Review Article



# Narrative review: current management and novel targeted therapies in intrahepatic cholangiocarcinoma

**Natalie M. Bath, Timothy M. Pawlik**

Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

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*Correspondence to:* Timothy M. Pawlik, MD, PhD, MPH, MTS, MBA, FACS, FRACS (Hon.). Professor of Surgery, Chair Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center, 395 W 12th Avenue, Columbus, OH 43210, USA. Email: tim.pawlik@osumc.edu.

**Background and Objective:** Intrahepatic cholangiocarcinoma (iCCA) is a rare hepatic malignancy with poor prognosis, which has seen an increased incidence over the last decade. Most patients present with advanced disease that is not amenable to surgical resection, and those who are able to undergo resection, frequently develop recurrent disease. With the rise of precision medicine, several targetable mutations have been described for iCCA and are currently under investigations. The development of improved targeted therapies is critical to prolonged overall survival (OS), and the use of targeted agents for iCCA is currently the focus of several ongoing randomized controlled trials. The objective of this review is to summarize current guidelines for diagnosis, surgical resection, and systemic treatment, which includes ongoing clinical trials investigated targeted therapies.

**Methods:** A comprehensive review was performed using MEDLINE/PubMed with the end search date of October 1, 2022. In PubMed the terms "intrahepatic cholangiocarcinoma," "bile duct cancer", "targeted therapies", and "clinical trials" were searched.

**Key Content and Findings:** The mainstay of treatment for iCCA is R0 resection with lymphadenectomy. Following surgical resection, new guidelines recommend 6 months of adjuvant capecitabine. Among patients with advanced or metastatic disease, systemic chemotherapy plays a significant role in prolonging survival for these patients.

**Conclusions:** Surgical resection represents the mainstay of treatment followed by 6 months of adjuvant capecitabine. While additional data is needed through randomized controlled trials, targeted therapies including fibroblast growth factor receptor (FGFR), isocitrate dehydrogenase (IDH), and erythroblastic oncogene B2 (ErbB2) inhibitors offer promising results as adjuncts to current standard of care in iCCA, particularly among individuals with unresectable disease. Future recommendations regarding the use of targeted therapy will emerge as clinical trial data become available.

**Keywords:** Intrahepatic cholangiocarcinoma (iCCA); bile duct cancer; targeted therapies; clinical trials

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## Introduction

### *Background*

Cholangiocarcinoma (CCA) is an aggressive albeit rare bile duct malignancy, which arises from epithelial cells of intrahepatic or extrahepatic bile ducts. CCAs are subdivided into three distinct categories based on the location of origin: intrahepatic (iCCA) arises above second order bile ducts; perihilar (pCCA) is located below second order bile ducts or common hepatic duct; and distal (dCCA) occurs in the common bile duct below the insertion of the cystic duct (1,2). pCCA and dCCA are commonly grouped together and termed "extrahepatic cholangiocarcinoma" (eCCA) (3). iCCA represents a category of bile duct cancers that is not only anatomically distinct, but also has its own unique molecular and clinical features. As a result, it is critical that the diagnosis, available treatment modalities, surgical options, and overall prognosis for iCCA are considered separately from eCCA.

### *Rationale and knowledge gap*

The mainstay of treatment for iCCA is surgical resection with curative intent (R0 resection) (4,5). Unfortunately, less than 20% of diagnosed patients are eligible for surgical resection as many patients present with advanced disease. Following R0 resection, 22% of patients will recur within 6 months of surgery. Furthermore, those who present with localized or regional disease face 5-year relative survival rates of 24% and 9%, respectively (6). In regards to systemic chemotherapy, the multi-center phase III BILCAP trial examined the efficacy of adjuvant chemotherapy in which a survival benefit was shown in a per-protocol analysis for capecitabine over observation [overall survival (OS) 53 months versus 36 months, P=0.028] (7). Despite this benefit, the overall responsiveness of iCCA to systemic chemotherapy remains widely variable with tumor responses seen to range from 10% to 30% (8,9).

### *Objective*

Due to the dismal OS for iCCA at all stages, there exists a significant need for novel molecular diagnostics and targeted therapies. Previous reviews have summarized the latest trends in molecular alterations and the development of targeted therapy in iCCA (3,10,11). These reviews are important in the context of highlighting new treatment regimens. Given the poor outcomes following standard treatment of iCCA, targeted therapy and systemic chemotherapy have been a topic of much interest in addition to surgical resection for resectable disease. The current clinical review addresses surgical resection and novel agents as potential management options to improve patient survival. In particular, many patients often do not present with resectable disease; therefore, novel agents are need to facilitate downstaging disease to make surgery possible. In addition, novel targeted agents may provide for more effective adjuvant therapy following surgery, as well as destination therapy for patients with unresectable disease. The current review addresses the diagnosis, staging, surgical management, late-breaking clinical trials and the current use of targeted therapies in the management of iCCA. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-109/rc).

## Methods

A comprehensive review was performed using MEDLINE/PubMed with the end search date of October 1, 2022. In PubMed the terms "intrahepatic cholangiocarcinoma", "bile duct cancer", "targeted therapies", and "clinical trials" were searched. Articles written in English from the above search terms were included. A review of the eligible literature was performed, and the most relevant, up-to-date articles were included (search strategy in *Table 1*).

## Epidemiology and risk factors

After hepatocellular carcinoma (HCC), iCCA is the second most common primary liver malignancy (9). The highest rates of iCCA are found the Eastern world, specifically in Thailand (85 per 100,000 population) and parts of China (7.6 per 100,000 population) (2,12). In the Western world, approximately 8,000 cases of CCA are diagnosed each year in the United States (1.7 per 100,000 population). Although rare, the incidence of iCCA has increased by an estimated 14% per year over several decades (4,6). This increase in incidence may be the result of improved diagnostic capabilities via imaging, molecular diagnostics, and pathology (13).

iCCA occurs in the setting chronic biliary inflammation and stasis; therefore, patients with disease that promote these processes are at an increased risk of developing iCCA. These disease processes differ in prevalence between Eastern and Western countries. In Western countries,

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | 1 October 2022 |
| Databases and other sources searched | MEDLINE/PubMed |
| Search terms used | Intrahepatic cholangiocarcinoma; bile duct cancer; targeted therapies; clinical trials |
| Timeframe | January 1, 1997–October 1, 2022 |
| Inclusion and exclusion criteria | Inclusion: reviews, clinical trials. Exclusion: language other than English |
| Selection process | Natalie M. Bath conducted search; consensus obtained amongst authors |

iCCA is commonly associated with primary sclerosing cholangitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cirrhosis, alcohol use, and smoking. In contrast, chronic bile duct calculi (hepatolithiasis), liver fluke infection, and viral hepatitis are more commonly endemic in Eastern countries and therefore are commonly seen in patients with iCCA (14,15). While conditions resulting in chronic biliary inflammation and stasis are commonly seen in patients with iCCA, the majority of tumors occur sporadically (16).

## Clinical presentation and evaluation

Like other biliary tract malignancies, patients with iCCA often present with abdominal discomfort, nausea, bloating, jaundice, or weight loss. Early tumors that have yet to cause these symptoms are frequently discovered incidentally on cross sectional imaging that was performed for other clinical indications. Evaluation should begin with a history and physical exam focusing on the presence of risk factors for chronic liver inflammation as mentioned above. Specifically, a history of any prior liver disease and personal and familial history of liver malignancies should be noted.

Beyond a focused history and physical exam, laboratory values and imaging play a primary role in the diagnosis and staging of iCCA. Laboratory values should include complete metabolic panel, coagulation studies, complete blood count, and tumor markers carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA). While not specific for cholangiocarcinoma, CA19-9 has been shown in a meta-analysis to have a sensitivity of 72% for cholangiocarcinoma (17). Important to note, CA19-9 is not produced by approximately 10% of the population and therefore would be an unreliable marker of disease in patient who are non-producers. Viral hepatitis panels should be considered as well.

Multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) with IV contrast are the most common cross-sectional imaging used in the diagnosis of iCCA and are critical to staging and in determining disease resectability. Resectability is based on location of the primary tumor, its relationship to nearby major vessels and bile ducts, presence of satellite lesions and distant metastases in the liver, and lymph node involvement (18,19). Chest CT should also be performed as part of staging. Esophagogastroduodenoscopy (EGD) and colonoscopy are recommended as part of initial work up since a mass diagnosed as adenocarcinoma may represent metastatic disease. Biopsy should only be performed once resectability status has been determined and is usually not necessary for patients undergoing resection.

While previously staged similar to HCC, a new staging classification was set forth initially in the revised 7$^{th}$ edition of the American Joint Committee on Cancer (AJCC) staging system, which focused on multiple tumors, vascular invasion, and lymph node metastasis (20). This classification was validated in 163 patients with resectable iCCA and was useful in predicting survival. With a median follow up of 34 months, patients with stage I disease did not reach median survival, stage II disease patients saw a median survival of 53 months, and 16 months for stage III disease (21).

## Surgical management

Early surgical referral is recommended for patients with newly diagnosed iCCA. Complete surgical resection is the only potentially curative treatment; unfortunately, most patients are found to have advanced disease at the time of diagnosis and are not surgical candidates. In addition to the initial work-up for iCCA as listed above, pre-operative evaluation should include an assessment of medical comorbidities, quality of underlying liver function, and

future liver remnant volume (7,22). Diagnostic laparoscopy should be considered at the time of surgery if no distant metastasis on imaging is seen. Contraindications to surgical resection include multifocal liver disease, lymph node metastasis outside of the porta hepatis, and distant metastasis as these findings typically indicate advanced disease.

### *Margin status*

While consensus has been reached regarding surgical resection, the optimal surgical margin remains uncertain. In an international cohort study of patients with resected ICC, margin status along with multifocality, vascular invasion, and lymph node metastasis were associated with worse survival (23). The Italian Intrahepatic Cholangiocarcinoma Study Group reported that margin-negative resection was associated with significantly higher survival rates and significantly lower recurrence rates. However, the width of the negative margin did not have a long-term impact on survival or recurrence (24). A multi-center retrospective study by Farges *et al.* reported that R1 resection (macroscopic positive margins) was the strongest independent predictor of poor outcome in lymph node negative (pN0) patients. However, in patients with metastatic lymph nodes, margin status did not have a significant impact on survival (25). In contrast to findings made by the Italian Study Group, Farges *et al.* noted that margin width greater than 5 mm was an independent predictor of survival in patients with lymph node negative disease.

### *Lymph node dissection*

Lymph node metastasis is an important prognostic indicator of patients with survival and guides adjuvant treatment options. Consequently, lymphadenectomy is recommended at the time of surgery (24,26). National Comprehensive Cancer Network (NCCN) guidelines recommend the removal of at least six lymph nodes that includes the area around the common hepatic artery and within the hepatoduodenal ligament. Additional evidence supports dissection of lymph node basins considered at-risk based on tumor location. For example, tumors located in the left hemi-liver may benefit from dissection along the lesser curvature of the stomach whereas the retro-pancreatic region would be considered an at-risk lymph node basin for the right hemi-liver (27-29).

## Systemic therapy

While surgical resection with negative margins represents the best option for patients to achieve long-term survival, recurrence of disease despite adequate surgical resection remains a common occurrence. The majority of recurrences after resection involve distant metastasis, which indicates the need for efficacious adjuvant systemic therapies (30). Due to the low incidence of biliary tract cancer, data examining adjuvant chemotherapy largely comes from two phase III randomized trials that have included both resected biliary tract and gallbladder cancer. These studies provide insight into the efficacy and safety of adjuvant chemotherapy regimens; however, it is important to keep in mind the results of these trials include biliary tract and gallbladder cancers, which each have distinct biologic behaviors.

### *BILCAP trial*

The phase III BILCAP study was a multicenter, prospective randomized controlled trial performed in the UK from 2006 to 2014. This trial included 447 patients (19% with iCCA, N=84) with resected CCA or gallbladder cancer who were randomized to receive adjuvant capecitabine or observation. Of note, 38% of patients underwent R1 resection and 47% had lymph node metastasis. Median OS was 51.1 months for the capecitabine arms and 36.4 months for the observation arm. This difference was statistically significant in the per-protocol analysis (HR 0.75; 95% CI: 0.58–0.97; P=0.028); however, no significant difference was seen in the intent-to-treat analysis. Relapse free survival was significantly longer in the capecitabine arm (24.4 versus 17.5 months) in both the intent-to-treat and per-protocol analysis (31). This trial demonstrated an improved OS when capecitabine was given in the adjuvant setting regardless of R0 or R1 resection. In follow up long-term analysis of the BILCAP data, capecitabine was associated with improved OS among resected patients. The impact of R status, grade, nodal status, and sex on prognosis was also confirmed (32). Consequently, international clinical practice guidelines were updated in 2019 to recommend adjuvant capecitabine for 6 months as the current standard of care following iCCA resection for most patients, especially those with high-risk features (7,33).

### *PRODIGE 12-ACCORD 18 trial*

PRODIGE 12-ACCORD 18 trial was conducted based

on data from ABC-02 in which dual gemcitabine/cisplatin regimen had become standard of care for unresectable biliary duct cancer. Therefore, PRODIGE 12-ACCORD sought to determine the benefit of dual gemcitabine/oxaliplatin (GEMOX) versus observation in resected CCA or gallbladder cancer. This multi-center randomized phase III trial was conducted from 2009 to 2014 and included 196 patients (43.9% iCCA, N=86). R0 resection was achieved in 87% of patients and 36% had lymph node metastasis. No significant different in median RFS or OS was noted between the two groups. As a result, dual adjuvant GEMOX has not been adopted in the adjuvant setting for biliary tract cancers (34).

### *Adjuvant radiation*

Although no randomized control trials exist to support the use of adjuvant radiation, there may be a role for adjuvant chemoradiation in patients with R1 resections and metastatic lymph nodes. SWOG S0809 was a prospective non-randomized phase II trial that included patients with eCCA or gallbladder cancer. Patients received adjuvant gemcitabine/capecitabine followed by capecitabine-based chemoradiation. OS at two years was 67% for patients who underwent an R0 resection versus 60% for R1 resection. However, this trial did not include patients with iCCA and therefore are not directly applicable (35). Additional studies are needed in order to elucidate the role of adjuvant radiation in iCCA.

### *Locoregional therapy*

Liver-directed therapies have been previously established in liver malignancies and there may have a role for intra-arterial therapy and Y-90 radioembolization for advanced iCCA (36). Specifically, hepatic intra-arterial pump therapy has been demonstrated to be safe and may lead to partial or complete disease control in up to 75% of patients, which subsequently may lead to prolonged OS (37). In a non-randomized phase II multi-center Y-90 Microspheres in Cholangiocarcinoma (MISPHEC) trial, 41 patients who had never received chemotherapy or intra-arterial therapy were included. Patients received gemcitabine/cisplatin with concomitant selective internal radiotherapy using glass Y-90 microspheres. This study reported a median OS of 22 months, and 22% of patients were down-staged to the point that disease was considered resectable (38). Intra-arterial therapy and Y-90 radioembolization are being investigated in the setting of advanced iCCA with additional future phase III trials.

### *Palliative treatment*

Unfortunately, most patients presenting with iCCA have advanced disease that is unresectable. Based on the phase III ABC-02 trial data, cisplatin plus gemcitabine versus gemcitabine alone was established as the standard of care for advanced biliary tract cancers (39). This trial randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive cisplatin plus gemcitabine versus gemcitabine alone. After a median follow-up of 8.2 months, median OS was superior in the cisplatin-gemcitabine group at 11.7 versus 8.1 months in the gemcitabine group (P<0.001). ABC-02 established cisplatin plus gemcitabine as the standard of care therapy for patients with advanced biliary tract tumors, including individuals with iCCA.

## Targeted therapy

Although gemcitabine has been established as first-line in the adjuvant setting or advanced CCA, many patients have disease progression on treatment. As a result of higher actionable genomic alterations seen in iCCA, increased interest in the development of new therapeutic options has developed through precision medicine. These targets include fibroblast growth factor receptor-2 (FGFR-2), isocitrate dehydrogenase-1 (IDH1), erythroblastic oncogene B2 (ErbB2), and B-Raf (BRAF). Many of these targeted therapies have received Food and Drug Administration (FDA) approval for use in the advanced or metastatic CCA setting; however, the efficacy of these agents over standard of care treatment is still being investigated.

### *FGFR2*

FGFR mutations have been identified in approximately 10–15% of patients with iCCA (40-42). FGFR is expressed on multiple cell types and has four transmembrane receptors (FGFR1-4). In the setting of cancer, the FGFR receptor binds growth factors, dimerizes, and then activates signaling pathways related to tumor proliferation, progression, cell survival, and migration (43-45). Binding of FGFR receptors leads to unregulated activation of cellular proliferation pathways including RAS-MAP kinase, JAK-STAT, and PI3-AKT-mTOR (9,40).

Pemigatinib is a potent oral inhibitor of FGFR1-3, and its safety and anti-tumor activity was investigated in phase II study FIGHT-202. This phase II study was a multi-center, open-label, single-arm trial conducted between 2017 and 2019 and included 146 enrolled patients who had previously been treated for locally advanced or metastatic CCA. Patients were placed into one of three cohorts: FGFR2 fusions/rearrangements; other FGF/FGFR alterations; or no FGF/FGFR alternations. Objective treatment response was noted in 35% of patients with FGFR2 fusions/rearrangements, 42% of patients had died (no deaths deemed to be treatment related), and 45% had a serious adverse event. Pemigatinib was approved in April 2020 by the US FDA for the treatment of patients previously treated for advanced CCA with a FGFR2 fusion or rearrangement. Based on this study, an international phase III study is currently recruiting patients to compare pemigatinib with gemcitabine/cisplatin as first-line therapy for unresectable or advanced CCA with FGFR2 fusions/rearrangements (43,46).

Infigratinib, another oral FGFR1-3 inhibitor, was evaluated in a multi-center, open-label phase II study in the setting of advanced or metastatic CCA in patients with FGFR2 or other FGFR mutations who had previously progressed on therapy. The primary endpoint was objective response rate by independent central review per RECIST, with duration of response. One hundred eight patients were included with 77% (N=83) having FGFR2 fusions. Overall response rate was 23.1% with 1 patient having complete response and 24 with partial response. Patients who were on earlier lines of therapy had improved responses with 34% response in second-line regimen and 13.8% in third and later-line treatments (47). With recent FDA approval for advanced or metastatic CCA, infigratinib is currently under investigation in a phase III trial against gemcitabine/cisplatin as first line therapy for advanced or metastatic CCA (48).

An irreversible FGFR1-4 inhibitor, FDA-approved futibatinib is currently undergoing clinical trial testing. A phase II study in 67 patients with FGFR aberrations in advanced iCCA, the overall response rate was 37.3% and disease control of 82%. Futibatinib is currently in phase III trials as first-line treatment for metastatic iCCA in patients with FGFR2 genomic fusions (43,49,50).

### *IDH*

IDH mutations are found in approximately 10–20% of iCCA patients (41,51). Preclinical models suggest that IDH mutation results in an abnormal response to hepatocyte injury and inflammation, and it also silences HNF4-alpha which acts as an anti-proliferative and tumor suppressor in hepatocyte differentiation. Preclinical models have demonstrated that IDH-associated silencing of HNF4-alpha results in a pro-neoplastic state found primarily in the biliary tract (9). Ivosidenib is an inhibitor of mutant IDH1and was evaluated in a randomized phase III trial conducted from 2017 to 2019. This multi-center, double-blind, placebo-controlled study included 230 patients with advanced IDH1-mutant CCA who had progressed on previous therapy and had received two or fewer treatment regimens. The primary end-point was progression-free survival and was significantly improved with ivosidenib to 2.7 months compared to 1.4 months in placebo (52). This trial established IDH as an actionable target in CCA, which has subsequently resulted in the US FDA approval of ivosidenib.

### *ErbB2*

ErbB2, commonly known as human epidermal growth factor receptor-2 (HER-2), is overexpressed in multiple tumor types including breast, gastroesophageal, and biliary tract cancers. Overexpression results in the spontaneous formation of multiple dimers, thereby increasing the activation by other dimers resulting in oncogenic pathways such as RAS-MAPK and PI3K-AKT (53,54). Lapatinib, erlotinib, pertuzumab, and trastuzumab are inhibitors of aberrant EGFR and HER. These drugs have been investigated in early phase trials; however, results are pending or have not demonstrated significant objective response (55,56).

### *BRAF*

BRAF mutations in iCCA are thought to exist in 1–3% of tumors (57). BRAF has a simplified mechanism of activation toward the MAPK pathway, which is crucial in the development of malignancies. Dabrafenib and trametinib have previously shown to have activity in BRAF-mutated cancer and were therefore examined in a phase 2 multi-center BRAF-mutated biliary tract cancers. Forty-three patients with BRAF-mutated biliary tract cancers were included in the study conducted from 2014 to 2018. Of these patients, 51% (N=22) were found to have an investigator-assessed overall response and 47% (N=20) were

**Table 2** Ongoing clinical trials investigating FGFR inhibitors in patients with iCCA (clinicaltrials.gov, accessed on 20 October 2022). Interventional drugs are FGFR2 inhibitors unless otherwise noted

| NCT, phase | Disease | Intervention | Tumor mutation | Primary outcome | Status |
|---|---|---|---|---|---|
| 03230318, II | Advanced iCCA | Derazantinib | FGFR2 | ORR, PFS | Active, not recruiting |
| 05565794, II | Advanced iCCA | Pemigatinib after SBRT | FGFR2 | ORR | Not yet recruiting |
| 05174650, II | Advanced iCCA | Atezolizumab (PD-L1 inhibitor) + derazantinib | FGFR2 | ORR | Recruiting |
| 04353375, II | Advanced iCCA | HMPL-453 (FGFR1-3 inhibitor) | FGFR2 | ORR | Not yet recruiting |
| 04526106, I/II | Advanced iCCA, solid tumors | RLY-4008 (FGFR2 inhibitor) | FGFR2 | ORR, MTD, adverse events | Recruiting |
| 05242822, I | iCCA, solid tumors | KIN-3248 (FGFR1-4 inhibitor) | FGFR2 +/– FGFR3 | DLT, adverse events, ORR, DCR, DOR, PFS | Recruiting |
| 05514912, II | Resectable iCCA | Arm A: infigratinib + nab-paclitaxel, cisplatin, gemcitabine. Arm B: nab-paclitaxel, cisplatin, gemcitabine | Arm A: FGFR2. Arm B: none | Feasibility; DLT; safety, tolerability | Not yet recruiting |
| 01752920, I/II | Locally advanced or metastatic solid tumors | Derazantinib | FGFR | Adverse events | Completed, has results |
| 05325866, I | Solid tumors | Bemarituzumab | FGFR2b | DLT, adverse events ORR | Recruiting |
| 04211168, II | Advanced biliary tract cancers | Toripalimab (anti-PD-1) + lenvatinib (FGFR1-4) | None | ORR, adverse events | Recruiting |

FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; NCT, national clinical trial; SBRT, stereotactic body radiation therapy; PD-L1, programmed death-ligand 1; PD-1, programmed cell death ligand 1; ORR, objective response rate; PFS, progression free survival; MTD, maximal tolerated dose; DLT, dose limiting toxicity; DCR, disease control rate; DOR, duration of response.

**Table 3** Ongoing clinical trials investigating IDH inhibitors in patients with iCCA (clinicaltrials.gov, accessed on 20 October 2022). Interventional drugs are IDH inhibitors unless otherwise noted

| NCT, phase | Disease | Intervention | Tumor mutation | Primary outcome | Status |
|---|---|---|---|---|---|
| 02428855, II | Advanced iCCA | Dasatinib | IDH | ORR | Completed |
| 02496741, I/II | iCCA, glioma, chondrosarcoma | Metformin + chloroquine | IDH1-2 | MTD | Completed |
| 02273739, I/II | iCCA, solid tumors, glioma, angioimmunoblastic T-cell lymphoma, chondrosarcoma | Enasidenib | IDH2 | Adverse events, DLT, ECOG PS | Completed |
| 03684811, I/II | Advanced solid tumors, glioma | FT-2102 (IDH1 inhibitor) | IDH1 | DLT, dose recommended, ORR | Completed |

IDH, isocitrate dehydrogenase; iCCA, intrahepatic cholangiocarcinoma; NCT, national clinical trial; ORR, objective response rate; MTD, maximal tolerated dose; DLT, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

found to have response by an independent reviewer (58). Dabrafenib plus trametinib showed promising activity and is undergoing additional investigation.

Optimal treatments in the adjuvant and advanced setting for iCCA have yet to be determined. Consequently, additional clinical trials are required to assess the efficacy and safety of targeted therapies. *Tables 2-5* summarize ongoing clinical trials investigating targeted therapies for iCCA. Important to note, the included trials focused on patients with specific tumor mutations; of note, trials that

**Table 4** Ongoing clinical trials investigating ErbB2/HER2 inhibitor in patients with iCCA (clinicaltrials.gov, accessed on 20 October 2022). Interventional drugs are HER2 inhibitors unless otherwise noted

| NCT, phase | Disease | Intervention | Tumor mutation | Primary outcome | Status |
|---|---|---|---|---|---|
| 04466891 II | Advanced biliary tract cancer | Zanidatamab | HER2 | ORR | Active, not recruiting |
| 03929666 II | Advanced GEC, advanced BTC, advanced CRC | Zanidatamab + standard of care | HER2 | DLT, adverse events, lab abnormalities, ORR | Active |

ErbB2, erythroblastic oncogene B2; HER2, human epidermal growth factor receptor-2; iCCA, intrahepatic cholangiocarcinoma; NCT, national clinical trial; GEC, gastroesophageal cancer; BTC, biliary tract tumors; CRC, colorectal cancer; ORR, objective response rate; DLT, drug limiting toxicity.

**Table 5** Ongoing clinical trials investigating BRAF inhibitors in patients with iCCA (clinicaltrials.gov, accessed on 20 October 2022). Interventional drugs are BRAF inhibitors unless otherwise noted

| NCT, phase | Disease | Intervention | Tumor mutation | Primary outcome | Status |
|---|---|---|---|---|---|
| 02465060, II | Advanced solid tumors, lymphomas | Dabrafenib mesylate | BRAF | ORR | Recruiting |

BRAF, B-raf; iCCA, intrahepatic cholangiocarcinoma; NCT, national clinical trial; ORR, objective response rate.

included patients without mutations were not included.

## Conclusions

iCCA is a rare biliary tract cancer that has seen increased prevalence over the past decade. Many patients present with advanced disease; however, surgical resection with lymphadenectomy remains the mainstay of treatment for resectable iCCA. Despite successful resection, many patients will recur long-term, indicating a significant need for improved systemic therapies. While chemotherapy is an important component of multi-modal treatment for iCCA, targeted therapies offer new mechanisms to help achieve improved rates of disease-free survival. As a result of these developments, it is critical for patients with iCCA to have genetic profiling completed. Current clinical trials are investigating actionable genomic alterations with the goal of improving safe and efficacious treatment for iCCA.

This review had several strengths and limitations. The current review provided a comprehensive summary of the diagnosis, surgical management, and use of systemic and targeted therapies—including an up-to-date review of ongoing clinical trials. These data are valuable to clinicians who treat patients with iCCA. Targeted therapy and personalized medicine have resulted in recent changes in treatment guidelines and offers patients with advanced disease additional options for treatment. While this review provided a summary of the latest evidence, the field of precision medicine continues to move quickly. As such, information included in the review was not exhaustive and not all currently recruiting clinical trials involving patients without targetable mutations were included.

### *Recommendations for iCCA management*

Patients with resectable iCCA should undergo surgical resection and receive adjuvant gemcitabine, which has been suggested to improve disease free and OS. Patients with unresectable disease or borderline resectable disease should be treated with cisplatin plus gemcitabine. The goal of systemic chemotherapy is to prolong survival, potentially convert unresectable disease to resectable disease, as well as test the biology of borderline resectable tumors to determine who may benefit from surgery. Among patients who do not respond to first line chemotherapy, targeted therapies should be strongly considered based on the molecular profile of the iCCA. Given the high incidence of recurrence and possible need for targeted therapy, all patients with iCCA should have molecular analysis of the tumor to identify potential targeted therapy that may benefit them in addition to standard of care chemotherapy.

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## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at https://

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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