Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial

Kohei Nakachi, Masafumi Ikeda, Masaru Konishi, Shogo Nomura, Hiroshi Katayama, Tomoko Kataoka, Akiko Todaka, Hiroaki Yanagimoto, Soichiro Morinaga, Shogo Kobayashi, Kazuaki Shimada, Yu Takahashi, Toshio Nakagohri, Kunihito Gotoh, Ken Kamata, Yasuhiro Shimizu, Makoto Ueno, Hiroshi Ishii, Takuji Okusaka, Junji Furuse, on behalf of the Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology Group (JCOG-HBPOG)

Summary

Background S-1 has shown promising efficacy with a mild toxicity profile in patients with advanced biliary tract cancer. The aim of this study was to evaluate whether adjuvant S-1 improved overall survival compared with observation for resected biliary tract cancer.

Methods This open-label, multicentre, randomised phase 3 trial was conducted in 38 Japanese hospitals. Patients aged 20–80 years who had histologically confirmed extrahepatic cholangiocarcinoma, gallbladder carcinoma, ampullary carcinoma, or intrahepatic cholangiocarcinoma in a resected specimen and had undergone no local residual tumour resection or microscopic residual tumour resection were randomly assigned (1:1) to undergo observation or to receive S-1 (ie, 40 mg, 50 mg, or 60 mg according to body surface area, orally administered twice daily for 4 weeks, followed by 2 weeks of rest for four cycles). Randomisation was performed by the minimisation method, using institution, primary tumour site, and lymph node metastasis as adjustment factors. The primary endpoint was overall survival and was assessed for all randomly assigned patients on an intention-to-treat basis. Safety was assessed in all eligible patients. For the S-1 group, all patients who began the protocol treatment were eligible for a safety assessment. This trial is registered with the University hospital Medical Information Network Clinical Trials Registry (UMIN000011688).

Findings Between Sept 9, 2013, and June 22, 2018, 440 patients were enrolled (observation group n=222 and S-1 group n=218). The data cutoff date was June 23, 2021. Median duration of follow-up was 45·4 months. In the primary analysis, the 3-year overall survival was 67·6% (95% CI 61·0–73·3%) in the observation group compared with 77·1% (70·9–82·1%) in the S-1 group (adjusted hazard ratio [HR] 0·69, 95% CI 0·51–0·94; one-sided p=0·0080). The 3-year relapse-free survival was 50·9% (95% CI 44·1–57·2%) in the observation group compared with 62·4% (55·6–68·4%) in the S-1 group (HR 0·80, 95% CI 0·61–1·04; two-sided p=0·088). The main grade 3–4 adverse events in the S-1 group were decreased neutrophil count (29 [14%]) and biliary tract infection (15 [7%]).

Interpretation Although long-term clinical benefit would be needed for a definitive conclusion, a significant improvement in survival suggested adjuvant S-1 could be considered a standard of care for resected biliary tract cancer in Asian patients.

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Introduction

The biliary tract contains the intrahepatic bile duct, extrahepatic bile duct, gallbladder, and ampulla of Vater. Biliary tract cancer is a generic name for a cancer that arises from these tissues. In Japanese cancer staging systems, extrahepatic cholangiocarcinoma (subclassified into perihilar or distal cholangiocarcinoma), gallbladder carcinoma, and ampullary carcinoma are classified as biliary tract cancer, and intrahepatic cholangiocarcinoma is classified as primary liver cancer.[1] In the TNM classification, each of these diseases is classified independently.[2] Although surgical resection is the only potentially curative treatment, the risk of relapse remains extremely high, particularly in the case of lymph node invasion or positive surgical margin. The reported 5-year overall survival is 30–50%.[3] When we planned this trial, no standard adjuvant chemotherapy had yet been established.[4–7] Results were reported from the Capecitabine Compared with Observation in Resected Biliary Tract Cancer (BILCAP) trial[8] conducted in the UK comparing capecitabine with observation. Although the primary endpoint of overall survival was not met in the intention-to-treat analysis, with a median overall survival of 51·1 months in the capecitabine group compared with 36·4 months in the observation group (adjusted hazard ratio [HR] 0·81, 95% CI 0·63–1·04; p=0·097), the prespecified per-protocol analysis suggested that capecitabine could improve overall survival (HR 0·75, 0·58–0·97; p=0·028).[8] Recently, long-term outcomes of the

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Department of Medical Oncology, Tochigi Cancer Center, Utsunomiya, Japan (K Nakachi MD); **Department of Hepatobiliary and Pancreatic Oncology** (K Nakachi, M Ikeda MD), **and Department of Hepatobiliary and Pancreatic Surgery** (M Konishi MD), **National Cancer Center Hospital East, Kashiwa, Japan; Japan Clinical Oncology Group Data Center** (S Nomura PhD), **Japan Clinical Oncology Group Operations Office** (H Katayama MD, T Kataoka PhD), **Clinical Research Support Office, Department of Hepatobiliary and Pancreatic Surgery** (K Shimada MD), **and Department of Hepatobiliary and Pancreatic Oncology** (T Okusaka MD), **National Cancer Center Hospital, Tokyo, Japan; Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan** (A Todaka MD); **Department of Surgery, Kansai Medical University, Hirakata, Japan** (H Yanagimoto MD); **Department of Hepato-Biliary and Pancreatic Surgery, Kanagawa Cancer Center, Yokohama, Japan** (S Morinaga MD); **Department of Gastroenterological Surgery, Osaka International Cancer Institute, Osaka, Japan** (S Kobayashi MD); **Division of Hepatobiliary and Pancreatic Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan** (Y Takahashi MD); **Department of Gastroenterological Surgery, Tokai University School of Medicine, Isehara, Kanagawa, Japan** (Prof T Nakagohri MD);

Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan (K Gotoh MD); **Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan** (K Kamata MD); **Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan** (Y Shimizu MD); **Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan** (M Ueno MD); **Gastrointestinal Medical Oncology, Chiba Cancer Center, Chiba, Japan** (H Ishii MD); **Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan** (Prof J Furuse MD)

Correspondence to: Dr Kohei Nakachi, Department of Medical Oncology, Tochigi Cancer Center, Utsunomiya 320–0834, Japan
knakachi@tochigi-cc.jp

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for research articles published using the terms "biliary tract cancer", "cholangiocarcinoma", "gall bladder carcinoma", "ampullary carcinoma", and "adjuvant" with the limitation of "clinical trial phase 3" between Jan 1, 2000, and Jun 30, 2022. Although the Capecitabine Compared with Observation in Resected Biliary Tract Cancer (BILCAP) study comparing capecitabine with observation did not meet the primary endpoint (ie, overall survival in intention-to treat analysis), sensitivity or per-protocol analysis indicated a benefit of adjuvant capecitabine. The American Society of Clinical Oncology guideline recommends capecitabine as adjuvant therapy on the basis of BILCAP results.

Added value of this study

To the best of our knowledge, this Adjuvant S-1 for Cholangiocarcinoma Trial (ASCOT) is the first randomised trial to show a significant survival benefit from adjuvant chemotherapy for this setting in an intention-to-treat analysis.Although ASCOT included only Japanese patients and S-1 is rarely used in Europe and in the USA, the benefit of oral fluoropyrimidine was shown in this setting.

Implications of all the available evidence

Oral fluoropyrimidine, S-1, or capecitabine, should be considered a control for future clinical trials. The results of the ongoing Adjuvant Chemotherapy with Gemcitabine and Cisplatin Compared to Standard of Care after Curative Intent Resection of Cholangiocarcinoma and Muscle Invasive Gall Bladder Carcinomatrial trial are expected to further improve prognosis. Adjuvant chemotherapy with S-1 could be considered a standard of care in Asian patients.

BILCAP study were reported, with similar results to those initially reported.[9] On the basis of such results, capecitabine has been considered a standard of care in European countries and the USA.

S-1 is an oral anticancer drug comprising a mixture of tegafur (a prodrug of fluorouracil), gimeracil, and oteracil potassium. Gimeracil inhibits dihydropyrimidine dehydrogenase activity, maintaining high concentrations of fluorouracil in blood and tumour tissue, and oteracil potassium suppresses phosphorylation of fluorouracil in the gastrointestinal tract, reducing gastrointestinal toxicity.[10] This drug has been shown to provide survival benefits when used as adjuvant chemotherapy in Japanese patients with pancreatic cancer[11] and gastric cancer.[12] In addition, Furuse and colleagues[13] conducted a phase 2 study of S-1 in 40 patients with advanced biliary tract cancer, and reported favourable efficacy of S-1, with a response rate of 35% and a median survival time of 9·2 months. S-1 in combination with gemcitabine was found to be non-inferior to gemcitabine plus cisplatin, and S-1 in combination with gemcitabine plus cisplatin was shown to be superior to gemcitabine plus cisplatin in the phase 3 trials for advanced biliary tract cancer.[14,15] We confirmed the feasibility of adjuvant therapy with S-1 in 33 patients with resected biliary tract cancer.[16] Among those patients, the 24-week protocol treatment was completed in 25 patients (76%). On the basis of the results, we conducted a randomised, phase 3 trial aiming to confirm the superiority of adjuvant S-1 over observation after curative resection of biliary tract cancer.

Methods

Study design and participants

This multicentre, open-label, randomised phase 3 Adjuvant S-1 for Cholangiocarcinoma Trial (ASCOT) was conducted at 38 Japanese hospitals participating in the Hepatobiliary Pancreatic Cancer Study Group of the Japan Clinical Oncology Group (JCOG; appendix pp 2–3). Eligible patients were 20–80 years old with histologically confirmed adenocarcinoma or adenosquamous carcinoma (ie, extrahepatic cholangiocarcinoma, gallbladder carcinoma, ampullary carcinoma, or intrahepatic cholangiocarcinoma) in a resected specimen, pathologically confirmed as T2–4, N0, M0 or T1–4, N1, M0 (for patients with extrahepatic cholangiocarcinoma, gallbladder carcinoma, or ampullary carcinoma), or T1–4, N0–1, M0 (for patients with intrahepatic cholangiocarcinoma) with no local residual tumour (R0) or microscopic residual tumour (R1) according to the 7th edition of Union for International Cancer Control classification,[2] and no distant metastases or moderate to severe ascites or pleural effusion according to findings from postoperative contrast-enhanced CT or MRI of upper abdomen and pelvis and CT of the chest. These imaging tests were mandatory before enrolment. All patients should have had radical surgical resection with curative intent, including pancreaticoduodenectomy, hepatectomy, bile duct resection, or cholecystectomy with D1 or more extensive lymphadenectomy according to the 5th edition of the Japanese Classification of Biliary Tract Carcinoma.[1] The extent of D1 regional lymphadenectomy is defined for each primary site and is provided in the protocol. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 or 1, within 2–10 weeks after resection, adequate organ functions (ie, absolute neutrophil count ≥1200 cells per μL; platelet count ≥100 000 cells per μL; haemoglobin ≥8·0 g/dL; total bilirubin ≤2·0 mg/dL; aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, serum creatinine ≤1·2 mg/dL; creatinine clearance ≥50 mL/min), and provision of written informed consent. The complete inclusion and exclusion

criteria are provided in the appendix (pp 4–5) and are also available in the protocol. The study protocol was reviewed for scientific and ethical content and was approved by the Japan Clinical Oncology Group Protocol Review Committee and the institutional review board of each participating hospital before initiation of the study. The Data and Safety Monitoring Committee monitored data and operation of the study. This study was undertaken in accordance with the international ethical recommendations stated in the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

Randomisation and masking

Using the Japan Clinical Oncology Group's web entry system (EPS Holdings, Tokyo, Japan) at the groups' Data Centre, enrolled patients were randomly assigned to either the observation or the S-1 group in a 1:1 ratio. Randomisation was performed by minimisation method, using institution, primary tumour site, and lymph node metastasis as adjustment factors. Patients, investigators, and the Japan Clinical Oncology Group Data and Safety Monitoring Committee were not masked to treatment assignment.

Procedures

Patients in the S-1 group received an oral dose of S-1 twice daily for 4 weeks, followed by a 2-week rest period. Three dose levels of S-1 were set according to body surface area: less than 1·25 m² 40 mg; 1·25 to less than 1·50 m² 50 mg; and 1·50 m² or more 60 mg twice a day. Patients with creatinine clearance levels of 50–60 mL/min received a 10 mg reduction in each dose of S-1 (ie, a 20 mg/day reduction). Treatment was continued for up to four cycles or 24 weeks. The criteria for dose modification are provided in the appendix (pp 6–8). Patients in the observation group received no anticancer treatment unless relapse was detected. Patients were followed up for 5 years after completion of patient accrual. Enhanced CT or MRI of the upper abdomen and pelvis, chest CT, and serum tumour marker levels (eg, carcinoembryonic antigen and carbohydrate antigen 19–9) were evaluated every 3 months until 3 years, and every 6 months until the end of 5 years after enrolment. Physical and laboratory examinations were performed once every 2–3 weeks in the S-1 group during protocol treatment, and every 4 weeks in the observation group until 24 weeks after enrolment. These examinations were then performed every 3 months until 3 years, and every 6 months until the end of 5 years after enrolment. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. S-1 was covered by health insurance and was not supported by the manufacturer.

Outcomes

The primary outcome was overall survival in all the randomised patients. The secondary outcomes were relapse-free survival, adverse events, proportion of treatment completion, and serious adverse events. Overall survival was calculated from the day of enrolment to the day of death from any cause, censored as of the last day the patient was documented to be alive. Relapse-free survival was calculated from the day of enrolment to the day of relapse or day of death from any cause, censored as of the last day the patient was documented to be alive without any evidence of relapse. The occurrence of second primary cancer and metachronous multiple cancer was not regarded as an event or censoring.

Statistical analysis

This study was designed to confirm the superiority of the S-1 over observation alone in improving overall survival. We assumed that the 3-year overall survival rate was 57% for the S-1 group and 47% for the observation group. As available data from previous clinical studies were scarce at the time, the 3-year survival rate for the study population was 47% among the patients with resected biliary tract cancers at the National Cancer Center Hospital East over a 10-year period from 1996 (unpublished data). The 10% difference corresponded to the expected HR for mortality of 0·74. With a one-sided alpha level of 0·05, 285 deaths were required to have 80% power. 440 patients were required with an enrolment period of 5 years and additional follow-up period of 3 years. One-sided alpha was adopted on the basis of a consideration that surgery alone remains the standard treatment when S-1 is inferior to observation. This consideration indicates that a statistical significance of inferiority of S-1 is not required for clinical decision making.

A blinded monitoring report was released in the second half of 2020. The data cutoff date was Sept 29, 2020. The report showed an estimated 3-year survival rate of 71·6%, much higher than expected. An extension of additional follow-up to 5 years (ie, 229 estimated deaths by September, 2023; power 73·7%) was discussed in late 2020, so that the primary analysis could be done on the basis of the 285 prespecified deaths, but we prioritised completion of the primary analysis in 2021 (with the originally planned additional follow-up period of 3 years). This decision was made because capecitabine became the standard treatment outside Japan on accont of the results from the BILCAP trial,[8] so surgery alone was considered unlikely to be recommended by 2023. Even if S-1 could not show a survival advantage statistically, we considered that it would be of benefit to both patients and researchers in Japan to publish the results as soon as possible and move on to the next steps. Consequently, the primary analysis was performed when 179 deaths occurred, representing 62·8% of total expected deaths.

We performed two planned interim analyses (both currently unpublished) and a primary analysis. The

first interim analysis was performed when one half of the initial planned sample size had been enrolled (on the basis of 11 deaths), and the second interim analysis was done when the planned 440 patients had been enrolled (on the basis of 116 deaths). The Lan-DeMets O'Brien & Fleming alpha spending function was used to adjust multiplicity due to the repeated testing for overall survival.[17] Because the projected prognosis was much better than expected, the primary analysis was undertaken without observing the targeted 285 deaths. On the basis of the observed deaths, all unspent alpha level was used for the primary analysis. The multiplicity-adjusted one-sided significance threshold for the primary analysis was 0·04931. The Japan Clinical Oncology Group Data and Safety Monitoring Committee, independently from investigators, reviewed the results of the two interim analyses and discussed whether the study should be terminated. The committee never joined a discussion on the timing of the primary analysis. All data reported here are based on the primary analysis.

Efficacy endpoints (ie, overall survival and relapse-free survival) were analysed for all randomly assigned patients on an intention-to-treat basis. Survival curves were estimated using the Kaplan-Meier method. The primary analysis was assessed by a stratified log-rank test. For overall survival, stratified Cox proportional-hazards model was applied to calculate HRs and associated CIs. The randomisation stratification factors excluding institutions were used for all stratified analyses. Except for the primary analysis for overall survival, unstratified log-rank tests and unstratified Cox proportional-hazards models were used, and all p values were reported as two sided. We undertook prespecified subgroup analyses for efficacy endpoints. Safety was assessed in all eligible patients. In the S-1 group, patients who were eligible to be assessed for safety were those who began the protocol treatment. Statistical analyses were completed by the Japan Clinical Oncology Group Data Center using SAS version 9·4 software. This trial is registered with the University hospital Medical Information Network Clinical Trials Registry (UMIN000011688).

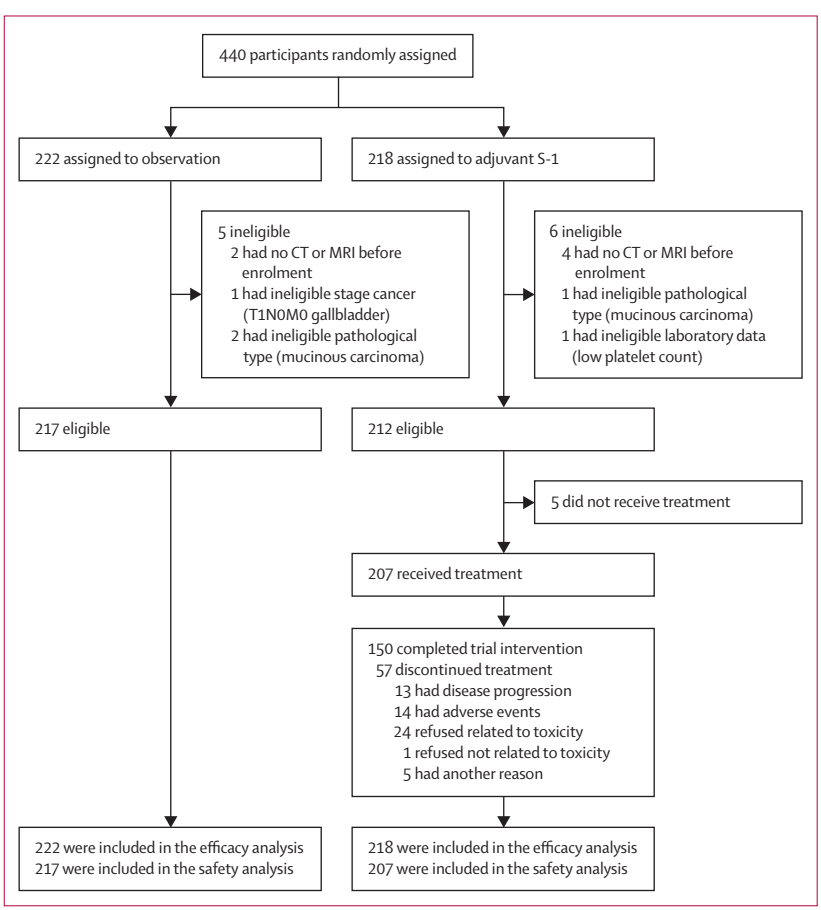

Figure 1: **Trial profile**

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 9, 2013, and June 22, 2018, 440 patients were enrolled and randomly assigned to the observation group (n=222) or the S-1 group (n=218) at 38 centres in Japan. After randomisation, five patients in the observation group and six patients in the S-1 group were found to be ineligible. The reasons for ineligibility were as follows: no CT or MRI before enrolment (six patients), mucinous carcinoma (three patients), stage 1 gallbladder cancer (one patient), and low platelet count (one patient). Five patients did not receive S-1 chemotherapy. As a result, 207 patients received at least one dose of S-1 (figure 1). Reasons for not receiving S-1 were as follows: patient declined to continue participation after randomisation (two patients), cerebral infarction (one patient), emergency orthopaedic surgery (one patient), and deterioration of diabetes (one patient).

Hepatectomy was performed in 186 (42%) of 440 patients, including major hepatectomy in 124 patients (right hepatectomy, n=61; left hepatectomy, n=44; right trisectionectomy, n=6; and left trisectionectomy, n=13; table 1). 227 (52%) patients had a pancreatoduodenectomy. Portal vein resection had been undertaken in 25 (6%) patients, and hepatic artery resection in 12 (3%) patients (appendix p 8). Median time between surgery and randomisation was 53 days (IQR 40–63 days) in the observation group and 53 days (41–63 days) in the S-1 group.

The data cutoff date was June 23, 2021. Median duration of follow-up for all enrolled patients was 45·4 months (IQR 32·1–60·1 months). Of 440 patients, 179 (41%) had died (100 [45%] in the observation group; 79 [36%] in the S-1 group). In the intention-to-treat analysis, overall

survival was longer in the S-1 group than in the observation group (HR 0·69, 95% CI 0·51–0·94; stratified log-rank test, one-sided p=0·0080; figure 2). The 3-year overall survival was 67·6% (95% CI, 61·0–73·3%) in the observation group and 77·1% (70·9–82·1) in the S-1 group. Median overall survival was 6·1 years (95% CI 4·2–not estimable [NE]) in the observation group and NE (95% CI 5·2–NE) in the S-1 group.

Of 440 patients 211 (48%) patients had disease relapse (115 [52%] in the observation group; 96 [44%] in the S-1 group). The HR for relapse-free survival in the S-1 group, as compared with the observation group, was 0·80 (95% CI 0·61–1·04; log-rank test, two-sided p=0·088; figure 2). The 3-year relapse-free survival was 50·9% in the observation group (95% CI 44·1–57·2%) and 62·4% in the S-1 group (55·6–68·4%). Median relapse-free survival was 3·5 years (95% CI 2·0–NE) in the observation group and 5·3 years (4·1–6·1) in the S-1 group. The most common site of first relapse was the liver, followed by lymph nodes. No significant differences were evident between groups (appendix p 9). Among patients who had relapse of disease, 102 (89%) of 115 patients in the observation group and 83 (86%) of 96 patients in the S-1 group had received any type of anticancer treatment. 89 (77%) patients in the observation group and 74 (77%) patients in the S-1 group received systemic chemotherapy, 71 (62%) in the observation group and 64 (67%) in the S-1 group received chemotherapy with gemcitabine plus cisplatin and five (4%) in the observation group and three (3%) in the S-1 group received chemotherapy with S-1 (appendix p 10).

Among 429 eligible patients, the HR for overall survival in the S-1 group compared with the observation group was 0·70 (95% CI 0·52–0·95) and the HR for relapse-free survival was 0·78 (0·60–1·02). Prespecified subgroup analyses among the intention-to-treat population for overall survival and relapse-free survival showed benefits of S-1 in female patients, and patients with lymph-node-positive and stage 3–4A disease (figure 3). No significant interactions were seen between the treatment group and any of the variables studied. Of 207 patients in the S-1 group safety population, 150 (72%) patients completed the protocol treatment. The remaining 57 patients discontinued treatment (reasons for discontinuation are provided in figure 1). Dose reduction was applied in 40 (19%) patients, with 33 (16%) patients requiring one dose reduction and seven (3%) patients requiring two dose reductions. Median time from initiation to dose reduction was 43 days (IQR 36–73·5). Median relative dose intensity was 96% (IQR 79–100). Relative dose intensity was more than 90% in 130 (63%) patients, 70–90% in 52 (25%) patients, and less than 70% in 25 patients (12%).

Common adverse events (ie, frequency ≥30%) of any grade in the S-1 group were decreased white blood cell counts, decreased neutrophil counts, anaemia, decreased platelet counts, hypoalbuminaemia, increased alkaline phosphatase, increased aspartate aminotransferase, increased alanine aminotransferase, fatigue, anorexia, and skin hyperpigmentation (table 2). The main grade 3 or 4 adverse events in the S-1 group

	Observation (n=222)	S-1 (n=218)
Age, years	70 (40–80)	68 (33–80)
Sex		
Female	70 (32%)	56 (26%)
Male	152 (68%)	162 (74%)
Eastern Cooperative Oncology Group performance status		
0	193 (87%)	191 (88%)
1	29 (13%)	27 (12%)
Primary tumour site		
Extrahepatic bile duct		
Perihilar	41 (18%)	46 (21%)
Distal	80 (36%)	78 (36%)
Gallbladder	33 (15%)	31 (14%)
Ampulla of Vater	37 (17%)	36 (17%)
Intrahepatic bile duct	31 (14%)	27 (12%)
Tumour stage*		
1	36 (16%)	36 (17%)
2	130 (59%)	126 (58%)
3	38 (17%)	37 (17%)
4A	18 (8%)	19 (9%)
Lymph node stage		
N0	132 (59%)	132 (61%)
N1	90 (41%)	86 (39%)
Histology		
Papillary	24 (11%)	14 (6%)
Well differentiated	65 (29%)	65 (30%)
Moderately differentiated	106 (48%)	113 (52%)
Poorly differentiated	19 (9%)	22 (10%)
Other	8 (3%)	4 (2%)
Resection status		
R0	189 (85%)	187 (86%)
R1	33 (15%)	31 (14%)
Surgery		
Hepatectomy	92 (41%)	94 (43%)
Pancreatoduodenectomy	112 (50%)	115 (53%)
Hepatopancreatoduodenectomy	6 (3%)	2 (1%)
Bile duct resection	12 (5%)	7 (3%)
Time from surgery to randomisation, days	53 (40–63)	53 (41–63)
Carcinoembryonic antigen, ng/mL	1·8 (1·3–2·6)	1·8 (1·3–2·5)
≤5 ng/mL	214 (96%)	213 (98%)
>5 ng/mL	8 (4%)	5 (2%)
Carbohydrate antigen 19–9, U/mL	9·9 (5·0–16·0)	11·2 (6·9–20·6)
≤37 U/mL	201 (91%)	194 (89%)
>37 U/mL	21 (9%)	24 (11%)

Data are n (%) or median (IQR). *Tumour stage was assessed according to TNM classification, 7th edition.

Table 1: **Baseline characteristics (intention-to-treat population)**

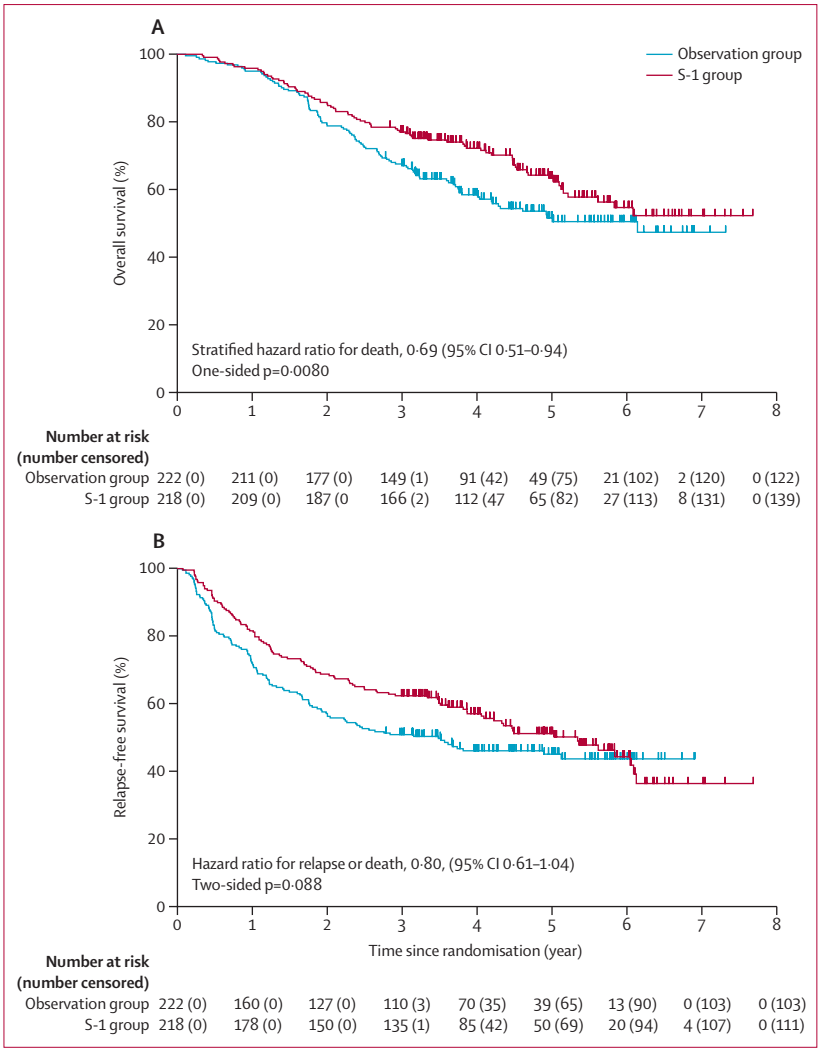

Figure 2: **Kaplan-Meier estimates of overall survival (A) and relapse-free survival (B) in the intention-to-treat population according to treatment group**
Tick marks indicate censored data.

were decreased neutrophil count 28 (14%) of 207 and biliary tract infection 15 (7%) of 207. Grade 4 non-haematological adverse events, such as increased blood bilirubin, increased aspartate aminotransferase, increased alanine aminotransferase, and biliary infection, were observed in five patients in the observation group and four patients in the S-1 group, with most adverse events only occuring in one or two patients. Of the four patients in the S-1 group, two events were considered related to S-1 (ie, myocardial infraction and Guillain-Barré syndrome). No treatment-related deaths occurred in either group.

Discussion

Our results showed that adjuvant therapy with S-1 prolonged survival among patients with resected biliary tract cancer compared with observation. This study represents the first randomised trial to show a statistically significant survival benefit from adjuvant chemotherapy for this setting in an intention-to-treat analysis. The HR of 0·69 observed in this study is the best among previously reported randomised trials of adjuvant biliary tract cancer.[4–8] The American Society of Clinical Oncology guideline recommends capecitabine as adjuvant therapy on the basis of the BILCAP trial results.[18] The guidelines commented that this recommendation was of moderate strength, due to the presence of only one randomised trial, the inconsistency of results between per-protocol and intention-to-treat analyses, and questions of generalisability to Asian populations. The results of this study complement the findings from the BILCAP study and strengthen the evidence for the effectiveness of oral fluoropyrimidines in adjuvant therapy.

Several explanations could account for the survival advantage of adjuvant therapy with S-1 in this study. First, S-1 was well tolerated, resulting in the high proportion of treatment completion of 150 (72%) of 207 among the safety population in the ASCOT trial, compared with 122 (58%) of 210 for capecitabine in the BILCAP trial,[8] and 61 (54%) of 114 for gemcitabine in the BCAT trial,[6] a Japanese randomised trial comparing gemcitabine and observation for extrahepatic cholangiocarcinoma. This proportion resulted in more patients benefiting from adjuvant therapy. The incidences of hand–foot syndrome (grade 3 20% *vs* 0%) and diarrhoea (8% *vs* 3%) leading to treatment discontinuation in BILCAP were lower in ASCOT. The proportion of treatment completion at 6 months was 78% in ACTS-GC[12] and 72% in JASPAC01,[11] similar to the present study. S-1 thus appears to offer a feasible and effective adjuvant chemotherapy for gastrointestinal cancer. Second, several differences in patient background were observed between ASCOT and BILCAP. Since both S-1 and capecitabine are more beneficial for patients with good performance status and R0 resection in the adjuvant setting, the inclusion of more patients with a performance status of 0 in ASCOT, 87% versus 45% in BILCAP, and with R0 resection in ASCOT, 88% versus 62% in BILCAP, might have contributed to the favourable results in ASCOT. The inclusion of more patients with a performance status of 0 might have also contributed to the favourable overall survival in the observation group in ASCOT (6·1 years *vs* 36 months in BILCAP). The effect of adjuvant S-1 was higher for patients with a performance status of 0 than for those with a performance status of 1 in subgroup analysis. Patients with a good performance status are thought to tolerate chemotherapy well, leading to the high proportion of treatment completion. The effect of S-1 was higher for R0 than for R1. The inclusion of more patients with R0 resection might have contributed to the favourable relapse-free survival in the observation group in ASCOT (median relapse-free survival 3·5 years *vs* 17·5 months in BILCAP). Ampullary carcinoma was included in the ASCOT study, but not in the BILCAP study, with a better HR for overall survival of 0·49 in the subgroup analysis. These differences

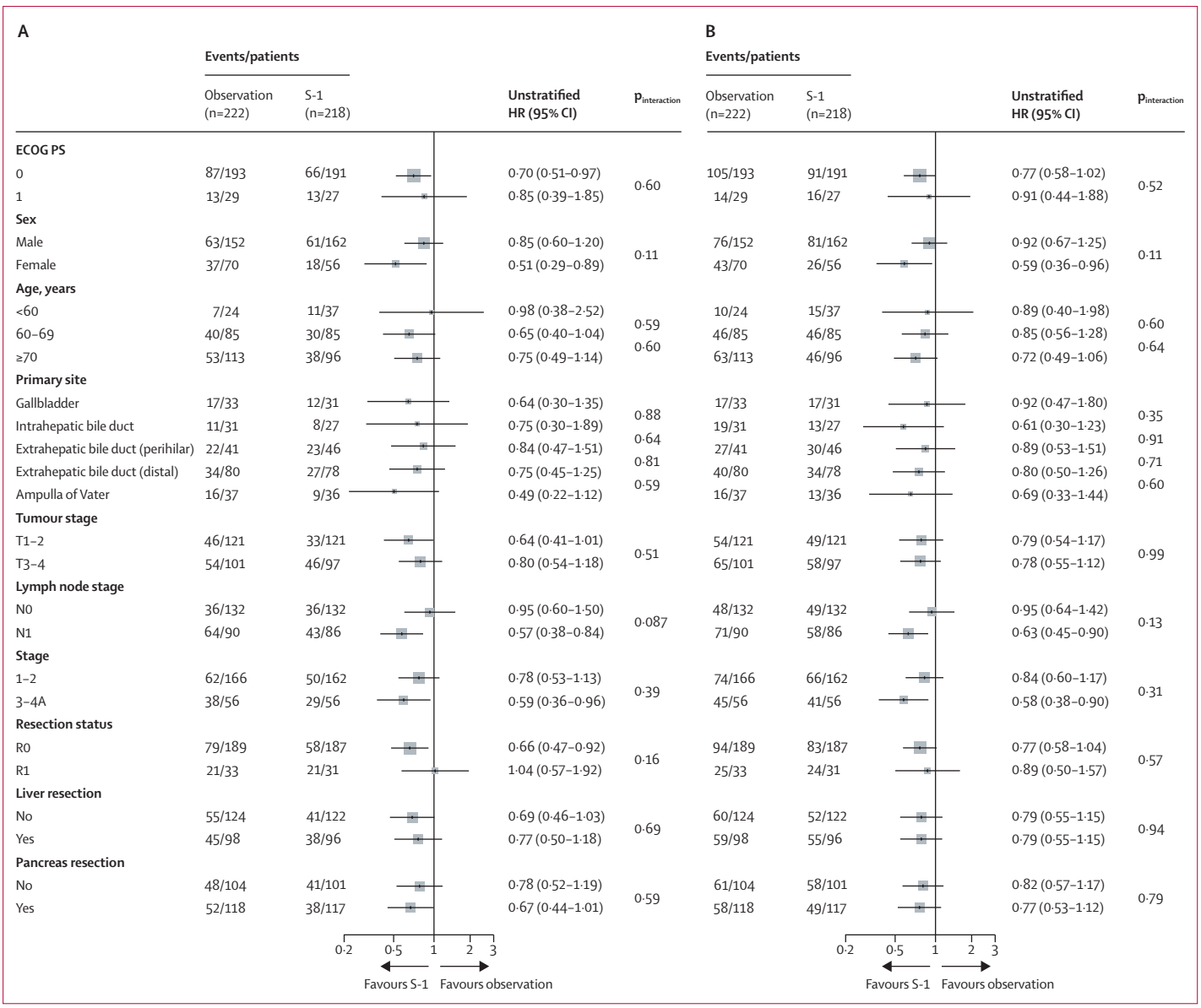

***Figure 3*: Forest plot of the treatment effect on overall survival (A) and relapse-free survival (B) in prespecified subgroup analyses**
The position of each square represents the point estimate of the treatment effect, and error bars represent 95% CIs. The sizes of squares are proportional to the precision of the estimates. HR=hazard ratio. ECOG PS=Eastern Cooperative Oncology Group performance status.

in background factors might have contributed to the favourable results in ASCOT. Third, both S-1 and capecitabine are oral fluoropyrimidines that exert antitumour activity in a time-dependent manner; so maintaining blood concentrations of fluorouracil seems important, particularly in eliminating minimal residual tumours, while keeping toxicity tolerable. S-1 contains oteracil potassium, which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, playing an important role in reducing gastrointestinal toxicities.

More potent postoperative adjuvant chemotherapies, such as combination regimens, are expected to be developed in the future. The PRODIGE 12 trial,[7] a randomised trial comparing a combination of gemcitabine plus oxaliplatin with surveillance, did not show a survival benefit. The STAMP trial,[19] a randomised phase 2 trial, showed that adjuvant gemcitabine plus cisplatin did not improve disease-free survival and overall survival compared with capecitabine for lymph-node-positive extrahepatic cholangiocarcinoma. The ACTICCA-01 study,[20] in which patients are randomly assigned to capecitabine compared with gemcitabine plus cisplatin, is ongoing and the results are anticipated. To make up for weaknesses in postoperative adjuvant therapy, preoperative neoadjuvant chemotherapy offers another direction for potentially resectable biliary tract

	Observation (n=217)			S-1 (n=207)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Decreased white blood cells	24 (11%)	1 (<1%)	0	88 (43%)	6 (3%)	0
Anaemia	163 (75%)	3 (1%)	1 (<1%)	193 (93%)	8 (4%)	1 (<1%)
Decreased platelet count	78 (36%)	1 (<1%)	0	140 (68%)	2 (1%)	0
Decreased neutrophil count	68 (31%)	3 (1%)	0	119 (57%)	28 (14%)	1 (<1%)
Hypoalbuminaemia	173 (80%)	5 (2%)	NA	194 (94%)	1 (<1%)	NA
Increased blood bilirubin	5 (2%)	3 (1%)	2 (1%)	50 (24%)	2 (1%)	2 (1%)
Increased alkaline phosphatase	141 (65%)	4 (2%)	0	130 (63%)	4 (2%)	0
Increased aspartate aminotransferase	99 (46%)	2 (1%)	4 (2%)	115 (56%)	6 (3%)	0
Increased alanine aminotransferase	69 (32%)	4 (2%)	2 (1%)	70 (34%)	3 (1%)	0
Increased creatinine	21 (10%)	0	0	29 (14%)	0	0
Febrile neutropenia	NA	0	0	NA	3 (1%)	0
Diarrhoea	5 (2%)	0	0	51 (25%)	6 (3%)	0
Mucositis oral	0	0	0	37 (18%)	2 (1%)	0
Biliary tract infection	NA	7 (3%)	1 (<1%)	NA	15 (7%)	0
Rash maculo-papular	3 (1%)	0	NA	22 (11%)	4 (2%)	NA
Palmar-plantar erythrodysesthesia syndrome	0	0	NA	9 (4%)	0	NA
Fever	32 (15%)	2 (1%)	0	50 (24%)	2 (1%)	0
Fatigue	8 (4%)	2 (1%)	NA	74 (36%)	6 (3%)	NA
Abdominal pain	11 (5%)	0	NA	21 (10%)	2 (1%)	NA
Nausea	3 (1%)	0	NA	59 (29%)	2 (1%)	NA
Vomiting	9 (4%)	0	0	10 (5%)	1 (<1%)	0
Anorexia	5 (2%)	1 (<1%)	0	87 (42%)	6 (3%)	0
Skin hyperpigmentation	0	NA	NA	75 (36%)	NA	NA
Dehydration	0	2 (1%)	0	2 (1%)	2 (1%)	0
Dysgeusia	2 (1%)	NA	NA	28 (14%)	NA	NA
Watering eyes	0	0	NA	38 (18%)	0	NA

Data are n (%). Adverse events experienced by three or more patients are reported. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. NA=not available.

Table 2: **Adverse events (safety population)**

cancer. The advantage of this approach is the availability of chemotherapy to all patients scheduled for surgery. The population that can receive postoperative adjuvant therapy is limited because of postoperative complications or exhaustion, so a substantial number of patients receive no benefit from postoperative adjuvant chemotherapy. Although the development of a more intensive postoperative adjuvant chemotherapy is difficult, the addition of preoperative chemotherapy is expected to enhance treatment efficacy. Biliary tract cancer is a heterogeneous disease category, and genomic profiles reportedly differ among primary lesions.[21] As specific targeted therapies depending on genomic alterations have already been developed for advanced biliary tract cancer,[22,23] similar targeted therapies are expected to be introduced to perioperative settings in the future.

A key limitation of the present study was that ASCOT was conducted only in Japanese patients. The pharmacokinetics and toxicity of S-1 have been suggested to differ in European and North American patients, particularly with regard to the occurrence of diarrhoea,[24] resulting in a need for dose adjustment.[25] A second limitation was that the statistical power for evaluations of relapse-free survival was low due to the small number of events, and the Kaplan-Meier curves crossed at 6 years. The 3-year relapse-free survival showed a sufficient difference (50·9% *vs* 62·4%). As relapse data after 3 years should be considered immature with many censored cases, we scheduled the final analysis for the 5-year follow-up. A third limitation was that the 3-year overall survival in the observation group observed in the ASCOT was 67·6%, representing a 20% improvement compared with the hypothesised 47%. That hypothesised value had been based on outcomes from more than 10 years earlier. Improvements in surgical management, as well as more appropriate patient selection due to advances in diagnostic imaging technology, presumably contributed to this discrepancy. The 3-year overall survival was consistent with that of the BCAT trial (65%).[6] This favourable overall survival is considered the current surgical outcome in Japan. Short follow-up time and a small number of events for the primary analysis are a fourth and fifth limitation; a final analysis of the 5-year follow-up is planned. The sixth limitation was that the trial is open-label; however, we consider that the trial design was ethically acceptable, the schedule of follow-up for death and relapse was the same manner for both groups, and the effect on overall survival and relapse-free survival was very limited.

In conclusion, adjuvant therapy with S-1 led to significantly longer overall survival than observation in Japanese patients with resected biliary tract cancer and was well tolerated in this setting. Although long-term clinical benefit would be needed for a definitive conclusion, S-1 could be considered a standard of care in Asian patients with resected biliary tract cancer.

Contributors

KN, MI, MK, HK, MU, HI, TO, and JF designed the trial, wrote the protocol, and coordinated the study. AT, HY, SM, SK, KS, YT, TN, KG, KK, and YS recruited patients and collected data. SN analysed the data. The first draft of the manuscript was prepared by KN and was based on the other authors' comments on the manuscript outline. Thereafter, the first draft was critically reviewed and revised by all authors. KN, MI, MK, HK, TK, and SN had access to the data, verified the underlying data, and contributed to the data interpretation and review, revision, and approval of the report.

Declaration of interests

KN has received grants from Delta-Fly Pharma and honoraria from Eisai, Yakult, AstraZeneca, and Ono. MI has received research funding from Eisai, Merck Biopharma, Eli Lilly Japan, Yakult, Ono, J-Pharma, AstraZeneca, Pfizer, Merus NV, NIHON SERVIER, Delta-Fly Pharma, Chiome Bioscience, Chugai, Bristol-Myers Squibb, Novartis, Bayer, Merck, and Syneos Health and honoraria from Eisai, Merck, Eli Lilly Japan, Yakult, Teijin Pharma, Ono, Incyte Biosciences Japan, NIHON SERVIER, Taiho, Chugai, Bristol-Myers Squibb, Novartis, Bayer, Takeda, EA Pharma, AstraZeneca, AbbVie, Abbott Japan, and Fujifilm Toyama Chemical. SN has received grants from AstraZeneca and Amgen and honoraria from AstraZeneca, Chugai, and Kyowa Hakko. AT has received honoraria from Ono Pharmaceutical, Yakult Honsha, and Taiho Pharmaceutical. MU has received grants from Taiho Pharmaceutical, AstraZeneca, Merck Biopharma, Merck, Astellas Pharma, Eisai, Ono Pharmaceutical, Incyte Biosciences Japan, Chugai Pharmaceutical, Delta-Fly Pharma, and Daiichi

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Data sharing

Qualified researchers can request access to study documents (including the clinical study report, the study protocol with any amendments, and the statistical analysis plan) that support the methods and findings reported in this Article.

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