World Journal of Gastrointestinal Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Oncol 2023 June 15; 15(6): 959-972

DOI: 10.4251/wjgo.v15.i6.959

ISSN 1948-5204 (online)

MINIREVIEWS

Paradigm shift of chemotherapy and systemic treatment for biliary tract cancer

Wattana Leowattana, Tawithep Leowattana, Pathomthep Leowattana

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Govindarajan KK, India; Hori T, Japan; Roy S, United States

Received: January 26, 2023
Peer-review started: January 26, 2023
First decision: April 11, 2023
Revised: April 14, 2023
Accepted: May 5, 2023
Article in press: May 5, 2023
Published online: June 15, 2023

Wattana Leowattana, Pathomthep Leowattana, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Rachatawee 10400, Bangkok, Thailand

Tawithep Leowattana, Department of Medicine, Faculty of Medicine, Srinakharinwirot University, Wattana 10110, Bangkok, Thailand

Corresponding author: Wattana Leowattana, BMed, MD, MSc, PhD, Full Professor, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajavithi Road, Rachatawee 10400, Bangkok, Thailand. wattana.leo@mahidol.ac.th

Abstract

Biliary tract cancers (BTC) are frequently identified at late stages and have a poor prognosis due to limited systemic treatment regimens. For more than a decade, the combination of gemcitabine and cis-platin has served as the first-line standard treatment. There are few choices for second-line chemo-therapy. Targeted treatment with fibroblast growth factor receptor 2 inhibitors, neurotrophic tyrosine receptor kinase inhibitors, and isocitrate dehydrogenase 1 inhibitors has had important results. Immune checkpoint inhibitors (ICI) such as pembrolizumab are only used in first-line treatment for microsatellite instability high patients. The TOPAZ-1 trial's outcome is encouraging, and there are several trials underway that might soon put targeted treatment and ICI combos into first-line options. Newer targets and agents for existing goals are being studied, which may represent a paradigm shift in BTC management. Due to a scarcity of targetable mutations and the higher toxicity profile of the current medications, the new category of drugs may occupy a significant role in BTC therapies.

Key Words: Biliary tract cancers; Gemcitabine and cisplatin combination; Fibroblast growth factor receptor 2 inhibitors; Isocitrate dehydrogenase 1 inhibitors; Neurotrophic tyrosine receptor kinase gene fusion inhibitors; Immune checkpoint inhibitors; Microsatellite instability high; Infrigatinib; Pemigatinib

Core Tip: There have been several developments in the field of advanced biliary tract cancer (BTC) therapy in recent years. First, the care of these hepatobiliary malignancies has improved as a result of better knowledge of the molecular basis of BTC. The Food and Drug Administration's approval of pemigatinib, infigratinib, and ivosidenib for fibroblast growth factor receptor 2-rearranged and isocitrate dehydrogenase 1-mutant cholangiocarcinoma illustrates the paradigm shift that the arrival of targeted agents has really brought about. Second, patients receiving modified fluorouracil, oxaliplatin, and liposomal irinotecan with fluorouracil-leucovorin, respectively, as second-line treatments after progressing to first-line cisplatin-gemcitabine, showed an overall survival advantage in the newly released Advanced Biliary Tract Cancer-06 and NIFTY studies.

Citation: Leowattana W, Leowattana T, Leowattana P. Paradigm shift of chemotherapy and systemic treatment for biliary tract cancer. *World J Gastrointest Oncol* 2023; 15(6): 959-972
URL: https://www.wjgnet.com/1948-5204/full/v15/i6/959.htm
DOI: https://dx.doi.org/10.4251/wjgo.v15.i6.959

INTRODUCTION

The term "biliary tract cancers" (BTCs) refers to a group of aggressive and invasive hepatobiliary tumors that include ampulla of Vater cancer (AVC), gallbladder carcinoma (GBC), perihilar cholangiocarcinoma (pCCA), distal cholangiocarcinoma (dCCA), and intrahepatic cholangiocarcinoma (iCCA). The anatomical location of iCCA is within the biliary tree, whereas dCCA and pCCA, which are sometimes combined under the term extrahepatic cholangiocarcinoma (eCCA), originate outside the liver[1-3]. Between BTC subgroups and geographical areas, incidence and causes differ. In high-income nations, the incidence of CCA is modest (between 0.35 and 2 cases per 100000 people), but it can be up to 40 times higher in areas of Thailand and China where the disease is endemic. The incidence of iCCA is increasing in high-income countries. Statistics from the United Kingdom, the United States, and other countries show a consistent and steady growth in incidence from 0.1 to 0.6 instances per 100000 people during the last 30 years[4-6]. Hepatitis B and C infection, primary sclerosing cholangitis, liver fluke infections, liver cirrhosis, hepatolithiasis, Caroli's disease, obesity-associated liver disease, and diabetes are risk factors that have historically been associated to the development of BTC. It should be highlighted that the epidemiological disparities in the occurrence of different BTC types worldwide are also reflected in these risk variables[7-9]. The median overall survival (OS) for BTCs is 12 mo. Depending on stage, the 5-year relative survival rate for iCCA is from 9% to 25%, for eCCA it is between 10% and 15%, and for GBC it is between 15% and 35%[10,11]. The basic principle of curative therapy is radical surgery with negative margins; patients with early-stage illness, however, usually show no symptoms. Regrettably, the majority of BTC patients present with advanced BTC, with just a tiny fraction of BTCs being identified with a resectable condition[12,13]. The current gold standard for first-line treatment is still combined chemotherapy (CT) with gemcitabine and cisplatin (Gem/Cis) and second-line leucovorin (LV) calcium (folinic acid), fluorouracil, and oxaliplatin (FOLFOX)[14,15]. However, there is no solid data concerning what to do next following the poor prognosis of chemotherapeutic treatment. The BTC landscape has recently witnessed the introduction of innovative medicines, including targeted medications like pemigatinib, infigratinib, and ivosidenib. Additionally, a number of cutting-edge therapies are being evaluated and have the potential to alter the therapeutic picture for these cancers, including immune checkpoint inhibitors (ICIs), either alone or in combination with other anticancer medicines[16-19]. In this review, we summarized recent clinical data on CT, targeted treatments, ICIs, and immunotherapy in the context of systemic treatment for BTCs.

CHEMOTHERAPY

First-line CT

Based on the outcomes of the Japanese BT22 Phase 2 and the Advanced Biliary Tract Cancer (ABC-02) Phase 3 studies, which showed that this combination was superior to gemcitabine alone, Gem/Cis is presently the recommended first-line treatment for patients with advanced BTC (aBTC)[14,20]. The results of this ground-breaking trial reported by Valle *et al*[21] showed that the combination of cisplatin and gemcitabine was associated with a longer median OS [11.7 mo *vs* 8.1 mo, HR: 0.64, 95% confidence interval (CI): 0.52-0.80; $P < 0.001$] and median progression-free survival (PFS) (8.0 mo *vs* 5.0 mo) compared with gemcitabine alone. Similar advantages of cisplatin-gemcitabine vs. gemcitabine monotherapy were also shown in the phase 2 BT22 study for Asian patients[22]. The efficacy of many combination CT treatments has been studied over the past ten years, including the triplet-agent

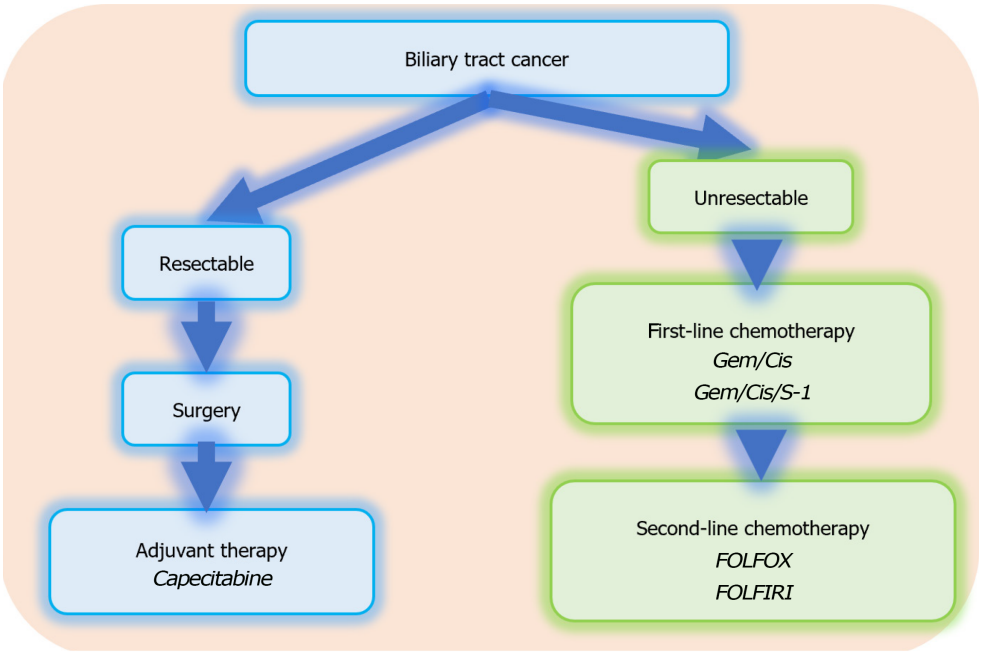
regimen, which combines Gem, Cis, and nab-paclitaxel (nab-P), and which has shown positive clinical results. Particularly, OS and PFS had medians of 19.2 and 11.8 mo, respectively[23,24]. In the real-world situation, Cheon *et al*[25] conducted a retrospective analysis in 178 Asian patients with advanced BTC to evaluate the treatment outcomes of Gem/Cis/nab-P. Gem/Cis/nab-P was administered as the initial course of treatment to 117 (65.7%) patients, whereas gemcitabine-based CT with nab-P was administered to 61 (34.3%) patients. The total objective response rate (ORR) for all patients was 42.1%, with a disease control rate (DCR) of 84.8%. In Korean patients with advanced BTC, they discovered that Gem/Cis/nab-P had positive real-life effectiveness and safety results that were consistent with the findings of the phase II study. However, Jung *et al*[26] evaluated the efficacy of triplet and normal doublet CT in a real-world scenario of 68 BTC patients and discovered that Gem/Cis/nab-P treatment did not increase PFS or OS compared to regular CT in patients with advanced BTC. They recommended that sizable randomized controlled studies are necessary to examine the advantages of triplet CT in advanced BTC.

A French team recently compared 5-fluorouracil (5-FU), oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) with the standard of care (SOC). One hundred and ninety-one patients with locally advanced or metastatic BTCs were randomized to receive either Gem/Cis for a maximum of 6 mo or infusional 5-FU without bolus, oxaliplatin, and irinotecan [modified FOLFIRINOX (mFOLFIRINOX)]. The study's primary OS endpoint was not met; the SOC in the first-line scenario was maintained with a median OS of 11.7 mo for mFOLFIRINOX and 13.8 mo for the Gem/Cis arm[27]. The development of S-1 in conjunction with platinum is ongoing in this line for BTC. In a phase 3 randomized controlled trial, the FUGA-BT study comprised 354 CT-unexperienced patients with recurrent or unresectable BTC with an ECOG of 0 or 1. OS is the primary endpoint of the non-inferiority study FUGA-BT, which compares Gem/S-1 to Gem/Cis. In Japanese patients, CT based on Gem/S-1 was not inferior to Gem/Cis. Patients allocated to the Gem/Cis group had a median OS of 13.4 mo, whereas those assigned to the S1-gemcitabine group had a median OS of 15.1 mo. Overall, there was good tolerability of the side effects, which did not substantially differ across treatment arms[28]. Recently, Ioka *et al*[29] conducted a multicenter, randomized phase 3 trial in 246 patients from 39 medical centers in Japan. Patients who had been enrolled were randomly assigned (1:1) to the Gem/Cis/S-1 (GCS) or Gem/Cis arm. The GCS regimen included 80 mg/m^2 of S-1 on days 1 through 7 every 2 wk, as well as infusions of cisplatin (25 mg/m^2) and gemcitabine (1000 mg/m^2) on day 1. OS was the main outcome, whereas PFS, ORR, and adverse events (AEs) were the secondary endpoints. They discovered that the median OS and 1-year OS rates in the GCS arm were 13.5 mo and 59.4%, respectively, whereas in the GC arm they were 12.6 mo and 53.7%. In the GCS arm, the median PFS was 7.4 mo, whereas in the GC arm, it was 5.5 mo. RR in the GCS arm was 41.5%, compared to 15.0% in the GC arm. AEs with a grade of 3 or below did not reveal any appreciable variations between the two arms. They stated that GCS may become the new first-line SOC for advanced BTC because it was the first regimen to show survival advantages as well as a higher RR than GC in a randomized phase 3 study (Figure 1).

Second-line CT

Combination regimens utilizing fluoropyrimidines, platinum salts, and other chemotherapies have been evaluated for the second-line situation. Results from a second-line randomized phase 3 trial were recently published. A United Kingdom population with locally advanced or metastatic BTC after progressing to first-line Gem/Cis CT with an ECOG 0-1 was involved in the open-label, phase 3 ABC-06 clinical research. The treatment of active symptom management plus FOLFOX or active symptom control alone was randomly allocated to 162 patients. Oxaliplatin (85 mg/m^2) was administered as a 2-h infusion on day 1 of the FOLFOX CT regimen, followed by a 2-h infusion of LV (175 mg/m^2/day), a 5-FU bolus (400 mg/m^2/day), and a 46-h infusion of 5-FU (2400 mg/m^2) every two weeks. OS among the population who were being treated intentionally was the main result. With 6.2 mo as opposed to 5.3 mo in the control group, FOLFOX slightly increased the median OS. Compared to 39% of patients in the control arm, 59% of patients in the experimental arm had grade 3/4 toxicities, such as fatigue and neutropenia. All subtypes of BTC tumors improved equally after FOLFOX in the subgroup study[30]. Patients who received FOLFOX as second-line treatment had a clinically significant increase in OS rates at 6 and 12 mo, despite the small absolute median OS difference between the two groups, and the study has produced clinical data for the first time in this context (Figure 1). For advanced BTCs, more cutting-edge CT regimens are being investigated in the second-line setting. A phase 2 study assigned 120 patients to either modified fluorouracil, and oxaliplatin (mFOLFOX) (5-FU 2400 mg/m^2 over 46 h, LV 100 mg/m^2 over 2 h, and oxaliplatin 100 mg/m^2 over 2 h, every 2 wk) or mFOLFIRI (5-FU 2400 mg/m^2 over 46 h, LV 100 mg/m^2 over 2 h, and irinotecan 150 mg/m^2 over 2 h, every 2 wk). The mFOLFOX group had a higher median OS (6.6 mo), ORR (5.9%), and median PFS (2.8 mo)[31].

A novel regimen, platinum-free liposomal irinotecan in combination with 5-FU/LV, has recently been studied in second-line BTC. In a randomized, open-label, phase IIb study, 174 Korean patients were randomly allocated to receive 5-FU/LV every two weeks or nal-IRI 70 mg/m^2 combined with 2400 mg/m^2 intravenous fluorouracil and intravenous LV 400 mg/m^2 for 46 h) (NIFTY study). When compared to 5 FU/LV, the nal-IRI with 5-FU/LV improved PFS and OS significantly. In comparison to the 5-FU/LV group, which had a median PFS of 5.5 mo *vs* 1.4 mo, the nal-IRI plus 5-FU/LV group had a median PFS of 3.9 mo and a median OS of 8.6 mo. Even though this clinical trial is in phase 2b, there are



DOI: 10.4251/wjgo.v15.i6.959

Figure 1 Treatment strategy in biliary tract cancers. FOLFIRI: 5-fluorouracil plus irinotecan; FOLFOX: 5-fluorouracil plus oxaliplatin; Gem/Cis: Gemcitabine plus cisplatin; Gem/Cis/S-1: Gemcitabine plus cisplatin plus S-1.

exactly the same number of participants as in the single-phase 3 study that has been conducted to date (ABC-06). In the nal-IRI plus 5-FU/LV group, 70% of patients and 31% of patients in the 5-FU/LV group experienced grade 3 side effects, such as neutropenia and asthenia. Despite the fact that these outcomes are encouraging, they must be validated in global phase 3 clinical studies[32]. In a phase 2 trial in 2018, irinotecan 180 mg/m^2 on day 1 combined with capecitabine 1000 mg/m^2 twice daily on days 1 through 10 (XELIRI-arm) or irinotecan 180 mg/m^2 on day 1 alone (IRI-arm) were the two therapy options given to 60 Gem/Cis refractory aBTC patients by Zheng *et al*[33] over the course of a cycle of 14 d. Treatments were continued until the condition became worse or the side effects became too severe. They discovered that the median PFS was 3.7 *vs* 2.4 mo, the 9-mo survival rate was 60.9% *vs* 32.0%, the median OS was 10.1 *vs* 7.3 mo, and the DCR was 63.3% *vs* 50.0% for the XELIRI-arm and IRI-arm, respectively. Leucopenia and neutropenia were the two grade 3 or 4 toxicities that were most prevalent.

Because of a number of factors, including the proportion of patients deemed suitable for third- or later-line treatment and the absence of agreement for second-line therapy prior to ABC-06 and NIFTY, few studies have looked at the usefulness of systemic CT in the third-line situation. There are few data on third-line CT for highly pretreated patients. As a result, the clinical choice of third-line CT in metastatic BTC remains complex and is based on a number of factors, including the patient's motivation, performance status, response to prior therapies, and quality of life[34,35].

TARGETED THERAPIES

More driving genes are being discovered because of the advancement of next-generation sequencing, which is assisting in the creation of new treatments as well as the explanation of the pathophysiology of BTC. In the BTC landscape, iCCA, eCCA, GBC, and AVC appear to differ significantly from one another based on this technology. Kirsten rat sarcoma virus (RAS), AT-rich interactive domain B mutations, and erb-b2 receptor tyrosine kinase 2 (ERBB2) are more common in eCCA and GBC, whereas isocitrate dehydrogenase (IDH)-1, IDH-2 mutations, and FGFR2 fusions or rearrangements are almost exclusively detected in intrahepatic variants[36,37].

FGFR2 inhibitors

According to several genetic studies, FGFR2 abnormalities are seen in about 15%–25% of iCCAs. Tyrosine kinase receptors known as FGFRs are implicated in regulating RAS, Janus kinase 2, and phosphoi-nositide 3-kinases (PI3K)/mammalian target of rapamycin pathways, and FGFR2 abnormalities affect cellular migration, angiogenesis, proliferation, and survival processes[38,39]. Numerous medications that target FGFR isoforms, including infigratinib, pemigatinib, derazantinib, erdafitinib (ATP-competitive, reversible inhibitors), and futibatinib (non-ATP-competitive, covalent

inhibitor), have been studied in iCCA patients during the past ten years[40,41]. In a phase 1 clinical trial with 3 CCA patients carrying FGFR2 abnormalities, the pan-FGFR tyrosine kinase inhibitor infigratinib was originally evaluated, and all patients had stable condition[42]. In a further phase 2 study, infigratinib was investigated in 61 gemcitabine-resistant CCA patients with *FGFR2* gene mutations, fusions, or amplifications. In the subset of CCAs with *FGFR2* gene fusions, the ORR and DCR, respectively, were 19% and 83%; the most frequently reported side effects were tiredness, hyperphosphatemia, baldness, and stomatitis[43]. Javle *et al*[44] recently published the complete data of this single-arm, phase 2 study, in which infigratinib showed a median PFS and OS of 7.3 mo and 12.2 mo, respectively (Table 1).

In a multicenter, open-label, single-arm phase 2 trial (FIGHT-202) with three cohorts: 107 patients with FGFR2 fusions or rearrangements, 20 patients with other FGFR alterations, or 18 patients without such changes, pemigatinib, another reversible inhibitor, was investigated. The main outcome measure was ORR in patients with FGFR2 fusions or rearrangements who took pemigatinib at least once. With three cases of full response and a median treatment time of 7.2 mo, ORR was observed in 35.5% (38/107) of patients with *FGFR2* gene fusions and/or rearrangements during the course of their median follow-up of 17.8 mo. The median PFS and OS for this cohort were 6.9 and 21.1 mo, respectively. The other two cohorts of CCA patients, however, did not have any responses; in patients with additional FGF/FGFR mutations, the median PFS was 2.1 mo and the median OS was 4.0 mo, whereas the median PFS in patients with FGFR wild type was 1.7 mo. Patients with *FGFR2* gene fusions and/or rearrangements had a median OS of 17.5 mo (95%CI: 14.4-22.9)[45]. Pemigatinib was given fast approval by the United States Food and Drug Administration for pretreated patients with metastatic CCA that included FGFR2 fusions or rearrangements as a consequence of the findings of FIGHT-202. Following these encouraging findings, in patients with FGFR2 rearrangements as the first-line scenario, the phase 3 FIGHT-302 and PROOF-301 investigations, in which both therapies are contrasted with Gem/Cis, are evaluating FGFR2 inhibitors[46,47].

In a phase 1/2 study (AR087-101) involving 29 CCA patients with *FGFR2* gene fusion, the pan-FGFR inhibitor derazantinib (ARQ087) was first analyzed. Two cases of therapy-naive CCA were included, although the bulk of the patients (n = 27) had had disease progression after at least one systemic treatment. According to the study's findings, with a median PFS of 5.7 mo, the ORR and DCR were 20.7% and 82.8%, respectively[48]. Erdafitinib (JNJ-42756493), a different pan-FGFR inhibitor, was studied in a phase 1 study and shown to be effective in CCA patients with FGFR mutations or gene fusions, with an ORR of 27.3% and an average response time of 11.4 mo[49]. Futibatinib (TAS-120), an irreversible, highly selective pan-FGFR inhibitor that can overcome resistance to ATP-competitive inhibitors, is the final potential drug. All iCCA patients (n = 3) exhibited a partial response in the first dose-escalation phase 1 study that included metastatic solid tumors with FGFR abnormalities[50]. Following the findings of this trial, 67 pretreatment iCCA patients with FGFR2 gene fusions or rearrangements were included in the FOENIX-CCA2 single-arm, multicenter, phase 2 trial. The findings of this trial showed that an ORR was noted in 42.0% of patients receiving futibatinib, with a median PFS of 9.0 mo and a median OS of 21.7 mo[51]. Futibatinib was associated with a number of the same treatment-related side effects as other FGFR inhibitors, such as diarrhea, hyperphosphatemia, alopecia, and dry mouth. The phase 3 FOENIX-CCA3 clinical research is evaluating futibatinib *vs* Gem/Cis as a first-line treatment for locally progressed, unresectable, or metastatic iCCA patients with FGFR2 gene fusions or rearrangements in light of the encouraging signs of efficacy reported in FOENIX-CCA2 (Figure 2).

IDH inhibitors

IDH mutations are very uncommon findings in the other BTC subtypes, such as eCCA and GBC; however, they have been documented in about 15% of all cases with iCCA. From a biological perspective, IDH mutations inhibit enhanced IDH1/2 activity, resulting in modifications to cellular metabolism and a buildup of the tumor metabolite 2-hydroxyglutaric acid (2-HG). IDH1/2 mutations in the isocitrate binding region reduce enzyme activity for oxidative decarboxylation of isocitrate to α-ketoglutarate. In turn, 2-HG alters DNA methylation and chromatin structure in a number of ways that hinder normal cell differentiation and promote cancer. This genetic change allows tumors to catalyze the conversion of α-ketoglutarate to 2-HG. This has recently been studied in patients with CCA, and several of these drugs have already demonstrated encouraging benefits in other malignancies with IDH mutations[52,53]. A number of IDH1/2 inhibitors, including ivosidenib, enasidenib, and others, have lately been investigated in CCA patients; some of these drugs have already shown notable benefit in other malignancies with IDH mutations.

An oral IDH1 targeted inhibitor called ivosidenib (AG-120) has demonstrated efficacy in preliminary clinical studies. The pivotal experiment that led to the approval of ivosidenib was the multicenter, randomized, double-blind, placebo-controlled ClarIDHy phase 3 study, patients with advanced, IDH1-mutant CCA who had progressed on up to two prior therapy regimens were enrolled. IDH1 mutations were prescreened in a total of 780 individuals, and 187 were randomly assigned to receive either 500 mg of ivosidenib once daily or a placebo. The majority of them were advanced iCCA at the time of randomization. In the ivosidenib group, the median PFS was 2.7 mo as opposed to 1.4 mo in the placebo group; this improvement was statistically significant. Ivosidenib's median OS was 10.3 mo while the placebo

Table 1 Summary of main clinical trials evaluating the targeted therapies in advanced biliary tract cancer patients

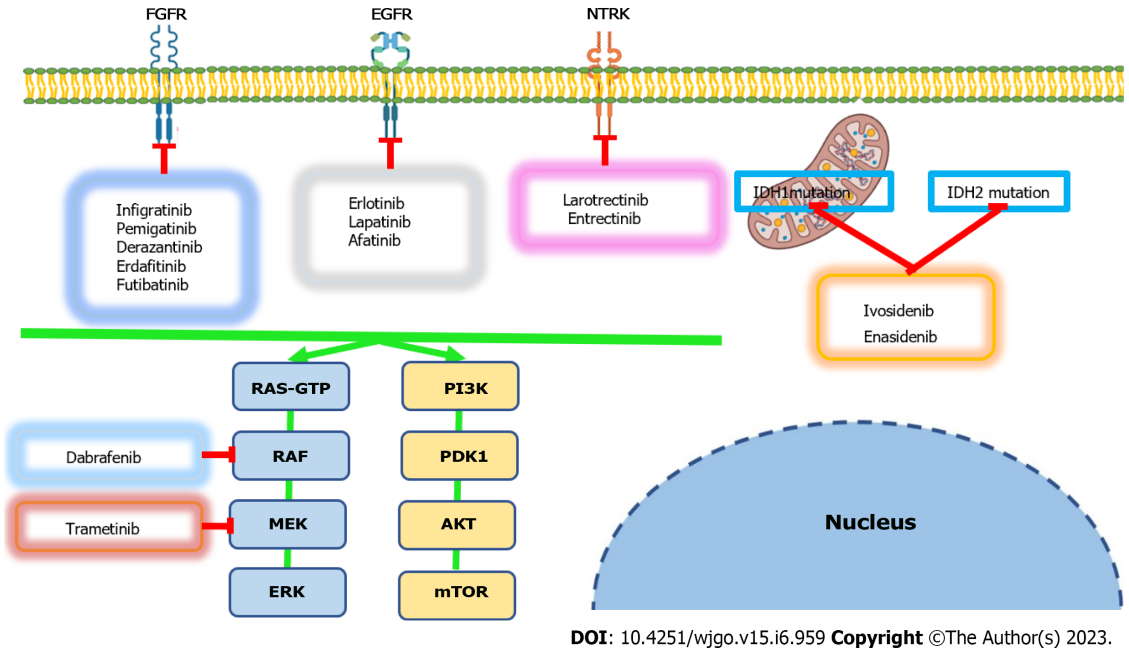
Ref.	Country	Drug(s)	Number of patients	Study phase	ORR (%)	Mean OS (months)	Mean PFS (months)	Adverse events
FGFR2 inhibitors								
Javle *et al* [44]	United States, Belgium, Spain, Germany, Singapore, Taiwan, and Thailand	Infigratinib (BGJ398)	108	2	23.1	12.2	7.3	Tiredness, baldness, hyperphosphatemia, and stomatitis
Abou-Alfa *et al*[45]	United States, France, Italy, Germany, Belgium, and South Korea	Pemigatinib (FIGHT-202)	146	2	35.5	21.1 (FGFR2 fusion)	6.9 (FGFR2 fusion)	Hypophosphatemia, arthralgia, stomatitis, hyponatremia, and abdominal pain
Mazzaferro *et al*[48]	United States and Italy	Derazantinib (AR087-101)	29	1/2	20.7	12.7	5.7	Fatigue, eye toxicity, hyperphosphatemia, and increase in ALT/AST
Bahleda *et al* [49]	United States, France, and Spain	Erdafitinib (JNJ-42756493)	11	1	27.0	12.0	7.5	Fatigue, eye toxicity, hyperphosphatemia, and increase in ALT/AST
Goyal *et al* [51]	United States, France, Spain, United Kingdom, Netherland, Japan, Germany, and South Korea	Futibatinib (TAS-120)	103	2	42.0	21.7	9.0	Hyperphosphatemia, diarrhea, fatigue, alopecia, and stomatitis
IDH inhibitors								
Zhu *et al*[54]	United States, China, Spain, United Kingdom, Ireland, and South Korea	Ivosidenib (AG-120)	187	3	51.0	10.3	2.7	Ascites, anemia, increase bilirubin level, and hyponatremia
BRAF inhibitors								
Subbiah *et al* [59]	United States, Denmark, United Kingdom, Austria, France, Italy, Spain, Germany, Netherland, Switzerland, Japan, and South Korea	Trametinib and Dabrafenib	43	2	47.0	14.0	9.0	Hypertension, reduced white blood cell count, and elevated gamma-glutamyl transferase
NTRK inhibitors								
Doebele *et al* [67]	United States, France, Italy, Spain, Germany, Australia, Hong Kong, Switzerland, Japan, and South Korea	Entrectinib	54	1/2	57.0	21.0	11.0	Anemia, increased weight, dyspnea, and fatigue

BRAF: B-Raf gene; FGFR2: Fibroblast growth factor receptor 2; IDH: Isocitrate dehydrogenase; NTRK: Neurotrophic tyrosine receptor kinase; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

group's median OS was 7.5 mo. The 57% crossover from placebo to ivosidenib, which was authorized on the basis of radiological advancement, may be the cause of the OS difference that was not statistically significant. Nausea, diarrhea, and exhaustion were common side effects that affected 41%, 35%, and 31% of individuals, respectively[54]. Rimini *et al*[55] presented the first real-world experience in 2022, with eight patients with previously treated locally advanced or metastatic IDH1-mutated CCA treated with ivosidenib after a median follow-up of 9.4 mo. They discovered that the median OS was not attained, while the median PFS from the commencement of therapy with ivosidenib was 4.4 mo. The DCR was 62.5%, with two patients attaining a partial response (at a rate of 25%). 12.5% of patients had side effects due to the therapy, however, none of grade 3 or higher were noted. Hypomagnesemia and a longer QT interval were the grade 2 AEs that were detected. They concluded that the effectiveness results were in line with those mentioned in the ClarIDHy study. Larger samples of real-world data are required to corroborate the findings[56]. Other IDH inhibitors, like as enasidenib (AG-221), and combination therapy combining these targeted drugs with additional anticancer drugs, such PARP inhibitors, are now being evaluated in IDH-mutated CCAs.

BRAF inhibitors

BRAF is a growth signal transduction protein kinase that belongs to the Raf kinase family. The mitogen-activated protein (MAP) kinase/extracellular signal-regulated kinases signaling system, which controls



DOI: 10.4251/wjgo.v15.i6.959

Figure 2 Targeted therapies used in systemic treatment for biliary tract cancers. AKT: Protein kinase B; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-related kinase; FGFR: Fibroblast growth factor receptor; GTP: Guanosine triphosphate; IDH1: Isocitrate dehydrogenase 1; IDH2: Isocitrate dehydrogenase 2; MEK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NTRK: Neurotrophic tyrosine receptor kinase; PI3K: Phosphoinositide-3-kinase; PKD1: Polycystic kidney disease 1; RAF: Raf proto-oncogene; RAS: RAS proto-oncogene.

cell division, differentiation, and secretion, is regulated by this protein. Approximately 5% of BTCs have been shown to contain BRAF gene alterations, particularly in iCCA. Fascinatingly, individuals with BRAFV600E mutations experience more aggressive clinical behavior, have more advanced tumors upon diagnosis, and are more likely to have lymph node involvement. Similar to other BRAF-mutated cancers, this situation has exhibited the early emergence of treatment resistance and transient responses to BRAF inhibitor monotherapy[57,58]. Consequently, combination therapies combining BRAF inhibitors and MEK inhibitors have been investigated. Subbiah *et al*[59] conducted a phase 2, open-label, single-arm study, the Rare Oncology Agnostic Research, to assess the effectiveness and safety of trametinib and dabrafenib in 43 patients, including 91% with iCCA, 2% with pCCA, 2% with GBC, and 2% with unclear origins. Independent analysis revealed a 47% ORR, a 9-mo median PFS, and a 14-mo median OS. These results demonstrated that, in contrast to metastatic colorectal cancer, where EGFR inhibition is crucial, BRAF inhibition is critical in BTC. Among patients taking dabrafenib with trametinib, hypertension (7%), a decrease in white blood cell count (7%), and an increase in gamma-glutamyl transferase (12%) were the most common grade 3 or 4 AEs. The dual-targeting treatment appears to produce better results than BRAF inhibition alone. Future research should concentrate on the use of combination drugs for early therapy.

EGFR inhibitors

Human EGFR2 (HER2) is a tumor-promoting growth factor receptor. EGFR, HER1 (ERBB1), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4) are all members of the same family. These transmembrane growth factor receptors activate downstream secondary messengers when their intracellular domains are phosphorylated, resulting in a variety of physiologic consequences. HER2 activation causes cancer by activating the MAP kinase and PI3K pathways, as well as a loss of cell polarity and adhesion and a disrupted cell cycle by activating cyclin D and inhibiting p27. The most active catalytic kinase is seen in HER2, especially when HER3 is involved. The HER2 protein has been shown to be overexpressed in 13% of GBCs and up to 18% of eCCA[60,61]. Although HER2 overexpression has been correlated with a poorer prognosis and a higher tendency to metastasize, it has also been associated with increased cytotoxic and targeted agent sensitivity. Javle *et al*[62] retrospectively analyzed patients with advanced GBC and CCA who had HER2/neu-directed therapy between 2007 and 2014 and who had HER2/neu genetic abnormalities or protein overexpression. HER2/neu-directed treatment (trastuzumab, lapatinib, or pertuzumab) had been administered to five patients with CCA and nine patients with GBC at some point throughout the research. Eight incidences of HER2/neu gene amplification or overexpression in GBC patients were found. With HER2/neu-directed treatment, these patients either had a full response (n = 1), a partial response (n = 4), or disease stability (n = 3). A HER2/neu mutation caused a patient who received lapatinib therapy to have a mixed response. Response times ranged from 8 to 168 wk (median 40 wk). The CCA cases in this series that were treated had a greater proportion of HER2/neu mutations,

and despite HER2/neu-directed treatment, these patients showed no radiological responses. They recommended that HER2/neu blocking is a promising therapeutic approach for patients with gene amplification for GBC and merits more investigation in multicenter research.

Neurotrophic tyrosine receptor kinase inhibitors

Three membrane-bound receptors known as tropomyosin receptor kinases (Trk A, B, and C) are encoded by the neurotrophic tyrosine receptor kinase genes (NTRK1-3), which are exceedingly uncommon in BTC (0.67%) and present in between 0.3% and 1% of all solid tumors. The cytoplasmic kinase is activated by neurotrophin binding, which also activates the MAPK, PI3K, and phospholipase C-γ1 pathways and downstream signaling cascades. One of the three *NTRK* genes can combine with a number of partners to form oncogenic fusions, which constitutively activate the Trk pathway and promote cancer[63-65]. Larotrectinib and entrectinib, two extremely specific small compounds that inhibit all three TRK proteins, were discovered and demonstrated efficacy in preliminary clinical studies. Larotrectinib (LOXO-101) phase 1 clinical trial, which recruited 55 patients, was analyzed, and it was revealed that the ORR was 75% and the median PFS was not attained until 9.9 mo. There were only 2 CCA patients included, and both had an ORR of 80%. One patient had a progressing condition[66]. Three entrectinib phase 1 or 2 clinical studies (STARTRK-1, STARTRK-2, and ALKA-372-001) were analyzed together. Fifty-four patients from 10 distinct NTRK fusion-positive tumor types were enrolled in all of the studies, which showed a median PFS of 12.9 mo and an ORR of 57%[67].

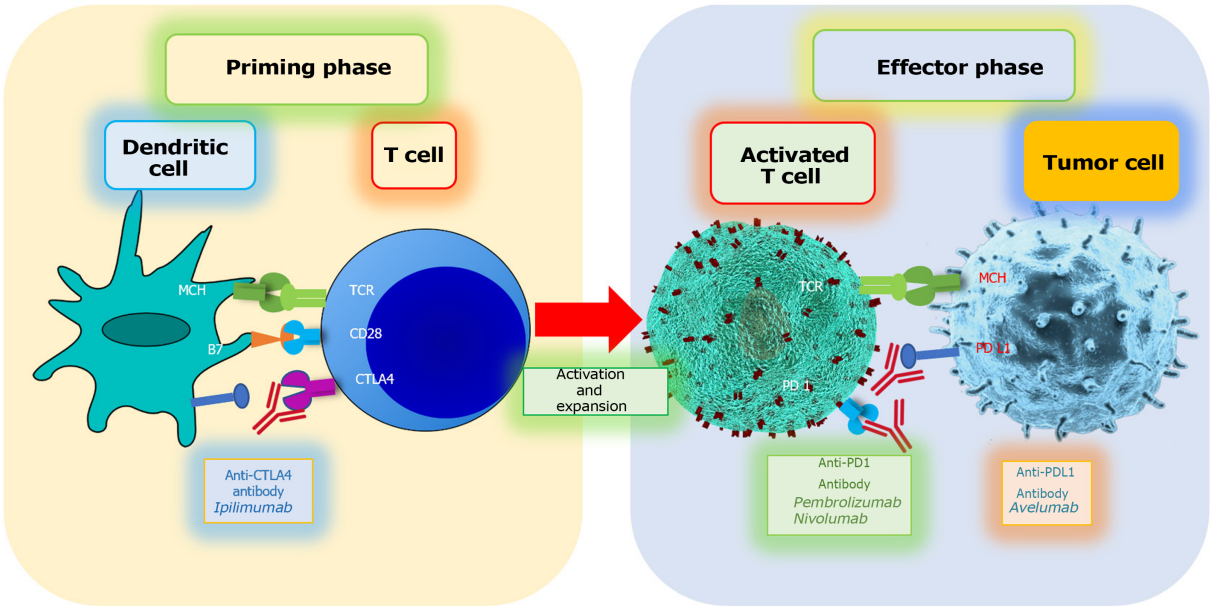
ICIS

The incorrect insertions or deletions that happen during DNA replication are recognized and corrected by the mismatch repair (MMR) mechanism. ICIs are particularly effective against cancers with a deficient MMR (dMMR) system because these cancers frequently have somatic mutations. Adenocarcinomas of the liver, cervix, endometrium, and gastrointestinal tract all have dMMR in more than 5% of cases. They are observed in localized phases more frequently (8%) than in metastatic stages (4%). Depending on the region and published series, dMMR accounts for 2%–18% of tumors in BTC. In contrast to eCCA or GBC (5%–8%), it is more common in iCCA (10%) and AVC (6%–20%)[68,69]. ICIs can boost anticancer activity by inhibiting immune system regulators like cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and lymphocyte activating gene 3. This results in increased cytotoxicity in T lymphocytes (Figure 3). ICIs have recently been tested in BTC, either by alone or in combination with other anticancer drugs[70-73].

Both the phase 1b and phase 2 KEYNOTE-158 studies used the PD-1 inhibitor pembrolizumab. In these two studies, a limited group of BTC patients who had already had treatment and whose conditions had gotten worse on traditional therapy were involved. The median PFS and OS for KEYNOTE-158 were 2.0 and 7.4 mo, respectively, whereas the ORR, median PFS, and median OS for KEYNOTE-028 were 13.0%, 1.8 mo, and 5.7 mo, respectively, in the intention-to-treat group. Microsatellite instability (MSI) status was used by the investigators to stratify their data, and patients with MSI-H/dMMR had an ORR of 40.9% with median PFS and OS of 4.2 and 24.3 mo, respectively [74]. Metastatic BTC was treated with nivolumab, a human immunoglobulin G4 monoclonal antibody that prevents PD-1 interaction with PD-L1 and PD-L2. Early results from a single-group, multicenter phase 2 study of nivolumab monotherapy showed partial responses in 10 of 45 patients with CCA who had previously received treatment, with 27 of them reaching a stable status. It is also worth noting that the median PFS and OS were 3.68 and 14.24 mo, respectively. Nivolumab was further assessed as a first-line treatment for patients with metastatic condition when combined with the traditional doublet Gem/Cis, with results indicating a median OS of 15.4 mo and a median PFS of 4.2 mo. Moreover, 11 out of 30 patients showed an objective response[75].

Ueno *et al*[76] performed a multicenter, open-label, phase 1 trial in 60 patients with BTCs to investigate the safety and tolerability of the ICI nivolumab as monotherapy or in combination with Gem/Cis CT. Nivolumab monotherapy (240 mg every 2 wk) was given to 30 patients with unresectable or recurrent BTC that was resistant or intolerant to Gem/Cis. Thirty CT-naive patients with unresectable or recurrent BTC were given nivolumab (240 mg every two weeks) in addition to Gem/Cis CT. In the monotherapy cohort, they found that the median OS was 5.2 mo, the median PFS was 1.4 mo, and just one patient out of thirty exhibited an objective response. Eleven out of 30 patients in the combination treatment cohort showed an objective response, and the median OS and PFS were 15.4 and 4.2 mo, respectively. They concluded that nivolumab showed evidence of therapeutic effectiveness in individuals with unresectable or recurrent BTC and had a tolerable safety profile. This preliminary evaluation of nivolumab for the treatment of advanced BTC offers encouraging data for upcoming larger randomized studies of nivolumab in this challenging malignancy.

Nivolumab was also investigated in a phase 2 trial on 54 patients with refractory BTC at doses of 240 mg intravenously every two weeks for 16 wk, followed by 480 mg intravenously every four weeks, until disease progression or unacceptable toxicity. According to the research, the ORR by central review was



DOI: 10.4251/wjgo.v15.i6.959 **Copyright** ©The Author(s) 2023.

Figure 3 The mechanisms of action of immune checkpoint inhibitors in cancer immunotherapy. CTLA-4: Cytotoxic T lymphocyte antigen 4; MHC: Major histocompatibility complex; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TCR: T cell receptor.

11%, the DCR was 50%, the median PFS was 3.7 mo, and the median OS was 14 mo. The median PFS and OS were higher for patients who were stratified by positive PD-L1 expression status than for patients who had PD-L1-negative expression[77]. Nivolumab and the anti-CTLA-4 drug ipilimumab were studied in combination in patients with advanced BTCs by Klein *et al*[78]. The median PFS was 2.9 mo, the ORR was 23%, 17 out of 39 patients had disease control, and the median OS was 5.7 mo. The ORR for patients with iCCA and GBC was 31%, while there was no response seen in individuals with eCCA, suggesting that the effectiveness of ICIs varied depending on the anatomic locations. In an advanced BTC patient without prior systemic treatment and an ECOG score of 0-1, Sahai *et al*[79] conducted a phase 2 randomized study to assess the impact of adding an anti-PD-1/PD-L1 antibody to either systemic CT or an anti-CTLA4 antibody. Nivolumab (360 mg) was given to patients in Arm A (35) on day one, along with Gem/Cis on days one and eight, every three weeks for six months, followed by Nivolumab (240 mg) every two weeks. Patients in Arm B (33) received nivolumab (240 mg) every two weeks, and Ipilimumab (1 mg/kg) every six weeks. They discovered that the 6-mo PFS rates in Arm A were 59.4% and Arm B was 21.2% for the observed main endpoint. The median PFS and OS in Arm A were 6.6 and 10.6 mo, respectively, while they were 3.9 and 8.2 mo in Arm B. The most common grade 3 or higher hematologic AE related to therapy was neutropenia (34.3%, Arm A), while tiredness (8.6%, Arm A) and elevated transaminases (9.1%, Arm B) were the most common nonhematologic AEs. They determined that when combined with CT or Ipilimumab, Nivolumab did not improve 6-mo PFS. Although both arms' median OS was less than 12 mo, Arm A's high OS rate at 2 years suggested benefit in a small patient cohort.

A phase 2 trial with advanced BTC examined gemcitabine and oxaliplatin (GEMOX) and the PD-1 antibody, camrelizumab. Fever and exhaustion were the side effects of therapy that occurred most frequently (both 73%). In 54% of patients, the combination produced an objective response. When compared to those for GEMOX alone, the median PFS was 6.1 mo and the median OS 11.8 mo[80]. Patients with advanced BTC were evaluated in a phase 2 research study in China using camrelizumab plus an oxaliplatin-based CT regimen. Similar to the ABC-02 study, the reported ORR was 16.3%, the median PFS was 5.3 mo, and the median OS was 12.4 mo. These encouraging findings imply that a novel first-line treatment for advanced BTC, camrelizumab plus oxaliplatin-based CT, may be possible [81]. In a phase 2 study, individuals with advanced BTC who had never had CT were given a combination of Gem/Cis plus durvalumab, with or without tremelimumab. Three regimens of CT and immunotherapy were administered to all patients, and the medication dosages across the regimens were all the same. They enrolled 128 patients; 32 in the Gem/Cis, followed by the Gem/Cis plus durvalumab and tremelimumab, 49 in the Gem/Cis plus durvalumab, and 47 in the Gem/Cis plus durvalumab and tremelimumab. The total median PFS was 12.1 mo and the median OS was 18.4 mo, which was encouraging compared with traditional CT. The research, however, lacked a control group. There were no appreciable changes in OS or PFS across the three regimens. After one cycle of therapy, the researchers discovered that lower PD-L1 expression in immune and tumor cells was linked to a shorter PFS. Immune cell PD-L1 expression was connected to the median OS. The findings suggested that PD-L1 expression variations following therapy may help predict clinical outcomes. Considering the

promising potential of CT combined with durvalumab in advanced BTC[82].

Peng *et al*[83] conducted a meta-analysis to assess the predictive and clinicopathological significance of the systemic immune-inflammation index (SII) in BTC. A combined study revealed that those with high SII levels had worse OS than people with low SII levels. Moreover, a higher SII was linked to lymph node metastases, TNM stage, and vascular invasion. In contrast, no significant relationship was discovered between a high SII and sex or tumor differentiation. These data indicated that high SII levels were associated with poor survival outcomes in individuals with BTC, as well as certain more malignant aspects of BTC.

CONCLUSION

Since BTC is frequently discovered at advanced stages, the disease is usually incurable. The best currently available, possibly curative treatment for a primary tumor found in the early stages in a subset of people is surgery; however, the treatment of advanced cancer is still in its early phases. As a result of biology's present understanding, new tactics are becoming possible because BTCs have several chemical changes that may be altered. Since several genetic abnormalities may be discovered and will affect our patients' outcomes, it is strongly recommended that all BTC patients receive a thorough molecular test before beginning systemic medication. There are several clinical trials taking place right now that use various methods to examine the safety and effectiveness of many medications in first- and second-line settings. Following the encouraging findings of phase 3 ABC-02, which showed an improvement in median OS compared with gemcitabine alone, the first-line recommended therapy is still Gem/Cis. However, the TOPAZ-1 clinical study, which revealed an improvement in OS, PFS, and ORR with immunotherapy combined with CT, has set a new course for patients who do not carry driver mutations. When compared to active symptom management, FOLFOX has demonstrated a little but statistically significant improvement in median OS. For BTC patients with certain genetic problems, targeted drugs such FGFR2, IDH1, and BRAF inhibitors have already demonstrated good outcomes in clinical trials. Targeted medicines, CT combinations, and ICIs are other approaches under investigation that will have an influence on the treatment of BTC in the future.

FOOTNOTES

Author contributions: Leowattana W wrote the paper; Leowattana T and Leowattana P collected the data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Thailand

ORCID number: Wattana Leowattana 0000-0003-4257-2480; Tawithep Leowattana 0000-0003-2316-3585.

S-Editor: Fan JR
L-Editor: A
P-Editor: Ji MX

REFERENCES

1 **Valle JW**, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet* 2021; **397**: 428-444 [PMID: 33516341 DOI: 10.1016/S0140-6736(21)00153-7]

2 **Bridgewater JA**, Goodman KA, Kalyan A, Mulcahy MF. Biliary Tract Cancer: Epidemiology, Radiotherapy, and Molecular Profiling. *Am Soc Clin Oncol Educ Book* 2016; **35**: e194-e203 [PMID: 27249723 DOI: 10.1200/EDBK_160831]

3 **Lendvai G**, Szekerczés T, Illyés I, Dóra R, Kontsek E, Gógl A, Kiss A, Werling K, Kovalszky I, Schaff Z, Borka K. Cholangiocarcinoma: Classification, Histopathology and Molecular Carcinogenesis. *Pathol Oncol Res* 2020; **26**: 3-15 [PMID: 30448973 DOI: 10.1007/s12253-018-0491-8]

4 **Saha SK**, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist* 2016; **21**: 594-599 [PMID: 27000463 DOI: 10.1634/theoncologist.2015-0446]

5 **West J**, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in

England and Wales 1971-2001. *Br J Cancer* 2006; **94**: 1751-1758 [PMID: 16736026 DOI: 10.1038/sj.bjc.6603127]

6 **Florio AA**, Ferlay J, Znaor A, Ruggieri D, Alvarez CS, Laversanne M, Bray F, McGlynn KA, Petrick JL. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. *Cancer* 2020; **126**: 2666-2678 [PMID: 32129902 DOI: 10.1002/cncr.32803]

7 **Massarweh NN**, El-Serag HB. Epidemiology of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *Cancer Control* 2017; **24**: 1073274817729245 [PMID: 28975830 DOI: 10.1177/1073274817729245]

8 **Clements O**, Eliahoo J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *J Hepatol* 2020; **72**: 95-103 [PMID: 31536748 DOI: 10.1016/j.jhep.2019.09.007]

9 **Sithithaworn P**, Yongvanit P, Duenngai K, Kiatsopit N, Pairojkul C. Roles of liver fluke infection as risk factor for cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2014; **21**: 301-308 [PMID: 24408775 DOI: 10.1002/jhbp.62]

10 **Spolverato G**, Kim Y, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, Clark Gamblin T, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Tran TB, Wallis Marsh J, Pawlik TM. Management and Outcomes of Patients with Recurrent Intrahepatic Cholangiocarcinoma Following Previous Curative-Intent Surgical Resection. *Ann Surg Oncol* 2016; **23**: 235-243 [PMID: 26059651 DOI: 10.1245/s10434-015-4642-9]

11 **Alabraba E**, Joshi H, Bird N, Griffin R, Sturgess R, Stern N, Sieberhagen C, Cross T, Camenzuli A, Davis R, Evans J, O'Grady E, Palmer D, Diaz-Nieto R, Fenwick S, Poston G, Malik H. Increased multimodality treatment options has improved survival for Hepatocellular carcinoma but poor survival for biliary tract cancers remains unchanged. *Eur J Surg Oncol* 2019; **45**: 1660-1667 [PMID: 31014988 DOI: 10.1016/j.ejso.2019.04.002]

12 **Tariq NU**, McNamara MG, Valle JW. Biliary tract cancers: current knowledge, clinical candidates and future challenges. *Cancer Manag Res* 2019; **11**: 2623-2642 [PMID: 31015767 DOI: 10.2147/CMAR.S157092]

13 **Rizzo A**, Brandi G. Pitfalls, challenges, and updates in adjuvant systemic treatment for resected biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 547-554 [PMID: 33571059 DOI: 10.1080/17474124.2021.1890031]

14 **Valle J**, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]

15 **Abdel-Rahman O**, Elsayed Z, Elhalawani H. Gemcitabine-based chemotherapy for advanced biliary tract carcinomas. *Cochrane Database Syst Rev* 2018; **4**: CD011746 [PMID: 29624208 DOI: 10.1002/14651858.CD011746.pub2]

16 **Chakrabarti S**, Kamgar M, Mahipal A. Targeted Therapies in Advanced Biliary Tract Cancer: An Evolving Paradigm. *Cancers (Basel)* 2020; **12** [PMID: 32722188 DOI: 10.3390/cancers12082039]

17 **Lamarca A**, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: Ready for "prime time" in biliary tract cancer. *J Hepatol* 2020; **73**: 170-185 [PMID: 32171892 DOI: 10.1016/j.jhep.2020.03.007]

18 **Rizzo A**, Ricci AD, Brandi G. Pemigatinib: Hot topics behind the first approval of a targeted therapy in cholangiocarcinoma. *Cancer Treat Res Commun* 2021; **27**: 100337 [PMID: 33611090 DOI: 10.1016/j.ctarc.2021.100337]

19 **Zhang W**, Shi J, Wang Y, Zhou H, Zhang Z, Han Z, Li G, Yang B, Cao G, Ke Y, Zhang T, Song T, QiangLi. Next-generation sequencing-guided molecular-targeted therapy and immunotherapy for biliary tract cancers. *Cancer Immunol Immunother* 2021; **70**: 1001-1014 [PMID: 33095329 DOI: 10.1007/s00262-020-02745-y]

20 **Okusaka T**, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, Nagino M, Kondo S, Nagaoka S, Funai J, Koshiji M, Nambu Y, Furuse J, Miyazaki M, Nimura Y. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 2010; **103**: 469-474 [PMID: 20628385 DOI: 10.1038/sj.bjc.6605779]

21 **Valle JW**, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, Bridgewater J, Okusaka T. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. *Ann Oncol* 2014; **25**: 391-398 [PMID: 24351397 DOI: 10.1093/annonc/mdt540]

22 **Furuse J**, Okusaka T, Bridgewater J, Taketsuna M, Wasan H, Koshiji M, Valle J. Lessons from the comparison of two randomized clinical trials using gemcitabine and cisplatin for advanced biliary tract cancer. *Crit Rev Oncol Hematol* 2011; **80**: 31-39 [PMID: 21094052 DOI: 10.1016/j.critrevonc.2010.10.009]

23 **Shroff RT**, Javle MM, Xiao L, Kaseb AO, Varadhachary GR, Wolff RA, Raghav KPS, Iwasaki M, Masci P, Ramanathan RK, Ahn DH, Bekaii-Saab TS, Borad MJ. Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. *JAMA Oncol* 2019; **5**: 824-830 [PMID: 30998813 DOI: 10.1001/jamaoncol.2019.0270]

24 **Roth MT**, Goff LW. Gemcitabine, Cisplatin, and nab-Paclitaxel for Patients With Advanced Biliary Tract Cancer: Closing the GAP. *JAMA Oncol* 2019; **5**: 831-832 [PMID: 30998823 DOI: 10.1001/jamaoncol.2019.0269]

25 **Cheon J**, Lee CK, Sang YB, Choi HJ, Kim MH, Ji JH, Ko KH, Kwon CI, Kim DJ, Choi SH, Kim C, Kang B, Chon HJ. Real-world efficacy and safety of nab-paclitaxel plus gemcitabine-cisplatin in patients with advanced biliary tract cancers: a multicenter retrospective analysis. *Ther Adv Med Oncol* 2021; **13**: 17588359211035983 [PMID: 34394748 DOI: 10.1177/17588359211035983]

26 **Jung K**, Park J, Jung JH, Lee JC, Kim J, Hwang JH. Real-World Outcomes of Gemcitabine, Cisplatin, and Nab-Paclitaxel Chemotherapy Regimen for Advanced Biliary Tract Cancer: A Propensity Score-Matched Analysis. *Gut Liver* 2022; **16**: 798-805 [PMID: 35000934 DOI: 10.5009/gnl210346]

27 **Phelip JM**, Desrame J, Edeline J, Barbier E, Terrebonne E, Michel P, Perrier H, Dahan L, Bourgeois V, Akouz FK, Soularue E, Ly VL, Molin Y, Lecomte T, Ghiringhelli F, Coriat R, Louafi S, Neuzillet C, Manfredi S, Malka D; PRODIGE 38 AMEBICA Investigators/Collaborators. Modified FOLFIRINOX Versus CISGEM Chemotherapy for Patients With Advanced Biliary Tract Cancer (PRODIGE 38 AMEBICA): A Randomized Phase II Study. *J Clin Oncol* 2022; **40**: 262-271 [PMID: 34662180 DOI: 10.1200/JCO.21.00679]

28 **Morizane C**, Okusaka T, Mizusawa J, Katayama H, Ueno M, Ikeda M, Ozaka M, Okano N, Sugimori K, Fukutomi A, Hara H, Mizuno N, Yanagimoto H, Wada K, Tobimatsu K, Yane K, Nakamori S, Yamaguchi H, Asagi A, Yukisawa S, Kojima Y, Kawabe K, Kawamoto Y, Sugimoto R, Iwai T, Nakamura K, Miyakawa H, Yamashita T, Hosokawa A, Ioka T, Kato N, Shioji K, Shimizu K, Nakagohri T, Kamata K, Ishii H, Furuse J; members of the Hepatobiliary and Pancreatic

Oncology Group of the Japan Clinical Oncology Group (JCOG-HBPOG). Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. *Ann Oncol* 2019; **30**: 1950-1958 [PMID: 31566666 DOI: 10.1093/annonc/mdz402]

29 **Ioka T**, Kanai M, Kobayashi S, Sakai D, Eguchi H, Baba H, Seo S, Taketomi A, Takayama T, Yamaue H, Takahashi M, Sho M, Kamei K, Fujimoto J, Toyoda M, Shimizu J, Goto T, Shindo Y, Yoshimura K, Hatano E, Nagano H; Kansai Hepatobiliary Oncology Group (KHBO). Randomized phase III study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401- MITSUBA). *J Hepatobiliary Pancreat Sci* 2023; **30**: 102-110 [PMID: 35900311 DOI: 10.1002/jhbp.1219]

30 **Lamarca A**, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters JS, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2021; **22**: 690-701 [PMID: 33798493 DOI: 10.1016/S1470-2045(21)00027-9]

31 **Choi IS**, Kim KH, Lee JH, Suh KJ, Kim JW, Park JH, Kim YJ, Kim JS, Kim JH. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. *Eur J Cancer* 2021; **154**: 288-295 [PMID: 34303267 DOI: 10.1016/j.ejca.2021.06.019]

32 **Yoo C**, Kim KP, Jeong JH, Kim I, Kang MJ, Cheon J, Kang BW, Ryu H, Lee JS, Kim KW, Abou-Alfa GK, Ryoo BY. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *Lancet Oncol* 2021; **22**: 1560-1572 [PMID: 34656226 DOI: 10.1016/S1470-2045(21)00486-1]

33 **Zheng Y**, Tu X, Zhao P, Jiang W, Liu L, Tong Z, Zhang H, Yan C, Fang W, Wang W. A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. *Br J Cancer* 2018; **119**: 291-295 [PMID: 29955136 DOI: 10.1038/s41416-018-0138-2]

34 **Zhang W**, Zhou H, Wang Y, Zhang Z, Cao G, Song T, Zhang T, Li Q. Systemic treatment of advanced or recurrent biliary tract cancer. *Biosci Trends* 2020; **14**: 328-341 [PMID: 32830166 DOI: 10.5582/bst.2020.03240]

35 **Rizzo A**, Ricci AD, Cusmai A, Acquafredda S, De Palma G, Brandi G, Palmiotti G. Systemic Treatment for Metastatic Biliary Tract Cancer: State of the Art and a Glimpse to the Future. *Curr Oncol* 2022; **29**: 551-564 [PMID: 35200550 DOI: 10.3390/curroncol29020050]

36 **Wakai T**, Nagahashi M, Shimada Y, Prasoon P, Sakata J. Genetic analysis in the clinical management of biliary tract cancer. *Ann Gastroenterol Surg* 2020; **4**: 316-323 [PMID: 32724874 DOI: 10.1002/ags3.12334]

37 **Berchuck JE**, Facchinetti F, DiToro DF, Baiev I, Majeed U, Reyes S, Chen C, Zhang K, Sharman R, Uson Junior PLS, Maurer J, Shroff RT, Pritchard CC, Wu MJ, Catenacci DVT, Javle M, Friboulet L, Hollebecque A, Bardeesy N, Zhu AX, Lennerz JK, Tan B, Borad M, Parikh AR, Kiedrowski LA, Kelley RK, Mody K, Juric D, Goyal L. The clinical landscape of cell-free DNA alterations in 1671 patients with advanced biliary tract cancer. *Ann Oncol* 2022; **33**: 1269-1283 [PMID: 36089135 DOI: 10.1016/j.annonc.2022.09.150]

38 **Arai Y**, Totoki Y, Hosoda F, Shirota T, Hama N, Nakamura H, Ojima H, Furuta K, Shimada K, Okusaka T, Kosuge T, Shibata T. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology* 2014; **59**: 1427-1434 [PMID: 24122810 DOI: 10.1002/hep.26890]

39 **Pu X**, Ye Q, Cai J, Yang X, Fu Y, Fan X, Wu H, Chen J, Qiu Y, Yue S. Typing FGFR2 translocation determines the response to targeted therapy of intrahepatic cholangiocarcinomas. *Cell Death Dis* 2021; **12**: 256 [PMID: 33692336 DOI: 10.1038/s41419-021-03548-4]

40 **Mirallas O**, López-Valbuena D, García-Illescas D, Fabregat-Franco C, Verdaguer H, Tabernero J, Macarulla T. Advances in the systemic treatment of therapeutic approaches in biliary tract cancer. *ESMO Open* 2022; **7**: 100503 [PMID: 35696747 DOI: 10.1016/j.esmoop.2022.100503]

41 **Aitcheson G**, Mahipal A, John BV. Targeting FGFR in intrahepatic cholangiocarcinoma [iCCA]: leading the way for precision medicine in biliary tract cancer [BTC]? *Expert Opin Investig Drugs* 2021; **30**: 463-477 [PMID: 33678096 DOI: 10.1080/13543784.2021.1900821]

42 **Nogova L**, Sequist LV, Perez Garcia JM, Andre F, Delord JP, Hidalgo M, Schellens JH, Cassier PA, Camidge DR, Schuler M, Vaishampayan U, Burris H, Tian GG, Campone M, Wainberg ZA, Lim WT, LoRusso P, Shapiro GI, Parker K, Chen X, Choudhury S, Ringeisen F, Graus-Porta D, Porter D, Isaacs R, Buettner R, Wolf J. Evaluation of BGJ398, a Fibroblast Growth Factor Receptor 1-3 Kinase Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in Fibroblast Growth Factor Receptors: Results of a Global Phase I, Dose-Escalation and Dose-Expansion Study. *J Clin Oncol* 2017; **35**: 157-165 [PMID: 27870574 DOI: 10.1200/JCO.2016.67.2048]

43 **Javle M**, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, Ramanathan RK, Goyal L, Sadeghi S, Macarulla T, El-Khoueiry A, Kelley RK, Borbath I, Choo SP, Oh DY, Philip PA, Chen LT, Reungwetwattana T, Van Cutsem E, Yeh KH, Ciombor K, Finn RS, Patel A, Sen S, Porter D, Isaacs R, Zhu AX, Abou-Alfa GK, Bekaii-Saab T. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. *J Clin Oncol* 2018; **36**: 276-282 [PMID: 29182496 DOI: 10.1200/JCO.2017.75.5009]

44 **Javle M**, Roychowdhury S, Kelley RK, Sadeghi S, Macarulla T, Weiss KH, Waldschmidt DT, Goyal L, Borbath I, El-Khoueiry A, Borad MJ, Yong WP, Philip PA, Bitzer M, Tanasanvimon S, Li A, Pande A, Soifer HS, Shepherd SP, Moran S, Zhu AX, Bekaii-Saab TS, Abou-Alfa GK. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol* 2021; **6**: 803-815 [PMID: 34358484 DOI: 10.1016/S2468-1253(21)00196-5]

45 **Abou-Alfa GK**, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, Oh DY, Dotan E, Catenacci DV, Van Cutsem E, Ji T, Lihou CF, Zhen H, Féliz L, Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2020; **21**: 671-684 [PMID: 32203698 DOI: 10.1016/S1470-2045(20)30109-1]

46 **Makawita S**, K Abou-Alfa G, Roychowdhury S, Sadeghi S, Borbath I, Goyal L, Cohn A, Lamarca A, Oh DY, Macarulla T, T Shroff R, Howland M, Li A, Cho T, Pande A, Javle M. Infigratinib in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF 301 trial. *Future Oncol* 2020; **16**: 2375-2384 [PMID: 32580579 DOI: 10.2217/fon-2020-0299]

47 **Bekaii-Saab TS**, Valle JW, Van Cutsem E, Rimassa L, Furuse J, Ioka T, Melisi D, Macarulla T, Bridgewater J, Wasan H, Borad MJ, Abou-Alfa GK, Jiang P, Lihou CF, Zhen H, Asatiani E, Féliz L, Vogel A. FIGHT-302: first-line pemigatinib vs gemcitabine plus cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements. *Future Oncol* 2020; **16**: 2385-2399 [PMID: 32677452 DOI: 10.2217/fon-2020-0429]

48 **Mazzaferro V**, El-Rayes BF, Droz Dit Busset M, Cotsoglou C, Harris WP, Damjanov N, Masi G, Rimassa L, Personeni N, Braiteh F, Zagonel V, Papadopoulos KP, Hall T, Wang Y, Schwartz B, Kazakin J, Bhoori S, de Braud F, Shaib WL. Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. *Br J Cancer* 2019; **120**: 165-171 [PMID: 30420614 DOI: 10.1038/s41416-018-0334-0]

49 **Bahleda R**, Italiano A, Hierro C, Mita A, Cervantes A, Chan N, Awad M, Calvo E, Moreno V, Govindan R, Spira A, Gonzalez M, Zhong B, Santiago-Walker A, Poggesi I, Parekh T, Xie H, Infante J, Tabernero J. Multicenter Phase I Study of Erdafitinib (JNJ-42756493), Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients with Advanced or Refractory Solid Tumors. *Clin Cancer Res* 2019; **25**: 4888-4897 [PMID: 31088831 DOI: 10.1158/1078-0432.CCR-18-3334]

50 **Bahleda R**, Meric-Bernstam F, Goyal L, Tran B, He Y, Yamamiya I, Benhadji KA, Matos I, Arkenau HT. Phase I, first-in-human study of futibatinib, a highly selective, irreversible FGFR1-4 inhibitor in patients with advanced solid tumors. *Ann Oncol* 2020; **31**: 1405-1412 [PMID: 32622884 DOI: 10.1016/j.annonc.2020.06.018]

51 **Goyal L**, Meric-Bernstam F, Hollebecque A, Valle JW, Morizane C, Karasic TB, Abrams TA, Furuse J, Kelley RK, Cassier PA, Klümpen HJ, Chang HM, Chen LT, Tabernero J, Oh DY, Mahipal A, Moehler M, Mitchell EP, Komatsu Y, Masuda K, Ahn D, Epstein RS, Halim AB, Fu Y, Salimi T, Wacheck V, He Y, Liu M, Benhadji KA, Bridgewater JA; FOENIX-CCA2 Study Investigators. Futibatinib for FGFR2-Rearranged Intrahepatic Cholangiocarcinoma. *N Engl J Med* 2023; **388**: 228-239 [PMID: 36652354 DOI: 10.1056/NEJMoa2206834]

52 **Boscoe AN**, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *J Gastrointest Oncol* 2019; **10**: 751-765 [PMID: 31392056 DOI: 10.21037/jgo.2019.03.10]

53 **Lee K**, Song YS, Shin Y, Wen X, Kim Y, Cho NY, Bae JM, Kang GH. Intrahepatic cholangiocarcinomas with IDH1/2 mutation-associated hypermethylation at selective genes and their clinicopathological features. *Sci Rep* 2020; **10**: 15820 [PMID: 32978444 DOI: 10.1038/s41598-020-72810-0]

54 **Zhu AX**, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DVT, Borad MJ, Bridgewater JA, Harris WP, Murphy AG, Oh DY, Whisenant JR, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Chamberlain CX, Aguado-Fraile E, Choe S, Wu B, Liu H, Gliser C, Pandya SS, Valle JW, Abou-Alfa GK. Final Overall Survival Efficacy Results of Ivosidenib for Patients With Advanced Cholangiocarcinoma With IDH1 Mutation: The Phase 3 Randomized Clinical ClarIDHy Trial. *JAMA Oncol* 2021; **7**: 1669-1677 [PMID: 34554208 DOI: 10.1001/jamaoncol.2021.3836]

55 **Rimini M**, Burgio V, Antonuzzo L, Rimassa L, Oneda E, Lavacchi D, Personeni N, Ratti F, Pedica F, Della Corte A, Persano M, De Cobelli F, Aldrighetti L, Scartozzi M, Cascinu S, Casadei-Gardini A. Real-World Data on Ivosidenib in Patients with Previously Treated Isocitrate Dehydrogenase 1-Mutated Intrahepatic Cholangiocarcinomas: An Early Exploratory Analysis. *Target Oncol* 2022; **17**: 591-596 [PMID: 36114954 DOI: 10.1007/s11523-022-00917-7]

56 **Casak SJ**, Pradhan S, Fashoyin-Aje LA, Ren Y, Shen YL, Xu Y, Chow ECY, Xiong Y, Zirklelbach JF, Liu J, Charlab R, Pierce WF, Fesenko N, Beaver JA, Pazdur R, Kluetz PG, Lemery SJ. FDA Approval Summary: Ivosidenib for the Treatment of Patients with Advanced Unresectable or Metastatic, Chemotherapy Refractory Cholangiocarcinoma with an IDH1 Mutation. *Clin Cancer Res* 2022; **28**: 2733-2737 [PMID: 35259259 DOI: 10.1158/1078-0432.CCR-21-4462]

57 **Weinberg BA**, Xiu J, Lindberg MR, Shields AF, Hwang JJ, Poorman K, Salem ME, Pishvaian MJ, Holcombe RF, Marshall JL, Morse MA. Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets. *J Gastrointest Oncol* 2019; **10**: 652-662 [PMID: 31392046 DOI: 10.21037/jgo.2018.08.18]

58 **Tsimafeyeu I**, Temper M. Cholangiocarcinoma: An Emerging Target for Molecular Therapy. *Gastrointest Tumors* 2021; **8**: 153-158 [PMID: 34722468 DOI: 10.1159/000517258]

59 **Subbiah V**, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, de Braud F, Prager GW, Greil R, Stein A, Fasolo A, Schellens JHM, Wen PY, Viele K, Boran AD, Gasal E, Burgess P, Ilankumaran P, Wainberg ZA. Dabrafenib plus trametinib in patients with BRAF(V600E)-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol* 2020; **21**: 1234-1243 [PMID: 32818466 DOI: 10.1016/S1470-2045(20)30321-1]

60 **Kim HJ**, Yoo TW, Park DI, Park JH, Cho YK, Sohn CI, Jeon WK, Kim BI, Kim MK, Chae SW, Sohn JH. Gene amplification and protein overexpression of HER-2/neu in human extrahepatic cholangiocarcinoma as detected by chromogenic in situ hybridization and immunohistochemistry: its prognostic implication in node-positive patients. *Ann Oncol* 2007; **18**: 892-897 [PMID: 17322545 DOI: 10.1093/annonc/mdm006]

61 **Detarya M**, Lert-Itthiporn W, Mahalapbutr P, Klaewkla M, Sorin S, Sawanyawisuth K, Silsirivanit A, Seubwai W, Wongkham C, Araki N, Wongkham S. Emerging roles of GALNT5 on promoting EGFR activation in cholangiocarcinoma: a mechanistic insight. *Am J Cancer Res* 2022; **12**: 4140-4159 [PMID: 36225633]

62 **Javle M**, Churi C, Kang HC, Shroff R, Janku F, Surapaneni R, Zuo M, Barrera C, Alshamsi H, Krishnan S, Mishra L, Wolff RA, Kaseb AO, Thomas MB, Siegel AB. HER2/neu-directed therapy for biliary tract cancer. *J Hematol Oncol* 2015; **8**: 58 [PMID: 26022204 DOI: 10.1186/s13045-015-0155-z]

63 **Javle M**, Borad MJ, Azad NS, Kurzrock R, Abou-Alfa GK, George B, Hainsworth J, Meric-Bernstam F, Swanton C, Sweeney CJ, Friedman CF, Bose R, Spigel DR, Wang Y, Levy J, Schulze K, Cuchelkar V, Patel A, Burris H. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol* 2021; **22**: 1290-1300 [PMID: 34339623 DOI: 10.1016/S1470-2045(21)00336-3]

64 **Okamura R**, Boichard A, Kato S, Sicklick JK, Bazhenova L, Kurzrock R. Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Malignancies: Implications for NTRK-Targeted Therapeutics. *JCO Precis Oncol* 2018; **2018** [PMID:

30637364 DOI: 10.1200/PO.18.00183]

65 **Grant CS**, Van Heerden JA. Anastomotic ulceration following subtotal and total pancreatectomy. *Ann Surg* 1979; **190**: 1-5 [PMID: 313757 DOI: 10.1038/s41379-019-0324-7]

66 **Drilon A**, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, Nathenson M, Doebele RC, Farago AF, Pappo AS, Turpin B, Dowlati A, Brose MS, Mascarenhas L, Federman N, Berlin J, El-Deiry WS, Baik C, Deeken J, Boni V, Nagasubramanian R, Taylor M, Rudzinski ER, Meric-Bernstam F, Sohal DPS, Ma PC, Raez LE, Hechtman JF, Benayed R, Ladanyi M, Tuch BB, Ebata K, Cruickshank S, Ku NC, Cox MC, Hawkins DS, Hong DS, Hyman DM. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018; **378**: 731-739 [PMID: 29466156 DOI: 10.1056/NEJMoa1714448]

67 **Doebele RC**, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, Blakely CM, Seto T, Cho BC, Tosi D, Besse B, Chawla SP, Bazhenova L, Krauss JC, Chae YK, Barve M, Garrido-Laguna I, Liu SV, Conkling P, John T, Fakih M, Sigal D, Loong HH, Buchschacher GL Jr, Garrido P, Nieva J, Steuer C, Overbeck TR, Bowles DW, Fox E, Riehl T, Chow-Maneval E, Simmons B, Cui N, Johnson A, Eng S, Wilson TR, Demetri GD; trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol* 2020; **21**: 271-282 [PMID: 31838007 DOI: 10.1016/S1470-2045(19)30691-6]

68 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]

69 **Zhao P**, Li L, Jiang X, Li Q. Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. *J Hematol Oncol* 2019; **12**: 54 [PMID: 31151482 DOI: 10.1186/s13045-019-0738-1]

70 **de Miguel M**, Calvo E. Clinical Challenges of Immune Checkpoint Inhibitors. *Cancer Cell* 2020; **38**: 326-333 [PMID: 32750319 DOI: 10.1016/j.ccell.2020.07.004]

71 **Goleva E**, Lyubchenko T, Kraehenbuehl L, Lacouture ME, Leung DYM, Kern JA. Our current understanding of checkpoint inhibitor therapy in cancer immunotherapy. *Ann Allergy Asthma Immunol* 2021; **126**: 630-638 [PMID: 33716146 DOI: 10.1016/j.anai.2021.03.003]

72 **Gani F**, Nagarajan N, Kim Y, Zhu Q, Luan L, Bhaijjee F, Anders RA, Pawlik TM. Program Death 1 Immune Checkpoint and Tumor Microenvironment: Implications for Patients With Intrahepatic Cholangiocarcinoma. *Ann Surg Oncol* 2016; **23**: 2610-2617 [PMID: 27012989 DOI: 10.1245/s10434-016-5101-y]

73 **Rizzo A**, Ricci AD, Brandi G. Recent advances of immunotherapy for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 527-536 [PMID: 33215952 DOI: 10.1080/17474124.2021.1853527]

74 **Piha-Paul SA**, Oh DY, Ueno M, Malka D, Chung HC, Nagrial A, Kelley RK, Ros W, Italiano A, Nakagawa K, Rugo HS, de Braud F, Varga AI, Hansen A, Wang H, Krishnan S, Norwood KG, Doi T. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. *Int J Cancer* 2020; **147**: 2190-2198 [PMID: 32359091 DOI: 10.1002/ijc.33013]

75 **Feng K**, Liu Y, Zhao Y, Yang Q, Dong L, Liu J, Li X, Zhao Z, Mei Q, Han W. Efficacy and biomarker analysis of nivolumab plus gemcitabine and cisplatin in patients with unresectable or metastatic biliary tract cancers: results from a phase II study. *J Immunother Cancer* 2020; **8** [PMID: 32487569 DOI: 10.1136/jitc-2019-000367]

76 **Ueno M**, Ikeda M, Morizane C, Kobayashi S, Ohno I, Kondo S, Okano N, Kimura K, Asada S, Namba Y, Okusaka T, Furuse J. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. *Lancet Gastroenterol Hepatol* 2019; **4**: 611-621 [PMID: 31109808 DOI: 10.1016/S2468-1253(19)30086-X]

77 **Kim RD**, Chung V, Alese OB, El-Rayes BF, Li D, Al-Toubah TE, Schell MJ, Zhou JM, Mahipal A, Kim BH, Kim DW. A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer. *JAMA Oncol* 2020; **6**: 888-894 [PMID: 32352498 DOI: 10.1001/jamaoncol.2020.0930]

78 **Klein O**, Kee D, Nagrial A, Markman B, Underhill C, Michael M, Jackett L, Lum C, Behren A, Palmer J, Tebbutt NC, Carlino MS, Cebon J. Evaluation of Combination Nivolumab and Ipilimumab Immunotherapy in Patients With Advanced Biliary Tract Cancers: Subgroup Analysis of a Phase 2 Nonrandomized Clinical Trial. *JAMA Oncol* 2020; **6**: 1405-1409 [PMID: 32729929 DOI: 10.1001/jamaoncol.2020.2814]

79 **Sahai V**, Griffith KA, Beg MS, Shaib WL, Mahalingam D, Zhen DB, Deming DA, Zalupski MM. A randomized phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer: BilT-01. *Cancer* 2022; **128**: 3523-3530 [PMID: 35895381 DOI: 10.1002/cncr.34394]

80 **Chen X**, Wu X, Wu H, Gu Y, Shao Y, Shao Q, Zhu F, Li X, Qian X, Hu J, Zhao F, Mao W, Sun J, Wang J, Han G, Li C, Xia Y, Seesaha PK, Zhu D, Li H, Zhang J, Wang G, Wang X, Shu Y. Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. *J Immunother Cancer* 2020; **8** [PMID: 33172881 DOI: 10.1136/jitc-2020-001240]

81 **Chen X**, Qin S, Gu S, Ren Z, Chen Z, Xiong J, Liu Y, Meng Z, Zhang X, Wang L, Zou J. Camrelizumab plus oxaliplatin-based chemotherapy as first-line therapy for advanced biliary tract cancer: A multicenter, phase 2 trial. *Int J Cancer* 2021; **149**: 1944-1954 [PMID: 34309846 DOI: 10.1002/ijc.33751]

82 **Oh DY**, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH, Nam AR, Oh KS, Kim JM, Lee Y, Guthrie V, McCoon P, Li W, Wu S, Zhang Q, Rebelatto MC, Kim JW. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. *Lancet Gastroenterol Hepatol* 2022; **7**: 522-532 [PMID: 35278356 DOI: 10.1016/S2468-1253(22)00043-7]

83 **Peng X**, Wang X, Hua L, Yang R. Prognostic and Clinical Value of the Systemic Immune-Inflammation Index in Biliary Tract Cancer: A Meta-Analysis. *J Immunol Res* 2022; **2022**: 6988489 [PMID: 36438200 DOI: 10.1155/2022/6988489]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com