyses

In post hoc analysis, there were 119 patients with enough tumor samples for NRAS and BRAF mutation analysis. NRAS mutations were detected in 9 tumors, in which best tumor response was 1 PR and 3 SD ≥16 weeks. Three tumors exhibited both KRAS and NRAS mutations. No BRAF mutations (V600E) were detected.

Table 1. Demographic and clinical characteristics of randomized patients

<table>
<thead>
<tr>
<th></th>
<th>C-GEMOX (N = 62)</th>
<th>GEMOX (N = 60)</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>61 (32–78)</td>
<td>59 (32–80)</td>
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</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (45%)</td>
<td>30 (50%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Female</td>
<td>34 (55%)</td>
<td>30 (50%)</td>
<td></td>
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<tr>
<td>ECOG PS</td>
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<td></td>
<td></td>
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<tr>
<td>0</td>
<td>18 (29%)</td>
<td>17 (28%)</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>44 (71%)</td>
<td>43 (72%)</td>
<td></td>
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<tr>
<td>Primary site</td>
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<td></td>
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<tr>
<td>Intrahepatic</td>
<td>44 (71%)</td>
<td>45 (75%)</td>
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<tr>
<td>Extrahepatic</td>
<td>9 (15%)</td>
<td>10 (17%)</td>
<td></td>
</tr>
<tr>
<td>Gallbladder</td>
<td>9 (15%)</td>
<td>5 (8%)</td>
<td></td>
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<tr>
<td>T stage</td>
<td></td>
<td></td>
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<tr>
<td>≤T3</td>
<td>49 (79%)</td>
<td>47 (78%)</td>
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<tr>
<td>T4</td>
<td>13 (21%)</td>
<td>13 (22%)</td>
<td></td>
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<tr>
<td>N stage</td>
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<tr>
<td>N0</td>
<td>15 (24%)</td>
<td>18 (30%)</td>
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<tr>
<td>N1</td>
<td>47 (76%)</td>
<td>42 (70%)</td>
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<tr>
<td>Disease status at entry</td>
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<tr>
<td>Locally advanced</td>
<td>23 (37%)</td>
<td>17 (28%)</td>
<td>0.34</td>
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<tr>
<td>Distant metastasis</td>
<td>39 (63%)</td>
<td>43 (72%)</td>
<td></td>
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<tr>
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<tr>
<td>No</td>
<td>35 (57%)</td>
<td>36 (60%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (44%)</td>
<td>24 (40%)</td>
<td></td>
</tr>
<tr>
<td>KRAS status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Negative</td>
<td>39 (63%)</td>
<td>39 (65%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Positive</td>
<td>23 (37%)</td>
<td>21 (35%)</td>
<td></td>
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<tr>
<td>EGFR expression*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>17 (28%)</td>
<td>28 (47%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Positive</td>
<td>43 (72%)</td>
<td>32 (53%)</td>
<td></td>
</tr>
</tbody>
</table>

*Only 120 tumors were available for EGFR expression assessment (60 in each arm).
**P was obtained by Fisher’s exact test, two-sided.
C-GEMOX, cetuximab plus gemcitabine and oxaliplatin; GEMOX, gemcitabine plus oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor.

A consistent trend favoring the C-GEMOX arm in terms of ORR and PFS was observed for all analyzed subgroups (supplementary Table S5 and Figure S1, available at Annals of Oncology online), the hazard ratio (HR) for PFS in patients with KRAS WT and mutated tumors was 0.65 (95% CI 0.41–1.03) and 0.73 (95% CI 0.39–1.35), respectively. Multivariate analyses of predictive or prognostic factors for ORR and PFS were shown in supplementary Figures S6–S7, available at Annals of Oncology online, in which C-GEMOX treatment was a borderline predictive factor for ORR (odds ratio = 2.60, 95% CI 0.96–7.06, P = 0.06) and a significant prognostic factor for PFS (HR = 0.67, 95% CI 0.45–0.98; P = 0.04).

Of patients with C-GEMOX, those with grade 2 or higher skin rashes had significantly better ORR, DCR, PFS, and OS than patients with less severe or no skin rashes (supplementary Table S8 and Figure S2, available at Annals of Oncology online).

Post hoc biomarker analyses

In post hoc analysis, there were 119 patients with enough tumor samples for NRAS and BRAF mutation analysis. NRAS mutations were detected in 9 tumors, in which best tumor response was 1 PR and 3 SD ≥16 weeks. Three tumors exhibited both KRAS and NRAS mutations. No BRAF mutations (V600E) were detected.

Figure 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) in all patients.
detected. Therapeutic efficacy based on RAS mutation (KRAS plus NRAS) was summarized in supplementary Table S5, available at Annals of Oncology online. Overall, the results were similar to the KRAS analysis in 122 patients.

discussion

This study is the first randomized trial to evaluate the efficacy of cetuximab plus chemotherapy stratified by tumor KRAS...
mutation status and the one in Asian ABTC patients, as shown Table 3. Addition of cetuximab only marginally, not significantly, improves the ORR and PFS of GEMOX chemotherapy in ABTC in this phase II trial. The results are largely consistent with that of two previous randomized trials evaluating adding either erlotinib or cetuximab to GEMOX in ABTC [9, 10].

The 36% of KRAS mutation rate in current study by the TaqMan® assay was similar to that of 41% by pyrosequencing in the report of Sohal et al. [17] and higher than the 10%–26% mutation rate in previous reports using direct sequencing [9, 15, 16, 19]. However, our analysis showed patients with KRAS-mutated ABTC had marginally lower responses and shorter survival than those with KRAS WT tumor, regardless of treatment group (supplementary Table S4, available at Annals of Oncology online). Whether KRAS mutation to be a negative prognostic factor for ABTC, as it did for IHCC after hepatectomy [19], requires further validation in larger study cohort. In addition, although patients with C-GEMOX did not achieve significantly better ORR and PFS than those with GEMOX alone, the trend of improvement in ORR and PFS with C-GEMOX was consistently observed in both KRAS WT and mutated subpopulations (supplementary Figure S1, available at Annals of Oncology online). A similar trend was also observed in the post hoc analysis of BINGO study in which, although not statistically significant, patients with C-GEMOX had numerical higher 4-month PFS rate when compared with patients with GEMOX alone regardless of KRAS mutation status [10]. Our post hoc analysis further demonstrated a similar trend in KRAS/NRAS WT and mutated subgroups (supplementary Table S5, available at Annals of Oncology online), indicating RAS mutation did not preclude the efficacy of cetuximab in ABTC.

We chose GEMOX as the backbone chemotherapy because modified GEMOX was the first regimen to demonstrate the survival benefit of systemic chemotherapy over best supportive care in ABTC patients and the experience of better compliance of GEMOX than GC in clinical practice [20]. However, we adopted the modified GEMOX by replacing the administration schedule of gemcitabine from 900 mg/m² bolus injection with 800 mg/m² FDR infusion, based on previously reported pharmacokinetic advantage of FDR [21]. With such a relatively low dose of gemcitabine and oxaliplatin regimen, our patients had comparable clinical outcomes with lower incidence of all grade sensory neuropathy and grade 3–4 neutropenia when compared with those with 100 mg/m² oxaliplatin and 1000 mg/m² gemcitabine in the Korean and BINGO trials [9, 10]. It is also interested to note that of patients with either GC or GEMOX in randomization trials for ABTC, the ORR and median PFS in trials from western countries (ABC02 and BINGO trials) were generally better than those from Asian countries (BT-22, Korean and current studies), with ORR of 23%–26% versus 15%–20% and PFS of 5.5–8.0 versus 4.1–5.8 months [9, 10, 22]. Whether the therapeutic effects of gemcitabine and platinum doublets in ABTC would be affected by ethnicity or the choice of platinum agent can only be answered by well-designed, prospective, large-scale randomization study.

In current study, the trend toward better therapeutic efficacy of C-GEMOX was not affected by the status of EGFR expression and KRAS mutation in ABTC. Recent studies linked the molecular abnormalities in cancer cells and the activation of EGFR signaling of intratumor mesenchymal stem cells with angiogenic and/or inflammatory responses in the tumor microenvironment, which can play crucial roles in cancer progression [23, 24]. Therefore, targeting EGFR-expressing stromal cells and the induction of antibody-dependent cell-mediated cytotoxicity are potential mechanisms to explain the effectiveness of cetuximab in EGFR-negative and/or KRAS-mutated tumors. A more comprehensive illustration of how molecular abnormalities regulate the tumor microenvironment will facilitate identification of optimal BTC patient subgroups for EGFR-targeted therapy.

The close correlation between the severity of skin rashes and cetuximab efficacy in current study was consistent with the findings in two previous studies of anti-EGFR therapy in ABTC, a Belgian study with cetuximab and a Korean study with erlotinib [9, 15]. These findings concur with the predictive role of skin rashes for EGFR antagonists in patients with mCRC and NSCLC [25, 26]. On the other hand, three trials combining chemotherapy with panitumumab in ABTC and the BINGO study did not describe such an association (Table 3) [10, 11, 17, 18].

There are several limitations in our study. First, randomized phase II trials can help balance patient heterogeneity and avoid selection bias; however, insufficient patient number frequently undermines the statistical power of such studies, especially when the effect of improvement is moderate or lower, as in the current study. Second, emerging data suggests that some BTC tumors could be driven by oncogenic alterations such as MET amplification, FGFR2 translocation, and ROS1 fusion, which might lead to anti-EGFR therapy resistance [27, 28, 29]. However, these biomarkers were not validated in ABTC studies, and not included at stratification or enrichment factors in current study.

In conclusion, C-GEMOX was well tolerated but failed to demonstrate significantly therapeutic superiority than GEMOX alone for ABTC in current randomized phase II trial. Further exploration of predictive and prognostic molecular biomarkers for selecting patients who will benefit most from EGFR-targeted therapy is warranted.

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disclosure

JSC received honorariums from Merck Serono, TTY Biopharm, and Sanofi. YC received an honorarium from TTY Biopharm. LTC received honorariums from Merck Serono, TTY Biopharm, and Sanofi, and also received study medication from TTY Biopharm for another investigator-initiated trial. All remaining authors have declared no conflicts of interest.

references