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Emerging Clinical Strategies in Cholangiocarcinoma: A Review on Targeted Therapy and Immunotherapy

Vanshika Gajjala
gvanshika2010@gmail.com

ABSTRACT

Cholangiocarcinoma (CCA) is a rare, highly heterogeneous, and aggressively malignant cluster of biliary tract cancers encompassing intrahepatic, perihilar, and distal subtypes. It disproportionately affects older adults, with roughly 75% of patients diagnosed at the age of 62 or older (Valle et al., 2021), and it is often diagnosed at an advanced, unresectable stage due to its clinically silent onset and deep anatomical seclusion. Five-year survival rates linger below 20%, largely because the foundational standard of care relies heavily on surgical resection and conventional cytotoxic chemotherapy, which has failed to provide durable survival benefits for most late-stage patients.

This review paper summarizes recent changes in the management of CCA. As the field moves from "one-size-fits-all" treatments towards highly personalized, biologically driven interventions, it has become crucial to synthesize the latest advancements in clinical and pre-clinical trials. Evidence was identified through a structured narrative literature search (see Methods) and is labelled by level of evidence throughout. This review compares biomarker-directed therapy with first-line chemoimmunotherapy using the endpoints appropriate to each. In previously treated patients with *FGFR2* fusions or rearrangements, *FGFR2* inhibitors achieved objective response rates of approximately 35% to 42% in single-arm studies, whereas the *IDH1* inhibitor ivosidenib mainly prolonged progression-free survival, with few objective responses. In contrast, the phase III trials TOPAZ-1 and KEYNOTE-966 enrolled broader biliary tract cancer (BTC) populations that included, but were not limited to, CCA, and reported modest overall survival gains with chemoimmunotherapy. Chemoimmunotherapy is now the first-line standard for advanced BTC, whereas biomarker-directed agents are generally used after progression on first-line treatment.

Furthermore, it addresses the limitations hindering these trials, including the logistical challenges of diagnostic tissue acquisition, the rarity of specific genetic cohorts, and the historical practice of pooling distinct anatomical subtypes into single clinical studies. This paper surveys emerging strategies in CCA research by exploring early-phase clinical and preclinical approaches, clearly separated from established evidence, designed to penetrate CCA's notoriously dense, immunosuppressive desmoplastic stroma. We conclude that further progress in CCA treatment depends on overcoming acquired resistance, democratizing access to comprehensive genomic profiling, and adopting adaptive, molecularly guided clinical trial designs that may extend survival and allow longer-term disease control in selected patients.

Keywords: *Cholangiocarcinoma; biliary tract cancer; intrahepatic cholangiocarcinoma; FGFR2 fusion; IDH1 mutation; targeted therapy; precision oncology; immune checkpoint inhibitors; chemoimmunotherapy; tumour microenvironment.*

INTRODUCTION

Biliary Tract Cancer (BTC) is a group of rare diseases among which CCA is a highly fatal condition that affects a higher proportion of geriatric populations, with roughly 75% of the patients diagnosed at the age of 62 or older (Valle et al., 2021). It belongs to a heterogeneous group of tumours within the bile ducts that connect the liver to the gallbladder and small intestine, to enable bile transport and digestion (Banales et al., 2020). CCA is rare; its annual incidence is estimated at roughly 0.3 to 6 per 100,000 people in most countries (Banales et al., 2020).

Due to a range of biological factors including DNA damage, accelerated cellular senescence and changes in the microenvironment, aging is a major risk factor for this highly malignant condition (Valle et al., 2021). Established risk factors for CCA include primary sclerosing cholangitis (PSC), biliary duct cysts, and chronic inflammation of the biliary tract, alongside parasitic liver fluke infections which remain a primary driver in specific geographic regions (Banales et al., 2020). Less well-established potential risk factors include metabolic conditions including obesity and diabetes, and chronic viral infections such as hepatitis B (HBV) and hepatitis C (HCV) (Clements et al., 2020). Beyond these triggers, other occupational and environmental exposures, such as thorium dioxide, arsenic, vinyl chloride, and cigarette smoking, have been linked to biliary tract malignancy (Clements et al., 2020). Other factors that may influence individual susceptibility to CCA include cirrhosis, inflammatory bowel disease (IBD), heavy alcohol consumption, and specific host genetic polymorphisms (Clements et al., 2020).

Furthermore, a substantial burden falls on older populations because of rising global life expectancy, and management of CCA is a major challenge in geriatric oncology, as about 80% of patients are diagnosed at an advanced stage (Banales et al., 2020). Currently, surgical resection is the only potentially curative treatment for CCA, and it is often combined with adjuvant chemotherapy or, in selected cases, radiotherapy (Lamarca et al., 2022). To add on, the prognosis of CCA is very poor, with 5-year survival rates typically under 20% (Banales et al., 2020). Hence substantial research is ongoing to effectively treat CCA at various stages.

This paper aims to discuss the current clinical and pre-clinical trials for CCA, given that surgical intervention and chemotherapy are not highly effective in late stage patients. Other trials on immunotherapy and targeted therapy to improve surgical rates will also be discussed. This paper will also discuss what is currently known of CCA and its biology, the current clinical interventions for alleviation of the disease and potential future directions in CCA treatment.

METHODS

This narrative review was based on a structured literature search. PubMed/MEDLINE and Google Scholar were searched for published studies, and ClinicalTrials.gov and American Society of Clinical

Oncology (ASCO) conference abstracts were searched for ongoing and unpublished trials. Articles published between January 2010 and December 2025 were considered, and the status of ongoing trials was verified on ClinicalTrials.gov in October 2026. Search terms combined "cholangiocarcinoma" or "biliary tract cancer" with "targeted therapy", "FGFR2", "IDH1", "immunotherapy", "immune checkpoint inhibitor" and "clinical trial"; additional terms (for example "CAR-T", "organoid", "nanoparticle" and "epigenetic") were used to identify the early-phase and preclinical approaches discussed. Further sources were identified from the reference lists of key reviews (Banales et al., 2016, 2020; Lamarca et al., 2022).

Studies were included if they were published in English and reported clinical, translational or preclinical findings on the diagnosis or treatment of cholangiocarcinoma or biliary tract cancer. Priority was given to phase II and III clinical trials, consensus statements, guidelines and systematic reviews. Case reports and opinion pieces were excluded, and conference abstracts and registry entries were used only to describe ongoing or unpublished trials. Ongoing trials were selected if they were registered for BTC or CCA and tested a biomarker-directed or immune-based strategy. Preclinical studies were included only where they illustrated an emerging approach relevant to the CCA tumour microenvironment, and they are reported separately from clinical evidence. Titles and abstracts were screened by the author, and no formal risk-of-bias assessment was performed; the review is therefore narrative rather than systematic.

Each study or therapy was then labelled by level of evidence (approved standard of care, completed phase III trial, completed phase II or single-arm study, ongoing trial, early-phase clinical study, or preclinical research), and these labels are used throughout the Results and Discussion. The term "BTC" is used when a study population included gallbladder cancer in addition to intrahepatic and extrahepatic CCA, and "CCA" when a study was restricted to cholangiocarcinoma; where available, the composition of each trial population is reported.

LITERATURE REVIEW

Anatomical subtypes of CCA

CCA is further divided into three different subtypes, depending on the origin of the tumour: intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA). Each of the subtypes has unique diagnostic and therapeutic pathways (Banales et al., 2020). For all the subtypes, the primary curative option is surgical resection, though the approaches differ for different subtypes (Banales et al., 2020).

Subtype iCCA develops within the liver parenchyma, so it is detected as a solid mass using non-invasive cross-sectional imaging. On the other hand, pCCA and dCCA are detected as flat, periductal structures using advanced preoperative multi-phase imaging, which can accurately show the complex biliary and vascular involvement (Banales et al., 2020).

Subtype iCCA frequently harbours *IDH1/2* mutations (approximately 10-20%) and FGFR2 fusions (approximately 10-16%) (Angerilli et al., 2023; Brandi et al., 2023). In contrast, extrahepatic subtypes such as dCCA and pCCA more often harbour *KRAS* mutations (up to 30%) and ERBB2 alterations (5-15%) (Jusakul et al., 2017). Other driver mutations like *TP53*, *CDKN2A* and *SMAD4* are also common

across all these subtypes (Jusakul et al., 2017). Across subtypes, CCA also shows shared epigenetic dysregulation, including promoter hypermethylation that silences tumour suppressor genes within the Wnt, TGF-β and PI3K signalling pathways (Goeppert et al., 2022; Jusakul et al., 2017). Population-based studies also indicate that Asian patients often have distinct mutational landscapes compared with Western patients (Jusakul et al., 2017). Together, these findings illustrate the complex molecular architecture of CCA, which underpins the development of precision therapeutic strategies.

When surgery is not feasible, systemic treatment is guided by both tumour genetics and anatomical location (Lamarca et al., 2022). For advanced disease of all subtypes, first-line treatment is gemcitabine plus cisplatin, now usually combined with an immune checkpoint inhibitor (Kelley et al., 2023; Oh et al., 2022). Biomarker-directed targeted therapy is generally used in later lines, after progression on first-line treatment, in patients whose tumours carry an actionable alteration; such alterations are more common in iCCA than in pCCA and dCCA, where palliative biliary stenting is also frequently needed (Lamarca et al., 2022). Because relapse after resection of extrahepatic tumours is common, better predictive tools, including emerging machine-learning models, are needed to identify patients who will benefit from surgical resection (Valle et al., 2021).

Prevalence, Prognosis and Diagnosis of CCA

CCA accounts for approximately 3% - 5% of all gastrointestinal cancers and global incidence rates are quite low in most high-income countries, ranging from about 0.3 to 2 cases per 100,000 individuals. Incidence is up to 40-fold higher in certain regions of China and Thailand, where liver fluke infections are endemic (Banales et al., 2020). An analysis of recent epidemiological trends suggests a rising incidence of intrahepatic CCA around the world along with the decline of extrahepatic CCA subtypes in many Western nations (Clements et al., 2020).

CCA has a poor prognosis because it frequently presents at an advanced stage (Valle et al., 2021). International data indicates that the baseline 3 year survival rate for iCCA is approximately 9% (Banales et al., 2020). For patients with metastatic BTC, evidence suggests that the median overall survival is often limited to 4.5 months, with about 41% of the patients surviving less than three months after initial diagnosis (Valle et al., 2021). Along with anatomical staging, genomic profiling suggests more about the molecular architecture of the tumour that heavily influences patient outcomes and therapeutic response (Jusakul et al., 2017).

Anatomical location strongly influences the clinical presentation of CCA, as early stage diseases are asymptomatic (Banales et al., 2016; National Cancer Institute, 2024). pCCA and dCCA often cause biliary obstruction, progressive jaundice, pruritus, dark urine and pale stools (National Cancer Institute, 2024; National Health Service, 2024). On the other hand, iCCA often causes non-specific symptoms like right-sided abdominal pain, fatigue, anorexia and weight loss (Banales et al., 2016; National Health Service, 2024). Furthermore, if biliary obstruction causes secondary infections, patients may have acute cholangitis with fever, chills, nausea and vomiting (National Cancer Institute, 2024).

Because of the tumour's growth pattern and deep anatomical location within the hepatobiliary tree, diagnosis of CCA is complex (Banales et al., 2016). CCA is frequently identified only after the onset of

obstructive symptoms as early-stage disease is often clinically silent. Clinicians often observe a cholestatic pattern that is characterized by elevations in direct bilirubin, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) as no single blood test is diagnostic (Banales et al., 2020). Serum tumour markers, particularly carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), are useful secondary indicators, although CA19-9 has limited specificity (Valle et al., 2021).

Recent CCA diagnostic paradigms have been exploring liquid biopsies, especially the analysis of cell-free DNA (cfDNA) and specialized proteins within the bile which can provide more information for early detection (Brito-Rocha et al., 2023).

Due to the aggressive nature of CCA, primary prevention is a public health priority (Shen & Shen, 2020). As the etiology of CCA is linked to chronic inflammation, prevention strategies must target modifiable risk factors (Shen & Shen, 2020). In Southeast Asia where liver flukes are a primary carcinogen, initiatives focus on reducing food-borne fluke infection through public education against eating raw fish to prevent chronic periductal fibrosis (Banales et al., 2020). Moreover in Western populations, prevention frameworks emphasize managing metabolic and lifestyle-driven conditions. Higher risk of CCA is associated with metabolic syndrome, which is a cluster of conditions including obesity, hypertension and dysglycemia (Clements et al., 2020). Addressing these metabolic factors, together with reducing tobacco use and alcohol consumption, may help reduce rising incidence rates (Clements et al., 2020; Shen & Shen, 2020).

Translational research highlights the potential for molecular chemoprevention, an example includes how regular low-dose aspirin use has been associated with lower CCA incidence in observational studies, possibly by inhibiting COX-2 overexpression and minimizing tumour angiogenesis (Marcano-Bonilla et al., 2022; Shen & Shen, 2020). To conclude, lifestyle modification and management of metabolic health are likely to contribute to reducing CCA risk, although most of the supporting evidence is observational.

Biomarkers

CA-19-9 levels frequently rise in non-cancerous conditions like liver cirrhosis, bile duct infections, and blocked bile ducts, making it an unreliable tool for diagnosing cancer (Banales et al., 2020). Molecular biomarker testing is increasingly used to detect actionable alterations in CCA, including *IDH1*, *BRAF* and *NTRK* mutations, along with *FGFR2* fusions and HER2/neu overexpression, which has improved the selection of patients for targeted therapies (Lamarca et al., 2022). The primary difficulty for a biomarker is the ability to differentiate between iCCA and hepatocellular carcinoma (Banales et al., 2020). Precision diagnostics are increasingly exploring liquid biopsies to analyse markers in urine, blood or bile, which may provide further insight into disease biology (Brito-Rocha et al., 2023).

Current treatment options for CCA

To evaluate complex biliary structure before surgical intervention, use of accurate preoperative anatomical mapping using 3D magnetic resonance cholangiopancreatography (MRCP) is essential (Banales et al., 2020). For small iCCA, liver transplantation is another potentially curative option, but has high recurrence rates (Valle et al., 2021). Because patients are at high risk of occult peritoneal and liver

metastases, staging laparoscopy is recommended before resection. Because most patients present with advanced disease, only a minority of newly diagnosed patients are eligible for resection (Valle et al., 2021).

Patient age is one factor that can influence treatment decisions for CCA, alongside performance status, comorbidities and tumour stage. Retrospective analyses reveal that older patients aged 70 and above are more likely to receive best supportive care than active intervention because of higher comorbidity burdens (Valle et al., 2021). While older age increases the risk of major postoperative morbidities, recent studies suggest that age alone should not exclude patients from curative-intent surgery (Valle et al., 2021). Selected older patients who undergo complex surgeries such as major hepatectomy can achieve survival similar to that of younger patients (Valle et al., 2021). Therefore, clinicians increasingly assess factors such as body mass index and functional reserve, rather than relying only on chronological age, to select patients best suited to aggressive interventions (Valle et al., 2021). As recurrence after resection is common, adjuvant therapy is important for improving patient outcomes (Banales et al., 2020).

After curative-intent surgery, six months of adjuvant capecitabine is the recommended standard of care, based on the phase III BILCAP trial (Primrose et al., 2019). Postoperative radiotherapy, sometimes combined with iridium-192 brachytherapy, may improve local control and survival in selected patients, although this evidence comes mainly from retrospective studies (Lamarca et al., 2022). For many patients with advanced or metastatic disease, radical surgery is not possible, and gemcitabine plus cisplatin (GemCis) became the standard first-line chemotherapy after the phase III ABC-02 trial in unresectable BTC (Valle et al., 2010); GemCis combined with durvalumab or pembrolizumab is now the preferred first-line regimen for advanced BTC, a group that includes CCA (Kelley et al., 2023; Oh et al., 2022). Emerging strategies that use targeted therapies and immunotherapies may further improve patient outcomes (Lamarca et al., 2022). Molecular profiling is recommended at diagnosis of advanced disease so that, after progression on first-line treatment, patients can be matched to targeted agents, specifically *FGFR2* inhibitors, *IDH1* inhibitors, *BRAF* inhibitors and HER2-targeting therapies (Lamarca et al., 2022). To further improve overall survival rates, discovery of standardized early-stage biomarkers is needed to ensure timely and effective interventions across all age groups (Banales et al., 2020).

Along with precision medicine, CRISPR/ Cas gene-editing technology is also an important preclinical research tool in CCA. Rather than being used as a standard patient treatment at this stage, CRISPR is primarily used to accelerate drug discovery and enhance early diagnostics (Banales et al., 2020). CRISPR-Cas9 screening is actively used in pre-clinical settings to identify essential gene-dependencies and therapeutic vulnerabilities such as valosin-containing protein (VCP), whose inhibition suppressed CCA growth in laboratory models (Banales et al., 2020). Recently, innovative diagnostic applications are integrating CRISPR/Cas systems with liquid biopsies. Experimental platforms allow the detection of extracellular vesicle-derived tumour biomarkers with single-nucleotide precision, a potential approach to early CCA detection that has not yet been clinically validated (Banales et al., 2020).

RESULTS AND DISCUSSION

The main limitations of current treatment options for CCA are the highly desmoplastic nature of tumours that restrict drug delivery and this results in high rates of post-surgical recurrence and the rapid development of chemoresistance (Elvevi et al., 2022). Therefore to overcome these existing limitations, many clinical trials for CCA have shifted towards precision medicine and immunotherapy (Lamarca et al., 2022). The two approaches differ in population, line of therapy and the endpoints on which benefit has been shown, so they are compared below by endpoint rather than as uniform categories. Among targeted agents, *FGFR2* inhibitors have produced high objective response rates in previously treated patients, whereas the *IDH1* inhibitor ivosidenib mainly improved progression-free survival (PFS); in both cases benefit is restricted to the minority of patients (approximately 15% to 20%) whose tumours carry a specific alteration (Elvevi et al., 2022). By contrast, the large phase III chemoimmunotherapy trials TOPAZ-1 and KEYNOTE-966 were conducted in broader, biomarker-unselected populations of patients with BTC, which included CCA but also gallbladder cancer, and showed lower response rates but a modest improvement in median overall survival (OS) that was durable in a subset of patients (Kelley et al., 2023; Oh et al., 2022).

Main types of clinical trials

A broad range of clinical trials is now changing the management of CCA. While the integration of first-line chemoimmunotherapy has improved baseline survival, researchers are now designing other trials to overcome the dense, fibrotic tumour microenvironment (TME) and combat acquired treatment resistance (Elvevi et al., 2022). Immunotherapy and targeted therapy have produced the most clinically relevant results to date. To distinguish levels of evidence, the subsections below label each therapy or study as approved standard of care, completed phase III trial, ongoing trial, early-phase clinical study, or preclinical research.

Targeted Therapies and Precision Medicine

Targeted therapies and precision medicine have substantially changed the design of clinical trials in CCA (Lamarca et al., 2022). In the past, clinical trials in advanced BTC, including CCA, relied on unselected patient cohorts treated with standard gemcitabine and cisplatin chemotherapy (Lamarca et al., 2022). Because median overall survival with this standard approach was under one year, researchers recognised the need to shift towards biologically driven clinical trials (Lamarca et al., 2022).

The main difference between precision medicine and targeted therapy is the scope and application of these trials. Precision medicine utilizes molecular profiling like next-generation sequencing (NGS) to identify specific gene alterations and to effectively match individual patients to most appropriate interventions (Lamarca et al., 2022). On the other hand, targeted therapy involves specific pharmacological agents like kinase inhibitors to inhibit these identified molecular drivers (Lamarca et al., 2022). In modern CCA clinical trials, targeted therapies act as precise intervention tools and precision medicine provides a strategic diagnostic framework.

As a result of these trials, CCA is increasingly sub-classified by molecular alterations as well as by anatomical location (Lamarca et al., 2022). Genomic sequencing reveals that a substantial proportion of

patients, mainly those with iCCA, carry actionable molecular alterations (Abou-Alfa et al., 2020a; Lamarca et al., 2022). Among these, the strongest evidence to date comes from trials targeting *FGFR2* fusions and *IDH1* mutations (Lamarca et al., 2022).

FGFR2 Inhibitors (approved; single-arm phase II evidence). Approximately 10% to 16% of iCCA cases have *FGFR2* fusions (Lamarca et al., 2022). In previously treated patients with FGFR2 fusions or rearrangements, the single-arm phase II trials FIGHT-202 (pemigatinib; objective response rate [ORR] 35.5%) and FOENIX-CCA2 (futibatinib; ORR 42%), together with a phase II study of infigratinib (ORR 23%), led to accelerated or conditional regulatory approvals (Abou-Alfa et al., 2020a; Goyal et al., 2023; Javle et al., 2021). In FIGHT-202, the disease control rate was 82%, the median duration of response (DOR) was 7.5 months and median PFS was 6.9 months; median OS was 21.1 months but was not yet mature at data cut-off (Abou-Alfa et al., 2020a). In FOENIX-CCA2, which enrolled only patients with iCCA, median DOR was 9.7 months, median PFS 9.0 months and median OS 21.7 months (Goyal et al., 2023). Because these were single-arm studies without a control group, their survival data cannot be compared directly with those of randomised trials.

IDH1 Inhibitors (approved; phase III evidence). Approximately 10% to 20% of iCCA cases have *IDH1* mutations that cause the production of an oncometabolite that drives tumourigenesis (Lamarca et al., 2022). In previously treated patients with this mutation, the randomised phase III ClarIDHy trial (n=187) found longer median progression-free survival (PFS) with the IDH1 inhibitor ivosidenib than with placebo (2.7 vs 1.4 months; hazard ratio [HR] 0.37), although objective responses were uncommon (ORR approximately 2%). The final analysis reported median OS of 10.3 vs 7.5 months, a difference that was not statistically significant without adjustment for crossover. These results led to its approval for previously treated IDH1-mutant CCA (Abou-Alfa et al., 2020b; Zhu et al., 2021). Ivosidenib's benefit is therefore best described as delayed progression and disease control rather than tumour shrinkage.

BRAF and Other Targets (tumour-agnostic approval; phase II basket evidence). Approximately 3% of iCCA cases have a rare *BRAF* V600E mutation. In the phase II ROAR basket trial, dabrafenib plus trametinib produced objective responses in approximately half of 43 patients with BRAF V600E-mutated BTC, suggesting that histology-agnostic basket trials can provide evidence for targeted therapy in small CCA populations (Subbiah et al., 2020).

Although *FGFR2* inhibitors can produce rapid tumour shrinkage, the clinical utility of targeted agents is restricted by the molecular subgroups they target, which typically represent only 15–20% of patients (Elvevi et al., 2022; Lamarca et al., 2022). Moreover, responses to *FGFR2* inhibitors can be deep but are frequently limited by the emergence of acquired resistance mutations, which underlines the need for serial genomic monitoring (Goyal et al., 2021).

To conclude, integrating precision medicine into clinical trial design ensures that targeted therapies are evaluated in the patient populations most likely to benefit, shifting later-line CCA treatment from uniform chemotherapy towards personalised approaches.

Immunotherapy

First-line treatment of advanced BTC, including CCA, has shifted from chemotherapy alone to chemoimmunotherapy (Kelley et al., 2023; Oh et al., 2022). Immunotherapy in solid tumours utilizes ICIs like programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, to prevent cancer cells from taking over the host's immune system and helps restore a tumour-directed T cell response (Lamarca et al., 2022). In the past, ICI monotherapy in previously treated BTC gave limited benefit; in the phase II KEYNOTE-158 study, pembrolizumab produced an objective response rate of 5.8% in 104 patients (Piha-Paul et al., 2020), which has been attributed to the tumour's immunosuppressive microenvironment (Lamarca et al., 2022). Therefore to overcome this problem, clinical trials began investigating combination strategies, hypothesizing that chemotherapy can cause favourable immunomodulatory effects within the tumour microenvironment which makes the cancer more susceptible to immune intervention (Lamarca et al., 2022). This approach was tested in two phase III trials, TOPAZ-1 and KEYNOTE-966, both of which met their primary overall survival endpoint.

The phase III TOPAZ-1 trial evaluated the addition of a PD-L1 inhibitor, durvalumab, to standard GemCis chemotherapy in 685 patients with previously untreated, unresectable or metastatic BTC. The population was not restricted to CCA: approximately 56% of patients had intrahepatic CCA, 19% extrahepatic CCA and 25% gallbladder cancer, and analyses by primary tumour site were exploratory (Oh et al., 2022). This trial demonstrated an increase in median OS (12.8 vs. 11.5 months; HR 0.80) and median progression-free survival (7.2 vs. 5.7 months) compared with chemotherapy alone (Oh et al., 2022). These results led to regulatory approvals in 2022, establishing durvalumab plus GemCis as a preferred first-line treatment for advanced BTC (Oh et al., 2022). In an updated analysis, the 3-year OS rate was approximately twice as high with durvalumab as with placebo plus GemCis (14.6% vs 6.9%) (Oh et al., 2024).

Following the TOPAZ-1 trial, the KEYNOTE-966 trial provided more validation of the chemoimmunotherapy approach. This phase III study investigated the effectiveness of pembrolizumab, which is a PD-1 inhibitor, combined with GemCis in 1,069 patients with previously untreated, unresectable or metastatic BTC; just under 60% had intrahepatic tumours, and the remainder had extrahepatic CCA or gallbladder cancer (Kelley et al., 2023). Just like TOPAZ-1, KEYNOTE-966 showed a statistically significant improvement in median OS (12.7 vs 10.9 months; HR 0.83) for the triple combination over standard chemotherapy (Kelley et al., 2023).

These two trials mark a significant change in the management of advanced BTC, including CCA (Lamarca et al., 2022). Taken together, they suggest that combining PD-1/PD-L1 inhibitors with frontline chemotherapy is beneficial, although the two regimens have not been compared head to head. The results of both major trials showed a 17% to 20% reduction in the risk of death and this solidified the role of ICIs in the first line setting (Kelley et al., 2023; Oh et al., 2022). Interestingly, neither trial showed a large increase in the number of objective tumour responses compared to chemotherapy alone (ORR 26.7% vs 18.7% in TOPAZ-1; about 29% in both arms of KEYNOTE-966). Instead, the main benefit was a modest improvement in survival, with some evidence of longer-lasting responses in a subset of patients (Oh et al., 2024). On the basis of these trials (n=685 and n=1,069), GemCis plus durvalumab or pembrolizumab is

now the preferred first-line treatment for most patients with advanced BTC (Kelley et al., 2023; Oh et al., 2022).

Novel Checkpoints and Combinations (early-phase and phase II studies). Researchers are also evaluating multi-targeted immunotherapies to enhance immune activation (the adjuvant ARTEMIDE-Biliary01 trial is described under Ongoing Phase III Trials). Some early-phase clinical trials are targeting alternative immune checkpoints like LAG-3 and TIM-3 and aim to reverse T-cell exhaustion in patients that demonstrate primary resistance to standard PD-1/PD-L1 blockade regimen (Lamarca et al., 2022).

Beyond durvalumab and pembrolizumab, researchers are also exploring other multi-targeted immunotherapy combinations. The randomised phase II IMbrave151 trial (n=162; previously untreated advanced BTC) compared atezolizumab (an anti-PD-L1 antibody) plus bevacizumab (an anti-VEGF antibody) with atezolizumab plus placebo, each combined with GemCis, on the hypothesis that VEGF inhibition might prepare the tumour microenvironment for superior immune infiltration (Macarulla et al., 2025). Median PFS was 8.3 vs 7.9 months (HR 0.67), but median OS was not improved (14.9 vs 14.6 months); as a proof-of-concept phase II trial, this result is hypothesis-generating (Macarulla et al., 2025). Moreover, early-phase trials have investigated dual Immune Checkpoint Inhibitor (ICI) alongside chemotherapy to stimulate a broader T-cell response against biliary tumors (Lamarca et al., 2022).

Comparison of Trials. The primary difference between chemoimmunotherapy and targeted therapy lies in the target population, the line of therapy and the endpoints on which benefit has been shown (Table 1).

These findings highlight a trade-off. *FGFR2* inhibitors can produce rapid responses in biologically defined subgroups, whereas ivosidenib mainly delays progression; targeted agents apply to fewer patients, and benefit is often limited by acquired resistance. Chemoimmunotherapy provides a modest survival benefit across broad, biomarker-unselected BTC populations, without the objective response rates seen with *FGFR2* inhibitors, although evidence suggests durable benefit in a subset of patients. Because the trials differ in design, population and line of therapy, these figures should not be compared directly. To conclude, current practice uses chemoimmunotherapy as first-line treatment for most patients, followed by biomarker-directed targeted therapy in later lines for those with actionable alterations.

Breadth of Target Population vs. Biomarker Selection. Durvalumab (TOPAZ-1) or pembrolizumab (KEYNOTE-966) added to frontline chemotherapy is approved for a broad, biomarker-unselected population of patients with advanced BTC, not only CCA (Kelley et al., 2023; Oh et al., 2022). Targeted therapies, on the other hand, are approved for highly defined molecular niches. Pemigatinib for *FGFR2* fusions or rearrangements and ivosidenib for *IDH1* mutations apply only to patients with these specific alterations, which typically represent only 15% to 20% of CCA patients (Elvevi et al., 2022; Lamarca et al., 2022).

Depth vs. Durability of Tumour Response. Chemoimmunotherapy provides a modest survival benefit across a broad population: in TOPAZ-1 and KEYNOTE-966, the risk of death was reduced by 17% to 20%, with median OS of approximately 13 months across more than 1,700 patients with BTC (Kelley et al., 2023; Oh et al., 2022). While objective response rates (ORR) increased only slightly with

immunotherapy in TOPAZ-1 and were unchanged in KEYNOTE-966, its main benefit appears to be durability in a subset of patients: in TOPAZ-1, survival curves show a tail suggesting that some patients may achieve prolonged disease control (Oh et al., 2024). *FGFR2* inhibitors, in contrast, achieve high ORRs, but median DOR was approximately 7.5 to 9.7 months in single-arm studies (Abou-Alfa et al., 2020a; Goyal et al., 2023), and ivosidenib's benefit is measured in PFS rather than response (Abou-Alfa et al., 2020b).

Table 1. *Key completed trials of chemoimmunotherapy and targeted therapy in* advanced biliary tract cancer, including cholangiocarcinoma

Trial	Therapy	Phase / design	Population and line	n	Key result	Evidence status
ABC-02	Gemcitabine + cisplatin vs gemcitabine	III, randomised	Unselected advanced BTC (CCA, gallbladder, ampullary); first line	410	Median OS 11.7 vs 8.1 months	Established backbone (Valle et al., 2010)
TOPAZ-1	Durvalumab + GemCis vs placebo + GemCis	III, randomised	Advanced BTC (iCCA 56%, eCCA 19%, gallbladder 25%); first line	685	Median OS 12.8 vs 11.5 months (HR 0.80); PFS 7.2 vs 5.7 months; ORR 26.7% vs 18.7%	Approved first line (Oh et al., 2022)
KEYNOTE-966	Pembrolizumab + GemCis vs placebo + GemCis	III, randomised	Advanced BTC (iCCA just under 60%; remainder eCCA and gallbladder); first line	1,069	Median OS 12.7 vs 10.9 months (HR 0.83); ORR about 29% in both arms	Approved first line (Kelley et al., 2023)
FIGHT-202	Pemigatinib	II, single-arm	CCA with FGFR2 fusion or rearrangement; previously treated	107	ORR 35.5%; DCR 82%; median DOR 7.5 months; PFS 6.9 months; OS 21.1 months (immature)	Accelerated approval, later line (Abou-Alfa et al., 2020a)
FOENIX-CCA2	Futibatinib	II, single-arm	iCCA only, with FGFR2 fusion or rearrangement; previously treated	103	ORR 42%; median DOR 9.7 months; PFS 9.0 months; OS 21.7 months	Accelerated approval, later line (Goyal et al., 2023)

ClarIDHy	Ivosidenib vs placebo	III, randomised	IDH1-mutant CCA; previously treated	187	Median PFS 2.7 vs 1.4 months (HR 0.37); ORR about 2%; OS 10.3 vs 7.5 months (not significant without crossover adjustment)	Approved, later line (Abou-Alfa et al., 2020b; Zhu et al., 2021)
ROAR (BTC cohort)	Dabrafenib + trametinib	II, single-arm basket	BRAF V600E BTC; previously treated	43	ORR about 50%	Tumour-agnostic approval (Subbiah et al., 2020)

BTC, biliary tract cancer; CCA, cholangiocarcinoma; DCR, disease control rate; DOR, duration of response; eCCA, extrahepatic CCA; GemCis, gemcitabine plus cisplatin; HR, hazard ratio; iCCA, intrahepatic CCA; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. Population composition is taken from the cited trial reports. Single-arm phase II results are not directly comparable with randomised phase III results.

By contrast, some targeted therapies can produce deep responses. In FGFR2 fusion-positive cohorts, FGFR2 inhibitors achieved ORRs of 35% to 42% in previously treated patients (Abou-Alfa et al., 2020a; Goyal et al., 2023), whereas objective responses to ivosidenib were uncommon (ORR approximately 2%) and its benefit was seen in PFS (Abou-Alfa et al., 2020b). However, the duration of *FGFR2* inhibitor responses is frequently shortened by the emergence of acquired secondary resistance mutations (Goyal et al., 2021).

Limitations of CCA Trials

Although the success of clinical trials in targeted therapy and immunotherapy has expanded treatment options for CCA, the execution and interpretation of these trials remain difficult because of several limitations (Banales et al., 2020). It is hard to create tests and treatments for this disease because the condition is rare, its physical makeup is complex, and it varies greatly between patients (Lamarca et al., 2022).

One of the main limitations is the difficulty of retrieving tissue samples for diagnosis and for measuring patient response. Moreover, because the biliary tract lies deep within the body, it is hard to obtain sufficient tumour tissue for genetic testing via fine-needle aspiration or endobiliary brushings. This makes it difficult to match patients with targeted therapies (Lamarca et al., 2022). For example, enrolment in trials such as the phase II FIGHT-202 study of pemigatinib depended on identifying patients with *FGFR2* fusions, which requires sufficient tissue sampling (Abou-Alfa et al., 2020a). Also, some tumors simply spread along the bile duct walls without forming a solid, measurable lump. Because of this, standard tumor measurement rules using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 are often

imprecise, complicating the Overall Response Rates (ORR) interpretation in trials like the ABC-02 chemotherapy study (Banales et al., 2020; Valle et al., 2010).

Because CCA is rare and is further divided into even smaller genetic subtypes, it is hard to recruit enough patients for clinical trials (Lamarca et al., 2022). For example, the phase III ClarIDHy trial of the IDH1 inhibitor ivosidenib required 49 sites across 6 countries to enrol 187 patients with this mutation (Abou-Alfa et al., 2020b; Zhu et al., 2021). Such broad, multinational recruitment increases trial costs and patient burden and highlights the strain of biomarker-driven trials in rare diseases. Moreover, past trial designs have struggled with CCA's inherent heterogeneity (Lamarca et al., 2022). In the past, clinical trials often pooled iCCA, pCCA and dCCA subtypes together to meet enrollment quotas (Banales et al., 2020). This approach did not account for differences in tumour biology and drug sensitivity between subtypes, which may have contributed to inconclusive results for some experimental drugs (Lamarca et al., 2022). The pivotal chemoimmunotherapy trials illustrate the same issue: TOPAZ-1 and KEYNOTE-966 enrolled intrahepatic CCA, extrahepatic CCA and gallbladder cancer together, so their headline results apply to BTC as a whole, and analyses of individual tumour sites remain exploratory (Kelley et al., 2023; Oh et al., 2022).

Finally, strict eligibility rules and highly selected patients mean that trial results may not match real-world outcomes. Patients with CCA mainly present at an advanced stage, with symptoms such as biliary obstruction, hepatic dysfunction or infection that limit the time available to achieve a treatment response and to measure time-to-event outcomes in trials (Banales et al., 2020). Moreover, strict eligibility excludes many patients and trials on specific biomarkers often yield extremely small cohorts. For example, in the biliary cohort of the phase II KEYNOTE-158 basket study (n=104), ORR was 6.6% (4 of 61) in PD-L1-expressing and 2.9% (1 of 34) in PD-L1-non-expressing tumours, so conclusions for either subgroup rest on very few responders (Piha-Paul et al., 2020).

To conclude, overcoming the current limitations of CCA trials is no easy task. Future studies should include more patients, make study locations more convenient to reduce patient burden, and use non-invasive molecular profiling strategies (Banales et al., 2020).

Other Treatment Strategies: Completed and Early-Phase Studies

While targeted therapies and ICIs currently dominate CCA research, other approaches are under investigation. These differ widely in their level of evidence: only the SWOG S1815 trial below is a completed randomised phase III study, whereas the remaining strategies are early-phase or preclinical and should not be regarded as equivalent.

First-Line Systemic Advancements (completed phase III trial). The foundational treatment for advanced BTC, including CCA, is gemcitabine plus cisplatin chemotherapy. The completed phase III SWOG S1815 trial tested the addition of nab-paclitaxel to this backbone; it did not significantly improve overall survival in the overall population, although an exploratory subgroup analysis suggested possible benefit in locally advanced disease (Shroff et al., 2024). Chemoimmunotherapy (checkpoint inhibitors combined with chemotherapy) has since become the first-line standard (see Immunotherapy), and

combinations of checkpoint inhibitors with tyrosine kinase inhibitors are being explored in treatment-naive patients (Elvevi et al., 2022).

Cellular Therapies and Cancer Vaccines (early-phase clinical studies). Experimental trials are investigating adoptive cell therapies as a way to penetrate the CCA microenvironment. Phase I and II trials of chimeric antigen receptor (CAR) T-cell therapies target antigens that are highly expressed in biliary tumours, such as mesothelin, MUC1 and EGFR (Elvevi et al., 2022). For example, a phase I study of EGFR-directed CAR-T cells in EGFR-positive advanced BTC (NCT01869166) reported that the therapy was safe and showed activity in some patients (Guo et al., 2018); no CAR-T therapy is approved for CCA.

Therapeutic cancer vaccines are also being explored. Early-phase trials investigating multi-peptide vaccines (targeting antigens like LY6K and TTK) or the OCV-C01 cocktail (targeting VEGFR1/2 and KIF20A) were generally well tolerated and induced T-cell responses, and some studies reported an association between immune response and longer survival in advanced BTC (Miyata et al., 2021). Researchers are also exploring mRNA platforms. For example, the personalized neoantigen mRNA vaccine iNeo-Vac-R01 is being investigated in a phase I study (NCT06956716) in combination with standard chemotherapy and a PD-1 inhibitor in advanced iCCA, with the aim of priming a tumour-specific immune response; the primary endpoint is safety and tolerability (ClinicalTrials.gov, 2025).

Epigenetics-Based Therapies (early clinical and preclinical evidence). In cholangiocarcinoma (CCA), unchecked cellular proliferation is often driven by aberrant DNA methylation silencing tumor suppressor genes like *p16*, *p15*, *CDH1*, and *MLH1*. Early studies are exploring hypomethylating agents to reverse this epigenetic silencing, which may halt tumor growth and restore tumor susceptibility to standard therapies (Goeppert et al., 2022). Furthermore, epigenome-wide sequencing of plasma and bile DNA methylation signatures is being investigated as a potential biomarker for early CCA detection (Goeppert et al., 2022).

Ongoing Trials and Preclinical Research

As the therapeutic landscape for CCA evolves, research is divided into two main areas: testing new drugs in patients and studying the underlying biology of the disease in the lab.

Ongoing Phase III Trials (results not yet reported). Several phase III trials are under way that could change standard practice, though their efficacy results have not yet been published. These trials aim to move targeted therapies and novel immunotherapies into earlier lines of treatment or to use them to overcome acquired resistance.

ARTEMIDE-Biliary01 (Phase III). This trial aims to investigate whether adding rilvegostomig, an experimental PD-1/TIGIT bispecific antibody to standard chemotherapy after surgery improves outcomes. Its aim is to determine whether this combination lowers the risk of recurrence in patients with resected BTC (intrahepatic or extrahepatic CCA, or gallbladder cancer) (Fan et al., 2024).

HERIZON-BTC-302 (Phase III). This trial aims to evaluate zanidatamab, combined with standard chemotherapy as a first-line treatment for HER2-positive advanced or metastatic BTC (a population not restricted to CCA), with the aim of establishing a biomarker-driven first-line option (Harding et al., 2025).

FIRST-308 (Phase III). This trial aims to test whether tinengotinib, a next-generation *FGFR* inhibitor, improves outcomes compared with physician's choice of chemotherapy in patients with *FGFR2* fusion- or rearrangement-positive CCA whose disease has progressed after chemotherapy and one prior *FGFR* inhibitor such as pemigatinib (ClinicalTrials.gov, 2023; Erul et al., 2024).

Preclinical Research (laboratory and animal models; not yet tested in patients). Before novel therapies are tested in patients, they are evaluated in preclinical settings using in vitro (cell-based) and in vivo (murine) models. Findings in this section are therefore hypothesis-generating and have not been shown to benefit patients. Current pre-clinical research in CCA is focused on developing personalized therapeutic screens and penetrating into the tumour's desmoplastic stroma.

Patient-Derived Organoids (PDOs) and Xenografts (PDXs). Traditional two-dimensional cell lines often fail to replicate the complex three-dimensional structure and microenvironment of human CCA. Researchers are therefore using PDOs, which are three-dimensional cultures derived from a patient's tumour, alongside murine PDX models. These models retain the patient's genetic and phenotypic profile, which allows drug-screening studies to identify tumour-specific vulnerabilities (Broutier et al., 2017; Lamarca et al., 2022).

Nanoparticle-Mediated Drug Delivery. As CCA has a dense, hypovascular stroma containing cancer-associated fibroblasts (CAFs) and dense extracellular matrix, systemic drugs face difficulty passing through the tumour bed. Nanomedicines such as lipid nanoparticles and polymeric micelles are being designed to cross this physical barrier and deliver cytotoxic or nucleic-acid payloads to the tumour while limiting exposure of healthy tissue; to date they have been tested mainly in cell-based and animal models (Lamarca et al., 2022). For example, doxorubicin-loaded polymeric (PLGA) nanoparticles showed enhanced drug delivery and anticancer activity in CCA and drug-resistant cells in vitro (Rattanaseth et al., 2025).

Advanced Cellular Therapies. CAR-T therapies are approved for several haematological cancers, but their success in solid tumours like CCA has been limited. Next-generation CAR-T and CAR-macrophage (CAR-M) cells are being optimised in preclinical mouse models; proposed targets include Claudin-18.2 and mesothelin. Some constructs are additionally engineered to secrete matrix-degrading enzymes, which may help immune cells degrade or penetrate the fibrotic CCA stroma and reach their targets (Lamarca et al., 2022). These approaches remain experimental, and their efficacy and safety in patients with CCA are unknown.

Future Directions for CCA Research

CCA research is changing quickly, moving beyond cytotoxic chemotherapy to incorporate precision oncology and immunotherapy into current treatment. Despite these advances, most patients with advanced disease still experience progression, and CCA remains a highly lethal malignancy. To improve outcomes

further, future research is aimed at addressing the historically neglected anatomical subtypes, overcoming biological barriers such as the desmoplastic stroma, and developing adaptive clinical trial designs.

Targeting Neglected Subtypes and Novel Pathways. In the past, precision medicine has benefited iCCA patients with prevalent actionable mutations like FGFR2 fusions and IDH1 mutations (Banales et al., 2020). By contrast, extrahepatic CCA is more often driven by KRAS mutations (Jusakul et al., 2017). As these targets were considered "undruggable" historically, these patients lacked biomarker-driven options. But, the advent of allele-specific KRAS G12C inhibitors and emerging pan-KRAS inhibitor may offer targeted options for these subtypes in future, although clinical evidence in BTC is still early-phase (Lamarca et al., 2022).

Dismantling the Desmoplastic Stroma. A major challenge in CCA is its desmoplasia which is a dense, fibrotic tumor microenvironment (TME) that is combined with cancer-associated fibroblasts (CAFs). This extracellular matrix acts as a physical barrier that may limit vascularization and restrict the entry of therapeutic agents and immune cells into the tumour core (Banales et al., 2020). Future research may focus increasingly on TME-modulating agents, that are designed to deplete CAFs or reduce the stromal matrix, which may sensitise the tumour to chemoimmunotherapy and novel cellular therapies.

Overcoming Acquired Resistance via Liquid Biopsies. Acquired resistance remains a common challenge even though targeted therapies can create deep initial responses. For instance, patients treated with first-generation FGFR inhibitors frequently developed secondary kinase domain mutations that were associated with disease progression (Goyal et al., 2021). A possible future direction in this field could be the integration of serial liquid biopsies (analyzing circulating tumor DNA) into routine clinical care and adaptive designs of trials. In principle, this approach could allow oncologists to track the molecular evolution of the tumour and switch to next-generation inhibitors before radiographic progression occurs, although this strategy remains investigational.

Moving to Curative-Intent Settings. Finally, researchers are testing immunotherapeutic and targeted agents in earlier, potentially curative stages. Moreover, future neoadjuvant and adjuvant trials aim to downstage borderline-resectable tumours and eradicate micrometastases, which may improve long-term survival in CCA (Lamarca et al., 2022).

The management of CCA is changing rapidly. By performing genomic profiling at diagnosis, clinicians can identify therapeutic targets and potential resistance mechanisms earlier. Coupled with adaptive trial designs, this may also allow earlier surgical intervention in selected patients. Future success will depend on synthesizing these advances into a clinical strategy that improves long-term outcomes for a larger proportion of patients with CCA.

CONCLUSION

Cholangiocarcinoma has long been regarded as one of the most challenging malignancies to treat; however, the therapeutic landscape is undergoing substantial change. The traditional approach of administering uniform chemotherapy to all patients regardless of tumor biology, has shifted towards more individualized treatment contingent upon patient-specific molecular and biological profiles. The

development of targeted agents such as *FGFR2* and *IDH1* inhibitors illustrates the potential of this shift: *FGFR2* inhibitors produced objective response rates of 35–42% in previously treated patients with *FGFR2* fusions or rearrangements, whereas ivosidenib prolonged progression-free survival in *IDH1*-mutant disease with few objective responses. However, only 15–20% of patients possess these specific alterations, and acquired resistance frequently develops even where initial responses are favourable, which limits the durability of such therapies.

Chemoimmunotherapy, on the other hand, presents different benefits. TOPAZ-1 and KEYNOTE-966, which enrolled broader populations of patients with BTC (including, but not limited to, CCA), did not achieve objective response rates as high as those of *FGFR2* inhibitors, but median overall survival was modestly improved, and chemoimmunotherapy is now the first-line standard, with biomarker-directed therapy generally reserved for later lines. Although these results are encouraging, substantial obstacles remain.

The acquisition of sufficient tumour tissue for genomic testing continues to constrain patient selection, the rarity of clinically actionable mutations complicates trial recruitment, and earlier trial designs frequently pooled anatomically and biologically distinct CCA subtypes, thereby confounding outcome interpretation. In parallel, investigators are pursuing complementary therapeutic strategies, including cellular therapies, mRNA-based vaccines and hypomethylating agents (all at early-phase or preclinical stages), aimed at overcoming the dense desmoplastic stroma that impedes drug and immune cell penetration into the tumour microenvironment. Preclinical tools such as patient-derived organoids and nanoparticle-based delivery systems may facilitate the translation of these approaches from laboratory investigation toward clinical application.

Future research priorities include extending precision-medicine approaches to the anatomical subtypes that have thus far received comparatively limited benefit, developing methods to detect acquired resistance prior to radiographic progression, and integrating these therapies into earlier stages of disease management where curative intent remains feasible. Should these efforts succeed, cholangiocarcinoma may transition from a near-uniformly fatal diagnosis toward a disease that can be controlled for longer in selected patients.

ABOUT THE AUTHOR

Vanshika Gajjala is an IBDP Year 1 student at Global Indian International School, Singapore. She takes interest in precision medicine and biology, hoping to explore how these areas intersect to improve patient outcomes. She plans to study Medicine in university, with a focus on oncology and human biology.

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