Gim *et al. Hepatoma Res* 2023;9:51
DOI: 10.20517/2394-5079.2023.90

Hepatoma Research

Review

Open Access

Challenges and opportunities for treating intrahepatic cholangiocarcinoma: targeted therapy

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How to cite this article: Gim G, Badri N. Challenges and opportunities for treating intrahepatic cholangiocarcinoma: targeted therapy. *Hepatoma Res* 2023;9:51. https://dx.doi.org/10.20517/2394-5079.2023.90

Received: 11 Aug 2023 **First Decision:** 16 Oct 2023 **Revised:** 13 Nov 2023 **Accepted:** 20 Dec 2023 **Published:** 31 Dec 2023

Academic Editors: Antonio Bertoletti, Hongping Xia **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

Over the last two decades, substantial progress has been made in the scope of molecular targeted therapy, leading to transformative advancements in the treatment of various malignancies, including biliary tract cancer (BTC). BTC represents a heterogeneous group of aggressive tumors with historically poor prognoses. However, recent discoveries of novel molecular alterations in BTC have provided new avenues for targeted therapeutic interventions, exemplified by the approval of pemigatinib, specifically designed for FGFR2 gene fusions or rearrangements in advanced BTC. Furthermore, subsequent regulatory approvals and ongoing clinical trials focusing on specific gene mutations have considerably expanded the array of treatment options available, augmenting the potential for personalized treatment strategies. In light of these developments, this review aims to furnish a comprehensive and up-to-date account of the molecular characteristics and potential targeted therapies in BTC. By presenting insights into novel therapeutic approaches and outlining prospective directions for translational and clinical investigations, this review seeks to contribute to the ongoing progress and optimization of therapeutic approaches in managing BTC.

Keywords: Cholangiocarcinoma, biliary tree cancer, biliary tract cancer, targeted therapy, immunotherapy, next-generation sequencing, bile duct neoplasms, hepatobiliary malignancy, intrahepatic cholangiocarcinoma

INTRODUCTION

Biliary tract cancer (BTC) is a heterogeneous group of biliary cancers that occur at various locations along the biliary tree, representing approximately 3% of gastrointestinal malignancies. BTC is divided into several main subtypes based on its location: intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA). These subtypes represent different locations along the biliary tree and contribute to the heterogeneity of BTC [Figure 1]. The incidence of BTC is steadily increasing worldwide[1]. Unfortunately, the prognosis for BTC remains grim due to delayed detection and the limited number of patients (approximately 30% or less) who qualify for curative surgery[2]. Furthermore, while several study results support the use of neoadjuvant therapy to potentially enhance survival and achieve a higher R0 resection rate, there is no unanimous consensus on its necessity[3]. Additionally, most patients are diagnosed at advanced stages with distant metastasis and extensive liver involvement. The rarity of the disease and the lack of effective treatments intensify the urgency to explore novel strategies for managing this devastating condition. The treatment of advanced BTC poses a significant challenge because the condition remains incurable and alternative treatment options are limited. As a result, the current approach focuses primarily on supportive care and systemic therapy to improve overall survival (OS) and enhance quality of life. Despite efforts, the prognosis for advanced BTC patients varies considerably, with reported median OS ranging from 4 to 12 months in different studies[4-6]. Therefore, the ongoing challenges in treating advanced or recurrent BTC underscore the necessity for further advancements in therapeutic interventions.

The gemcitabine and cisplatin combination regimen has long been the standard systemic therapy for advanced BTC, based on the findings of the ABC-02 study[6]. This phase 3 trial compared the efficacy of gemcitabine alone versus gemcitabine plus cisplatin and showed better OS and progression-free survival (PFS) with the combined therapy. Patients received gemcitabine plus cisplatin for approximately 8 cycles, followed by close surveillance. It also showed a better response rate (RR) in the combination regimen group than in the gemcitabine monotherapy group (26.1 % and 15.5 %, respectively). Subgroup analysis revealed the benefits of the combination therapy across different tumor locations, including intrahepatic, extrahepatic, and gallbladder. These findings established the gemcitabine and cisplatin therapy as the standard systemic treatment for advanced BTC.

In the pursuit of enhancing treatment outcomes, the TOPAZ-1 study investigated the addition of immunotherapy to chemotherapy for advanced BTC[7]. The study included patients who received up to 8 cycles of gemcitabine/cisplatin plus durvalumab, followed by durvalumab maintenance, compared to those who received gemcitabine/cisplatin followed by placebo. The results demonstrated a positive outcome with durvalumab, showing a median OS of 12.8 months compared to 11.5 months with placebo (hazard ratio [HR] of 0.80; 95% confidence interval [CI]: 0.66-0.97 months; $P = 0.021$). The study also showed a higher RR in the durvalumab group compared to the placebo group [26.7% and 18.7%, respectively, odds ratio of 1.60, (95%CI: 1.11-2.31)]. Subgroup analyses based on sex, PD-L1 expression, tumor location (intrahepatic *vs.* extrahepatic or gallbladder), and Asian *vs.* non-Asian populations all showed benefits from the combination therapy. Additionally, the PFS was improved in durvalumab group. Consequently, the combination of gemcitabine/cisplatin plus durvalumab has emerged as a new frontline standard of treatment for advanced BTC, presenting a promising advancement in treatment options.

Despite the advancements made in systemic treatment over time, the prognosis of the disease remains unfavorable as it continues to worsen despite undergoing initial treatment. Unfortunately, only a limited number of patients with BTC who experience disease progression following their first-line therapy are eligible to undergo second-line chemotherapy, further limiting their treatment opportunities. According to

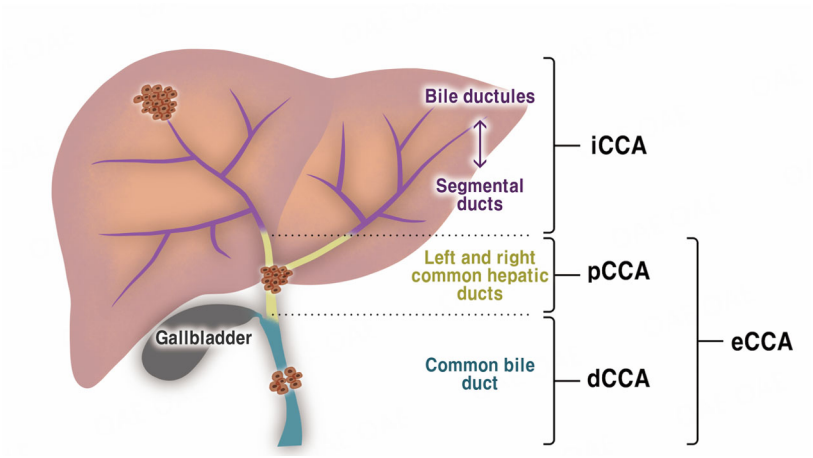

Figure 1. Illustration of the anatomical sites of BTC includes intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA). iCCA refers to malignancies located in the periphery of the second-order bile ducts, while pCCA originates in the right or left hepatic duct and/or at their junction. On the other hand, dCCA involves the common bile duct. Each subtype of BTC occupies a distinct anatomical position within the biliary tract. The collective term extrahepatic cholangiocarcinoma (eCCA) is used to encompass both pCCA and dCCA.

the TOPAZ-1 trial, 42.5% of patients received subsequent anticancer therapy following immune-chemotherapy[7]. There are several factors that contribute to the limitation of advancing beyond the first line of treatment. One such factor is the insufficient remaining healthy liver parenchyma, which significantly restricts the feasibility of receiving cytotoxic systemic treatments, often resulting in poor outcomes. Additionally, the overall performance status of patients with advanced or metastatic BTC tends to be generally poor, further complicating treatment decisions and options. Infection poses another significant barrier to overcome, as advanced BTC is often complicated by cholangitis, sepsis, and other issues associated with the biliary tree.

When patients with BTC experience disease progression on the first line of therapy and are able to proceed to second-line systemic treatment, the decision regarding the subsequent line of therapy becomes complex. This complexity arises from the absence of a well-defined global treatment standard for this stage. The ABC-06 trial has shown improved survival in patients who received second-line therapy with folinic acid, fluorouracil, and oxaliplatin (FOLFOX) in combination with active symptom control (ASC) compared to ASC alone[4]. However, despite these advancements, the efficacy and prognosis remain discouraging, with median OS at 6.2 months with FOLFOX.

Due to the discouraging prognosis and limited treatment options in BTC, advancements in molecular techniques like next-generation sequencing (NGS) have paved the way for alternative approaches. Moreover, patients with BTC display significant variations in their molecular characteristics and genetic abnormalities, which can vary depending on their specific anatomic locations [Table 1]. This diversity in molecular features makes BTC a potential candidate for targeted therapy. As a result, molecular analysis has now become a routine part of diagnostic testing for advanced BTC cases, providing valuable insights for treatment decisions and enhancing treatment efficacy. In the upcoming section, we will delve into diverse targeted therapies for BTC, exploring their effectiveness and research findings in the context of this challenging cancer.

Table 1. The prevalence of genetic alterations in BTC based on the anatomic sites

Genetic Alteration	Anatomic Site		
	iCCA	eCCA	GBC
IDH1,2 Mutation	13%-30%[8,9]	4.7%[10]	-
FGFR2 Fusion	10%-15%[11]	-	-
BRAF V600E Mutation	1.5%[12]	-	0.5%[12]
HER2 Alteration	2.2%[13]	7.5%[13]	12.6%[13]
KRAS G12C Mutation	1.2% across all sites[14]		
NTRK Fusion	0.75% across all sites[15]		
RET Fusion	0.15%[16]	0.11%[16]	-
MSI-H/dMMR	2.06%[17]	4%[10]	5%[18]
TMB-H	4% across all sites[19]		

BTC: biliary tract cancer; dMMR: mismatch repair deficient; eCCA: extrahepatic cholangiocarcinoma; FGFR: fibroblast growth factor receptor; GBC: gallbladder cancer; HER2: human epidermal growth factor receptor 2; iCCA: intrahepatic cholangiocarcinoma; IDH: isocitrate dehydrogenase; KRAS: Kirsten rat sarcoma viral oncogene homolog; MSI-H: microsatellite instability-high; NTRK: neurotrophic tyrosine receptor kinase; RET: rearranged during transfection; TMB-H: high tumor mutational burden.

TARGETED THERAPIES FOR BILIARY TRACT CANCER

Isocitrate dehydrogenase inhibitors

IDH gene mutations are frequently observed in approximately 13%-30% of iCCA cases, establishing them as the most prevalent targetable mutations in BTC[8,9]. Extensive research has focused on the IDH gene in various cancers, particularly acute myeloid leukemia and other myeloid malignancies. Although the exact mechanisms underlying the oncogenic effects of IDH mutations remain unclear, it is believed that these mutations contribute to the excessive accumulation of metabolites associated with cancer development[20]. Specifically, IDH1 mutations have been shown to enhance the conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG), leading to the accumulation of 2-HG and potentially impairing cell differentiation, as well as promoting the proliferation of tumor cells.

Ivosidenib, an oral IDH1 inhibitor, is currently recommended by the National Comprehensive Cancer Network (NCCN) as a second-line therapy for advanced, unresectable, and metastatic BTC harboring IDH1 mutations[21]. The approval of ivosidenib by the Food and Drug Administration (FDA) was based on the compelling results of the phase III CLARIDHY study[22]. This trial showed a statistically significant improvement in PFS for patients randomized to ivosidenib, with a HR of 0.37 (95%CI: 0.25-0.54; $P < 0.000$)[9]. The most common treatment-related adverse events (TRAE) observed was ascites, which were observed in 9% of treated patients compared to 7% in the placebo arm, while the patients' quality of life did not appear to be significantly affected. The most common grade 3 or worse adverse event observed in both the ivosidenib and placebo groups was ascites, occurring in 7% of patients in each group. Furthermore, serious adverse events were reported in 30% of patients who received ivosidenib and in 22% of patients in the placebo group. A summary of targeted therapies for CCA is provided in [Table 2].

Several ongoing early-phase trials are assessing other IDH inhibitors in IDH mutant tumors including BTC such as LY3410738 (NCT04521686)[23], HMPL-306 (NCT04762602)[24], and IDH305 (NCT02381886)[25]. Additionally, there is an ongoing study (NCT04088188) evaluating the addition of ivosidenib with gemcitabine and cisplatin as a treatment for advanced BTC patients[26]. Although it is a phase I study, it holds the potential to provide valuable insights into the efficacy of combining targeted therapy and chemotherapy in the management of advanced BTC. A summary of ongoing targeted therapy trials with data is provided in [Table 3].

Table 2. Approved targeted therapies for BTC

Target	Drug	Trial name	Patient number (*n*)	ORR	mPFS (months)	mOS (months)	Grade ≥ 3 TRAE
IDH	Ivosidenib	ClarIDHy	187	-	2.7	10.3	53%
FGFR	Pemigatinib	FIGHT-202	146 (107 FGFR R/F + 20 FGFR-O + 18 FGFR-N + 1 unassigned)	35.5% (in FGFR R/F)	6.9 (in FGFR R/F)	21.1 (in FGFR R/F)	64%
	Futibatinib	FOENIX-CCA2	103	41.7%	8.9	20.0	73.1%
BRAF/MEK	Dabrafenib/ Trametinib	ROAR	43	51%	9	14	53%
HER2	Trastuzumab/ Pertuzumab*	MyPathway	39	23 (0% in iCCA)	4 (2.6 in iCCA)	10.9 (3.9 in iCCA)	46%
TRK	Larotrectinib	LOXO-TRK-14001, SCOUT, NAVIGATE	244	69%	29.4	NR	20%
	Entrectinib	ALKA, STARTRK-1, STARTRK-2	150	61.3%	13.8	37.1	-
RET	Pralsetinib*	ARROW	23 including 3 BTC	57%	7.4	13.6	69%
	Selpercatinib	LIBRETTO-001	41 including 2 BTC	43.9%	13.2	18.0	38%

**Not FDA-approved for BTC but recommended by NCCN.* BTC: biliary tract cancer; FGFR-N: no FGF/FGFR alterations; FGFR-O: other FGF/FGFR alteration; FGFR R/F: FGFR2 fusions or rearrangements; iCCA: intrahepatic cholangiocarcinoma; mOS: median overall survival; mPFS: median progression-free survival; NR: not reached; ORR: objective response rate; TRAE: treatment-related adverse event.

The promising data on IDH inhibitors in BTC hold potential, but challenges, especially regarding acquired resistance, must be addressed. Studies are investigating the mechanisms of secondary resistance to IDH inhibitors. However, the molecular underpinnings of this resistance are not yet fully elucidated. Several studies have found mutant IDH isoform switching as a potential mechanism of acquired resistance to IDH-targeted therapy[31,32]. Nonetheless, additional research is necessary to gain a comprehensive grasp of these molecular processes.

Fibroblast growth factor receptor inhibitors

FGFR is a cell surface receptor that transmits signals from fibroblast growth factors, playing an essential role in regulating cell proliferation, tissue maturation, and cellular differentiation[33]. Continuous activation of FGFRs can lead to the proliferation of cancer cells. Activation of FGFRs can occur via different mechanisms, including gene amplification, which results in the overexpression of receptors, activating mutations, or translocations that create activating gene fusions[34]. Among all FGFR alterations, FGFR2 fusions exhibit the highest frequency in BTC, being detected in approximately 10%-15% of patients with iCCA, while being comparatively rare in other subtypes[35,36]. Several pan-FGFR inhibitors and selective FGFR inhibitors have been undergoing investigation. The data obtained from registrational studies provide compelling evidence that FGFR2 fusions, as the most prevalent alterations in BTC, significantly contribute to the therapeutic efficacy observed in this disease[37,38].

Pemigatinib and futibatinib are two FGFR inhibitors currently available for patients with pretreated BTC who have FGFR2 fusions or rearrangements[39]. In April 2020, the FDA granted accelerated approval to an oral inhibitor of FGFR1-3, pemigatinib, as a therapy option for previously treated advanced BTC patients who tested positive for FGFR2 fusion or FGFR2 rearrangement, based on the findings of the phase II FLIGHT-202 study[40,41]. The final analysis of the study, with a median follow-up duration of 45.4 months, showed a disease control rate (DCR) of 82.4% (95%CI: 73.9%-89.1%) and a median OS of 17.5 months (95%CI: 14.4-22.9 months)[42]. Based on the promising data mentioned earlier, a phase III randomized study, FIGHT-302 (NCT03656536), is currently underway to evaluate pemigatinib as a frontline treatment for advanced BTC patients, comparing it with the combination of gemcitabine and cisplatin[43].

Table 3. Ongoing targeted therapy trials in BTC

Target	Drug/Name of trial	Phase	Trial ID	Outcome	Note
IDH	LY3410738	I	NCT04521686		LY3410738 is a dual IDH1/2 inhibitor
	HMPL-306	I	NCT04762602		HMPL-306 is a dual IDH1/2 inhibitor
	IDH305	I	NCT02381886		IDH1R132-mutant tumors are eligible
	ivosidenib + gemcitabine + cisplatin	I	NCT04088188		
FGFR	Futibatinib/ FOENIX-CCA3	III	NCT04093362		Futibatinib versus Gemcitabine + Cisplatin as a first-line in advanced BTC with FGFR2 gene rearrangement
	Derazabtinib/ FIDES-01	II	NCT03230318	In FGFR2 fusion group: ORR 21.4%, mPFS 8.0 months, mOS 17.2 months[27]	Derazabtinib is a pan-selective FGFR inhibitor
	RLY-4008/ ReFocus	I/II	NCT04526106	ORR 88.2%[28]	RLY-4008 is a highly selective FGFR2 inhibitor
	Pemigatinib/ FIGHT-302	III	NCT03656536		Pemigatinib versus Gemcitabine/Cisplatin as a frontline in advanced BTC with FGFR2 rearrangement
	KIN-3248	I/Ib	NCT05242822		KIN-3248 is a selective small molecule pan-FGFR inhibitor
	Bemarituzumab	Ib/II	NCT05325866		Bemarituzumab is a humanized IgG1 monoclonal antibody against FGFR2b
BRAF	ABM-1310	I	NCT05501912 NCT04190628		ABM-1310 is a small molecule BRAF inhibitor
	BGB-3245	Ia/Ib	NCT04249843		BGB-3245 is a small molecule inhibitor of RAF monomer and dimer
HER2	Trastuzumab deruxtecan/ HERB	II	JMA-IIA00423	ORR 36.4%, DCR 81.8%, mPFS 4.4 months, mOS 7.1 months. Grade ≥ 3 TRAEs in 81.3% of patients[29]	
	Zanidatamab/ HERIZON-BTC-01	IIb	NCT04466891	ORR 41.3%, DCR 68.8%, mPFS 5.5 months, OS at 9 months of 69.9%[30]	Zanidatamab is a HER2-targeted bispecific antibody
	DB-1303	I/IIa	NCT05150691		DB-1303 is an ADC consisting of a humanized anti-HER2 IgG1 monoclonal antibody
	Tucatinib + trastuzumab and oxaliplatin-based therapy or pembrolizumab-containing combinations	Ib/II	NCT04430738		
	CT-0508	I	NCT04660929		CT-0508 is a CAR-macrophage

ADC: antibody-drug conjugate; BTC: biliary tract cancer; CAR: chimeric antigen receptor; mOS: median overall survival; mPFS: median progression-free survival; ORR: objective response rate; TRAE: treatment-related adverse event.

Futibatinib, an oral agent that inhibits FGFR 1-4, has received accelerated approval from the FDA in September 2022[44]. This decision was based on the demonstrated efficacy in patients with previously treated advanced or metastatic iCCA with FGFR fusions or rearrangements, as shown in the data from the phase II FOENIX-CCA2 trial[45]. An updated analysis data, with a median follow-up of 25 months, revealed an objective response rate (ORR) of 41.7% with a DCR of 82.5%[46]. The median duration of response (DOR) was 9.5 months, while the median PFS was 8.9 months. Furthermore, the mature median OS was recorded as 20.0 months. Similarly to pemigatinib, a phase III clinical trial (FOENIX-CCA3, NCT04093362) is currently underway. This trial is evaluating futibatinib as a frontline option for locally advanced, metastatic, or recurrent unresectable iCCA with FGFR2 rearrangements. The trial aims to compare the efficacy of futibatinib with the doublet of gemcitabine and cisplatin.

Both studies evaluating pemigatinib and futibatinib showed a similar side effect profile. Hyperphosphatemia, alopecia, and diarrhea were the most frequent TRAEs noted with both drugs. In the case of pemigatinib, these side effects were mostly in grade 1 or 2. Among grade 3 or more severe adverse events, hypophosphatemia was the most frequently reported, occurring in 14.3% of cases[42]. Similarly, for futibatinib, the most common grade 3 TRAE was hyperphosphatemia, seen in 30% of participants[45]. Additionally, other notable grade 3 adverse events included increased aspartate aminotransferase levels (7%), stomatitis (6%), and fatigue (6%).

Several ongoing trials hold the potential to provide promising data in the near future. One of these is the phase II FIDES-01 study, investigating derazantinib, a pan-selective FGFR inhibitor, in patients with pretreated iCCA harboring FGFR2 fusion ($FGFR2^{F}$) or FGFR mutation/amplification ($FGFR2^{M/A}$). Data from the 2022 ESMO Congress showed a higher ORR of 21.4% (95%CI: 13.9%-30.5%) in $FGFR2^{F}$ compared to 6.5% in $FGFR2^{M/A}$ cohort (95%CI: 0.8%-21.4%)[29]. The median OS was documented as 17.2 months (95%CI: 12.5%-22.4%) and the median PFS reached 8.0 months (95% CI: 5.5%-8.3%) in $FGFR2^{F}$ patients.

In the ongoing ReFocus trial (NCT04526106), RLY-4008, a highly selective FGFR2 inhibitor, is being evaluated in advanced solid tumors, including FGFR inhibitor-naïve BTC. Preliminary data from the 2022 ESMO Congress showed a promising ORR of 88.2% (95%CI: 63.6%-98.5%) in 17 patients who received the recommended phase 2 doses[30]. Notably, one patient achieved a near-complete response and underwent curative tumor resection. The encouraging findings underscore the significance of further monitoring the ongoing development of RLY-4008 as a potential treatment option for advanced stages and potentially in the neoadjuvant setting.

The encouraging data on FGFR inhibitors in BTC holds promise, but there are significant challenges to overcome, particularly concerning acquired resistance to these inhibitors. Numerous preclinical investigations have been conducted to identify the underlying mechanisms of resistance, including bypass signaling, epithelial-mesenchymal transition (EMT), and the development of secondary FGFR mutations, commonly referred to as gatekeeper mutations[47]. However, it is vital to acknowledge that the majority of research in this area has primarily centered on urothelial, lung, and gastric cancer cell lines, potentially not encompassing the complete range of resistance mechanisms observed in BTC. Moreover, in vitro cell models may not entirely capture the heterogeneity and complexity of human disease, adding another layer of consideration in interpreting the findings and applying them to BTC treatment strategies.

BRAF inhibitors

The mitogen-activated protein kinase (MAPK) signaling pathway, which includes the RAS/RAF/MEK/ERK pathway, plays an essential role in cellular proliferation and survival[48]. BRAF, an oncogene, activates the RAS/RAF/MEK pathway. BRAF mutations, particularly the V600E mutation, are commonly observed in various solid tumors, including colorectal malignancy, non-small cell lung cancer (NSCLC), and melanoma[49,50]. The BRAF V600E mutation activates BRAF, resulting in tumor growth and metastasis[51]. BRAF activating mutations are rare in BTC, comprising approximately 5.5% of cases, with 1.5% of BRAF V600E mutation in iCCA and 0.5% of BRAF V600E in GBC[12].

Combining the RAF inhibitor, dabrafenib, with the MEK inhibitor, trametinib, has shown encouraging results in the treatment of BRAF-mutated BTC. The phase II ROAR trial investigated the effectiveness of combining dabrafenib and trametinib in patients with advanced solid tumors harboring the BRAFV600E mutation who had experienced the progression of disease after prior treatment[52]. The trial showed a significant ORR of 51%, with a mean OS of 14 months and a mean PFS of 9 months. The dabrafenib and

trametinib combination regimen demonstrated manageable side effects. In light of these results, the FDA approved dabrafenib plus trametinib as a subsequent line of therapy for BTC with BRAFV600E mutations[53].

Ongoing phase 1 trials are exploring the response to selective BRAF inhibitors, such as ABM-1310 (NCT05501912, NCT04190628) and BGB-3245 (NCT04249843), in patients with BRAFV600-mutated solid tumors, including BTCs. Additionally, more studies are needed to evaluate the effectiveness of targeted therapies in patients with concurrent TP53 and BRAFV600E mutations, as initial findings suggest a more aggressive disease and reduced clinical benefits[54].

Similar to other targeted therapies, the challenge of overcoming resistance to BRAF inhibitors persists. As evidenced by PFS data, a significant proportion of patients initially responsive to BRAF inhibitors eventually face resistance, necessitating adjustments in treatment strategies. While several potential mechanisms have been proposed, the majority of investigations have revolved around melanoma and a limited range of lung cancer cohorts. Nevertheless, a comprehensive analysis of these findings offers relevant insights that can be extrapolated to BTC patient populations. Notably, one of the potential mechanisms involves the reactivation of the MAPK pathway[55-57], often occurring due to alterations affecting the drug target itself, such as BRAF copy number gains and MEK2 mutations[58-60].

As discussed earlier, combination treatment involving BRAF inhibitors and MEK inhibitors has shown promising results. However, despite this encouraging observation, the development of acquired resistance to combination therapy remains an inevitable challenge. A study conducted within a melanoma cohort has highlighted that the mammalian target of rapamycin (mTOR) activation could potentially contribute to the acquired resistance seen with combined BRAF and MEK inhibition[61]. The mTOR kinase plays an important role in cellular proliferation, and aberrant mTOR activation has been noted across various cancer types[62,63]. Given that both the MAPK/ERK and PI3K/AKT signaling pathways converge into the mTOR complex 1, this pathway could hold significance for the effectiveness of targeted therapy in patients with BRAF-mutant melanoma[61]. This potentially implies that the inclusion of an mTOR inhibitor might effectively restore sensitivity to BRAF or MEK inhibitors, prompting further exploration for potential therapeutic interventions.

Human epidermal growth factor receptor 2 inhibitors

HER2, encoded by the ERBB2 gene, is a receptor tyrosine kinase involved in crucial oncogenesis signaling pathways. Its dysregulation is well-documented in cancer development[64]. Besides its well-known significance in breast cancer, emerging evidence suggests its involvement in BTC[65]. HER2 expression shows ethnic variations, with a higher prevalence in Asian patients (28.4%) compared to Western patients (19.7%)[66]. Additionally, HER2 positivity rates in BTC vary based on tumor location, with reported alteration rates of 2.2% in iCCA, 7.5% in eCCA, and 12.6% in GBC[13]. Detection of HER2 amplification in BTC can be achieved through various testing modalities, including immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and NGS techniques, with NGS providing the advantage of simultaneously evaluating multiple molecular alterations, including HER2 activating mutations, particularly when diagnostic tissue is limited. However, IHC and FISH remain the more commonly employed methods[67].

Pertuzumab and trastuzumab, two monoclonal antibodies targeting HER2, have shown promise in treating HER2-positive malignancies[68]. In a phase II MyPathway study (NCT02091141) involving previously treated HER2-amplified and overexpressed metastatic BTC patients, the pertuzumab and trastuzumab combination

demonstrated an ORR of 23% (95%CI: 11%-39%), a median PFS of 4.0 months (95%CI: 1.8-5.7 months), and a median DOR of 10.8 months (95%CI: 0.7-25.4 months)[69]. Adverse events of grade 3 or higher were documented in 46% of patients, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases being the most common. Although the dual anti-HER2 therapy for HER2-positive BTC has not received FDA approval, it is included as an option in the NCCN guidelines for patients who have undergone prior treatment[21]. To further confirm and establish the efficacy of the HER2-targeted treatment in subsequent lines of therapy for BTC, future randomized controlled trials are essential.

Trastuzumab deruxtecan (T-DXd) has demonstrated encouraging anti-cancer efficacy in advanced solid tumors that are HER2-positive, including BTC[70]. A phase I study involving advanced HER2 mutant solid tumors, excluding breast and gastric cancers, showed an ORR of 28.3%, and the median PFS reached 7.2 months (95%CI: 4.8-11.1 months). The HERB phase II study, which focused on BTCs, revealed an ORR of 36.4% (95%CI: 19.6%-56.1%) in patients with HER2-positive BTCs, along with a DCR of 81.8% (95%CI: 59.7%-94.8%). The study also revealed a median OS of 7.1 months (95%CI: 4.7-14.6 months) and a median PFS of 4.4 months (95%CI: 2.8-8.3 months)[31]. However, the safety analysis revealed that 81.3% of patients had grade 3 or higher TRAEs, with cytopenia being common. Of particular concern, approximately 25% of patients developed interstitial lung disease (ILD), along with significant gastrointestinal and myelosuppression toxicities. This highlights the need for further investigation and follow-up.

Zanidatamab, a HER2-targeted bispecific antibody, underwent evaluation in the phase IIb HERIZON-BTC-01 study (NCT04466891) in patients with HER2-amplified, locally advanced, unresectable, or metastatic BTC. Among the 87 patients, 41.3% of participants had an objective response, with a DCR of 68.8% (95%CI: 57.4%-78.7%). The median PFS reached 5.5 months (95%CI: 3.7-7.2 months), and data for median OS were not yet mature at the time of data cutoff. However, the OS at 9 months reached 69.9% (95%CI: 57.8%-79.1%)[32].

Despite remarkable advances in HER2-targeted therapy, resistance continues to pose challenges in HER2-positive BTCs. While resistance studies are primarily focused on breast and gastrointestinal cancers, they provide valuable insights into potential resistance mechanisms in BTC. Notably, the intrapatient and intertumor heterogeneity of HER2 expression is considered a critical factor contributing to primary resistance[71,72]. Furthermore, HER2 positivity in BTC often coincides with other oncogenic drivers such as FGFR, MET, and KRAS alterations, known to impart resistance to anti-HER2 therapy in in vitro studies[73].

Encouragingly, a small case series demonstrated the successful reversal of trastuzumab resistance by combining HER2 blockade with inhibition of the secondary driver mutation[74]. Additionally, in studies involving gastric cancer patients, loss of HER2 has been linked to potential acquired resistance to anti-HER2 therapy[75,76]. Notably, the SUMMIT study evaluated an irreversible pan-HER tyrosine kinase inhibitor, neratinib, in HER2-mutant advanced BTC, showing antitumor activity but not meeting the primary endpoint; in one GBC patient, loss of HER2 amplification and reduction in VAF of the original HER2 mutation were demonstrated through biopsy and NGS[77]. Combinatorial approaches, continuous monitoring of HER2 alterations, and adaptive treatment regimens may offer potential solutions to improve clinical outcomes and enhance the efficacy of HER2-targeted therapy in the management of BTCs.

Tropomyosin receptor kinase inhibitors

The neurotrophic tropomyosin kinase receptors (NTRK or TRK) family is a group of transmembrane tyrosine kinases that hold significance in the development of neurons. These receptors are encoded by the genes NTRK1, NTRK2, and NTRK3. In 1986, the first identification of somatic fusions involving the NTRK

genes was reported in a colorectal cancer patient. Subsequently, it was uncovered that mutations in NTRK genes, most commonly NTRK fusions, are associated with oncogenesis in various tumor types. The NTRK mutations are more common in patients with lung cancers and soft tissue tumors[78]. The estimated prevalence of NTRK fusions in BTC is 0.75%[15].

To date, the FDA has approved two first-generation NTRK inhibitors as first-line and subsequent line of therapy in patients with NTRK fusion-positive BTC: larotrectinib[79] and entrectinib[80]. In November 2018, the FDA granted accelerated approval to Larotrectinib based on results from three multicenter clinical trials: LOXO-TRK-14001, SCOUT, and NAVIGATE. A pooled analysis of the three studies showed an ORR of 69% (95%CI: 63-75), with more than one-fourth of the cases (26%) achieving a complete response (CR)[81]. The response has shown considerable durability, with a median DOR of 32.9 months (95%CI: 27.3-41.7). The median PFS reached 29.4 months (95%CI: 19.3-34.3). The median was not reached at a median follow-up of 32.2 months. The TRAEs were primarily in grade 1 or 2, and 20% of patients had grade 3 or 4 adverse events, leading to treatment discontinuation in five cases.

Entrectinib was approved by the FDA in the subsequent year for adults and pediatric patients who have solid tumors with NTRK gene fusion based on favoring data from three multicenter, single-arm clinical trials: ALKA, STARTRK-1 (NCT02097810) and STARTRK-2 (NCT02568267)[82]. An updated pooled analysis data of the three phase 1-2 trials from the 2022 ASCO annual meeting has demonstrated meaningful clinical response and good tolerability[83]. The ORR was 61.3% (95%CI: 53.1%-69.2%), with more than one-fourth of those who had responses achieving a CR. The median DOR reached 20.0 months (95%CI: 13.2-31.1 months) and the PFS reached 13.8 months (95%CI: 10.1-20.0 months). At a median survival follow-up of 30.6 months, the median OS reached 37.1 months (95%CI: 27.2-NE). Moreover, the TRAEs were mainly grade 1-2: dysgeusia (36.6%), diarrhea (29.8%), and weight gain (28.5%). A total of 7.2% of patients needed to discontinue the treatment due to adverse events.

While a significant portion of patients with NTRK fusion-positive cancers achieve enduring disease control, the emergence of resistance to TRK inhibition remains a substantial challenge[84]. This emphasizes the critical need to develop second-generation TRK inhibitors and/or explore strategies to counter this resistance mechanism. A recent study examining post-progression tumor tissue through NGS from patients treated with first-generation TRK inhibitors found that the majority displayed on-target resistance (83%) as opposed to off-target resistance (11%) or an unidentifiable mechanism (6%)[85]. Among patients exhibiting on-target resistance, mutations primarily affected the solvent front (87%) and, to a lesser extent, the gatekeeper region (13%). The sequential use of next-generation therapy appears to impact the pattern of mutation occurrence and development. At present, several next-generation TRK inhibitors, such as selitrectinib, repotrectinib, and taletrectinib, are undergoing evaluation in clinical trials due to their promising preclinical activity[86]. These innovative agents hold considerable potential in addressing the resistance challenge that may arise with the use of first-generation TRK inhibitors.

RET inhibitors

For over three decades following the identification of the RET gene that encodes the receptor tyrosine kinase, mutations in the RET gene have been identified as actionable drivers of oncogenesis[87]. Specific RET fusion proteins can initiate tumorigenesis and progression of cancer by stimulating subsequent signaling cascades, ultimately resulting in unregulated cell growth. While RET gene fusions are relatively rare in BTC, they are identified in around 1% to 2% of other types of cancer, such as NSCLC and thyroid cancers, indicating the promise of targeting RET kinase in therapeutic interventions[88]. Activating aberrations in RET, including mutations, fusions/rearrangements, or amplifications, are found in about 1.8% of all tumors,

with a favorable response observed in many cases to RET-directed therapy[89]. Despite the overall rarity of RET aberrations, their significance in driving oncogenesis highlights the need for further research and understanding in order to explore potential therapeutic interventions.

Pralsetinib, a selective RET receptor tyrosine kinase inhibitor, has shown encouraging results in the phase 1/2 ARROW trial, where it was evaluated in patients with solid tumors carrying RET fusions, including BTC[90]. The study showed an ORR of 57% (95%CI: 35%-77%), with a DOR of 11.7 months (95%CI: 5.5-19.0 months). The median PFS reached 7.4 months (95%CI: 5.1-13.6 months) and the median OS reached 13.6 months (95%CI: 7.5-NE) with a median follow-up of 23.5 months. Among the three BTC patients, two participants had objective responses. In the safety analysis of 29 eligible patients, 20 patients (69%) experienced grade ≥ 3 TRAEs, with the most frequent any-grade TRAEs being abnormal liver function tests. Based on these findings, pralsetinib was approved by the FDA for advanced or metastatic RET-fusion-positive lung and thyroid cancers[91,92]. While pralsetinib has not received FDA approval as a tumor-agnostic drug, it is listed as a recommended option in the NCCN guidelines for both first-line and subsequent-line treatment of RET-positive BTC[21].

Selpercatinib, a highly selective RET kinase inhibitor, was approved by the FDA for the treatment of any RET-mutated solid tumors following promising data from the LIBRETTO-001 trial, a phase 1/2 basket trial assessing its efficacy in solid tumors with RET fusion, regardless of their primary location[93,94]. Among 41 efficacy-evaluable patients, the ORR reached 43.9% (95%CI: 28.5-60.36), with a DOR of 24.5 months (95%CI: 9.2-NE), including two BTC patients, one of whom had a response. The PFS was 13.2 months (95%CI: 7.4-26.6) and the OS reached 18.0 months (95%CI: 10.7-NE). 38% of patients had grade ≥ 3 TRAEs, with hypertension and abnormal liver function tests being frequently observed as grade 3 TRAEs. Selpercatinib is currently recommended in the NCCN guidelines for both progressive and first-line treatment of RET-positive BTC[21]. Furthermore, its CNS activity highlights its potential in treating locally advanced or metastatic solid tumors harboring RET fusions.

RET fusions exhibit diverse patterns, and the impact of fusion partners and breakpoints on drug response is not fully understood[95]. Despite an initial positive response, acquired resistance to RET inhibition treatment inevitably emerges[96]. While data on acquired resistance to RET inhibitors is growing, a comprehensive understanding is not yet matured. Recent data in lung and thyroid cancer patients suggest that primary and acquired resistance mechanisms converge on MAPK pathway activation[97]. Therefore, employing a sequential approach to RET-targeted therapy could require a combination of treatments involving inhibitors that target distinct MAPK pathways. Furthermore, it appears necessary to reevaluate the characterization of tumors treated with RET inhibitors when they show progression under RET inhibitor therapy.

IMMUNOTHERAPIES FOR BILIARY TRACT CANCER

High tumor mutational burden

Programmed cell death ligand-1(PD-L1) is an immune checkpoint ligand that allows cancer cells to evade immune recognition[98]. Immunotherapy targeting PD-L1 or its receptor, programmed cell death 1 (PD-1), has shown promising results in various cancers. Hypermutated tumors with a high tumor mutational burden (TMB) are particularly responsive to immune checkpoint inhibitors[99,100]. TMB is the number of somatic gene mutations present in a tumor and it serves as a biomarker for predicting the response to immunotherapy[101]. TMB-H, with a threshold of ≥ 10 mutations per megabase, indicates a high probability of neoantigen formation and has been associated with improved outcomes in several cancer types. Approximately 4% of all subtypes of BTCs are estimated to have TMB-H[19].

Pembrolizumab, an immune checkpoint inhibitor targeting PD-1 receptors, was approved by the FDA for the treatment of TMB-H tumors[102]. The KEYNOTE-158 trial assessed pembrolizumab in TMB-H tumors across various sites[103]. The study revealed a 29% ORR (95%CI: 21%-39%). Additionally, 57% of participants achieved a DOR lasting 12 months or longer, and 50% attained a DOR of 24 months or longer. Although there were 63 BTC patients in the KEYNOTE-158 trial, none of them had high TMB. However, two out of the 63 patients had objective responses.

Recent data from the phase II CheckMate-848 study (NCT03668119) demonstrated promising results using nivolumab and ipilimumab in patients with previously treated advanced or metastatic TMB-H solid tumors[104]. The ORR was 35.5% (95%CI: 24.1%-47.8%) in the group with tissue TMB-H and 22.5% (95%CI: 13.9%-33.2%) in the group with blood TMB-H. Based on the above findings, the current NCCN guidelines list nivolumab and ipilimumab combination therapy as frontline and subsequent-line treatment for TMB-H BTCs, and pembrolizumab is listed as a subsequent-line treatment for TMB-H BTCs[21].

High microsatellite instability and mismatch repair deficient

Tumors with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H) levels show increased neoantigen production and CD8+ T cell infiltration[105]. MSI-H/dMMR leads to difficulties in repairing DNA replication errors, causing mutations. The MSI-H/dMMR is identified in about 2.06% of iCCA patients[17].

Pembrolizumab has received full FDA approval for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors, who have progressed after prior treatment and have limited alternative options[106]. The approval is based on data from multiple trials, including KEYNOTE-158 (NCT02628067), KEYNOTE-164 (NCT02460198), and KEYNOTE-051 (NCT02332668), involving 504 patients with over 30 types of tumors. An integrated analysis of these studies revealed that, at a median follow-up of 20.1 months, pembrolizumab achieved an ORR of 33.3% (95%CI: 29.2%-37.6%), comprising a CR rate of 10.3% and a partial response rate of 23.0%. According to the NCCN guidelines, pembrolizumab is currently listed as both a first-line and subsequent-line treatment option for MSI-H/dMMR tumors[21].

Dostarlimab, another anti-PD-1 monoclonal antibody, was assessed in the phase I GARNET trial. This study included 106 patients who had advanced solid tumors, and two of them had MSI-H/dMMR BTCs[107]. The trial showed that an ORR at 38.7% (95%CI: 29.4%-48.6%) in patients with dMMR and CR was around 7.5%. A median DOR was not reached with a median follow-up of 12.4 months. About 8.3% of patients experienced at least one grade 3 or higher adverse event, with the most common being an elevated lipase level. Based on this, the FDA approved dostarlimab for recurrent or advanced solid tumors with MSI-H/dMMR, which have progressed after previous lines of therapy and do not qualify for suitable alternative treatment options[108].

Adoptive immunotherapy

While immune checkpoint inhibitors have made notable progress, their effectiveness in treating BTC remains unsatisfactory. Another promising approach in the field of BTC immunotherapy is Chimeric Antigen Receptor (CAR) T-cell therapy, which is currently being evaluated. CAR T-cell therapy has demonstrated exceptional efficacy in the treatment of hematologic cancers, having received regulatory approval for conditions such as B-cell lymphoma. However, expanding the use of CAR T-cell treatment to solid tumors, such as BTC, presents unique challenges due to these tumors' ability to exclude T cells from the tumor microenvironment and avoid immune system recognition.

Researchers have been actively exploring the potential of introducing highly potent cancer-specific T cells into solid tumors as an innovative strategy. Encouraging findings have been observed, particularly with fourth-generation anti-CD133 CAR T-cells, which have demonstrated significant effectiveness against BTC cells expressing CD133[109]. Additionally, the combination of CAR T therapies targeting both EGFR and CD133 in a cocktail immunotherapy approach has produced promising outcomes in advanced BTC patients[110]. Furthermore, a phase I study (NCT01869166) involving EGFR-specific CAR T cells for EGFR-mutated advanced BTC has shown favorable results, including a 5.8% CR rate and stable disease in 58.8% of patients[111].

Moreover, at the 2023 ASCO meeting, results from a phase I trial using gavocabtagene autoleucel, an autologous genetically engineered anti-mesothelin T cell receptor fusion construct cell therapy, were presented[112]. This trial focused on patients with refractory mesothelioma and other mesothelin-expressing solid tumors, including BTC. The results were promising, with an ORR of 21% and a DCR of 77% among the 32 patients who participated in the study, including one patient with BTC. Furthermore, the 6-month OS rate reached 70.2%. These findings suggest a potential avenue for effective treatment in patients with mesothelioma patients and other mesothelin-expressing solid tumors, offering hope in the fight against these challenging malignancies. Nevertheless, concerns about the toxicity of CAR T-cell therapy in BTC persist, mainly due to potential toxicity and endothelial damage, emphasizing the imperative for further investigation and the conduct of clinical trials.

In conclusion, while CAR T-cell therapy has significantly advanced the treatment of hematologic malignancies, its application for solid tumors, including BTC, brings forth a landscape filled with both promise and hurdles. Research involving CAR T cells targeting specific antigens such as CD133 and EGFR has demonstrated effectiveness in both preclinical and clinical contexts, instilling hope for patients with conditions like BTC. Nonetheless, persisting safety concerns and the imperative for more extensive research underscore the continuous endeavors to enhance the potential of CAR T-cell therapies for solid tumors, with the ultimate goal of improving their efficacy while mitigating potential adverse effects.

CHALLENGES AND POTENTIALS OF TARGETED THERAPIES

Sequencing of cancer genomics

The evolution of targeted therapy is closely intertwined with the advancements in DNA sequencing technology used in cancer cells. Cancer, being a genomic disease, is often influenced by both somatic and germline mutations, highlighting the crucial need to comprehend cancer's genomic sequencing in order to uncover its origins and develop personalized treatment approaches. Recent progress and cost reductions in NGS have greatly accelerated the transformation of cancer genomic data into practical clinical applications. It allows simultaneous analysis of hundreds or thousands of genes, empowering the implementation of molecularly targeted therapy based on the insights gained from the results.

NGS technology has enabled the identification of genomic profiles for individual cancer cells, paving the way for personalized treatment approaches. However, the diversity of tumor genomic sub-categories identified by NGS makes it exceedingly difficult to conduct randomized controlled trials with an adequate number of patients for each specific sub-category[113]. Furthermore, the intratumoral environment consists of diverse and heterogeneous cells, resulting in variations in genomic profiles and mutation data among these cells. As a consequence, there are concerns about the feasibility of relying solely on sequencing results to determine the most suitable targeted therapy[114].

Resistance and potential overcome strategies

The iCCA develops resistance to treatments, which is closely associated with cancer-related mortality, although the precise mechanisms underlying this resistance are not fully understood. During cancer treatment, adaptive changes lead to acquired resistance, involving mechanisms such as genetic alterations, changes in the tumor's microenvironment, metabolic reprogramming, and loss of the treatment target[115,116].

One of the investigational methods to elucidate the development of acquired resistance in cancer, as observed in targeted therapy, involves analyzing the molecular differences between tumor samples before and after acquiring resistance[117]. By comparing the resistant tumor sample with the pre-treatment tumor sample at the molecular level, we can identify whether the resistance is due to changes in previously actionable mutations or the emergence of new mutations. This comprehensive analysis can potentially provide insights into the underlying causes of resistance and guide the modification of treatment strategies accordingly.

Furthermore, to overcome acquired resistance driven by tumor genetic alterations, exploring the next generation of inhibitors and researching strategies for combination treatments appears to be essential. By focusing on these areas of investigation, we can aim to develop more effective approaches to combat acquired resistance and enhance the overall efficacy of cancer therapies.

Determining the sequence of treatment

We have thoroughly reviewed various systemic treatment options for advanced iCCA, along with the foundational research data. While we are aware of the several options available, the next consideration and decision-making process involve the prioritization and sequence of these treatment modalities. As previously mentioned, any systemic treatment may initially demonstrate a favorable response but ultimately develop acquired resistance due to various factors, necessitating a change in treatment.

Given the relatively recent use of targeted therapies and the rarity of actionable mutations among the iCCA patient population, conducting head-to-head comparing trials between targeted therapy and chemotherapy and/or immunotherapy is challenging. Consequently, selecting treatment strategies tailored to individual patient situations is essential. Elements shaping these individualized decisions encompass factors such as the extent of tumor burden, the urgency of treatment initiation takes into account the time required for sequencing the tumor genome, the patient's medical history, drug accessibility, financial aspects, anticipated toxicity, patient performance status, and anticipated treatment response.

In many cases, combining chemotherapy with immunotherapy would be a preferable first-line treatment while awaiting tumor genomic information. However, as the tumor progresses, established guidelines for selecting second-line therapy remain absent due to limited supportive data. Tailored to the unique context of individual patients, second-line treatment might encompass targeted therapy, immunotherapy, or FOLFOX, with reference to the ABC-06 trial findings, alongside the consideration of other cytotoxic chemotherapy treatments. Although direct comparative prospective study data could be lacking, using targeted therapy upfront and reserving FOLFOX could be a reasonable approach if the patient has any indication for targeted therapy. Targeted therapies are generally perceived as more tolerable and can exhibit considerable effectiveness, particularly when administered early, potentially yielding enhanced patient outcomes. The investigation into the sequencing of treatment strategies demands further exploration.

Potential role as neoadjuvant and adjuvant therapy

In patients with iCCA, complete resection is regarded as the sole definitive curative option, although its feasibility is limited for many due to the advanced disease at diagnosis. While not conclusively established,

based on current data, hepatic resection with negative margins is considered the preferred surgical goal[118]. The available research data on neoadjuvant and adjuvant chemotherapy in resectable iCCA presents challenges in drawing definitive conclusions. A study result by Buettner *et al.* showed similar OS and PFS between patients with perioperative chemotherapy and those without, although this needs to be cautiously interpreted due to low neoadjuvant treatment patient numbers and possible selection bias effect[119]. Conversely, more recent research indicates that neoadjuvant therapy, particularly in stage II-III disease, may lead to enhanced OS[120-122]. Moreover, the optimal adjuvant treatment strategy for resected iCCA remains uncertain due to limited clinical trial data supporting a standard regimen.

The efficacy of targeted therapy as neoadjuvant or adjuvant treatment for resectable disease remains an unexplored area of research. The challenges of limited early-stage detections and infrequent actionable mutations hinder the conduct of studies in this domain. Moreover, the effects of targeted therapy on tumor downstaging, survival benefits, recurrence-free survival, and potential adverse events leading to unfavorable outcomes require further elucidation.

In an attempt to address this, a clinical trial (NCT05514912) is underway to evaluate chemo-targeted therapy for resectable intrahepatic cholangiocarcinoma using infigratinib in combination with chemotherapy in FGFR2 fusion-positive iCCA[123]. The study aims to provide valuable insights into the treatment efficacy for this specific patient subset. To our knowledge, there are currently no ongoing clinical trials investigating the efficacy of targeted therapy or combination treatments with targeted therapy in an adjuvant setting. Additional research is needed to address these uncertainties and shed light on potential treatment strategies.

CONCLUSION

In summary, iCCA remains a formidable challenge with historically poor outcomes. However, recent advancements in targeted therapies and immunotherapy offer hope for improved treatment strategies and better patient outcomes.

Targeted therapies, such as FGFR inhibitors, IDH inhibitors, and HER2 inhibitors, are demonstrating promising results in iCCA treatment by specifically targeting genetic alterations. These therapies provide personalized treatments, offering the potential for more effective responses and increased survival rates among iCCA patients.

Immunotherapies, including PD-L1 inhibitors and CAR T-cell therapy, have garnered significant attention as emerging treatment modalities in the context of BTC. Numerous ongoing research endeavors are focused on these approaches. Immune checkpoint inhibitors have gained FDA approvals for iCCA with TMB-H and MSI-H/dMMR, expanding the therapeutic options available for advanced or metastatic disease.

Despite these breakthroughs, challenges such as conducting large trials, overcoming acquired resistance, and optimizing treatment sequencing remain. Addressing these areas requires ongoing research and investigation. In conclusion, while iCCA treatment remains challenging, recent progress in targeted therapies and immunotherapy brings optimism. By advancing scientific understanding and clinical practice, we can pave the way for better outcomes for iCCA patients.

DECLARATIONS

Acknowledgments

I would like to acknowledge Donghyun Gim for providing assistance with creating the figure.

Authors' contributions

Conceptualization: Badri N
Writing-original draft preparation: Gim G
Writing-review and editing: Badri N
Supervision: Badri N
Read and agreed to the published version of the manuscript: Gim G, Badri N

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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