Targeted Oncology (2023) 18:51–76
https://doi.org/10.1007/s11523-022-00942-6

REVIEW ARTICLE

Optimizing Patient Pathways in Advanced Biliary Tract Cancers: Recent Advances and a French Perspective

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Accepted: 8 December 2022 / Published online: 6 February 2023

Abstract

Biliary tract cancers (BTCs) are a heterogeneous group of tumors that are rare in Western countries and have a poor prognosis. Three subgroups are defined by their anatomical location (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma) and exhibit distinct clinical, molecular, and epidemiologic characteristics. Most patients are diagnosed at an advanced disease stage and are not eligible for curative-intent resection. In addition to first- and second-line chemotherapies (CisGem and FOLFOX, respectively), biologic therapies are now available that target specific genomic alterations identified in BTC. To date, targets include alterations in the genes for isocitrate dehydrogenase (*IDH*) 1, fibroblast growth factor receptor (*FGFR*) 2, v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), human epidermal growth factor receptor 2 (*HER2* or *ERRB2*), and neurotrophic tyrosine receptor kinase (*NTRK*), and for those leading to DNA mismatch repair deficiency. Therapies targeting these genomic alterations have demonstrated clinical benefit for patients with BTC. Despite these therapeutic advancements, genomic diagnostic modalities are not widely used in France, owing to a lack of clinician awareness, local availability of routine genomic testing, and difficulties in obtaining health insurance reimbursement. The addition of durvalumab, a monoclonal antibody targeting the immune checkpoint programmed cell death ligand-1, to CisGem in the first-line treatment of advanced BTC has shown an overall survival benefit in the TOPAZ-1 trial. Given the high mortality rates associated with BTC and the life-prolonging therapeutic options now available, it is hoped that the data presented here will support updates to the clinical management of BTC in France.

Key Points

Biliary tract cancers (BTCs) are a rare heterogeneous group of aggressive epithelial cancers that, due to a lack of symptoms in the early stage of disease, are typically diagnosed at an advanced stage when the disease is unresectable or has metastasized.

While treatments for this advanced disease are limited, recent advances that offer the opportunity for more personalized therapy for patients with BTC include therapies specific to the more common genetic alterations, as well as immunotherapies that mediate immune recognition of the tumors.

This review comprises data from recent publications on the efficacy of treatment options, in addition to expert opinions on the current state of BTC treatment in France.

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1 Introduction

Biliary tract cancers (BTCs), which include cholangiocarcinomas (CCAs) and gallbladder carcinomas (GBCs), represent a heterogeneous group of aggressive epithelial cancers, with different clinical, molecular and epidemiological characteristics depending on their anatomical location [1, 2]. BTCs are rare in Western countries, but can be endemic in parts of Asia [3]. CCAs are categorized into three distinct groups, based on their anatomical location [4]. Intrahepatic CCA (iCCA) occurs in the periphery of second-order bile ducts, and the two subtypes of extrahepatic CCA (eCCA)—perihilar CCA (pCCA) and distal CCA (dCCA)—arise at the right and/or left hepatic duct and/or at their junction, and the common bile duct, respectively [4]. According to the 2019 World Health Organization (WHO) classification of digestive tumors, iCCAs are divided into two main subtypes: adenocarcinoma/large duct type, which resembles eCCA, and adenocarcinoma/small duct type, which shares characteristics with hepatocellular carcinoma (HCC) [5].

Surgery is the only potentially curative treatment, but is possible only for the minority of patients who are diagnosed with localized BTC. However, relapse rates in patients who have undergone curative-intent surgery are high. Due to the lack of symptoms in the early stages of disease (particularly for iCCA), approximately half to two-thirds of CCA cases are diagnosed at an advanced stage, at which time the condition is unresectable or has metastasized [2, 6, 7]. In these cases, management is palliative, relying on best supportive care (BSC) alone or combined with systemic therapy and/or local therapies (e.g., stereotactic radiotherapy, hepatic arterial therapies), and recommended treatment options past first-line therapy have been limited [2, 8]. However, recent advances include therapies specific to the more common genetic alterations, as well as immunotherapies that mediate immune recognition of the tumors. These novel therapeutic targets offer the opportunity for more personalized therapy for BTC patients in the future.

The following review comprises data from recent publications on the efficacy of treatment options in addition to expert opinions on the current state of CCA, with a particular focus on the impact and management of CCA in France. Therapeutic options that are still under evaluation are summarized. In addition, evidence is presented on the importance of investigating molecular abnormalities in patients with BTC and the therapeutic value these have, with the opportunity to personalize care for patients with CCA.

2 Epidemiology of Biliary Tract Cancer

BTC is a rare cancer, but its incidence overall has generally tended to increase in recent decades [4]. In France, the incidence of CCA (any subtype) has been reported to be 1.4 (for men) and 0.7 (for women) cases per 100,000 person-years (between 1976 and 2005), with eCCA being more common than iCCA (0.5–1.1 vs. 0.2–0.4 per 100,000 person-years) [7].

Risk factors associated predominantly with iCCA include chronic non-alcoholic liver disease, infection with hepatitis C virus, liver flukes, metabolic syndromes (such as type 2 diabetes mellitus and obesity), and infection with hepatitis B virus [9, 10]. Particularly in the presence of cirrhosis, alcoholic and fatty liver disease drastically increases the risk of developing BTC, particularly iCCA [9]. Approximately one-third of patients with iCCA have cirrhosis [11]. The overlapping etiologic factors between HCC and iCCA, and the shared nucleotide substitutions observed in HCC and iCCA related to chronic hepatitis [12], suggest a common cell of origin (biliary epithelial cells, liver progenitor cells, or hepatocytes) and different pathways of oncogenesis. Notch activation has been implicated in the conversion of normal hepatocytes into malignant cholangiocytes [13]. A recent study also highlights the importance of the microenvironment in hepatocellular or biliary tumoral orientation in relation to specific epigenetic signatures [14].

Other factors associated with increased risk of developing either iCCA or eCCA include gallstones, chronic inflammatory diseases of the bile ducts (particularly primary sclerosing cholangitis (PSC)), and Lynch syndrome [10, 15, 16]. PSC frequently coexists with inflammatory bowel disease (IBD), and the risk of CCA increases with the duration of IBD and with the need for colectomy [17]. On the other hand, smoking, choledocholithiasis, cholelithiasis, and cholecystolithiasis show a greater association with eCCA than iCCA [9]. Differences in BTC incidence between geographic regions are likely due to particular risk factors having a higher prevalence within certain areas. For instance, biliary parasitic infections have been reported as a prominent risk factor for BTC in East Asian countries such as Thailand, and sclerosing cholangitis and metabolic liver disease have been reported as some of the most common risk factors in Western nations [10, 18, 19].

In Western countries, including the United Kingdom (UK) and the United States of America (USA), the incidence of iCCA is increasing while the incidence of eCCA remains relatively stable [20–22]. A recent retrospective analysis of a French nationwide hospital database estimated the incidence of newly diagnosed iCCA as 1,825 patients per year (3650 new cases between 2014 and 2015) [23]. The study investigators noted this was higher than the incidence of iCCA recorded in earlier French registry studies [24].

As BTC is generally diagnosed at an advanced stage, with limited therapeutic options available, it is associated with a poor prognosis. The ENSCCA registry, a multicenter observational study of 2234 patients with a histologically proven diagnosis of CCA between 2010 and 2019 in 26 hospitals and 11 European countries (iCCA: 1243; pCCA: 592; dCCA: 399),

showed that at diagnosis, 42.2% of patients had local disease, 29.4% had locally advanced disease, and 28.4% had metastatic disease [25]. Patients undergoing resection (50.3%) had the best outcomes, particularly with negative-resection margin (R0) (median overall survival (OS): 45.1 months); however, margin involvement (R1) (hazard ratio (HR): 1.92; 95% confidence interval (CI), 1.53–2.41; median OS: 24.7 months) and lymph node invasion (HR: 2.13; 95% CI: 1.55–2.94; median OS: 23.3 months) compromised prognosis. Among patients with unresectable disease (49.6%), the median OS was 10.6 months for those receiving active palliative therapies, mostly chemotherapy (26.2%), and 4.0 months for those receiving BSC (20.6%). iCCA was associated with a worse outcome than pCCA or dCCA. Eastern Cooperative Oncology Group (ECOG) performance status (PS), metastatic disease, and serum carbohydrate antigen (CA) 19-9 levels were independent prognostic factors. The relative survival rate in France for patients with all subtypes and stages of BTC was reported to be 25% at 1 year, 10% at 3 years, and 7% at 5 years, with the majority of cases found to be unresectable or metastatic at diagnosis. For patients with advanced disease, the 5-year survival rate was < 5% [7]. The abovementioned French nationwide study underlines the aggressive nature of BTC, with one-quarter of patients dying during their first hospital stay and two-thirds of patients not having access to active treatment (receiving only BSC) [23].

The age-standardized annual mortality rates attributable to iCCA increased across 32 European countries from 2002 to 2013, with the exception of Finland, which had an 8% decrease in mortality for men and a 14% decrease in mortality for women. After Hong Kong, France had the highest age-standardized mortality rate for iCCA in men (1.78 in 100,000) and one of the highest age-standardized mortality rates for iCCA in women (1.04 in 100,000). In contrast, the age-standardized annual mortality rates attributable to eCCA decreased across most of the European countries among both men and women (Fig. 1). The countries with the lowest rates of eCCA mortality in men and women included France (0.07 in 100,000 and 0.05 in 100,000, respectively), along with other central and northern European countries [26]. The reason for the lower mortality rate with eCCA than iCCA may be that it is associated with a higher incidence of obstructive jaundice at presentation, prompting earlier diagnosis. Metastasis can be more frequently associated with iCCA, and it is speculated that this may be due to patients presenting with more advanced disease at diagnosis [7]. Ultimately, there has been no significant improvement over the last 30 years in early diagnosis of BTC, and updates are needed in therapeutic management to improve patient outcomes in France.

3 Current Treatments for BTC

3.1 Biliary Drainage and Surgical Resection

Only 30–50% [25] of patients diagnosed with CCA are suitable for resection, which is the only potentially curative

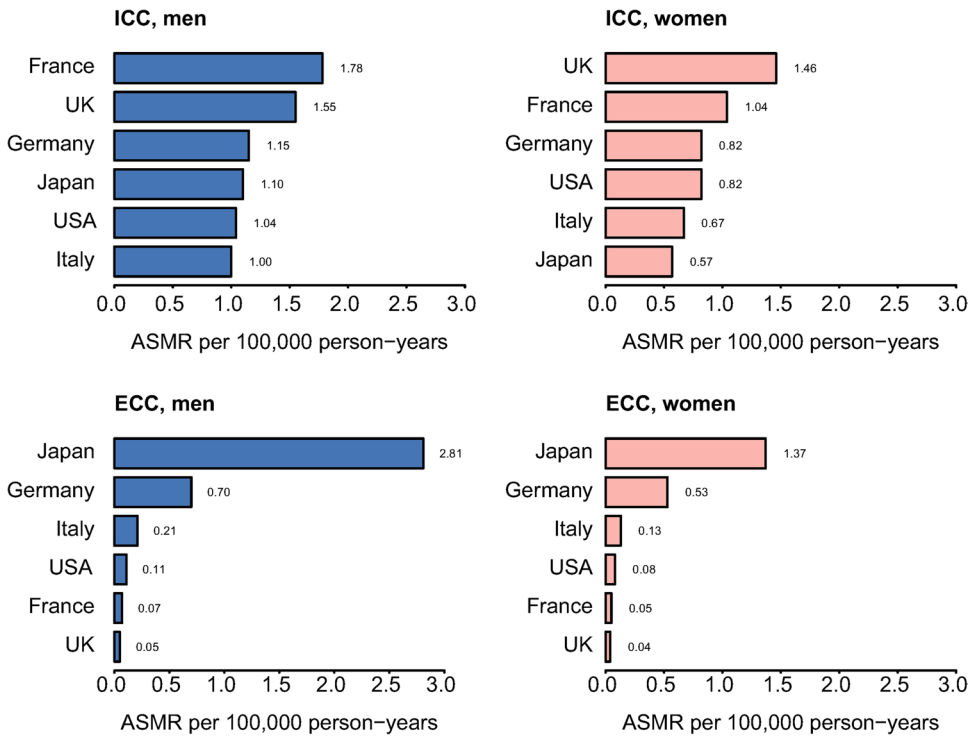


Fig. 1 Age-standardized mortality rates per 100,000 patients across selected countries, broken down according to intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, as well as according to men and women, in 2015 [26]. Reprinted from *J Hepatol*, 71, Bertuccio P, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma, 104–14, Copyright (2019), with permission from Elsevier. *ASMR* age-standardized mortality rates, *ECC* extrahepatic cholangiocarcinoma, *ICC* intrahepatic cholangiocarcinoma

treatment [27]. For patients with resectable pCCA, biliary drainage may be used to flush the bile ducts in order to alleviate cholestasis, and this can be performed prior to surgical resection, but is not without risk of complications such as infection or the seeding of metastatic cells [28, 29]. Biliary drainage may also be performed in patients with unresectable CCA and is beneficial for patients who are deteriorating and cannot be treated with chemotherapy. In these patients, biliary drainage may improve the patient's quality of life (QoL) and allows the initiation of chemotherapy [30].

For the minority of patients who are able to undergo surgical resection, postoperative relapses are frequent and 5-year OS after surgery is only 25–35% [27, 31, 32]. Some of the main prognostic factors in patients with resected BTC are lymph node metastasis, depth of tumor invasion, and positive surgical margins [33–35].

3.2 Adjuvant Therapy

Adjuvant therapy has become a widely used option for patients who have undergone surgical resection, although a standard treatment approach in this setting has not yet been established [36]. No benefit with gemcitabine plus oxaliplatin (GEMOX) adjuvant therapy was observed in a French phase 3 trial (PRODIGE 12-ACCORD 18) in resected patients with BTC compared with surgery alone [37]. This finding was supported by a Japanese phase 3 trial (BCAT), which also did not show benefit of gemcitabine monotherapy over surveillance in resected eCCA [38].

More favorable results were obtained with adjuvant capecitabine (a fluoropyrimidine pro-drug) in a British phase 3 trial (BILCAP) that included 447 patients with BTC after curative-intent resection [39, 40]. Patients were randomized to either an observation group or capecitabine treatment for 24 weeks [39]. Although a survival improvement was noted in the capecitabine group relative to the observation group (median OS of 49.6 vs. 36.1 months), the difference between active treatment and the observation group did not reach statistical significance (HR: 0.84; 95% CI: 0.67–1.06). However, the OS benefit became statistically significant following adjustment for prognostic factors including tumor grade and stage (HR: 0.74; 95% CI: 0.59–0.94) [40], and a recurrence-free survival (RFS) benefit was shown in the first 24 months post-randomization (HR: 0.74; 95% CI: 0.57–0.96) [39]. Despite the lack of significance for the primary endpoint in this study, 6 months of adjuvant chemotherapy with capecitabine has been recommended in international [41] and French [42] clinical practice guidelines in patients with surgically resected BTC. Recently, the results of two randomized trials presented in congress (but not yet published) have reinforced the place of fluoropyrimidines in the adjuvant treatment of BTC. A South Korean randomized phase 2 trial (STAMP) in 101 patients with resected lymph node-positive eCCA failed to demonstrate a benefit of adjuvant cisplatin plus gemcitabine (CisGem regimen) over capecitabine [43]. Median disease-free survival (primary endpoint) was 14.3 months in the CisGem arm and 11.1 months in the capecitabine arm (HR: 0.96; 95% CI: 0.71–1.30; $P = 0.86$), and median OS was 35.7 months in both arms (HR: 1.08; 95% CI: 0.72–1.64; $P = 0.81$). A Japanese phase 3 trial (ASCOT) showed an OS benefit (HR: 0.69; 95% CI: 0.51–0.94) over surveillance alone after curative-intent resection of BTC with S-1, an oral fluoropyrimidine combination consisting of tegafur, gimeracil, and oteracil, which is widely used in Asia but not validated in Western populations [44]. However, RFS was not significantly improved (HR: 0.80; 95% CI: 0.61–1.04). The results of this study, although not transposable to the European population, reinforce the rationale for using a fluoropyrimidine in adjuvant therapy.

To date, data from real-world clinical practice settings in France on the use of adjuvant therapy, especially capecitabine, are lacking. In our experience, a relatively high proportion of patients may receive adjuvant chemotherapy; however, there is no overall information on exposure and dose/intensity of adjuvant treatment, and this gap in knowledge needs to be addressed.

3.3 Locoregional Treatment

For patients with unresectable iCCA, which generally presents as a liver-only or liver-predominant disease, locoregional treatments are a promising therapeutic option that may be used in addition to chemotherapy [45]. Radioembolization (also known as selective internal radiotherapy (SIRT)) involves the administration of Yttrium-90 (^{90}Y)–labelled microspheres into the hepatic arteries to treat both primary liver tumors and metastases. A phase 2 trial in 41 patients with locally advanced, unresectable iCCA receiving SIRT combined with CisGem reported a centrally confirmed best overall response rate (ORR) of 39% at 3 months (90% CI: 26−53%) and a disease control rate (DCR) of 98% [46]. After a median follow-up of 36 months, median progression-free survival (PFS) was 14 (95% CI: 8–17) months, suggesting that the combination of chemotherapy with SIRT was beneficial for a significant proportion of patients. Furthermore, some patients were able to be downstaged, allowing for curative-intent secondary resection. Glass radiolabeled microspheres for the treatment of iCCA are now reimbursed in France [47].

Hepatic arterial infusion of chemotherapy (HAI) involves the delivery of chemotherapy directly into the liver. In a

phase 2 trial, 38 patients with unresectable iCCA received HAI with floxuridine (FUDR, a fluoropyrimidine) plus intravenous gemcitabine-oxaliplatin combination chemotherapy (GEMOX regimen) [48]. The 6-month PFS rate was 80%. After a median follow-up of 30.5 months, partial radiographic response was observed in 58% of patients and DCR was 84%. In France, floxuridine is no longer used for HAI, which rather relies on oxaliplatin via implantable catheters and ports in patients with liver metastases as well as iCCA. An ongoing French phase 2 trial (GEMOXIA-02; NCT03364530) is evaluating HAI gemcitabine plus oxaliplatin in patients with iCCA who failed prior first-line systemic chemotherapy. A US phase 2 trial (NCT04251715) is currently recruiting patients with liver-dominant, unresectable iCCA to investigate the efficacy and safety of induction systemic chemotherapy with modified FOLFIRINOX (mFOLFIRINOX; oxaliplatin, irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV)), followed by HAI with floxuridine and dexamethasone given concurrently with systemic modified FOLFIRI (irinotecan, 5-FU, and LV).

Other loco-regional treatments include external beam radiation therapy (EBRT), including stereotactic body radiotherapy, which delivers high-dose radiation beams to a tumor with high precision while limiting toxicity to surrounding tissue [49]. However, chemoradiotherapy with EBRT (50 Gy) plus 5-FU/cisplatin failed to show an improvement in PFS compared with GEMOX in a French randomized phase 2 trial of patients with locally advanced BTC, with a median PFS of 5.8 versus 11.0 months (HR: 0.65; 95% CI: 0.32–1.33) [50]; this trial was stopped early due to low patient recruitment. Transarterial chemoembolization (TACE) allows for the selective delivery of antitumor agents via the hepatic artery and has also been reported to limit toxicity in healthy tissue [51]. TACE using irinotecan-loaded beads was compared with CisGem in a randomized trial and showed an improved median OS of 33.7 versus 12.6 months, respectively ($P = 0.048$) [45].

Radiologically guided ablative procedures (e.g., radiofrequency ablation) have been advocated for the treatment of small (< 3 cm) single lesions when surgical resection is not an option [27]. Data from a meta-analysis that investigated the efficacy of locoregional therapies showed good outcomes for patients undergoing ablation, with a complete response rate of 93.3% and a median OS of 30.2 months [45]. Due to the quality of the studies investigated within the meta-analysis, ablation was the only strategy that received a strong recommendation. For EBRT and intra-arterial therapies, the pooled ORR from the meta-analysis was 23.4–41.3%, with a pooled mean OS of 14.1–21.3 months.

While evidence supporting the use of loco-regional therapies is mounting, there is still a relatively limited amount of robust data. French guidelines recommend that these therapies should be discussed on a case-by-case basis in patients with liver-only (or liver-dominant) iCCA, in combination with first-line systemic chemotherapy or as monotherapy following first-line treatment failure [42]. The results of two trials are currently awaited: a phase 3 trial (SIRCCA; NCT02807181) investigating first-line SIRT in patients with unresectable iCCA, and a randomized phase 2 trial (ABC-07; ISRCTN identifier 10639376) investigating EBRT.

3.4 First-Line Chemotherapy for Advanced BTC

Gemcitabine monotherapy has previously been used to treat patients with advanced BTC. An analysis of 100 cases (of whom 23 had iCCA and 25 had eCCA) demonstrated modest efficacy with an ORR of 7% (95% CI: 2.9–13.9) and median OS of 7.3 (95% CI: 5.4–9.2) months [52].

The gold-standard, first-line therapy for BTC is a CisGem regimen for 6 months, which has been shown to be more effective than gemcitabine alone in patients with locally advanced or metastatic BTC [53, 54], and is now the chemotherapy backbone for any new regimens being investigated in this setting. A pivotal UK phase 3 trial (ABC-02) demonstrated a significant PFS and OS benefit of CisGem over gemcitabine, regardless of the primary tumor site (Table 1) [53]. Of note, patients with an altered ECOG PS of 2 did not seem to benefit from the doublet chemotherapy to the same extent as those with a preserved ECOG PS of 0 or 1 [55]. Similarly, a Japanese randomized phase 2 study (BT-22) showed higher 1-year OS rate (39.0% vs. 31.0%) and median OS (11.2 vs. 7.7 months) with CisGem compared with gemcitabine [54].

Trials investigating alternative combinations for first-line treatment of BTC are also summarized in Table 1 [56–62]. A single-center phase 3 study conducted in India suggested that gemcitabine and oxaliplatin doublet (a modified GEMOX regimen) provided similar outcomes compared with CisGem in patients with unresectable GBC [61]. A systematic review of 33 studies (1470 patients) compared CisGem and GEMOX for the treatment of advanced BTC [63]. The weighted median OS was 9.7 months for the CisGem group and 9.5 months for the GEMOX group. However, the CisGem combination was associated with higher toxicity compared with GEMOX [63]. A South Korean phase 3 study showed non-inferiority of capecitabine plus oxaliplatin (CAPOX) versus GEMOX in terms of 6-month PFS, and no significant differences in OS and ORR [57]. In a Japanese phase 3 trial (FUGA-BT), gemcitabine plus S-1 was non-inferior to CisGem [58]. Recently, a German randomized phase 2 study (NIFE) showed similar results with CisGem and the combination of nanoliposomal-irinotecan (Nal-IRI) plus 5-FU and LV in patients with advanced BTC (Table 1) [59]. Subgroup analyses suggested that the latter combination was of particular benefit in patients with eCCA, but this should be interpreted with caution due to the small number of patients.

Table 1 Selected trials investigating therapies for first-line use in patients with advanced biliary tract cancers

Selected study	Phase	N	Treatment	Primary endpoint outcomes
GERCOR, 2004 [50]	2	33[a]	GEMOX	ORR in evaluable patients: 35.5% (95% CI: 18.7–52.3)
ABC-02, 2010 [53]	3R	410	CisGem vs. gemcitabine	mOS: 11.7 mo for CisGem vs. 8.1 mo for gemcitabine HR: 0.64 (95% CI: 0.52–0.80; $P < 0.001$)
ABC-03, 2015 [66]	2R	124	CisGem + cediranib vs. CisGem	mPFS: 8.0 mo (95% CI: 6.5–9.3) with CisGem + cediranib vs. 7.4 mo (95% CI: 5.7–8.5) with CisGem HR: 0.93 (95% CI: 0.65–1.35; $P = 0.72$)
BINGO, 2014 [64]	2R	150	CisGem + cetuximab vs. CisGem	4-mo PFS: 63% (95% CI: 52–74) with CisGem + cetuximab vs. 54% (95% CI: 43–65) with CisGem
BT-22, 2010 [54]	2R	83	CisGem vs. gemcitabine	1-y OS: 39% with CisGem vs. 31% with gemcitabine
Kim et al., 2019 [57]	3R	222	CAPOX vs. GEMOX	6-mo PFS: 44.5% (95% CI: 12–16) with GEMOX vs. 46.7% (95% CI: 12–16) with CAPOX
Lee et al., 2012 [65]	3R	268	GEMOX vs. GEMOX + erlotinib	mPFS: 4.2 mo (95% CI: 2.7–5.7) with GEMOX vs. 5.8 mo (95% CI: 4.6–7.0) with GEMOX + erlotinib HR: 0.80 (95% CI: 0.61–1.03; $P = 0.087$)
Morizane et al., 2019 [58]	3R	354	CisGem vs. gemcitabine + S-1	mOS: 13.4 mo with CisGem vs. 15.1 mo with gemcitabine + S-1 HR: 0.945 (90% CI: 0.78–1.15; $P = 0.046$ for non-inferiority)
Schroff et al., 2019 [62]	2	62	CisGem + Nab-paclitaxel	PFS: 11.8 mo (95% CI: 6.0–15.6)
Sharma et al., 2019 [61]	3R	260[b]	CisGem vs. modified GEMOX	mOS: 9 mo with GEMOX vs. 8.3 mo with CisGem HR: 0.78 (95% CI: 0.60–1.02; $P = 0.057$)
NIFE, 2021 [59]	2R	91	Nal-IRI/5-FU/LV vs. CisGem	mPFS: 5.98 mo (95% CI: 2.37–9.59) with nal-IRI/5-FU/LV vs. 6.87 mo (95% CI: 2.46–7.82) with CisGem
PRODIGE 38 AMEBICA, 2022 [60]	2R	191[c]	CisGem	6-month PFS: 47.3% (90% CI: 38.4–56.3)
			mFOLFIRINOX	6-month PFS: 44.6% (90% CI: 35.7–53.7)
KHBO1401-MITSUBA, 2018 [67]	3R	246	CisGem-S-1 vs. CisGem	mOS: 13.5 mo with CisGem-S-1 vs. 12.6 mo with CisGem; HR: 0.791 (90% CI: 0.620–0.996; P = 0.046)

5-FU 5-fluorouracil, *CAPOX* capecitabine + oxaliplatin, *CI* confidence interval, *CisGem* cisplatin + gemcitabine, *ECOG PS* Eastern Cooperative Oncology group performance status, *GBC* gallbladder cancer, *GEMOX* gemcitabine + oxaliplatin, *HR* hazard ratio, *LV* leucovorin, *mFOLFIRINOX* oxaliplatin irinotecan and infusional 5-FU, *m* median, *mo* month, *nal-IRI* nanoliposomal irinotecan, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *R* randomized, *y* year

[a]The GERCOR study investigated first-, second- and third-line use; however, only group A patients received only first-line use and results presented in the paper are not separated out by treatment stage, hence only results for Group A are presented here

[b]Included patients with GBC only

[c]Patients had ECOG PS 0–1

Triplet chemotherapy regimens have also been evaluated in the treatment of patients with advanced BTC. All randomized trials that had evaluated a triple-agent therapy combining cisplatin-platinum with another molecule (mostly epidermal growth factor receptor inhibitors [64, 65] or antiangiogenic agents [66]) had been negative so far (Table 1). For instance, a French randomized phase 2 trial (PRODIGE 38 AMEBICA) in patients with advanced BTC and an ECOG PS of 0 or 1 failed to demonstrate a benefit of mFOLFIRINOX over CisGem in terms of 6-month PFS rate (the primary endpoint) or OS (median: 11.7 months in the mFOLFIRINOX group and 13.8 months in the CisGem group) [60]. Of note, exploratory subgroup analyses suggested that CisGem was superior to mFOLFIRINOX for patients with iCCA (HR: 0.58; 95% CI: 0.39–0.85; $P < 0.1$). The only exception to date came from Japan, where the cisplatin, gemcitabine, and S-1 triplet regimen improved OS compared with CisGem (median: 13.5 vs. 12.6 months; HR: 0.791; 90% CI: 0.620–0.996; $P = 0.046$) [67]. Among a number of non-randomized phase 2 studies that have assessed triplet chemotherapy regimens, oxaliplatin, irinotecan, and S-1 provided encouraging results, with an ORR of 50% and median PFS and OS of 6.8 months and 12.5 months, respectively [68]. In a US study, cisplatin, gemcitabine, and nanoparticle albumin-bound–paclitaxel provided an ORR of 45%, a median PFS of 11.8 months, and a median OS of 19.2 months (95% CI: 13.2 to not estimable) [62]. This regimen is currently being compared with CisGem in the US SWOG-1815 phase 3 study (NCT03768414).

GEMOX was developed in France and has historically been the preferred regimen in our country for the treatment

of advanced BTC after the results of a phase 2 study [56]; however, CisGem is increasingly used in routine practice [60, 69–73]. As a result, GEMOX may be used preferentially for patients who could be susceptible to hearing loss or abnormal renal function (with creatinine clearance > 30 mL/min).

The optimal duration of CisGem has not been clearly established. The ABC-02 trial showed a benefit for treatment with CisGem for up to 24 weeks, but median OS was not markedly different in the BT-22 trial in patients given CisGem for twice the duration (48 weeks); median OS was 11.4 months for the CisGem group in the BT-22 trial and 11.2 months in the ABC-02 trial [53, 54]. A South Korean study retrospectively analyzed data from 120 patients with advanced BTC who continued gemcitabine after six to eight CisGem cycles (maintenance group) compared with 111 patients who received no further maintenance chemotherapy after CisGem [74]. The median OS in the maintenance group was not significantly different from that in the observation group (22.4 months; 95% CI: 17.0–27.8 and 20.5 months; 95% CI: 15.4–25.6, respectively; $P = 0.162$); nevertheless, maintenance gemcitabine monotherapy is frequently administered in routine practice in France and elsewhere.

According to French [42] and European Society of Medical Oncology (ESMO) clinical practice guidelines [55] for BTC, systemic chemotherapy is the treatment of choice for patients with advanced disease; combination chemotherapy is recommended for patients with an ECOG PS of 0–1 and gemcitabine monotherapy for patients with an ECOG PS of 2. The recommended combination regimen for patients with an ECOG PS of 0–1 is CisGem.

3.5 Second-Line and Beyond Chemotherapy for Advanced BTC

FOLFOX (oxaliplatin, 5-FU and LV) is the reference second-line chemotherapy regimen for patients with advanced BTC, based on the findings of a UK phase 3 study (ABC-06) (Table 2) [75]. This study compared FOLFOX plus active symptom control (ASC, which included analgesia, biliary drainage, anti-emetics, antibiotics, steroids, other palliative treatment for symptom control, palliative radiotherapy, or blood transfusion) with ASC alone in patients with advanced BTC who had progressed on or after treatment with CisGem. This study demonstrated a significant, though modest, improvement in OS (median OS gain < 1 month) with FOLFOX plus ASC versus ASC alone, along with an ORR of 5% and a median PFS of 4 months. However, the 12-month OS rate was more than doubled in the FOLFOX group compared with the control group (25.9% vs. 11.4%), and FOLFOX was active even in patients resistant to CisGem. Interestingly, FOLFOX seemed less beneficial in patients with eCCA than in those with iCCA, with HRs of 0.84 (95% CI: 0.45–1.57) and 0.64 (95% CI: 0.38–1.06), respectively. Despite its modest efficacy results, the ABC-06 trial may have far-reaching implications for clinical practice. Its impact may be reminiscent of the effects of the study by Burris and colleagues in 1997, which showed a modest, albeit undisputed, benefit for more than a decade of gemcitabine over 5-FU as first-line treatment for advanced pancreatic cancer [76]. In France, the recommendation of FOLFOX as the second-line standard-of-care for BTC [42] may have hastened the shift from GEMOX to CisGem as first-line therapy.

Nal-IRI in combination with 5-FU and LV was investigated in South Korea in patients with metastatic BTC after progression on CisGem in a randomized phase 2 study (NIFTY) (Table 2) [77]. The Nal-IRI-5-FU-LV combination significantly improved PFS (7.1 vs. 1.4 months; HR:

Table 2 Main randomized trials investigating second-line chemotherapy in patients with biliary tract cancers

Study	Phase	Patient group	N	Treatment	Primary endpoint outcomes
ABC-06, 2021 [75]	3	Advanced BTC	162	FOLFOX (up to 12 cycles) + ASC vs. ASC	mOS: 6.2 mo (95% CI: 5.4–7.6) with ASC + FOLFOX vs. 5.3 mo (95% CI: 4.1–5.8) with ASC Adjusted HR: 0.69 (95% CI: 0.50–0.97; $P = 0.031$)
NIFTY, 2021 [77]	2R	Metastatic BTC	178	Nal-IRI + 5-FU/LV vs. 5-FU/LV	mPFS: 7.1 mo (95% CI: 3.6–8.8) with nal-IRI + 5-FU/LV vs. 1.4 mo (95% CI: 1.2–1.5) with FU/LV HR: 0.56 (95% CI: 0.39–0.81; $P = 0.0019$)
NALIRICC, 2022 [78]	2	Metastatic BTC	100	Nal-IRI + 5-FU/LV vs. 5-FU/LV	mPFS: 2.8 mo with nal-IRI + 5-FU/LV vs. 2.3 mo with 5-FU/LV

5-FU 5-fluorouracil, *ASC* active symptom control, *BTC* biliary tract cancer, *CI* confidence interval, *FOLFOX* leucovorin + 5-FU + oxaliplatin, *HR* hazard ratio, *LV* leucovorin, *m* median, *mo* month, *nal-IRI* nanoliposomal irinotecan, *OS* overall survival, *PFS* progression-free survival, *R* randomized

0.56; 95% CI: 0.39–0.81; $P = 0.0019$) and OS (8.6 vs. 5.5 months; HR: 0.68; 95% CI: 0.48–0.98; $P = 0.035$) compared with 5-FU-LV [77]. Of note, the median OS in the 5-FU-LV group was close to that in the FOLFOX group in the ABC-06 study [75] (5.5 and 6.2 months, respectively), raising the question of whether the ABC-06 trial would have been positive if the comparator had been 5-FU-LV instead of ASC. The NIFTY results suggest that the Nal-IRI-5-FU-LV regimen is a promising second-line treatment option; however, these findings were not confirmed in a Western population. NALIRICC (NCT03043547) was a randomized phase 2 study that compared the efficacy and safety of Nal-IRI-5-FU-LV with that of 5-FU-LV in German patients with metastatic BTC who had progressed after first-line gemcitabine-based therapy [78]. The results of this study (presented at the 2022 ESMO conference) showed that, despite an improved ORR in the Nal-IRI-5-FU-LV arm (14.3% vs. 3.9%), there was no difference in median PFS (the primary endpoint) between patients receiving Nal-IRI-5-FU-LV and those receiving 5-FU-LV (2.8 vs. 2.3 months). Moreover, median OS tended to be longer in the group receiving 5-FU-LV than in those receiving Nal-IRI-5-FU-LV (8.2 vs. 6.9 months) [78].

To date, no randomized trial of chemotherapy has been reported for patients with BTC whose disease progressed after two systemic treatment lines. As a consequence, no recommendation has been made in this setting in French [42] and European [70] guidelines.

3.6 Comparing Treatment in France With Global Practice

A cancer registry study in France found that, during the 5 years between 2001 and 2005, 14.2% of BTC patients underwent curative-intent surgery, 21.6% had palliative radiation therapy and/or chemotherapy, and 60.3% had BSC [7]. Between 1996 and 2005, only 15.9% of patients received adjuvant therapy. Interestingly, the proportion of patients receiving BSC decreased between 1976 and 2005, and the proportion of patients receiving palliative chemotherapy and/or radiotherapy, as well as curative-intent resection, increased over this period [7]. However, this shift has somewhat plateaued more recently, as attested by the above-mentioned French nation-wide hospital database study of 3650 newly diagnosed iCCA cases (assessed between 2014 and 2015), in which 11.2% of patients underwent surgery, 23.8% received chemotherapy, and 65.0% received BSC [23]. Patient care was mainly provided by general hospitals (59.8%), rather than university hospitals (15.0%) and private (19.2%) or cancer centers (6.0%). In all, 28.4% of patients were admitted via the emergency room. A palliative care code was associated with the first hospital stay in 25% of patients and with a subsequent hospital stay in 60%. Of note, a total of 655 centers were involved in the patient's first hospital stay and 28.8% of patients received care in low-volume hospitals (less than five patients with iCCA during the 2014–15 period), which represented 446 (68%) of the 655 centers, with a small proportion of patients being referred to high-volume centers, except for surgery. These findings reflect the marked decentralization of the French healthcare system. Comparatively, a retrospective US study of patients with iCCA who underwent surgical resection between 2000 and 2014 showed that 17% of patients received radiation therapy and 40% received chemotherapy, with the use of chemotherapy significantly increasing over time [79].

4 Targeted Therapies and Ongoing Trials

In recent years, substantial advances in the molecular characterization of BTC have occurred. BTC should now be viewed as a "target-rich" disease, with up to 40% of cases harboring targetable genomic alterations [80–82]. Certain mutations are common to all CCA subtypes and others are exclusive to certain subtypes. Some of the most common genomic alterations, including those involving the genes for isocitrate dehydrogenase 1 (*IDH1*), isocitrate dehydrogenase 2 (*IDH2*), and fibroblast growth factor receptor 2 (*FGFR2*), have been found to occur almost exclusively in iCCA. The *IDH1* and *IDH2* mutations, as well as *FGFR2* rearrangements/fusions, have been detected in approximately < 5–20% of iCCAs [80, 82–84], with *IDH1* the more common of the *IDH* mutations (up to 20% *IDH1* vs. < 5% *IDH2* in iCCA). Table 3 summarizes the genomic alterations that are relevant to BTC and the agents currently approved for use [85–94].

4.1 *IDH* Mutations

Under normal circumstances, the IDH1 and IDH2 enzymes catalyze the conversion of isocitrate to α-ketoglutarate; however, the mutated forms instead catalyze the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent conversion of α-ketoglutarate to D-2-hydroxyglutarate (D-2HG), which is an oncometabolite (Fig. 2) [95–97]. Numerous pro-tumor effects are seen as the α-ketoglutarate-dependent enzymes are competitively inhibited by D-2HG. These effects include a decrease in NADPH and glutathione, resulting in increased reactive oxygen species, DNA damage, inhibition of DNA repair mechanisms, and epigenetic dysregulation [97].

IDH mutations have been reported across other tumor types besides iCCA, including glioma, chondrosarcoma, and acute myelogenous leukemia. Both *IDH1* and *IDH2* mutations are the predominant gene alterations in iCCA [83]. Recent genomic profiling data from iCCA samples

Table 3 Second-line treatments approved for patients with BTC who harbor specific genomic alterations

	Biomarker	Key trial	Trial design	Patients	Primary endpoint	Indication as per US FDA approval
Larotrectinib	*NTRK* gene fusion	NAVIGATE [87]	Basket trial (single arm)	55 (CCA: 2)	ORR: 75% (95% CI: 61–85)	Tumor agnostic (all solid tumors harboring an *NTRK* gene fusion) [88]
Entrectinib	*NTRK* gene fusion	STARTRK-2 [122]	Basket trial (single arm)	155	ORR: 61.3% (95% CI: 53.1–69.2)	Tumor agnostic (all solid tumors harboring an *NTRK* gene fusion) [91]
Pembrolizumab	dMMR/ MSI-H	KEYNOTE-158 [93]	Basket trial (single arm)	233 (BTC: 22)	ORR: 34.3% (95% CI: 28.3–40.8) ORR for BTC: 40.9% (95% CI: 20.7–63.6)	Tumor agnostic (all dMMR/MSI-H solid tumors) [89]
Pemigatinib	*FGFR2* gene fusion	FIGHT-202 [86]	BTC-specific trial (single arm)	107 (CCA only)	ORR: 35.5% (95% CI: 26.5–45.4)	Previously treated, unresectable locally advanced or metastatic CCA harboring an *FGFR2* gene fusion [92]
Infigratinib	*FGFR2* gene fusion	NCT02150967 [106]	Single arm	122	ORR: 23.1% (95% CI: 15.6–32.2)	Previously treated, unresectable locally advanced or metastatic CCA with a *FGFR2* fusion or other rearrangement [163]
Futibatinib	*FGFR2* gene fusion	FOENIX-CCA2 [108]	Single arm	103	ORR: 41.7% (95% CI not provided)	Previously treated, unresectable locally advanced or metastatic intrahepatic CCA harboring *FGFR2* fusions or other rearrangements [164]
Ivosidenib	*IDH* mutation	ClarIDHy [85, 94]	BTC-specific trial (randomized, placebo-controlled phase 3)	185 (CCA only) Updated results: 187 (ivosidenib: 126)	mPFS: 2.7 mo with ivosidenib vs. 1.4 mo with placebo HR 0.37 (95% CI: 0.25–0.54; P<0.0001 one-sided) 6-mo PFS: 32% (95% CI: 23–42) with ivosidenib vs. 0% with placebo Updated results: mOS: 10.3 mo with ivosidenib vs. 7.5 mo with placebo (without adjusting for 70% of crossover) HR: 0.79 (95% CI: 0.56–1.12; $P = 0.09$ one-sided)	Previously treated, unresectable locally advanced or metastatic CCA harboring an *IDH1* mutation [90]

BTC biliary tract cancer, *CCA* cholangiocarcinoma, *CI*: confidence interval, *dMMR* DNA mismatch repair deficiency, *FGFR2* fibroblast growth factor receptor 2, *HR* hazard ratio, *IDH* isocitrate dehydrogenase, *m* median, *mo* months, *MSI-H* microsatellite instability-high, *NTRK* neurotrophic tyrosine receptor kinase, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *US FDA* United States Food and Drug Administration

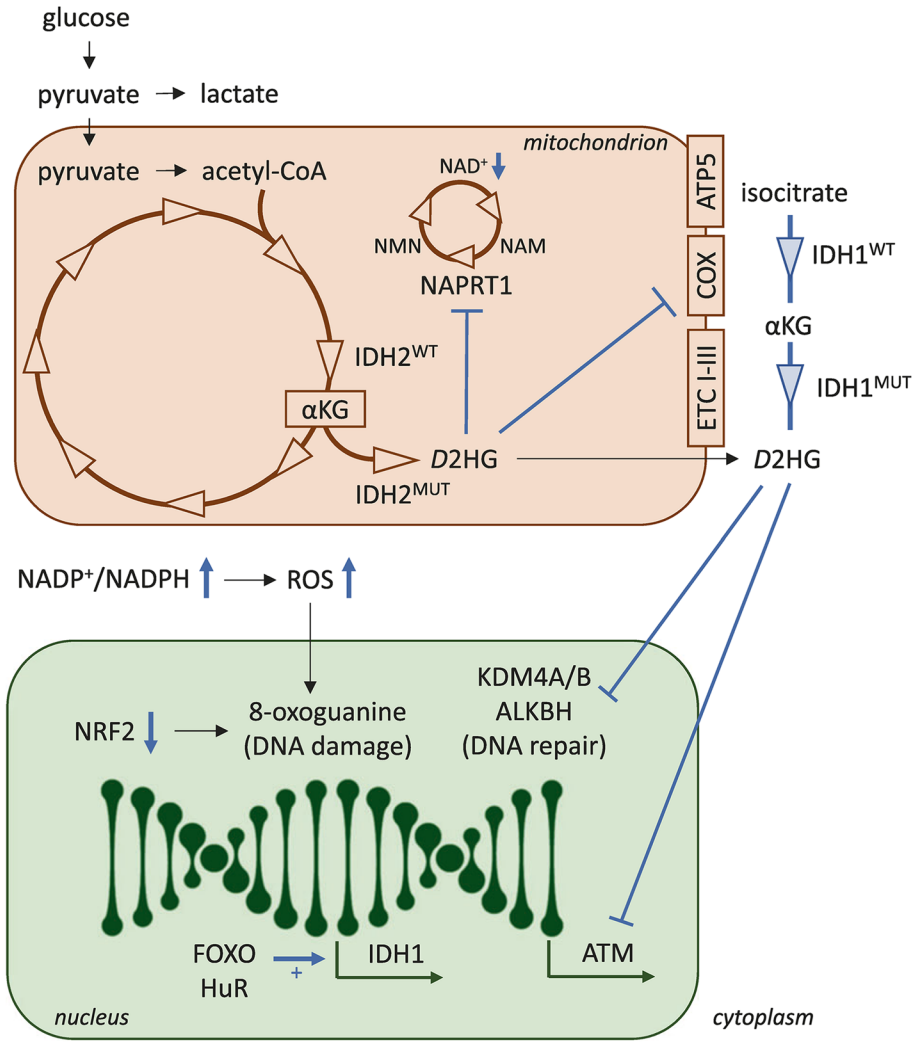


Fig. 2 Effects of *IDH1/2* mutations and D-2HG accumulation on cellular metabolism, redox states, and DNA damage repair [97]. Material from: Molenaar RJ, et al. Wild-type and mutated IDH1/2 enzymes and therapy responses. *Oncogene*. Published 2018 by Springer Nature, reproduced with permission of SNCSC. *αKG* α-ketoglutarate, *ALKBH* alkylation repair homolog, *ATM* ataxia-telangiectasia mutated, *ATP5* adenosine triphosphate synthase, *CoA* coenzyme A, *COX* cytochrome C oxidase, *D-2HG* D-2-hydroxyglutarate, *ETC* electron transport chain, *FOXO* forkhead box proteins, *HuR* human antigen R, *IDH* isocitrate dehydrogenase, *KDM* lysine histone demethylase, *mut* mutation, *NAD(P)* nicotinamide dinucleotide (phosphate), *NAD(P)H* nicotinamide dinucleotide (phosphate), reduced, *NAM* nicotinamide, *NAMPT* nicotinamide phosphoribosyltransferase, *NAPRT1* nicotinate phosphoribosyltransferase domain containing 1, *NMN* nicotinamide mononucleotide, *NRF2* nuclear factor (erythroid-derived 2)-like, *ROS* reactive oxygen species, *wt* wildtype

have indicated that *IDH1* and *IDH2* mutations have various genetic locations, and are mutually exclusive, suggesting that *IDH1* and *IDH2* mutations are driver oncogenes in iCCA [98]. Of note, a meta-analysis of 45 studies determined that *IDH1* mutations were more prevalent than *IDH2* mutations in CCA, and that *IDH1* mutations were significantly more frequent in non-Asian than in Asian patients (weighted mean, 16.5% vs. 8.8%; $P < 0.001$) [99]. In patients with advanced iCCA, *IDH* mutations have not been found to be associated with patient prognosis [100].

Ivosidenib is a potent targeted inhibitor of the *IDH1* mutant enzyme and was approved in the USA in August 2021 for use in patients with CCA, based on the findings from a double-blind, placebo-controlled phase 3 trial (ClarIDHy) (Table 3) [85, 94]. The ClarIDHy trial was conducted across six countries, including France, and demonstrated that in addition to being well tolerated, ivosidenib improved PFS (the primary endpoint) compared with placebo in chemorefractory, *IDH1*-mutated CCA (Fig. 3) [85]. Patients taking ivosidenib (n = 124) had significantly improved PFS compared with those in the placebo group ($n = 61$), with a median PFS of 2.7 (95% CI: 1.6–4.2) months versus 1.4 (95% CI: 1.4–1.6) months, respectively (HR: 0.37; 95% CI: 0.25–0.54; $P < 0.0001$ one-sided). The PFS rate was 32% (95% CI: 23–42) at 6 months and 22% (95% CI: 13–32) at 12 months for ivosidenib, whereas no patients in the placebo group were free from progression at 6 months or later [85]. Median OS was 10.3 (95% CI: 7.8–12.4) months with ivosidenib ($n = 126$) and 7.5 (95% CI: 4.8–11.1) months with placebo ($n = 61$; HR: 0.79; 95% CI: 0.56–1.12; $P = 0.09$ one-sided). In an OS analysis adjusted for crossover to ivosidenib (70% of patients in the placebo group), the placebo group had an adjusted median OS of 5.1 (95% CI: 3.8–7.6) months (HR: 0.49; 95% CI: 0.34–0.70; $P < 0.001$ one-sided) [94]. While long-term follow-up in ClarIDHy of patient health-related QoL (HRQoL) was limited by small sample size, initial results suggested that patients treated with ivosidenib were likely to maintain their baseline HRQoL scores, and none experienced a clinically meaningful deterioration in the domain of physical functioning

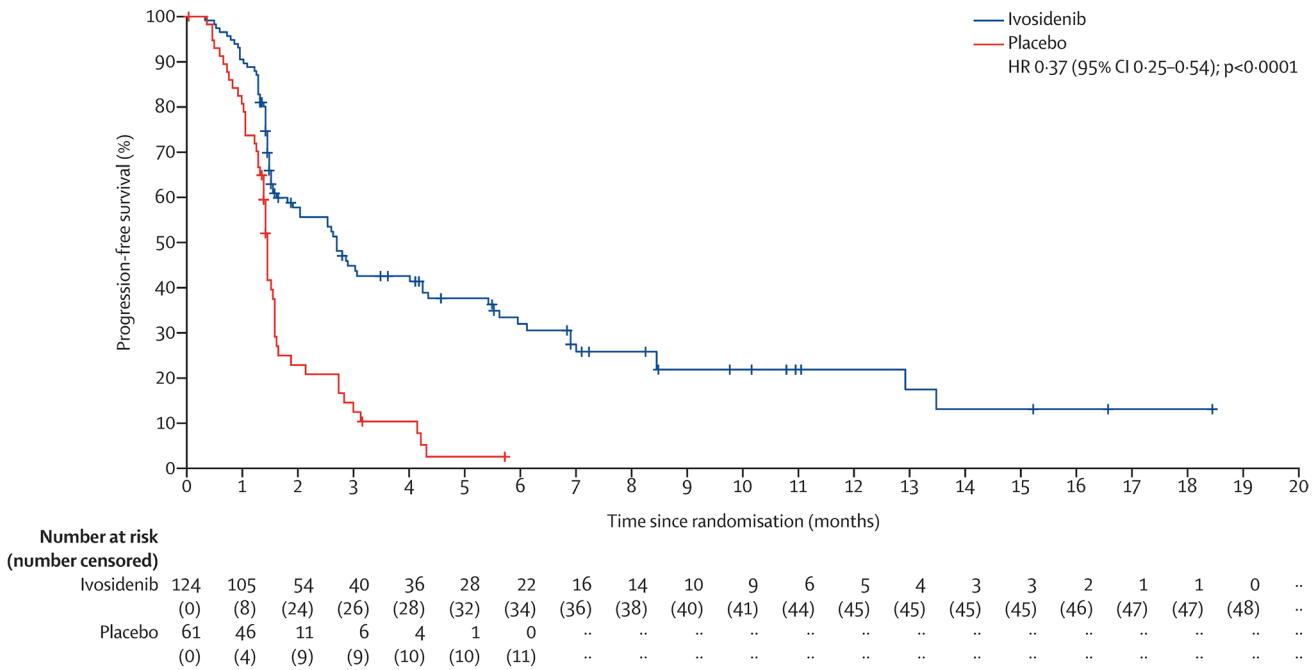


Fig. 3 Kaplan-Meier plot of the probability of progression-free survival in the intention-to-treat population comparing ivosidenib and placebo groups [85]. Reprinted from *Lancet Oncol*, 21, Abou-Alfa GK, et al. Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study, 796-807, Copyright (2020), with permission from Elsevier. *CI* confidence interval, *HR* hazard ratio

[101]. In the latest French and ESMO guidelines [42, 55], ivosidenib is recommended for patients with CCA and *IDH1* mutations who have progressed after at least one prior line of systemic chemotherapy.

4.2 *FGFR* Alterations

Fibroblast growth factors (FGFs) control a range of cellular processes, including the regulation of cellular survival, proliferation, migration, and differentiation, through their high-affinity binding to four tyrosine kinase receptors (FGFRs) [102]. Genomic alterations in *FGFR* genes, including chromosomal translocations, amplifications, and gain-of-function mutations, have been associated with a range of cancers, including BTC [103, 104]. Interestingly, *FGFR2* alterations are generally—but not absolutely—mutually exclusive with *IDH* mutations [82]. Occurring almost exclusively in iCCA, translocations of *FGFR2* are present in about 13.6% of iCCA patients, and result in activation of mitogen-activated protein kinase-promoting tumorigenesis, allowing anchorage-independent growth [103].

Pemigatinib is a selective, potent, oral inhibitor of FGFR1, 2, and 3 [105]. The FIGHT-202 study, a multicenter, open-label, phase 2 study, examined the effects of pemigatinib on outcomes in chemorefractory patients with iCCA, most of whom had *FGFR2* fusions/rearrangements (Table 3) [86]. Among the 107 patients with *FGFR2* fusions or rearrangements, 38 had an objective response (three with complete response and 35 with partial response (Fig. 4)) for an ORR (the primary study endpoint) of 35.5% (95% CI: 26.5–45.4%). The median duration of response was 7.5 months, and the median OS was 21.1 months. Of 103 patients with *FGFR2* fusions or rearrangements and post-baseline tumor measurements, 91 (88%) had a decrease from baseline in target lesion size. For patients with *FGFR2* fusions or rearrangements, objective responses were seen across all demographic and disease subgroups assessed. None of the patients with other *FGF/FGFR* alterations ($n = 20$) nor those without an *FGF/FGFR* alteration ($n = 18$) had an objective response, but stable disease was reported in eight patients with another *FGF/FGFR* alteration, as well as in four patients without an *FGF/FGFR* alteration [86].

Several other *FGFR* inhibitors are currently under investigation for use in patients with iCCA. Infigratinib has shown a manageable safety profile and preliminary clinical activity against iCCA tumors with *FGFR* alterations in a phase 2 study [106]. Patients with confirmed *FGFR2* or other *FGFR* alterations had an ORR of 23.1% (95% CI: 15.6–32.2), with one complete response and 24 partial responses seen [106]. Derazantinib is another multi-kinase inhibitor currently undergoing phase 2 assessment [107]. Data showed that, in addition to a manageable safety profile, derazantinib showed good antitumor activity in patients with *FGFR2*

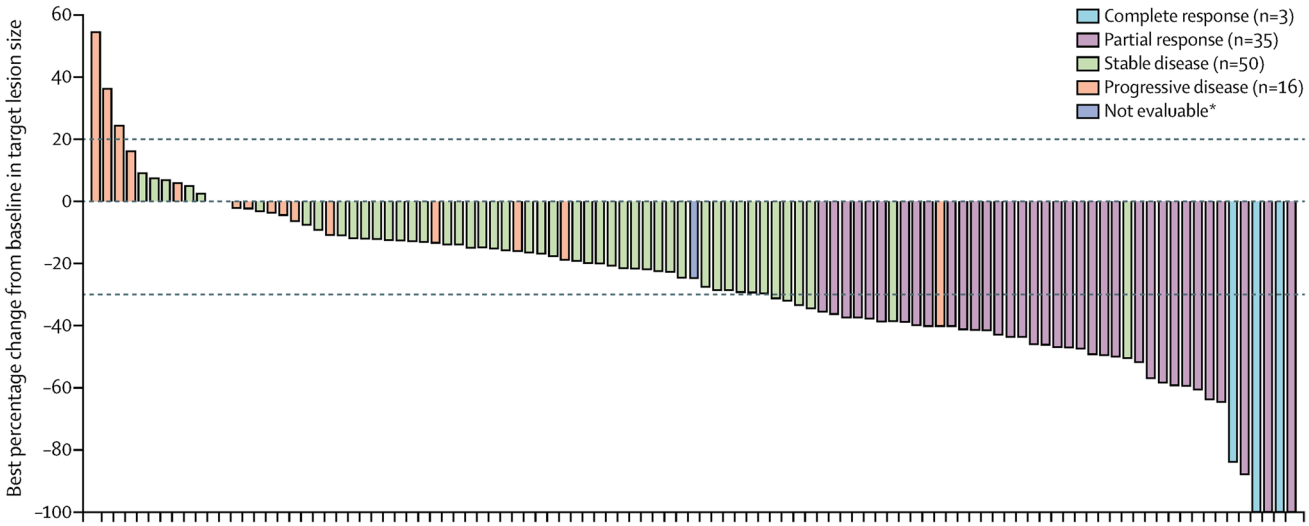


Fig. 4 Best percentage change from baseline in target lesion size for individual patients with fibroblast growth factor receptor 2 (*FGFR2*) fusions or rearrangements in the FIGHT-202 study of pemigatinib [86]. Colored bars indicate confirmed responses assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST. Reprinted from *Lancet Oncol*, 21, Abou-Alfa GK, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study, 671-84, Copyright (2020), with permission from Elsevier

fusion-positive, advanced iCCA who had progressed on first-line chemotherapy, with an ORR of 20.7% and a DCR of 82.8%. Futibatinib, an FGFR 1–4 inhibitor, has been investigated in the phase 2 FOENIX-CCA2 trial, the results of which were presented at the 2022 American Society of Clinical Oncology conference [108]. In 103 patients with iCCA and *FGFR2* alterations, the ORR (the primary study endpoint) was 41.7%, DCR was 82.5%, median PFS was 8.9 months, and median OS was 20 months, with 12-month PFS and OS rates of 35.4% and 73.1%, respectively [108]. Futibatinib had a tolerable safety profile, with hyperphosphatemia being the most common adverse event (85%). Another *FGFR* inhibitor, erdafitinib, is currently under investigation in a phase 2a study to assess its efficacy and safety in Asian patients with advanced CCA who have *FGFR* alterations [109]. Interim findings showed, in addition to an acceptable safety profile, six partial responses and four stable disease responses in the 12 evaluable patients treated with erdafitinib (ORR of 50% and DCR of 83.3%). Of the ten patients who were *FGFR*-positive, the ORR was 60% and the DCR was 100%. Several ongoing phase 3 studies are comparing FGFR inhibition with pemigatinib (FIGHT-302; NCT03656536), infigratinib (PROOF; NCT03773302), or futibatinib (FOENIX-CCA3; NCT04093362) to CisGem as first-line therapy for patients with advanced iCCA harboring *FGFR2* rearrangements. The 2022 French and ESMO guidelines now recommend FGFR inhibitors (e.g., pemigatinib, futibatinib, infigratinib) for patients with CCA and *FGFR2* fusions who have progressed after at least one prior line of systemic chemotherapy [42, 55].

Next-generation FGFR2 inhibitors are also in development. Preliminary results from the phase 1/2 REFOCUS study of RLY-4008 (presented at the 2022 ESMO conference) reported a confirmed ORR of 82.4% and DCR of 100% at the recommended phase 2 dose ($n = 17$ patients), with 88.2% of patients remaining on treatment with this dose [110]. Further data are awaited with interest.

Data are also needed on the optimal sequencing of FGFR inhibitors. A retrospective US study suggested that patients who progress after one FGFR inhibitor can receive treatment with another FGFR inhibitor, with similar outcomes to patients receiving post-FGFR inhibitor chemotherapy [111]. However, only about 50% of patients are eligible for a second course of FGFR inhibitor treatment after disease progression.

4.3 Mismatch Repair Deficiency/Microsatellite Instability

The DNA mismatch repair (MMR) system is one of the cellular DNA repair mechanisms that maintain genomic integrity during cell division [112]. A proficient system is denoted as pMMR. A deficient MMR system (dMMR phenotype) is unable to repair replication errors, which are particularly frequent in repeated sequences such as microsatellites. These recurring sequences of DNA are about 10–60 base pairs long, each made of repeating units of one to five base pair motifs [112]. Microsatellite instability (MSI) can result from MMR malfunction, leading to uncontrolled microsatellite lengths. The MSI genotype has been observed

in multiple cancers. dMMR tumors present with a high MSI (MSI-H), due to varying lengths in microsatellite sequences and frameshift mutations resulting in truncated or abnormal (highly immunogenic) proteins, as well as the activation of oncogenes [112].

The proportion of MSI-H status among BTC patients is controversial. A whole exome-sequencing analysis found dMMR or MSI-H status in 36% of 260 patients with BTC [80]. A systematic review estimated that 10%, 5–13%, and 5% of iCCA, eCCA, and GBC cases, respectively, harbor dMMR and/or MSI-H [113]. Even lower proportions of 1–2% have been reported [112, 114, 115].

dMMR/MSI-H tumors are sensitive to immune checkpoint blockade with anti-programmed death 1 receptor (PD-1) antibodies, regardless of the cancer's tissue of origin [116, 117]. Pembrolizumab, a monoclonal antibody that binds to PD-1, was shown in the KEYNOTE-158 study (Table 3) to have durable antitumor activity, as well as an acceptable safety profile, in patients with CCA who were not responding to other therapies, with two complete responses and seven partial responses among 22 patients (ORR: 40.9%) [93]. Based on these data, the 2022 French and ESMO guidelines recommend pembrolizumab in patients with MSI-H/dMMR who show progression after, or intolerance to, prior treatments [42, 55].

4.4 *NTRK* Gene Fusion

Neurotrophin receptor tyrosine kinase (*NTRK*) gene fusions are found in > 90% of cases of several rare tumors (e.g., infantile fibrosarcoma, secretory breast carcinoma, and mammary analogue secretory carcinoma), but with a low frequency (< 1–5%) in most other tumor types, and are considered to be tumor-agnostic alterations. The *NTRK1*, *NTRK2*, and *NTRK3* genes encode the tropomyosin receptor kinase (TRK) proteins, which are members of the tyrosine kinase family. Following a fusion event, these overexpressed chimeric proteins can drive oncogenic transformation via ligand-independent activation of the TRKs [118, 119]. *NTRK* gene fusions are reported to account for approximately 2% of all genetic alterations in advanced BTC [120]. A recent retrospective study assessing next-generation sequencing (NGS) results of 29 patients with various cancers that were *NTRK* gene fusion-positive, determined that the frequency of co-occurrence of *NTRK* fusion with MSI-H was 17.6% and co-occurrence of *NTRK* fusion with a high tumor mutation burden (> 20 mutations/Mb) biomarker was 20.7% [121]. While this result has yet to be validated in patients with BTC, it may inform future diagnostic and therapeutic strategies.

Both larotrectinib and entrectinib target *NTRK* fusions. In a clinical study, patients treated with larotrectinib showed a significant objective response across a range of *NTRK* fusion-positive cancers (Table 3). Only two patients in that study had CCA: one had a decrease in tumor size and the other had progressive disease [87]. Data to date from the STARTRK-2 study showed that patients with a range of advanced *NTRK* fusion-positive solid tumors (including one patient with CCA) also had a high response rate with entrectinib [122]. Despite the lack of data, the French and ESMO guidelines recommend NTRK inhibitors for BTC patients with *NTRK* fusions who have progressed after, or are intolerant to, prior therapy [42, 55].

4.5 *HER2* Overexpression

One of the other targets of interest in the second-line setting is human epidermal growth factor receptor (HER2) [123]. *HER2* (*ERBB2*) amplification, overexpression, or both are observed in approximately 15–30% of GBC, eCCA, and ampullary carcinomas, and in 4–5% of iCCA cases [6, 82, 124–126].

Recently published were the findings from the MyPathway trial, which investigated the efficacy of a dual anti-HER2 regimen, pertuzumab + trastuzumab, in previously treated patients with metastatic BTC who had either or both *HER2* amplification and overexpression [127]. In this non-randomized, multicenter, open-label phase 2a trial, nine of the 39 enrolled patients achieved a partial response (ORR: 23%; 95% CI: 11–39).

A phase 2 study investigated the efficacy of FOLFOX plus trastuzumab as second-line or third-line treatment for patients with HER2-positive BTC that had progressed despite chemotherapy with gemcitabine and cisplatin [128]. Of the 34 patients enrolled, ten patients had a partial response and 17 had stable disease, to give an ORR (primary study endpoint) of 29.4% (95% CI: 16.7–46.3) and a DCR of 79.4% (95% CI: 62.9–89.9). Median PFS was 5.1 (95% CI: 3.6–6.7) months and median OS was 10.7 (95% CI: 7.9–not reached) months.

Zanidatamab is a bispecific *HER2*-targeted antibody that is accessible in France via an early access program. A phase 1 study, investigating the safety and preliminary efficacy of zanidatamab in BTC patients with centrally confirmed *HER2* overexpression has demonstrated acceptable tolerability and promising and durable anti-tumor activity with this agent [129]. In this non-randomized, multicenter study, eight of the 17 patients evaluable for response had a response (ORR: 47%; 95% CI: 23–72); further randomized clinical trials are ongoing in this population (NCT04466891).

The HERB study investigated the efficacy and tolerability of trastuzumab deruxtecan, an antibody-drug conjugate consisting of the humanized monoclonal antibody trastuzumab covalently linked to the topoisomerase I inhibitor, deruxtecan, in patients with *HER2*-expressing BTC who were refractory or intolerant to a gemcitabine-containing regimen [130]. In this investigator-initiated, multicenter, single-arm

phase 2 trial, two and six of the 22 enrolled HER2-positive patients achieved a complete and partial response, respectively (ORR: 36.4%; 90% CI: 19.6–56.1; $P = 0.01$) and the DCR was 81.8%. Median OS was 7.1 months. Interestingly, this study reported promising results even in the subgroup of HER2-low patients ($n = 8$), who had a DCR of 75.0% and a median OS of 8.9 months [130].

While these results are promising, physicians need to be aware of accuracy problems inherent in HER2 testing, with high rates of discordance (20–25%) between central and local readings observed in breast cancer studies [131]. Moreover, the pattern of HER2 staining on immunohistochemistry in breast cancer is different from that in digestive tract cancers, and the optimal testing modality and criteria for HER2 overexpression in BTC have yet to be defined [132]. Studies to date in BTC have used the HER2 expression criteria defined for gastroesophageal cancer [125, 126].

The 2022 French and ESMO guidelines state that HER2-directed therapies "*can be considered*" (rather than recommended) in patients with progressive advanced disease and relevant genetic alterations [42, 55], noting that none of these treatments have yet been approved for use in BTC by the European Medicines Agency or the US Food and Drug Administration [55].

4.6 *BRAF V600E* Mutation

The prevalence of v-raf murine sarcoma viral oncogene homolog B1 (*BRAF)* mutations in patients with BTC is relatively low, with the vast majority being BRAFV600E (~ 3%) [133].

The combination of dabrafenib (a BRAF inhibitor) and trametinib (a mitogen-activated protein kinase (MEK) inhibitor) is under investigation in the Rare Oncology Agnostic Research (ROAR; NCT02034110) basket trial as a potential regimen for patients with BRAFV600E-mutated, advanced BTC. This is a phase 2, open-label, single-arm, multicenter trial. An investigator-assessed objective response was observed in 22 of the 43 evaluable patients to date, with an ORR of 51% (95% CI: 36–67%) [134]. Of note, these results support "classical" BRAF therapeutic manipulation in BRAFV600E-mutated BTC, i.e., BRAF inhibition potentiated by downstream MEK inhibition without the need for negative feedback loop inhibition via an epidermal growth factor receptor inhibitor such as in advanced colorectal cancer.

At the time of writing, dabrafenib-trametinib is approved for BTC in the USA, but not in Europe. Nevertheless, the current French and ESMO guidelines recommend this treatment for patients with progressive BTC after systemic therapy and *BRAFV600E* mutations [42, 55].

4.7 ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) Ranking of Therapies

To assist with the determination of the best available therapy based on genomic markers, ESMO developed the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) system [135]. This system ranks and matches genomic alterations with targeted therapies according to their clinical utility, as shown in Table 4 [135].

The ESMO Precision Medicine Working Group currently recommends NGS for a range of genomic alterations with actionable targets (Table 5) [120]. *IDH1* mutations in advanced CCA have received an IA rating [120], indicating that the evidence thoroughly supports the use of the *IDH1*-targeted therapy for patients with this mutation. *FGFR2* fusions received an IB rating in advanced CCA based on results from the FIGHT-202 trial of pemigatinib [86]. This rating supports the use of targeted therapy in this group, albeit without the same level of evidence as ivosidenib. Other rankings for less common mutations include MSI-H and *NTRK* (both with a rating of IC), as well as *BRAF*, which has a ranking of IIB. Certain genomic alterations, such as *HER2*, were not listed, but could be now considered as IIB due to specific trial data [127]. This highlights the importance of genetic sequencing of tumor samples, which is recommended by the French and ESMO guidelines [42, 55, 120], to identify patients who may benefit from targeted therapy, to screen patients for inclusion in clinical trials, and to further drug research and capture valuable data. An improved understanding of genetic alterations and their possible associations will lead to better treatments.

4.8 Trials Investigating Targeted Therapies and Immunotherapies

Numerous trials are currently underway to investigate targeted therapies for first-line use in patients with BTC (Table 6). In addition to the targets already recommended by the ESMO Precision Working Group, targets such as programmed cell death ligand 1 (PD-L1) are under active investigation. Monoclonal antibodies targeting immune regulatory checkpoint molecules, such as PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), as well as associated ligands, have been shown to be effective against various tumors by mediating immune recognition of the tumor [136–138]. Consequently, agents targeting PD-1/PD-L1 and CTLA-4 are being increasingly studied, despite reports that an effective antitumor response may be induced in < 30% of patients [139].

An international phase 3 study (TOPAZ-1) compared CisGem in combination with the anti-PD-L1 monoclonal antibody durvalumab ($n = 341$) with CisGem + placebo

Table 4 The European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) [135] Reprinted from *Ann Oncol*, 29(9). Mateo J, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). 1895-902, 2018, Copyright 2018, with permission from Elsevier

ESCAT evidence tier	Required level of evidence	Clinical implications
I Ready for routine use	I-A: prospective, randomized clinical trials show the alteration-drug match in a specific tumor type results in a clinically meaningful improvement of a survival end point I-B: prospective, non-randomized clinical trials show that the alteration-drug match in a specific tumor type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 I-C: clinical trials across tumor types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumor types	Access to the treatment should be considered standard of care
II: Investigational	II-A: retrospective studies show patients with the specific alteration in a specific tumor type experience clinically meaningful benefit with matched drug compared with alteration-negative patients II-B: prospective clinical trial(s) show the alteration-drug match in a specific tumor type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial
III: Hypothetical target	III-A: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumor type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types III-B: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data	Clinical trials to be discussed with patients
	IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical in vitro or in vivo models IV-B: actionability predicted in silico	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
IV: Combination development	V: Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Clinical trials assessing drug combination strategies could be considered
	X: No evidence that the genomic alteration is therapeutically actionable	The finding should not be taken into account for clinical decision

Table 5 Genomic alterations that are, or may be, present in biliary tract cancer, and for which there is a targeted therapy and for which next-generation sequencing is indicated [120]

Gene alterations	ESCAT score	Available or potential targeted therapy[a]
IDH1 mutations	IA	Ivosidenib
FGFR2 fusions	IB	Infigratinib, pemigatinib, futibatinib, derazantinib, erdafitinib
dMMR/MSI	IC	Pembrolizumab, nivolumab
NTRK fusions	IC	Entrectinib, larotrectinib
BRAF^{V600E} mutations	IIB	Encorafenib, dabrafenib, vemurafenib
ERBB2 (*HER2*) amplifications, mutations	IIIIA	Trastuzumab, pertuzumab, tucatinib, lapatinib, neratinib, trastuzumab deruxtecan, trastuzumab emtansine, afatinib, dacomitinib
PIK3CA hotspot mutations	IIIA	Alpelisib, copanlisib
BRCA 1/2 mutations	IIIA	Olaparib
MET amplification	IIIA	Crizotinib, capmatinib
KRAS G12C	–	Adagrasib
RET	–	Selpercatinib, pralsetinib

BRAF v-raf murine sarcoma viral oncogene homolog B1, *BRCA* breast cancer gene, *CCA* cholangiocarcinoma, *ERBB2* erb-b2 receptor tyrosine kinase 2, *ESCAT ESMO* The European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets, *dMMR* DNA mismatch repair deficiency, *FGFR2* fibroblast growth factor receptor 2, *HER2* human epidermal growth factor receptor 2, *IDH* isocitrate dehydrogenase, *KRAS* Kirsten rat sarcoma virus, *MET* mesenchymal epithelial transition factor receptor, *MSI* microsatellite instability, *NTRK* neurotrophic tyrosine receptor kinase, *PIK3CA* phosphatidylinositol-45-bisphosphate 3-kinase catalytic subunit alpha, *RET* rearranged during transfection

[a]May include agents studied/approved in indications other than CCA; see individual prescribing information for details

Table 6 Ongoing trials evaluating first-line therapies for patients with advanced biliary tract cancer including cholangiocarcinoma, targeting genomic alterations

Acronym	Phase	Drug	Drug target	Description	Patients	NCT number
KEYNOTE-966	3	Pembrolizumab	PD-1	Main study: pembrolizumab or placebo + CisGem for patients with advanced BTC Extension: (in China) pembrolizumab or placebo + CisGem for patients with advanced BTC	Main study: 1048[a] Extension: 160[a]	Main study: NCT04003636; Extension: NCT04924062
FOENIX-CCA3	3	Futibatinib	*FGFR2*	Futibatinib vs. CisGem for patients with advanced CCA harboring *FGFR2* gene rearrangements	216	NCT04093362
PROOF[b]	3	Infigratinib	*FGFR2*	Infigratinib vs. CisGem for patients with advanced CCA with *FGFR2* gene fusions/translocations	300[a]	NCT03773302
FIGHT-302	3	Pemigatinib	*FGFR*	Pemigatinib vs. CisGem for patients with advanced CCA with *FGFR2* rearrangements	432	NCT03656536
ZWI-ZW25-201	2/3	Zanidatamab	*HER2*	Zanidatamab + standard first-line combination chemotherapy for patients with advanced HER2-expressing gastrointestinal cancers including BTC	362	NCT03929666

BTC biliary tract cancer, *CCA* cholangiocarcinoma, *CisGem* cisplatin + gemcitabine, *FGFR2* fibroblast growth factor receptor 2, *HER2* human epidermal growth factor receptor 2, *PD-1* programmed cell death protein 1

[a]Estimated enrollment

[b]Trial prematurely stopped for commercial reasons

($n = 344$) in patients with advanced BTC. The addition of durvalumab significantly prolonged OS (median: 12.8 vs. 11.5 months; HR: 0.80; 95% CI: 0.66–0.97; $P = 0.021$), and PFS (median: 7.2 vs. 5.7 months; HR: 0.75; 95% CI: 0.64–0.89; $P = 0.001$); ORR were 26.7% versus 18.7%, respectively [140, 141]. Although durvalumab is approved in the USA for BTC and was approved very recently in Europe (December 2022), it is not currently reimbursed in France for this indication (although in the latter, an early access program has been recently implemented). Another phase 3 study (KEYNOTE 966) investigating an anti-PD-1 monoclonal antibody (pembrolizumab) in patients with previously

Table 7 Ongoing trials evaluating second-line therapies for patients with advanced biliary tract cancer targeting genomic alterations

Phase	N[a]	Drug	Drug target	Patient population	NCT number
2	143	Derazantinib	FGFR2	*FGFR2* mutated iCCA	NCT03230318
2	160	Infigratinib	FGFR2	CCA with *FGFR* genetic alteration	NCT02150967
2	50	Infigratinib	FGFR2	Solid tumors including CCA	NCT04233567
2	386	Futibatinib	FGFR2	Advanced solid tumors harboring FGF/FGFR aberrations	NCT02052778
2	61	Ramucirumab	VEGFR2	BTC	NCT02520141
1/2	30	Tivozanib	VEGFR	BTC	NCT04645160
3	50	Bortezomib vs. BSC	PTEN	iCCA	NCT03345303
2/3	298	Surufatinib vs. capecitabine	VEGFR, FGFR1, CSF1R	BTC	NCT03873532
2	100	Zanidatamab	HER2	*HER2*-amplified BTC	NCT04466891
2	70	Pyrotinib	HER2	*HER2*-altered BTC	NCT04571710
2	74	Ceralasertib + olaparib or durvalumab	ATR + (PARP or PD-L1)	BTC	NCT04298021
2	26	Ceralasertib or durvalumab	ATR + PD-L1	BTC, previously treated with immunotherapy	NCT04298008
2	55	Apatinib	Multi-kinase	BTC	NCT03427242
2/3	39	Apatinib	Multi-kinase	BTC	NCT03144856
2	43	Regorafenib	Multi-kinase	BTC	NCT02053376
1/2	740	Adagrasib	KRAS G12C	Advanced solid tumors with *KRAS* G12C mutation	NCT03785249

ATR ataxia telangiectasia and Rad3-related protein, *BSC* best supportive care, *BTC* biliary tract cancer, *CCA* cholangiocarcinoma, *CSF1R* colony stimulating factor 1 receptor, *FGFR2* fibroblast growth factor receptor 2, *HER2* human epidermal growth factor receptor 2, *iCCA* intrahepatic cholangiocarcinoma, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *PARP* poly (ADP-ribose) polymerase, *PD-L1* programmed cell death ligand 1, *PTEN* phosphatase and tensin homolog, *VEGFR2* vascular endothelial growth factor receptor 2

[a]Estimated enrolment

untreated BTC is currently underway. That double-blind trial is expected to enroll 1,048 patients, who will be randomized to receive either CisGem + pembrolizumab or CisGem + placebo. The primary endpoints are PFS and OS [142].

Numerous trials are also underway to evaluate targeted therapies in the second-line setting (Table 7). These include therapies targeting FGFR2 and vascular endothelial growth factor (VEGF). VEGF is a common cancer target and has been found to be overexpressed in BTC – one study reported VEGF overexpression in 53.8% of iCCA cases and 59.2% of eCCA cases [1]. Treatment with VEGF inhibitors helps to prevent angiogenesis and VEGF-related tumor metastasis. Single-arm studies investigating therapies for iCCA include the MATCH Screening trial (NCT02465060), which is investigating the multi-targeted receptor tyrosine kinase inhibitor sunitinib, among other targeted therapies, as a possible treatment for patients with advanced, refractory solid tumors, including iCCA.

Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations occur with widely varying frequencies among solid cancers from 0% to up to 90% of pancreatic cancers, but only a minority are *KRAS* G12C mutations. In the phase 2 KRYSTAL-1 trial (NCT05162443), four (50%) of the eight pretreated patients with BTC experienced a partial response with adagrasib, a *KRAS* G12C-selective inhibitor [143]. Enrollment in this study continues, and an early access program has been initiated in patient populations with *KRAS* G12C–mutant solid tumors. In addition, other studies are starting to evaluate drugs that target the other *KRAS* mutations in pancreatic and other cancers, starting with *KRAS* G12D (MRTX1133), which is the most common alteration.

As shown in Table 8, various trials are now underway investigating the use of combination of targeted therapies, mostly with immune checkpoint inhibitors.

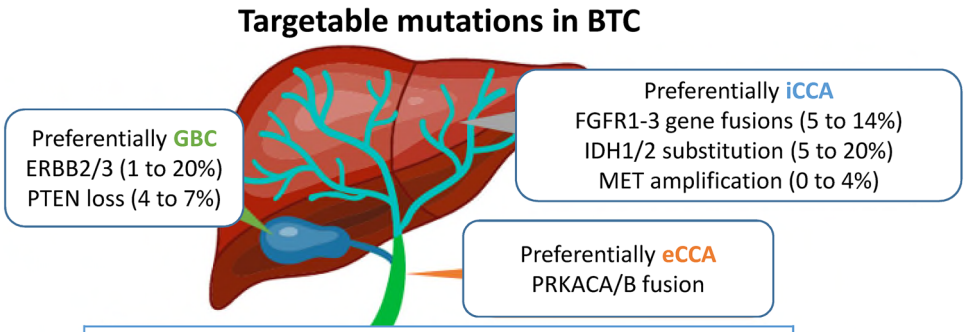
5 Detecting Molecular Alterations in BTC: The French Perspective

Despite the advances in molecular precision oncology and data demonstrating the value of genomic testing in patients with BTC, to date, routine testing for the more common genomic alterations has not been implemented in France (Fig. 5). However, this is likely to change with the inclusion in the latest French and ESMO guidelines of specific recommendations around molecular testing and targeted therapies for common mutations, such as *IDH* mutations and *FGFR2* fusions [42, 55]. Therefore, it is crucial that patients have their tumors tested for these common genetic alterations [83, 103]. Differences in the incidence of certain genomic alterations between types of BTC mean that not all mutations need to be tested for. *IDH* mutations, for instance, appear almost

Table 8 Trials evaluating second-line targeted treatment combinations for patients with advanced biliary tract cancers

Study details	Phase	N	Drug	Drug target	Patient population	NCT number
Yoo et al. 2020 [165]	2	159	Bintrafusp alpha (M7824)	PD-L1 + TGF-βR	BTC	NCT03833661
Baretti et al. 2018 [166]	2	44	Entinostat + nivolumab	PD-1 + HDAC1/3	CCA and pancreatic cancer	NCT03250273
LEAP-005 Lwin et al. 2020 [167]	2R	187	Pembrolizumab + lenvatinib vs. lenvatinib	PD-1 + multi-kinase	Various solid tumors including BTC	NCT03797326
NCT04550624	2	40	Pembrolizumab + lenvatinib	PD-1 + multi-kinase	CCA	NCT04550624
NCT04976634	2	400	Pembrolizumab + lenvatinib + belzutifan	PD-1 + multi-kinase + HIF-2α	Various solid tumors including BTC	NCT04976634
IMMUNO-BIL Boilève et al. 2021 [168]	2	106	Durvalumab + tremelimumab with or without paclitaxel	PD-L1 + CTLA-4	BTC	NCT03704480
NCT04720131	2	39	Camrelizumab + apatinib + capecitabine	PD-L1 + multi-kinase	BTC	NCT04720131
NCT03092895	2	152	SHR-1210 + apatinib vs. FOLFOX or GemOx	PD-L1 + multi-kinase	Primary liver cancer or BTC	NCT03092895

BTC biliary tract cancer, *CCA* cholangiocarcinoma, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *FOLFOX* leucovorin + 5-fluorouracil + oxaliplatin, GemOx, gemcitabine + oxaliplatin, *HDAC1/3* histone deacetylases 1/3, *HIF-2α* hypoxia inducible factor-like factor 2α, *PD-1*, programmed cell death protein 1, *PD-L1* programmed cell death ligand 1, *R* randomized, *TGF-βR* transforming growth factor beta receptor



All BTC subtypes			
Alteration frequency (%)	**iCCA**	**eCCA**	**GBC**
KRAS	9 to 35%	12 to 47%	11 to 19%
CDKN2A/B	1 to 18%	0 to 17%	0 to 19%
PI3K/mTOR	4 to 16%	4 to 25%	7 to 14%
TP53	3 to 32%	18 to 45%	43 to 46%
BRAF	4 to 22%	3%	0 to 33%
MGMT methylation	38%	26%	62%
dMMR/MSI-H	1 to 10%	1 to 13%	1 to 36%
***NTRK* gene fusions**	0 to 3.6% (all subtypes)		

Fig. 5 Selected targetable mutations in biliary tract cancers presenting rates, as well as those more common within particular subtypes [80, 113, 118, 157–161]. *BRAF* proto-oncogene B-Raf, *BTC* biliary tract cancer, *CDKN2A/B* cyclin-dependent kinase inhibitor 2A/B, *dMMR/MSI-H* deficient mismatch repair/microsatellite instability-high, *eCCA* extrahepatic cholangiocarcinoma, *ERBB* erb-b2 receptor tyrosine kinase, *FGFR* fibroblast growth factor receptor, *GBC* gallbladder cancer, *iCCA* intrahepatic cholangiocarcinoma, *IDH* isocitrate dehydrogenase, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *MET* MET proto-oncogene receptor tyrosine kinase, *MGMT* methylguanine-DNA methyltransferase, *mTOR* mammalian target of rapamycin, *NTRK* neurotrophic tyrosine receptor kinase, *PI3K* phosphoinositide 3-kinase, *PRKACA/B* protein kinase A/B catalytic subunit, *PTEN* phosphatase and tensin homolog, *TP53* tumor protein P53

exclusively in iCCA, so routine testing for these mutations in GBC or eCCA is not worthwhile [144]. However, it is important to note that *IDH1* mutations might be found in eCCA and GBC, although infrequently (0.4–1.4%) [145]. In addition, it is frequently difficult in clinical practice to determine at an advanced stage the exact type of BTC (e.g., GBC invading the liver or pCCA). Lastly, a gene-by-gene approach may be cumbersome and time-consuming, a concern owing to the poor prognosis of advanced BTC, with a median OS still < 1 year.

Although a range of diagnostic modalities are available for the evaluation of genomic alterations, the ESMO Precision Medicine Working Group recommends the use of routine NGS on tumor samples to detect mutations [120]. NGS is widely used in cancer diagnosis due to its sensitivity, specificity, and high-throughput speed, and is becoming progressively more affordable [146]. Given the possibility of translocations (*FGFR2*) and mutations (*IDH1* and *IDH2*), it is important to use a combined DNA and RNA NGS approach [55]. RNA NGS is used to identify fusion transcriptions, as the sensitivity of DNA NGS is lower for these genomic alterations and inadequate coverage of introns can result in the reporting of false-negative results [147, 148]. Of note, RNA NGS can also detect mutations. Both DNA and RNA NGS should be conducted as early as possible and ideally at the beginning of first-line treatment.

The most common clinical specimens are formalin-fixed paraffin-embedded (FFPE) tumor samples, and it is possible to extract RNA and DNA from these to perform genomic tests [149, 150]. Performing genomic tests on DNA and RNA from frozen tissue is also possible [151].

In cases where neither frozen nor FFPE samples are available, circulating tumoral DNA can be tested instead. However, while studies have demonstrated the feasibility of detecting *IDH1* mutations in plasma samples (with a reported concordance of detection between tissue and plasma in 84% and 92% of samples [152, 153]), and even *FGFR2* fusions, with a reported concordance of detection between tissue and plasma in 87% of samples [154], this diagnostic modality is not yet validated for routine use.

Increased plasma 2HG levels are pathognomonic of *IDH* mutations in both acute myeloid leukemia as well as CCA [155]. Recently, a small study determined that D-2HG enantiomers were significantly elevated in patients with iCCA and *IDH* mutations compared with patients who had *IDH* wild-type CCA, with sensitivity and specificity both reported at near 100% [156]. The levels of serum D-2HG correlated with tumor response to treatment and burden [156]. Consequently, D-2HG enantiomers and similar biomarkers are expected to become available for the identification of patients who would benefit from *IDH*-targeting therapy. Although this assay requires the use of a mass spectrometer, its rapidity (9-min run per sample), accuracy, precision, and low cost fulfil eligibility criteria for routine clinical use. It is hoped that future developments will make genetic tests such as this more accessible, so that they may be used in routine clinical practice.

It is recommended that a tumor genomic test be performed upon initial diagnosis [42]. The advantage of the early implementation of molecular testing is that there can be a delay before results of the molecular tests arrive (tumor sample retrieval, processing, and shipping, test turnaround time), which in our experience may be up to 3–4 weeks. Given the high mortality associated with BTC, any time gained is extremely valuable, particularly if this means the patient is a candidate for a targeted therapy, which would be expected to have a positive impact on survival.

Although the French National Cancer Institute has set up a network of tumoral somatic genetic platforms, and despite understanding the importance of genetic testing in patients with BTC, only a fraction of these patients are able to access molecular testing in France. This is due to the complexity of the reimbursement process. These genetic tests are not reimbursed directly by the French health insurance, which discourages some centers from carrying out these tumoral analyses. It should be noted that the notion of individual affordability has no meaning in France, where the principle of equity and the 100% coverage of *approved* drugs and tests by the national healthcare system of long-term illnesses, including cancer, prohibit a patient from paying directly for these drugs or tests at his or her own expense. Information must be provided to patients and gastroenterologists/oncologists in order to promote access to these innovative therapies. There is also a need for improved coordination between oncologists in local hospitals and those in the larger cancer centers, as well as between oncologists and pathologists, to improve patient care [146].

6 Conclusions

Among BTCs, the incidence of iCCA is increasing and this form of cancer represents an important clinical issue, as it is associated with poor prognosis and currently has limited recommended therapeutic options, with chemoresistance increasingly seen in clinics. New developments offer hope for these cases, with the advent of genomic sequencing and targeted therapies for specific genomic alterations. Up to 40% of patients with CCA have a molecular alteration and many of these are treatment targets, but there is no routine rapid diagnostic testing available to identify these patients. In France, there is an imbalance in healthcare resource access between settings, with patients treated at smaller, community hospitals less likely to access the full diagnostic and therapeutic options available to patients treated at large, expert centers. While differences in the management

of these cases have been noted between healthcare providers in France, improving communication between centers and encouraging interdisciplinary coordination in patient management could lessen the burden on individual centers and allow for optimal patient management. The use of new diagnostic modalities, coupled with more personalized, targeted treatment options, is expected to reduce the high mortality rates seen in France and improve patient outcomes.

Acknowledgements The authors would like to thank Megan Newman who provided medical writing assistance with the first draft of this article on behalf of Springer Healthcare Communications. This medical writing assistance was funded by Servier, France.

Declarations

Funding The open access fee for publication of this article was funded by Servier, France.

Authorship The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. The authors played equal roles in the initial discussions and contributions to the paper and reviewed the successive drafts.

Disclosures CN has received consulting fees/honoraria from Amgen, AstraZeneca, Baxter, Bristol Myers Squibb (BMS), Fresenius Kabi, Incyte Biosciences, Merck, MSD, Mylan, Novartis, Nutricia, Pierre Fabre, Roche, Sanofi, and Servier; research funding from Roche and AstraZeneca; and clinical trial funding from OSE Immunotherapeutics, AstraZeneca, BMS, Fresenius Kabi, and Nutricia. PA has received consulting fees from Amgen, AstraZeneca, Baxter, Bayer, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, and Viatris; honoraria for lectures from Amgen, Bayer, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, and Viatris; and travel expenses from Amgen, Pierre Fabre Oncologie, Roche, and Servier. EA: None disclosed. JE has received consulting fees from MSD, Eisai, BMS, AstraZeneca, Bayer, Roche, Ipsen, Basilea, Merck Serono, Incyte, Servier, and Beigene; travel expenses from Amgen; and research funding (institutional) from BMS and Beigene. XA has received fees from Bayer, Ipsen, Eisai, Gilead, and Servier; and travel expenses from Gilead, Viatris, and Ipsen. JCS has received consulting fees from BMS, Servier, Merck Serono, Pierre Fabre Oncologie, Astellas, Incyte and AstraZeneca; and honoraria for lectures from Amgen, Bayer, BMS, MSD, and AstraZeneca. AT has received consulting fees from Servier, Merck Serono, Pierre Fabre Oncologie, and Viatris; and travel expenses from Merck Serono, Sanofi, and AstraZeneca. RC: None disclosed. DM has received consulting fees/honoraria from AbbVie, Amgen, AstraZeneca, Bayer, BMS, Foundation Medicine, Incyte, Leo Pharma, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, Taiho, and Viatris; and travel expenses from Amgen, Bayer, BMS, Merck Serono, MSD, Pierre Fabre Oncologie, Roche, Sanofi, Servier, and Viatris.

Compliance with ethical guidelines This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the authors.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

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