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An Overview of the Therapeutic Development of Cholangiocarcinoma with Special Emphasis on Targeted and Biologic Therapies

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Abstract

Purpose of Review Cholangiocarcinoma remains difficult to treat with a poor prognosis. Nevertheless, the treatment landscape is rapidly evolving to include chemotherapy, immunotherapy, and targeted therapies. This paper will summarize recent developments in targeted therapies.

Recent Findings Gemcitabine/cisplatin plus durvalumab or pembrolizumab is the standard first-line treatment for patients with advanced cholangiocarcinoma. Multiple alterations have been identified with corresponding approved targeted agents, including fibroblast growth factor receptor inhibitors pemigatinib, infigratinib, and futibatinib; the isocitrate dehydrogenase 1 inhibitor ivosidenib; and the inhibitors of encoded kinases of *NTRK1-3* entrectinib and larotrectinib. In tumors with microsatellite instability or deficient mismatch repair, pembrolizumab is approved. Dabrafenib and trametinib also received tumor agnostic approval for BRAF V600E mutations. Additional emerging targets include HER2 and DNA repair pathways.

Summary Multiple targeted therapies are currently approved in the treatment of advanced cholangiocarcinoma, and many more molecular alterations or pathways have been identified as promising therapeutic targets.

Keywords Cholangiocarcinoma; Molecular targeted therapy · Chemotherapy · ctDNA

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Introduction

Cholangiocarcinoma is an uncommon invasive carcinoma arising from the bile duct epithelium; when advanced, it carries a poor prognosis [1••, 2, 3]. For more than a decade, chemotherapy, specifically gemcitabine and cisplatin (GemCis), was the standard first-line combination for all advanced cholangiocarcinoma patients with an overall median survival of 11.7 months (hazard ratio (HR), 0.64; 95% CI, 0.52–0.80) [4]. The recent addition of durvalumab, an anti-programmed death-ligant 1 (PD-L1) antibody, to GemCis extended median survival from 11.5 to 12.8 months (HR 0.80, 95% CI 0.66–0.97) [5••], while the addition of pembrolizumab, a programmed cell death protein 1 (PD-1) antibody, to GemCis improved survival from 10.9 to 12.7 months (HR 0.83, 95% CI 0.72–0.95) [6••]. Excitingly, the treatment landscape for advanced cholangiocarcinoma continues to rapidly change and evolve.

In recent years, novel sequencing technologies have allowed us to molecularly subtype this rare and serious disease [7–9] and develop targeted therapies that prolong life. These genomic studies have revealed more than 50% of

patients with cholangiocarcinoma harbor genomic alterations that are targetable [10]. In this review, we provide an update on approved and emerging targeted therapies in cholangiocarcinoma as well as discuss relevant ongoing clinical trials.

Classification and Epidemiology

Cholangiocarcinoma is rare, although the worldwide incidence is increasing [11]. It represents less than 1% of all malignancies and about 10–15% of all primary liver malignancies [3]. In the USA and Europe, the incidence of cholangiocarcinoma is approximately 0.3–3.5 per 100,000 person years, while in Asia, the incidence is higher around 90–115 per 100,000 person years [2, 3, 12]. The most common risk factors for cholangiocarcinoma include older age, primary sclerosing cholangitis, biliary cysts and stones, cirrhosis, and liver infections, including liver flukes (*Opisthorchis viverrini*), hepatitis B virus, and hepatitis C virus. Other risk factors include cholelithiasis, obesity, diabetes, inflammatory bowel disease, tobacco smoking, and alcohol use. The varied incidence reflects varied distribution of the risk factors; in western countries, cholangiocarcinoma is often associated with chronic inflammation, while in Southeast Asia, liver flukes pose a significant risk [1••, 2, 3, 13–15].

Histologically, most cholangiocarcinomas are adenocarcinomas [1••]. Cholangiocarcinoma is classified as intrahepatic or extrahepatic. Intrahepatic cholangiocarcinoma represents about 5–20% of all cholangiocarcinomas, is located within the parenchyma of the liver, and is further divided pathologically into mass-forming, periductal-infiltrating, and intra-ductal-growing [1••, 2, 3]. Extrahepatic cholangiocarcinoma is the more common subtype and is further subclassified into hilar tumors and distal tumors. Pathologic subtypes of extrahepatic cholangiocarcinoma include sclerosing, nodular, and papillary [1••, 2, 3]. Molecular distinctions exist within each of these classifications and give rise to treatment implications [16].

Clinical Presentation and Evaluation

Cholangiocarcinoma lacks early and specific symptoms and may be entirely asymptomatic; as such, it is often detected at advanced stages of disease, limiting therapeutic options [17]. If present, symptoms are usually nonspecific, including abdominal pain or fullness, weight loss, and fatigue [1••, 2, 18]. Extrahepatic cholangiocarcinoma may present with symptoms of obstructive jaundice.

Cholangiocarcinoma may be found incidentally due to abnormal liver function tests or a concerning mass on imaging. Diagnostic tests should include a complete metabolic panel, complete blood count, and tumor markers including carbohydrate antigen (CA 19–9), carcinoembryonic antigen (CEA) and alpha feto-protein (AFP). Elevated CA 19–9 and CEA may lend support to a diagnosis of cholangiocarcinoma but are not specific and may be elevated from biliary inflammation or obstruction. Imaging studies to consider include contrast-enhanced multiphasic abdominal and pelvis computed tomography (CT) and/or contrast-enhanced multiphasic abdominal and pelvis magnetic resonance imaging (MRI), which can be paired with magnetic resonance cholangiopancreatography (MRCP). These advanced imaging modalities can delineate intrahepatic involvement, biliary tree involvement, vascular involvement, presence of satellite lesions or distant metastases, perihilar and portal lymph node involvement, and resectability [1••, 2, 19]. A CT of the chest is also recommended for staging purposes [1••, 2, 3].

Overview on Treatments

Most patients present initially with advanced disease with a minority of patients eligible for surgical resection [20]. Generally, contraindications for definitive resection include main hepatic portal vein or arterial invasion, invasion in adjacent organs, lymph node metastases beyond the porta hepatis, and distant metastases [1••, 21]. Adjuvant therapy is recommended for almost all patients [1••, 3]. For patients with microscopic residual disease (considered an R1 resection margin) and/or positive regional lymph node disease, adjuvant chemotherapy or chemoradiation is recommended [22]. The BILCAP phase III clinical trial points to capecitabine, an oral fluoropyrimidine, as the standard option recommended by national and international guidelines [1••, 3, 23••]. Other options may include gemcitabine [24]. Adjuvant chemotherapy after definitive resection may decrease all-cause mortality yet an overall survival benefit remains unclear, as randomized trials have shown conflicting results [23••, 25–27]. In the BILCAP study, the primary endpoint of improved survival in the intention-to-treat analysis was not met, with a median overall survival was 51.1 months (95% CI 34.6–59.1) in the capecitabine group compared with 36.4 months (29.7–44.5) in the observation group (adjusted hazard ratio [HR] 0.81, 95% CI 0.63–1.04; $p=0.097$). In a protocol-specified sensitivity analysis, however, which adjusted for minimization factors and nodal status, grade, and gender, the overall survival HR was 0.71 (95% CI 0.55–0.92; $p=0.01$), suggesting a benefit. S-1, a mixture of tegafur (a prodrug of fluorouracil), gimeracil, and oteracil potassium, showed increased progression-free and overall survival in the adjuvant setting in Japan [28]. Adjuvant chemoradiation is an alternative option to discuss with patients after multidisciplinary review [29]. Chemotherapy regimens used during concurrent radiation are generally fluoropyrimidine-based and radiation typically

involves external beam radiation therapy (EBRT) with intensity-modulated radiation therapy (IMRT) [1••]. Adjuvant chemoradiation may reduce mortality in high-risk patients after resection [30]. Despite curative-intent resection, more than 60% of patients relapse and systemic therapy is the standard therapy thereafter [26].

A small subset of patients with perihilar-hilar disease who are not eligible for resection may be candidates for liver transplant, which may be curative [1••, 21, 31, 32]. The recurrence-free survival rate at 5 years following neoadjuvant therapy and liver transplantation for perihilar cholangiocarcinoma can be as high as 65% [33]. Fluoropyrimidine-based chemoradiation is another option for nonmetastatic unresectable intrahepatic or extrahepatic cholangiocarcinoma [1••]. Chemoradiation may have improved overall survival compared to chemotherapy alone and has the potential to convert unresectable disease to resectable disease [34, 35]. In addition to systemic therapies, locoregional therapies are appropriate for select patients, namely, those with intrahepatic nonmetastatic unresectable or metastatic cholangiocarcinoma. Options for locoregional therapies include external beam radiotherapy, arterially directed therapies such as Y-90, and radiofrequency ablation [1••, 3, 21, 36–38].

Systemic treatment modalities include chemotherapy, immunotherapy, and targeted therapy. Currently, GemCis plus durvalumab is the standard first line treatment for advanced cholangiocarcinoma [5••]. The long-awaited, front-line results from the phase III SWOG 1815 trial compared triplet therapy with GemCis plus nab-paclitaxel versus GemCis reported disappointing results not meeting its primary endpoint: median survival was 14 months versus 12.7 months, $p = 0.65$ [39••].

A recent phase III clinical trial KEYNOTE 966 evaluating GemCis with or without pembrolizumab, an anti-PD-1 antibody, in the frontline for cholangiocarcinoma did meet its primary endpoint of overall survival. The triplet reported an OS of 12.7 months compared to the doublet of 10.9 months (HR 0.83, 95% CI 0.72–0.95, $p = 0.0034$) with no new safety signals [6••]. It appears that the combination of immunotherapy with chemotherapy is here to stay.

In the last few years, next-generation-sequencing of tumors has afforded novel agents that are now FDA approved. Other emerging and investigational targeted agents are in the pipeline. The remaining review will focus on these targeted agents.

Targeted Therapies in Cholangiocarcinoma

Targeted therapies interfere with identified driver molecules for cancer cell growth and propagation which are specific to or have a higher expression on cancer cells, and therefore theoretically limit the impact on normal tissues [26]. The major classes of targeted therapies include monoclonal antibodies, small molecule inhibitors, and antibody–drug conjugates. Monoclonal antibodies target cancer antigens to recruit immune cells, while small molecular inhibitors interfere with cellular signaling within the cancer cells [40].

Approved Targets

FGFR

Fibroblast growth factor receptors (FGFR) are a family of four receptor tyrosine kinases (FGFR1–4) that are important targets in cholangiocarcinoma. These transmembrane receptors normally exist in an autoinhibited state with their activity regulated by members of the fibroblast growth factor (FGF) family. Binding of their ligand leads to dimerization of the extracellular domain, which engages multiple downstream signaling pathways, including RAS-MAPK, PI3K-AKT, PLCγ, and STAT [41]. Within malignant cells, the structure of FGFR2 is disrupted such that the affinity for the ligand is increased, the kinase can dimerize independent of its ligand, and the autoinhibited state is interrupted. Taken together, these alterations result in constitutive activation of FGFR2, and downstream signaling cascades of this kinase have been shown to drive the survival and growth of intrahepatic cholangiocarcinoma cells [42]. FGFR2 fusions or rearrangements occur in 11–12% of patients with intrahepatic cholangiocarcinoma and are more common in patients younger than 65 [43]. For patients with a fusion or rearrangement of FGFR2, multiple targeted treatments have received accelerated approval in previously treated disease, including pemigatinib, infigratinib, and futibatinib [1••, 3]. Survival has been reported to be longer than 20 months with most of these agents [44, 45••]

Pemigatinib, an oral inhibitor of FGFR1–3, was the first FGFR inhibitor to receive accelerated FDA approval in April 2020. Phase II clinical trials have evaluated its use in patients with previously treated locally advanced or metastatic disease. Phase II data revealed that 35.5% (95% CI 26.5–45.4%) of patients achieve an objective response, with three having achieved a complete response [44]. Among responders, the median duration of response was 7.5 months (95% CI 5.7–14.5), and 37% of patients retained a response at 12 months. The most common adverse event was hyperphosphatemia [44]. A phase III clinical trial to assess pemigatinib vs chemotherapy as a first-line agent for advanced cholangiocarcinoma with FGFR2 rearrangements is ongoing [46].

Unlike the other FGFR inhibitors, futibatinib is an irreversible inhibitor of FGFR1-4. This distinct property makes futibatinib less susceptible to on-target resistance mutations (particularly V565I and V565L gatekeeper mutations) and reduces the emergence of drug-resistance

clones [47]. Phase II data revealed a 42% objective response rate (95% CI 32–52%), including one patient with a complete response. Among responders, the median duration of response was 9.7 months (95% CI 7.6–17.0), and 14% of responders retained that response at 12 months. The most frequent adverse events were hyperphosphatemia, alopecia, dry mouth, diarrhea, dry skin, and fatigue [45••]. This drug received accelerated FDA approval in September 2022 [48].

Other novel and highly selective FGFR inhibitors are actively being investigated. RLY-4008 is a highly selective and potent FGFR2 inhibitor that is designed to target both driver alterations and FGFR resistance mutations. The early results from the ReFocus phase 1/2 study presented at European Society for Medical Oncology 2022 demonstrated an impressive objective response rate of 88% among 38 patients with majority of responses are still ongoing [49]. Others include a phase II trial of E7090 (also called tasurgratinib), an oral selective tyrosine kinase inhibitor of FGFR1-3 (NCT04238715), and a phase II RAGNAR trial (erdafitinib) (NCT04083976) in patients with unresectable or metastatic cholangiocarcinoma and other solid tumors. These agents may have the potential to overcome resistance to by binding to the active kinase domain.

Infigratinib is another oral inhibitor of FGFR1–3 and was also evaluated in patients with previously treated advanced or metastatic disease. In a phase II trial, 23.1% of patients had an objective response (95% CI 15.6–32.2%), including one who had a complete response. Among responders, the median duration of response was 5 months (IQR 3.7–9.3). The most common adverse events were hyperphosphatemia, stomatitis, fatigue, and alopecia [50]. Infigratinib did receive accelerated FDA approval in 2021; however, the confirmatory phase III trial has been discontinued due to difficulties in recruiting and enrolling patients. Thus, this drug is no longer available on the market [51].

Finally, derazantinib (ARQ 087) is an oral multi-kinase inhibitor with pan-FGFR activity that was studied in a phase I/II clinical trial among patients with previously treated advanced FGFR2 gene fusion-positive cholangiocarcinoma. The response rate was 20.7%, and the mean duration of response was 4.6 months (95% CI 2.3–8.9). The median progression-free survival was 5.7 months (95% 4.0–9.2). The most common adverse events were dry mouth, nausea, fatigue, and asthenia [52].

IDH

An estimated 13% of patients with intrahepatic cholangiocarcinoma harbor isocitrate dehydrogenase 1 (IDH1) mutations [53]. Mutations in this enzyme result in a loss of normal catalytic activity and production of an abnormal metabolite, which results in abnormal histone and DNA methylation, eventually leading to tumorigenesis [54].

Ivosidenib is an oral targeted inhibitor of mutated IDH1. A phase III trial evaluated ivosidenib versus placebo in patients with previously treated unresectable or metastatic cholangiocarcinoma. The objective response rate was 2%, though 51% of patients who received ivosidenib achieved stable disease. Median progression-free survival was improved with ivosidenib at 2.7 months (95% CI 1.6–4.2) versus 1.4 months with placebo (HR 0.37, 95% CI 0.25–0.54, $p < 0.0001$). Median overall survival was 10.3 months (95% CI 7.8–12.4 months) for ivosidenib versus 5.1 months (95% CI, 3.8–7.6 months) for placebo (HR 0.49, 95% CI 0.34–0.70, $p < 0.001$) after adjusting for crossover. The overall most common adverse events were nausea, diarrhea, and fatigue, and the most common grade 3 or worse adverse event was ascites [55, 56].

NTRK

Fusions of genes in the *NTRK* family, including *NTRK1-3*, lead to expression of their encoded kinases, tropomyosin receptor kinases (TRKs) A-C, with rearrangements that lead to constitutive activity of the kinase. These kinases are involved in the regulation of cell proliferation, differentiation, and survival, such that the gene fusions act as oncogenic drivers [57]. Among a cohort of patients with cholangiocarcinoma in Thailand, about a third of patients were found to have expression of TRK with gene fusions by immunohistochemistry (IHC) [58]. However, in a series from Belgium, about 13% of samples screened by IHC were positive but the rate was much lower — 0.75% — when confirmatory next-generation sequencing was performed [59]. Entrectinib and larotrectinib are approved therapy option in all solid tumor patients with *NTRK* gene fusions.

Entrectinib is an oral inhibitor of TRKA-C (and also ROS1 and ALK) and notably crosses the blood–brain barrier. Two phase I clinical trials have evaluated entrectinib in metastatic or locally advanced *NTRK* fusion-positive solid tumors, and a phase II clinical trial is ongoing. An analysis of these three studies pooled, which notably included one participant with cholangiocarcinoma, revealed an objective response in 57% of participants (95% CI 43.2–70.8%), including four participants who had a complete response. The single participant with cholangiocarcinoma had a partial response. The median duration of response was 10 months (95% CI 7.1–not estimable). The most common adverse events were dysgeusia, constipation, and fatigue, and the most frequent grade 3–4 adverse events were anemia, increased weight, dyspnea, and fatigue [60].

Similarly, larotrectinib, another small molecule inhibitor of TRKA-C, has been evaluated in solid tumors. A study of the first 55 enrolled patients across a phase I clinical trial of adults, a phase I-II clinical trial of children, and a phase II "basket" study of adults included participants with locally

advanced or metastatic solid tumors, including two participants with cholangiocarcinoma. This study found an overall response rate of 75% (95% CI 61–85%), including seven participants who had a complete response. One participant with cholangiocarcinoma had progressive disease and the other had a partial response. The median duration of response had not been reached after a median follow-up of 8.3 months; however, at 1 year, 71% of responses were ongoing. Most common adverse events of any grade included increased ALT or AST levels, fatigue, nausea/vomiting, and dizziness, and the most common grade 3–4 adverse events were anemia, AST/ALT elevations, weight increase, and a decrease in neutrophil count. This study also evaluated mechanisms of acquired resistance in participants who experienced disease progression and found kinase domain mutations affecting the *NTRK* gene [61].

DNA Mismatch Repair

Immunotherapy is often prescribed to patients with tumors with microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) [1••, 3]. Deficient mismatch repair occurs in about 5% of biliary tract cancers [62]. In a study of multiple, previously treated tumor types with dMMR, including four patients with cholangiocarcinoma, pembrolizumab, a monoclonal antibody against programmed cell death protein-1 (PD-1), induced an objective response rate of 53% (95% CI 42–64%) [63]. A similar study of pembrolizumab, which included 22 participants with cholangiocarcinoma, found an objective response rate of 34.3% (95% CI 28.3–40.8%) and the median duration of response had not been reached at a median follow-up of 13.4 months. The most common treatment-related adverse events were fatigue, pruritus, diarrhea, and asthenia; of note, three patients had a grade 4 treatment-related adverse event, which included one patient with Guillain–Barre syndrome, one with an increased ALT, and one with a decreased neutrophil count and enterocolitis [64]. As such, pembrolizumab is currently approved for subsequent therapy in advanced biliary tract cancer in tumors with dMMR or MSI-H [1••].

With PD-1 and PDL-1 inhibitors such as durvalumab — and soon pembrolizumab — being used more frequently in the first-line setting for patients with metastatic disease, the sequencing of immunotherapy and its role in a later-line setting promises to become a topic of future research. Furthermore, although in non-small cell lung cancer patients with tumors that have specific driver mutations tend to manifest poorer responses with immunotherapy, such observations have not yet been reported in detail in patients with cholangiocarcinoma. These observations again underscore the importance of determining how best to administer and sequence these therapeutic agents.

Emerging Targets

HER2

Human epidermal growth factor receptor 2 (HER2), also known as receptor tyrosine-protein kinase erbB-2 (ERBB2), is a member of the epidermal growth factor receptor family. It is a transmembrane tyrosine kinase, which, when dimerized and autophosphorylated, actives multiple downstream signaling cascades. Predictably, when HER2 is amplified or overexpressed, this dysregulation can spur the growth and spread of malignant cells [65]. About a quarter of patients with biliary tract cancers have HER2 overexpression and/or amplification; this was more likely in extrahepatic rather than intrahepatic cholangiocarcinoma [65].

Trastuzumab and pertuzumab are both monoclonal antibodies that target HER2, although they bind to different domains of the protein. A phase IIa basket study involving the combination trastuzumab and pertuzumab in participants with metastatic HER2-positive biliary tract cancer, which includes HER2 amplification, overexpression, or both, demonstrated an objective response rate of 23% (95% CI 11–39%), all of which were partial responses. Median duration of response was 10.8 months (95% CI 0.7–25.4). By subgroup, the objective response rate was 0% for intrahepatic cholangiocarcinoma and 29% for extrahepatic cholangiocarcinoma. Progression-free survival was 4 months (95% CI 1.8–5.7), and overall survival was 10.9 months (95% CI 5.2–15.6). Most common adverse events were diarrhea and increased liver enzymes. There were no grade 4–5 treatment-related adverse events [66].

The safety of a new bispecific monoclonal antibody against two domains of HER2, zanidatamab, has been studied in biliary tract cancers [67]. In a phase I clinical trial, zanidatamab was studied in locally advanced or metastatic HER2-expressing or HER2-amplified solid tumors, including intrahepatic and extrahepatic cholangiocarcinoma. Of note, most patients were heavily pre-treated, including with previous HER2-targeted therapy. Among those with biliary tract cancers, 38% experienced an objective response (95% CI 18–62%) with a median duration of response of 8.5 months (95% CI 3.2–not estimable) and progression-free survival of 3.5 months (95% CI 1.8–6.7). There were no dose-limiting toxicities reported. The most common reported adverse event was diarrhea with no grade 3 adverse events in the biliary cancer participants [67]. There is an ongoing phase II trial (HERIZON-BTC-01; NCT04466891) to study the use of zanidatamab monotherapy in previously treated HER2-positive biliary tract cancers.

Neratinib is an irreversible pan-HER oral tyrosine kinase inhibitor which was recently studied in a phase II basket trial which included a cohort with biliary tract cancer, the

vast majority of whom had received prior therapies. This study found an objective response rate of 16% (95% CI 4.5–36.1%), and the median progression-free and overall survival for the cholangiocarcinoma group was 1.4 months (95% CI 0.5–9.1) and 5.4 months (95% CI 0.8–16.2), respectively [68].

Finally, a phase II clinical trial of trastuzumab-deruxtecan, an antibody–drug conjugate with an anti-HER2 antibody and a topoisomerase I inhibitor, in advanced biliary tract cancers is underway [69••].

BRAF

The *BRAF* gene encodes the B-Raf protein, which is a serine/threonine protein kinase that plays a role in regulating intracellular signaling pathways that affect cell division and differentiation. Most mutations lead to a valine to glutamic acid substitution at codon 600, designated V600E, which mimics phosphorylation of the activation site and therefore increases kinase activity [70]. *BRAF* V600E mutations have been found in about 5% of biliary tract cancers and are associated with worse outcomes [71].

The combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor results in sequential kinase inhibition within a signaling pathway. In the ROAR trial, a phase II clinical trial of dabrafenib and trametinib in BRAF-V600E-mutated metastatic, advanced, or recurrent biliary tract cancer after previous treatments, 51% of patients experienced an overall response (95% CI 36–67%), and notably among those who experienced a response, 67% (95% CI 17–57%) and 36% (95% 2–33%) had an ongoing response at 6 and 12 months, respectively. The median duration of treatment was 8 months (range 2–34 months), and the overall survival was 14 months (95% CI 10–33). The most common all-cause grade 3 or 4 adverse event was increased γ-glutamyltransferase [72••].

A summary of clinical trials of the approved and emerging targets is displayed in Table 1.

Potential Targets Under Investigation

DNA Damage Repair

IDH-1 and IDH-2 mutations induce production of tumorigenic metabolites, as previously discussed. These mutations also induce a deficit in homologous recombination, which has been shown to make tumor cells sensitive to poly(adenosine 5′-diphosphate-ribose) polymerase (PARP) inhibitors in in vivo models [73]. Several studies are underway to evaluate PARP inhibitors in tumors with IDH mutations [74]. An ongoing phase II clinical trial (NCT03212274) is investigating the efficacy of olaparib for patients with advanced tumors harboring IDH1 or IDH2 mutations, including those with cholangiocarcinoma. Another non-randomized phase II clinical trial (UF-STO-ETI-001) is underway to assess the agent niraparib, also a PARP inhibitor, in patients with several different solid tumors, including cholangiocarcinoma, with mutations in BAP1, a ubiquitin ligase, and other proteins involved in DNA repair (NCT03207347).

Immunotherapy has also been trialed in patients with DNA damage repair mutations. One study evaluated a small cohort of patients with a variety of DNA damage repair mutations (BRCA1, BRCA2, RAD51C, RAD51D, ATM, and PALB2) and advanced pancreaticobiliary malignancies treated with combined ipilimumab and nivolumab. It found that of the 8 patients evaluated, 6 achieved disease control (75% response rate), including two patients with a complete response, one of which had cholangiocarcinoma. Notably, the two patients with a complete response had a long duration of response at 19–22 months [75••]. A retrospective study evaluated patients with solid tumors who had received combination therapy with a PARP inhibitor and PD-1 inhibitor observed a 22.2% objective response rate (95% CI 8.0–36.5%). The median progression-free and overall surgical was 4.6 months (95% CI 2.5–6.0) and 9.4 months (95% CI 4.7–14.0), respectively. This study included 3 participants with cholangiocarcinoma; that subset had a 33.3% response rate [76].

Additional DNA damage repair pathways under evaluation include ATR, a kinase involved in DNA damage response, and Wee1, which regulates the cell-cycle. In combination, inhibition of these targets in vivo shows a synergistic effect in disrupting mitosis [77]. Multiple phase II studies are underway targeting ATR and Wee1 (as monotherapy or in combination with PARP inhibitors) in cholangiocarcinoma (NCT03878095, NCT04298021) [78].

A summary of the various molecular pathways discussed, and their therapeutic targets are displayed in Fig. 1, and ongoing clinical trials of targeted therapy in cholangiocarcinoma are summarized in Table 2.

Challenges and Future Directions

Multiple challenges exist in implementing and optimizing the use of targeted therapies. Tissue acquisition has been challenging, such that next-generation sequencing and identification of targetable mutations have been limited. Oftentimes, biopsies are not adequate to generate the necessary sequencing data. A long turnaround time for results of 4 to 8 weeks has further delayed management decisions and trial enrollment. In view of the rarity of these cancers coupled with the rarity of these genetic changes, clinical trials with FGFR inhibitors in the front-line setting have encountered difficulty recruiting patients—and recruitment remains

Table 1 Selective FDA approved and emerging targeted and biologic therapies

FDA approved in cholangiocarcinoma					FDA approved in solid tumors			Not FDA approved in cholangiocarcinoma or solid tumors overall
Target	FGFR gene fusion or rearrangement			IDH1 mutation	NTRK gene fusion		BRAF-V600E mutation	HER-2-amplified or overexpressed
Therapy	Pemigatinib	Infigratinib	Futibatinib	Ivosidenib	Entrectinib	Larotrectinib	Dabrafenib and trametinib	Pertuzumab plus trastuzumab
ORR (95% CI)	35.5% (26.5–45.4)	23.1% (15.6–32.2)	42% (32–52)	2% (not listed)	57% (43.2–70.8)	75% (61–85)	51% (36–67)	23% (11–39)
mDOR (months) (95% CI)	7.5 (5.7–14.5)	5.0 (3.7–9.3)	9.7 (7.6–17)	2.8 (0.1–34.4)	10 (7.1–not estimable)	Not reached at median follow-up of 8.3 months	9 (6–14)	10.8 (0.7–25.4)
mPFS (months) (95% CI)	6.9 (6.2–9.6)	7.3 (5.6–7.6)	9.0 (6.9–13.1)	2.7 (1.6–4.2)	11 (8.0–not estimable)	Not reached at median follow-up 9.9 months	9 (5–10)	4.0 (1.8–5.7)
mOS (months) (95% CI)	21.1 (14.8–not estimable)	12.2 (10.7–14.9)	21.7 (14.5–not reached)	10.3 (7.8–12.4)	21 (14.9–not estimable)	Unknown	14 (10–33)	10.9 (5.2–15.6)
Adverse Events (Grades 3–4, ≥ 5% prevalence)	Hypophosphatemia (12%), arthralgia (6%), stomatitis (5%), hyponatremia (5%), abdominal pain (5%), and fatigue (5%)	Stomatitis (15%), hyponatremia (13%), hypophosphatemia (12%), hyperphosphatemia (10%), palmer-plantar erythrodysesthesia syndrome (6%), hypercalcemia (5%), increased lipase (5%)	Hyperphosphatemia (30%), increased AST (7%), fatigue (6%), stomatitis (6%), palmar-plantar erythrodysesthesia syndrome (5%)	Ascites (9%), anemia (7%), increased bilirubin (6%), hyponatremia (6%)	Anemia (11%), increased weight (7%), dyspnea (6%)	Anemia (11%), decreased neutrophil count (7%), increased weight (7%), increased AST or ALT (7%)	Increased GGT (12%), pyrexia (7%), decreased WBC count (7%), hypertension (7%), hyponatremia (7%), increased AST (5%), increased ALP (5%), hyperglycemia (5%), cholangitis (5%), increased weight (5%), increased bilirubin (5%), neutropenia (5%), increased AST (5%)	Increased AST (13%), increased ALT 13%), increased ALP (10%), increased bilirubin 8%), abdominal pain (8%), ascites (5%), hyponatremia (5%)

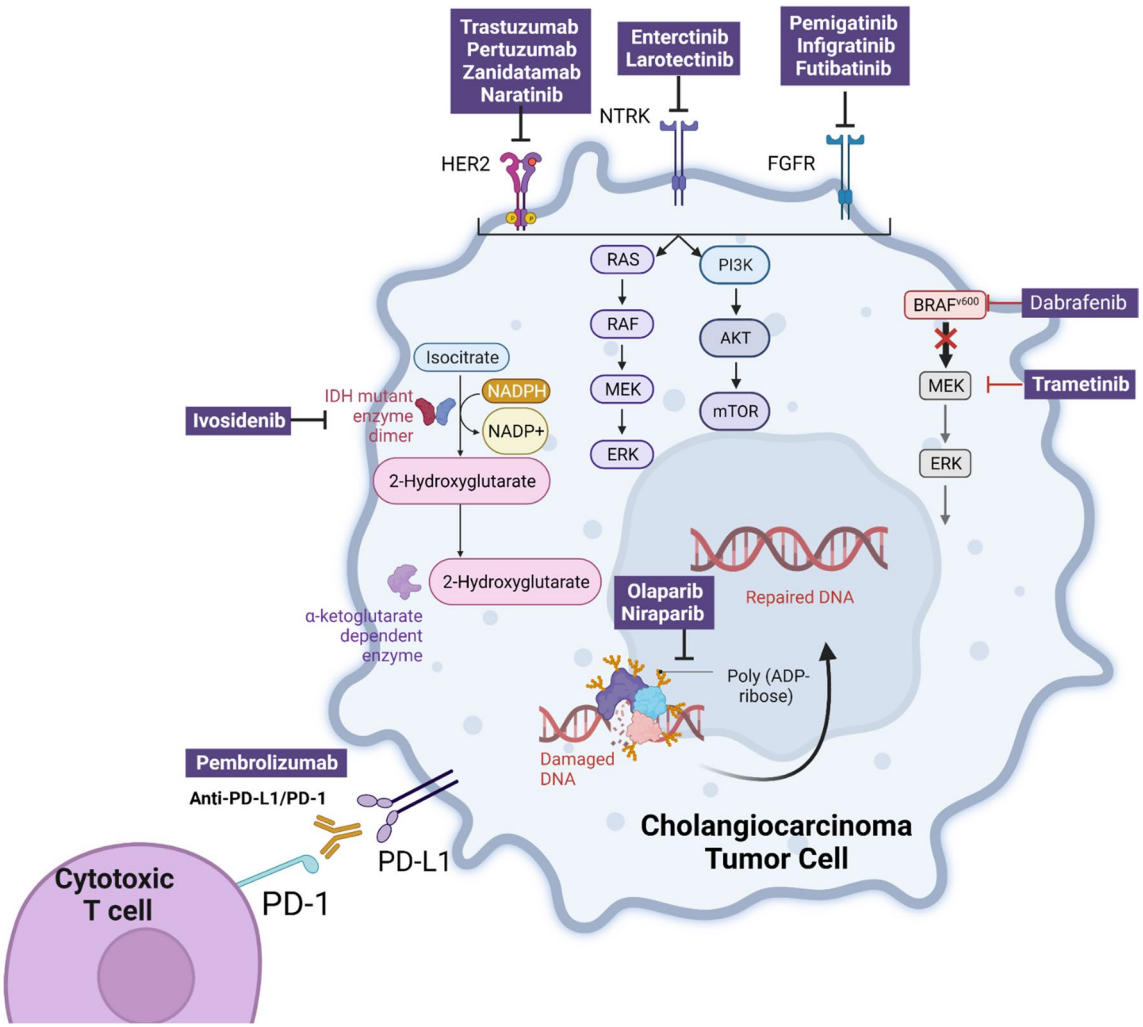

Fig. 1 Molecular pathways involved in tumorigenesis and their therapeutic targets

ongoing (for example, NCT03656536, NCT04093362). Furthermore, the role and optimal sequencing in the neoadjuvant and adjuvant settings are yet to be determined. Ongoing studies of targeted therapies compared to approved first-line chemotherapy regimens may lend support to using targeted therapies first-line [46, 79]. Finally, although many patients respond initially to targeted therapies, most ultimately acquire a resistance to the drug, often driven by secondary mutations [80].

Several approaches are being implemented to overcome some of these challenges. First, as next-generation testing becomes more readily available, clinicians are increasingly performing such testing earlier—with turnaround times as fast as 7–10 days [81]. Second, "liquid biopsies" to assess for circulating tumor DNA are becoming more attractive as this testing is less invasive and could potentially replace those instances where tissue sampling is deemed inadequate; in clinical practice, these liquid biopsies are used to diagnose early disease, monitor for recurrence, and identify therapeutically actionable mutations [82]. The concordance of circulating tumor DNA with next-generation sequencing of tumor tissue is approximately 40–74%, with variation across studies, tumor types, tissue biopsy sites, and disease stage with higher concordance in more advanced disease [83–85]. Additional research will be required to identify the mechanisms behind acquired resistance and to develop additional therapeutics to address this resistance; previous strategies tested in clinical trials include simultaneous inhibition of co-occurring driver mutations or simultaneous blockade of multiple proteins within a pathway [86]. For example, in patient-derived models of cholangiocarcinoma, inhibition of EGFR has been shown to overcome resistance in tumors with FGFR2 pathway aberrations [87]. New research charting the spectrum of co-mutations suggests predictable mechanisms of resistance to allow for rational drug design for combination therapies [43].

Table 2 Ongoing clinical trials of targeted or biologic therapy in cholangiocarcinoma

Drug(s)	Clinical trial phase	Clinical trial identifier	Line of therapy
FGFR inhibitors			
Pemigatinib (vs gemcitabine + cisplatin)	III	NCT03656536	First-line
Futibatinib (vs gemcitabine + cisplatin)	III	NCT04093362	First-line
Tasurgratinib (E7090)	II	NCT04238715	Second-line or greater
Derazantinib	II	NCT03230318	Second-line or greater
Gunagratinib (ICP-192)	II	NCT05678270	Second-line or greater
HMPL-453	II	NCT04353375	Second-line or greater
3D185	II	NCT05039892	Second-line or greater
Erdafitinib (JNJ-42756493)	II	NCT04083976	Second-line or greater
TT-00420	II	NCT04919642	Second-line or greater
Nab-paclitaxel, cisplatin, and gemcitabine ± Infigratinib	II	NCT05514912	No line of therapy specified
RLY-4008	I/II	NCT04526106	No line of therapy specified
TT-00420 ± Nab-paclitaxel	I/II	NCT04742959	No line of therapy specified
TT-00420 ± atezolizumab or Nab-Paclitaxel	I/II	NCT05253053	Refractory to all standard therapy
Infigratinib + atezolizumab + bevacizumab	I	NCT05510427	Refractory to all standard therapy
KIN-3248	I	NCT05242822	No line of therapy specified
CPL304110	I	NCT04149691	Refractory to all standard therapy
Bemarituzumab (anti-FGFR2b antibody)	I	NCT05325866	Second-line or greater
IDH inhibitors			
Dasatinib	II	NCT02428855	Second-line or greater
Olutasidenib (FT-2102) ± gemcitabine/cisplatin	I/II	NCT03684811	Second-line or greater
Enasidenib (AG-221)	I/II	NCT02273739	Second-line or greater
LY3410738 ± gemcitabine/cisplatin or durvalumab	I	NCT04521686	Second- or third-line
HMPL-306	I	NCT04762602	Second-line or greater
IDH305	I	NCT02381886	No line of therapy specified
NTRK			
Entrectinib (RXDX-101)	II	NCT02568267	No line of therapy specified
HER2			
Trastuzumab	II	NCT03613168 NCT02999672 NCT00478140	First-line Second-line or greater First- or second-line
Varlitinib (ASLAN001)	II	NCT02609958	Second-line or greater
Zanidatamab (ZW25)	II	NCT04466891 NCT03929666	Second-line or greater First-line
Lapatinib	II	NCT00107536	First- or second-line
Tucatinib + trastuzumab (+ chemoimmunotherapy)	I/II	NCT04430738	No line of therapy specified
A166	I/II	NCT03602079	No line of therapy specified
DB-1303	I/II	NCT05150691	Second-line or greater
IL-12 + trastuzumab	I	NCT00004074	Second-line or greater
ZW49	I	NCT03821233	Refractory to all standard of care treatments
BRAF			
Atezolizumab ± cobimetinib	II	NCT03201458	Second- or third-line
ABM-1310	I	NCT05501912 NCT04190628	No line of therapy specified; Second-line or greater
VEGF/VEGF receptor			
Erlotinib + bevacizumab	II	NCT00350753 NCT00356889	No line of therapy specified First-line
Apatinib	II	NCT03251443 NCT04454905	Second-line or greater No line of therapy specified
Bevacizumab + gemcitabine + capecitabine	II	NCT01007552	First-line

Table 2 (continued)

Drug(s)	Clinical trial phase	Clinical trial identifier	Line of therapy
Atezolizumab + tivozanib	I/II	NCT05000294	Second-line or greater
Gemcitabine/cisplatin ± bevacizumab + atezolizumab	II	NCT05211323	First-line
PI3K/AKT/mTOR			
MK2206	II	NCT01425879	Second-line or greater
DNA damage repair			
Olaparib	II	NCT03212274	Second-line or greater
Olaparib + durvalumab	II	NCT03991832	First-, second- or third-line
Olaparib + ceralasertib (AZD6738)	II	NCT03878095	Second-line or greater
Niraparib	II	NCT03207347	Refractory to all standard therapy
Olaparib and ceralasertib (AZD6738)	II	NCT03878095	Second-line or greater
AZD6738 and Durvalumab or AZD6738 and Olaparib	II	NCT04298021	Second-line

Future directions will include novel therapeutic strategies, including oncolytic viruses (NCT05124002, NCT03225989), chimeric antigen receptor T cells (CAR-T) (NCT04951141, NCT03633773, NCT04660929), and small interfering RNA (siRNA) [88]. Preliminary work already suggests that CAR-T therapy in cholangiocarcinoma is feasible [89, 90].

The future and the treatment landscape for cholangiocarcinoma is promising; however, we must also address critical questions on financial toxicity, which remains a significant barrier to personalized treatment [91], particularly when targeted and other therapies are allowing cancer patients to live longer. In a study of Medicare beneficiaries with new cancer diagnoses, out-of-pocket costs totaled nearly a quarter of total household income [92]. Barriers to access for these and other therapies remain in place, especially relevant for minorities and those without insurance coverage [93]. Key players including government, industry, and public–private partnerships must work together to tackle the ongoing disparity seen in cancer care among minorities [94]. The availability of these life-saving drugs will mean very little when patients have no means of accessing them.

Conclusion

Cancer therapy in patients with advanced cholangiocarcinoma is no longer limited to chemotherapy alone. Greater understanding of molecular pathways have opened the door to more personalized targeted therapies, including the use of agents that target molecular alterations in FGFR fusions, IDH mutations, NTRK fusion, and HER2 receptor overexpression. Targeted therapies have allowed patients to live longer with this rare and often lethal malignancy and have generated further innovation.

Declarations

Conflict of Interest HMB is a Paul Calabresi Scholar at the Mayo Clinic Cancer Center and acknowledges K-12 grant program, K12CA090628. MJB has received grants and consulting fees from Servier, Taiho, QED, Relay therapeutics, Astra Zeneca, Kinnate, PUMA, Loxo, Incyte, Zymeworks, and Merck. AJ has received honorarium from Pfizer, BMJ, Meter Health, and Novartis. NHT is a recipient of the K23MD017217 grant and has received consulting fees from Helsinn. All other authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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