Review Article
How to incorporate new agents into precise medicine for cholangiocarcinoma?

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Abstract: Cholangiocarcinoma, a rare and aggressive form of cancer originating from the bile ducts in the liver, poses a significant challenge for treatment. However, the emergence of precision medicine has brought newfound hope for more effective therapies. Several precision medicine approaches have demonstrated promise in the treatment of cholangiocarcinoma. One such approach is targeted therapy, which involves utilizing drugs that specifically target the genetic mutations or alterations present in the tumor cells. In the case of cholangiocarcinoma, mutations in the IDH1 and IDH2 genes are frequently observed. Immunotherapy is another precision medicine approach being explored for the treatment of cholangiocarcinoma. Immune checkpoint inhibitors like pembrolizumab and nivolumab can be used to bolster the body’s immune response against cancer cells. While the response to immunotherapy can vary among individuals, studies have shown promising results, particularly in patients with high levels of tumor-infiltrating lymphocytes or microsatellite instability. Moreover, molecular profiling of cholangiocarcinoma tumors can play a crucial role in identifying potential targets for precision medicine. Through advanced next-generation sequencing techniques, specific gene alterations or dysregulations in pathways can be identified, potentially guiding treatment decisions. This personalized approach enables tailored treatment plans based on the unique genetic characteristics of each patient’s tumor. In conclusion, the advent of precision medicine has opened up new avenues for the treatment of cholangiocarcinoma. Targeted therapy and immunotherapy have exhibited promising results, and further molecular profiling is expected to uncover additional therapeutic options. Such advancements represent a significant step forward in the quest to enhance outcomes for individuals affected by cholangiocarcinoma.

Keywords: Cholangiocarcinoma, targeted therapy, precise medicine

Introduction

Cholangiocarcinoma (CCA) is a highly diverse tumor that can develop in various parts of the biliary tract system, both within and outside the liver. The location of the tumor determines its subtype, which includes intrahepatic (iCCA), perihilar (pCCA), and distal extrahepatic (dCCA). Each subtype has unique characteristics that greatly influence the prognosis of the disease [1]. Intrahepatic CCA specifically refers to tumors located within the liver parenchyma near the second-order bile ducts. Perihilar CCA is situated between the insertion site of the cystic duct and the common bile duct, away from the second-order bile ducts. Distal CCA is found in the common bile duct beyond the insertion site of the cystic duct. In the past, perihilar CCA and distal CCA were collectively classified as extrahepatic cholangiocarcinoma (eCCA) [2]. On a global scale, CCA accounts for roughly 3% of all gastrointestinal malignancies and is the second most common form of primary liver cancer, following hepatocellular carcinoma, comprising 10-15% of cases. Unfortunately, mortality rates for CCA have been steadily increasing over the past few decades, experiencing a 36% rise in the United States between
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1999 and 2014 alone. Since 2013, over 7000 deaths have been attributed to this devastating disease [3].

In recent years, the US Food and Drug Administration (FDA) has given its approval to targeted therapies for the treatment of cholangiocarcinoma (CCA). The growing interest in these therapies stems from their unique ability to selectively target cancer cells, all the while safeguarding healthy cells nearby [4]. This document aims to delve into the most recent advancements in highly mutated agents for CCA, showcasing their potential to usher in a new era of precision medicine for this particular type of cancer.

Isocitrate dehydrogenase 1 and 2 mutations

IDH1 and IDH2 are the metabolic genes that undergo the most frequent mutations in human cancers, making them a significant focus of research. In the realm of epithelial malignancies, particularly iCCA, IDH mutations are prevalent. Studies have revealed that IDH1 mutations are present in approximately 10-20% of iCCA patients [5-7]. IDH inhibitors could potentially play a substantial role as a targeted therapy against CCA, particularly iCCA.

Ivosidenib, an IDH1 inhibitor, received FDA approval in August 2021 for the treatment of locally advanced or metastatic CCA in adult patients with the IDH1 mutation who have previously undergone treatment [8]. The results of a phase III clinical trial (ClariDHy, NCT02989857) demonstrated significant benefits of ivosidenib in patients with advanced or metastatic CCA and IDH1 mutation who had received up to two prior chemotherapy regimens, particularly in terms of progression-free survival (PFS). These results were based on 90% of patients who were iCCA in the ivosidenib group and 95% in the placebo group, and R132C mutation of IDH1 was the commonest type (ivosidenib: 68%, placebo: 74%). Patients were randomly assigned to receive either ivosidenib or placebo in a 2:1 ratio, with the option to switch from placebo to ivosidenib after disease progression. Out of the 185 patients who were randomized (91% with iCCA), 124 were given ivosidenib and 61 were given placebo. The primary endpoint of progression-free survival (PFS) was achieved, with an HR of 0.37 (95% CI: 0.25-0.54; P < 0.001) and median PFS of 2.7 months and 1.4 months for ivosidenib and placebo, respectively. Although the difference in median PFS may not appear significant, the PFS rates at 6 and 12 months were notably higher in the ivosidenib group (32.0% and 21.9% at 6 and 12 months, respectively) compared to the placebo group (0% at both time points). Ivosidenib also had an impact on overall survival (OS), with a median OS of 10.8 months in the ivosidenib group compared to 6 months in the placebo group, when adjusted for cross-over (HR 0.46; P = 0.0008). The unadjusted OS in the placebo group, where 57% of patients crossed over to ivosidenib, was 9.7 months [9]. The toxicity profile was in keeping with the previously reported findings Ivosidenib also showcased notable enhancements in various quality-of-life measures, including pain, emotional and cognitive functioning, anxiety, and tiredness. The most frequently reported all-grade treatment-emergent adverse events (TEAE) associated with ivosidenib was nausea (42%), while ascites (9%), anemia (7%), increased blood bilirubin level (6%), and hypotension (6%) were the most common grade 3 events [10]. These findings prompted the NCCN to recommend the use of ivosidenib for patients with CCAs who have the IDH1 mutation and are refractory to chemotherapy [11].

The clinical findings have revealed that ivosidenib demonstrates a nature of enhanced safety and yields improved progression-free survival (PFS), along with a promising potential for overall survival (OS), even amongst patients involved in crossover during the study. This treatment proves to be beneficial for patients with advanced IDH1-mutated cholangiocarcinoma (CCA), and it has recently obtained approval from the FDA. Enasidenib, a specific IDH2 inhibitor, has also garnered approval from the FDA for acute myeloid leukemia and is currently under investigation for its potential application in CCA (NCT02273739) [12]. Vorasidenib, an oral brain-penetrant inhibitor of mutant IDH1 and IDH2 enzymes, showed preliminary activity in IDH-mutant gliomas [13]. However, the natural application of enasidenib and vorasidenib in the treatment of CCA is still pending clinical trials.

Fibroblast growth factor receptor fusions

Fibroblast growth factor receptors (FGFR) have a significant impact on the development of
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Intrahepatic cholangiocarcinoma (iCCA) [14]. 10-20% of iCCAs have been found to have FGFR1, FGFR2, FGFR3, FGFR4, and FGFR2 fusions. FGFR2 proteins, when constantly activated, promote cell proliferation by stimulating the pathway and exhibit point mutations, amplification, or overexpression [15, 16]. FGFR2 fusions, a specific pattern of genetic alteration, are present in 10-15% of iCCA but very minimally in eCCA [16]. With all this in mind, pharmacologic targeting against the FGFR pathway, such as with FGFR inhibitors, has gained much attention with the development of multiple inhibitors and various clinical trials.

Although the first-generation FGFR inhibitors target multiple receptors, they lack strong anti-FGFR inhibition and often result in harmful side effects. As a result, several new inhibitors of FGFR isoforms 1-3 have emerged as promising treatments for advanced CCAs with FGFR2 gene fusions. These inhibitors, such as erdafitinib, infgratinib, pemigatinib, derazantinib, and the non-ATP-competitive inhibitor futibatinib, have demonstrated therapeutic benefits [17].

Infgratinib is a competitive tyrosine kinase inhibitor specific to FGFR1-3. Receptor tyrosine kinase inhibitors have also revolutionized cancer therapy in recent decades, with now over 40 compounds approved by the FDA for cancer therapy. The multicenter, open-label, phase II study (NCT02150967) evaluated the effectiveness of infgratinib in patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangement and previously treated with at least one gemcitabine-containing regimen. Among the 61 patients enrolled in the study, demonstrated that overall response rate (ORR) of 14.8% and a disease control rate (DCR) of 75.4%. The FGFR2 alternation type contributes to the final results, including fusion (78.7%), mutation (13.1%), and application (4.9%). The Common adverse events observed in the patients included hyperphosphatemia (72.1%), fatigue (36.1%), stomatitis (29.5%), and alopecia (26.2%). Moreover, grade 3 or 4 treatment-related adverse events were reported in 41% of patients [18]. In a subgroup analysis of patients with FGFR2 gene fusions or rearrangements, an independent central review evaluated an objective response rate of 23.1%. Common treatment-related adverse events of any grade in this subgroup included hyperphosphatemia (77%), stomatitis (54%), and ocular toxicity such as dry eyes (34%) [19]. In May 2021, the FDA approved Infgratinib for patients with FGFR2 fusion-positive cholangiocarcinoma [20]. Currently, an ongoing phase III study (PROOF 301, NCT3773302) is assessing the use of Infgratinib as a first-line therapy [21].

The results of a phase II study (FIGHT-202, NCT02924376) on pemigatinib, an ATP-competitive FGFR kinase inhibitor, have shown promise for patients with advanced cholangiocarcinoma who have undergone previous treatment, particularly for iCCA (89%). Among the participants, 73.3% had FGFR2 fusions or rearrangements, while 13.7% had other FGFR alterations. All patients had previously received at least one line of systemic therapy, with 39.0% having received two or more lines for advanced/metastatic disease. Patients with FGFR2 fusions or rearrangements had a response rate of 35.5%, while no objective responses were seen in patients without these genetic alterations. The median progression-free survival (PFS) was 6.9 months for patients with FGFR2 fusions or rearrangements, compared to 1.7 and 2.1 months for those without these alterations. Median overall survival (OS) was 17.5 months for patients with FGFR2 fusions or rearrangements, compared to 6.7 and 4.0 months for those without. The 12-month survival rates were 68%, 23%, and 13% for these groups, respectively. Further analysis confirmed sustained responses and tolerability with pemigatinib, with patients who responded and had FGFR2 rearrangements/fusions experiencing twice the OS compared to non-responders (median 30.1 versus 13.7 months). Pemigatinib was well-tolerated, with the most common all-cause grade ≥ 3 treatment-emergent adverse events being fatigue (5.4%), diarrhea (3.4%), and nausea (2%). About 10.2% of patients discontinued pemigatinib due to adverse events. One of the most common TEAE associated with this treatment was hyperphosphatemia, occurring in 60% of the patients and 49% of the patients in the study unfortunately died, the majority of deaths result from disease progression (42%). However, no deaths were deemed to be treatment-related [22]. These findings have led to the approval of pemigatinib by the FDA for patients with advanced cholangiocarcinoma and positive FGFR2 fusions [23].
To further explore the potential of pemigatinib, a phase III study, FIGHT-302, is currently underway. This study aims to compare pemigatinib with gemcitabine plus cisplatin chemotherapy as a first-line treatment option for patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangements. The ultimate goal of this study is to offer these patients a new and improved first-line treatment option [24].

Derazantinib, also known as ARQ 087, is a potent inhibitor of FGFR2, FGFR1, and FGFR3 kinases, taken orally and demonstrating strong efficacy against these targets [25]. Phase 1/2 study, adult patients with unresectable iCCA and FGFR2 fusion who had experienced disease progression and were intolerant to or ineligible for first-line chemotherapy were enrolled (NCT01752920). The study revealed that ORR of 20.7% and DCR of 82.8%. 93.1% of patients experienced TEAE, the most common were asthenia/fatigue (69.0%), eye toxicity (41.4%), and hyperphosphatemia (75.9%). Additionally, 27.6% of patients experienced grade ≥ 3 TEAE [26].

In 2019, Erdafitinib was granted approval by the FDA as a therapy for individuals diagnosed with locally advanced or metastatic urothelial carcinoma. This endorsement was primarily due to the noteworthy clinical efficacy and safety exhibited by Erdafitinib, which acts as a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor [27].

Futibatinib, also known as TAS-120, is a type of medication that belongs to the irreversible pan-FGFR inhibitor class. Its main function is to inhibit the phosphorylation of FGFR and block downstream signaling pathways. It has shown promising results in clinical studies involving patients with CCA who have FGFR2 gene fusions/rearrangements or mutations. Phase I study has shown activity in cohorts of patients with FGF/FGFR aberrations beyond FGFR2 fusions with ORR of 15.6 and DCR of 71.9% in these patients [28]. Subsequently, in the phase II FOENIX-CCA2 trial (NCT02052778), futibatinib was tested on patients specifically diagnosed with iCCA and FGFR2 fusions/rearrangements. Out of all the patients participating in the trial, 78% had FGFR2 fusions, while 22% had FGFR2 rearrangements. The results showed encouraging news that ORR was 41.7% and DCR was 82.5%. The most common treatment-related adverse events (TRAE) reported during this trial were hyperphosphatemia (85%), alopecia (33%), and dry mouth (30%) [29]. Currently, an ongoing open-label, randomized phase III trial called FOENIX-CCA3 (NCT04093362) is comparing the efficacy of futibatinib with the standard therapy of gemcitabine plus cisplatin as a first-line treatment for patients with advanced iCCA and an FGFR2 rearrangement. The objective of this trial is to assess the superiority of futibatinib compared to the standard therapy in terms of OS and PFS [30]. Excitingly, on September 30, 2022, futibatinib received approval from the United States for the treatment of adult patients with previously treated, locally advanced, or metastatic intrahepatic cholangiocarcinoma with FGFR2 fusion or rearrangement [31]. This approval offers hope to patients suffering from this condition, as futibatinib provides a novel treatment option that specifically targets the genetic alterations associated with cholangiocarcinoma.

As stated, FGFR inhibitors have shown promising results in the treatment of CCA, particularly in patients with FGFR2 fusions or rearrangements. The safety profile of these inhibitors is manageable, with hyperphosphatemia being a common side effect. Nail changes, mucosal dryness, ocular toxicity, and gastrointestinal issues are also potential side effects that need to be carefully monitored and managed. Despite these potential challenges, the preliminary data on FGFR inhibitors in advanced iCCA is encouraging. Further research is needed to determine the impact of different fusion partners and mutations on the efficacy of FGFR inhibitors in iCCA. With proper management of side effects, FGFR inhibitors have the potential to be a valuable second-line treatment option for patients with advanced or metastatic CCA.

**BRAF mutations**

Mutation of the BRAF gene is one way in which the MAPK pathway can become constitutively activated. Mutations in the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene, including exon 11 mutations (G469A and V600E), are found in approximately 1% to 7% of cholangiocarcinoma (CCAs), most commonly iCCA [14, 32]. The BRAFV600E inhibitor, Vemurafenib, was tested in a phase II basket study involving eight patients with CCA. The study
reported one partial response (PR) and five cases of stable disease (SD) in the CCA group [33]. For patients with BRAF\textsuperscript{V600E} mutations, a combination therapy targeting both BRAF (dabrafenib) and MEK (trametinib) has shown promising results in solid tumors. This approach was tested in the ROAR basket clinical trial, with a subgroup of 33 patients with biliary tract cancer. The study revealed partial response rates of 42% and 36% based on investigator and independent assessments, respectively. The most commonly observed TEAE was an increase in γ-glutamyl transferase, affecting 12% of patients [34]. Based on these findings, the combination of dabrafenib and trametinib is included as a treatment option for patients with BRAF\textsuperscript{V600E}-mutated CCA in the NCCN guidelines [34]; nevertheless, these drugs are not currently approved for this indication.

Human EGFR2

Human EGFR2 (HER2) is a receptor that plays a crucial role in promoting the growth of cancer cells. It is a member of a receptor family that consists of EGFR, HER1 (ERBB1), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4). Upon phosphorylation in their inner domains, these receptors activate secondary messengers that lead to a variety of biological effects [35]. The activation of HER2 has been linked to the development of tumors through the activation of the MAPK and PI3K pathways, as well as the loss of cell polarity and adhesion. Additionally, it disrupts the cell cycle by activating cyclin D and inhibiting p27 [36]. Recent studies have revealed that the HER2 protein is overexpressed in 36.4% of gallbladder cancer cases and up to 18% of extrahepatic cholangiocarcinoma cases [37, 38]. The overexpression of HER2 in these cases has been associated with a poorer prognosis and an increased likelihood of metastasis. Various clinical trials have been conducted to investigate the effectiveness of drugs targeting HER2 in the treatment of biliary tract cancer (BTC). For example, the My Pathway trial (NCT02091141) examined the combination of trastuzumab and pertuzumab in 39 patients with HER2-positive BTC. The trial showed an objective response rate (ORR) of 23%, a progression-free survival (PFS) of 4 months, and an overall survival (OS) of 10.9 months [39]. Another trial, the phase II SUMMIT trial (NCT01953926), evaluated the efficacy of neratinib as a monotherapy in 25 patients with BTC and HER2 mutations. The trial demonstrated an ORR of 12%, a median PFS of 2.8 months, and a median OS of 5.4 months [40]. Currently, there are multiple clinical trials underway to further explore HER2-directed therapies for various solid tumors. These trials include the MATCH trial (NCT02465060), which investigates the effectiveness of different tyrosine kinase inhibitors in HER2-positive tumors, and the TAPUR trial (NCT02693535), which evaluates the efficacy of multiple TKIs, such as trastuzumab and pembrolizumab, in HER2-positive tumors.

Zanidatamab, a humanized, bispecific monoclonal antibody, utilizes a unique approach by targeting two distinct regions of the HER2 protein. Zanidatamab can bind to the two extracellular domains of HER2 which leads to receptor clustering, receptor internalization, and downregulation, in turn leading to the inhibition of uncontrolled downstream signaling and the prevention of malignant growth. This novel therapeutic agent is currently being evaluated in the HERIZON-BTC-01 trial (NCT04466891) to assess the efficacy of zanidatamab in patients with HER2-amplified, unresectable, locally advanced, or metastatic biliary tract cancer who have experienced disease progression following previous treatment with gemcitabine-based therapy. The results confirmed ORR of 41.3% determined by independent central review and 74% of patients discontinued treatment owing to radiographic progression. Moreover, it is worth highlighting that no grade 4 TEAE or treatment-related deaths and 18% of patients who had grade 3 TEAE were reported during the trial. This signifies the favorable safety profile of zanidatamab, further supporting its potential as a viable treatment option for patients with advanced biliary tract cancer [41].

Neurotrophic tyrosine receptor kinase fusions

NTRK genes are responsible for producing various neurotrophic tyrosine receptor kinase proteins, including TrkA, B, and C. These proteins are activated by the binding of neurotrophins, which then initiate a series of signaling pathways such as RAS/RAF/MEK/ERK mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), and phospholipase C-γ1 [42]. NTRK fusions have been identified in
3.5% of patients with iCCA. Although NTRK fusion genes are not common in patients with CCA, data from solid tumor patients indicate that TRK inhibitors like entrectinib or larotrectinib could be beneficial for treatment [43-46]. Based on NCCN guidelines, these inhibitors are recommended as first or later-line therapy for patients with NTRK gene fusion-positive CCA [47]. Clinical trials have demonstrated that both larotrectinib and entrectinib, which target all three TRK proteins, have shown significant activity. Phase I trial of larotrectinib (NCT02122913) with 55 patients, the ORR was 79%, the mPFS was 28.3 months, and the progression-free rate at 12 months was 67%. The trial included only two CCA patients, with one showing progressive disease and the other achieving a partial response (PR) of 80% [46]. A combined analysis of three ongoing phase I or II trials of entrectinib (STARTRK-1:NCT02097810, STARTRK-2:NCT02568267, and ALKA-372-001:NCT02650401) included a total of 54 patients with 10 different NTRK fusion-positive tumor types. The analysis revealed a median PFS of 12.9 months (IQR 8.77-18.76) and an ORR of 57% (95% CI: 43.2-70.8%). Only one CCA patient was included in the analysis, who achieved a PR with a 40% reduction in tumor size [45].

**BRCA mutations**

BRCA mutations are found in a small proportion of CCA cases, with BRCA1 mutations present in only 0.4% of iCCA and 2.6% of eCCA cases, and BRCA2 mutations in 2.0% of iCCA and 2.6% of eCCA cases [48]. Several studies have demonstrated that CCA patients with BRCA1 or BRCA2 mutations can achieve significant relief when treated with poly(ADP) ribose polymerase (PARP) inhibitors [49-51]. Currently, several phase II studies are underway to investigate the effectiveness of PARP inhibitors in patients with biliary tract cancers (NCT04298021; NCT04306367; NCT04895046). The National Comprehensive Cancer Network (NCCN) recommends olaparib as the primary PARP inhibitor for BRCA-mutated pancreatic cancer or biliary tract cancers [52]. Rucaparib, which has been approved for ovarian and prostate cancer, is also being studied as a maintenance therapy for individuals with BRCA mutations [53]. In recent findings, veliparib, another PARP inhibitor, has shown promise in advanced ovarian cancer with BRCA mutations when used in combination with first-line chemotherapy, resulting in a notable increase in progression-free survival (PFS) [54]. Additionally, AZD 5305, a novel and highly selective PARP inhibitor, is currently undergoing evaluation in the phase I/IIa PETRA trial (NCT04644068) [55].

**KRAS mutations**

KRAS mutations are present in 9% to 40% of CCA, including specific mutations such as KRAS G12C or KRAS G12D mutations [56, 57]. The KRISTAL-1 study (NCT03600883) is a phase I/II study that aims to evaluate the effectiveness of adagrasib, a KRAS G12C inhibitor, in patients with advanced solid tumors carrying the KRASG12C mutation. Out of the 42 participants in the study, 8 had biliary tract cancer. Preliminary findings show that adagrasib has demonstrated promising clinical activity, with ORR of 32.2% and DCR of 88.1% in patients with “other” tumors, including those with biliary tract cancer. The median PFS was 6.3 months [58]. In a recent study (NCT03785249) investigating the use of adagrasib for the treatment of biliary tract cancer with the KRASG12C mutation, objective responses were observed in 5 patients, resulting in an ORR of 41.7%. The median duration of response was 5.3 months (95% CI: 2.8-7.3), and the median progression-free survival was 7.4 months (95% CI: 5.3-8.6) [59]. Although KRASG12D shows potential as a target for the treatment of solid tumors, additional research is necessary to determine its effectiveness and safety specifically for CCA [60].

**MMR/MSI/tumor mutational burden**

CCA is one type of solid tumor that may not express MMR proteins, leading to hypermutation and MSI during DNA replication [61]. Immunohistochemistry (IHC) is used to detect MMR protein expression, while molecular testing confirms the status of MSI stability [62, 63]. It is important to note that the terms MSI-high and MSI-low are no longer recommended, and MSI-low tumors are now classified as microsatellite stable [63]. When samples lack coordinated expression of at least one MMR protein and show MSI during molecular testing, they are classified as MMR-deficient (dMMR). dMMR occurs in approximately 6% of CCAs, while MSI occurs in 1%-2% [62-64]. These tumor charac-
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Characteristics identify a subgroup of patients who may benefit from treatment with pembrolizumab, a PD-1/L1 inhibitor, based on data from the KEYNOTE-158 study [64]. Pembrolizumab is approved in the United States for MSI-high or dMMR solid tumors of any type, and the NCCN guidelines recommend its use as a first- or later-line treatment for patients with unresectable or metastatic CCA [65]. Pembrolizumab in combination with gemcitabine and cisplatin (KEYNOTE-966 study) could be a new treatment option for patients with previously untreated metastatic or unresectable biliary tract cancer [71].

Tumor mutational burden (TMB), which measures the number of mutations in coding DNA, is associated with microsatellite instability (MSI) in certain types of tumors [63, 66]. However, this relationship does not seem to apply to patients with biliary tract cancers. In a study by Weinberg et al., only 2%-3% of patients with CCA had a high TMB, defined as >17 mutations per megabase. In contrast, the KEYNOTE-158 study found that patients with solid tumors and a high TMB responded better to pembrolizumab. This led to the approval of pembrolizumab in the United States for patients with solid tumors and high TMB [67]. However, it’s worth noting that none of the patients in the KEYNOTE-158 study had biliary cancer, so it remains uncertain whether this approach would be effective for CCA patients.

At present, the European Medicines Agency (EMA) has not approved the utilization of biomarkers such as MMR (mismatch repair), MSI (microsatellite instability), and TMB (tumor mutational burden) in conjunction with corresponding therapies.

Future perspectives and conclusions

Genomic profiling of cholangiocarcinoma tumors can unveil potentially targetable mutations and alterations that could be effectively treated with specific drugs or immunotherapies. As current strategies are still advancing, there is a pressing need to uncover new driving factors and actionable alterations. It is crucial to further explore the efficacy of these approaches beyond just providing palliative care, such as in adjuvant or neoadjuvant settings, and to investigate potential synergies with chemotherapy and immunotherapy. Moreover, comprehending both primary and acquired resistance mechanisms is vital, as well as developing strategies to combat them.

As Figure 1 presented those genetic alterations in intrahepatic and extrahepatic cholangiocarcinoma (CCA) [7, 68-70], the Precision Medicine era in biliary tract cancers has predominantly focused on intrahepatic cholangiocarcinoma (iCCA), particularly emphasizing FGFR and IDH mutations. Figure 2 depicted that tumor signaling pathways and targeted therapies for cholangiocarcinoma (CCA). Moreover, phase III trials have demonstrated the efficacy of IDH1 inhibitors in treating CCA with IDH1 mutations that have progressed after chemotherapy. Additionally, FGFR inhibitors have shown promise in iCCA cases with FGFR2 fusions in phase II trials, with ongoing confirmatory studies.
More investigation is necessary to comprehend resistance mechanisms and consider utilizing these treatments in diverse scenarios, potentially in combination with other agents. Ivosidenib is recommended as a second-line treatment for adult patients with locally advanced or metastatic CCA who have the IDH1 mutation and have already received prior thera-
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Table 1. Relevant clinical studies for targeted therapies with FDA approval for CCA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Study</th>
<th>ORR</th>
<th>DCR</th>
<th>Clinical indication</th>
<th>Grade ≥ 3 TRAE</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivosidenib</td>
<td>IDH1 inhibitor</td>
<td>NCT02989857</td>
<td>2%</td>
<td>53%</td>
<td>IDH1 mutation</td>
<td>7%</td>
<td>2.7 months</td>
<td>10.3 months</td>
</tr>
<tr>
<td>Infigratnib</td>
<td>FGFR inhibitor</td>
<td>NCT02150967</td>
<td>14.8%</td>
<td>75.4%</td>
<td>FGFR2 fusions/rearrangement</td>
<td>66.2%</td>
<td>5.8 months</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pemigatinib</td>
<td>FGFR inhibitor</td>
<td>NCT02924376</td>
<td>35.5%</td>
<td>82%</td>
<td>FGFR2 fusions</td>
<td>68.7%</td>
<td>6.9 months</td>
<td>21.1 months</td>
</tr>
<tr>
<td>Derazantinib</td>
<td>FGFR inhibitor</td>
<td>NCT01752920</td>
<td>20.7%</td>
<td>82.8%</td>
<td>FGFR2 fusion</td>
<td>27.6%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Futibatinib</td>
<td>FGFR inhibitor</td>
<td>NCT02052778</td>
<td>15.6%</td>
<td>71.9%</td>
<td>FGFR2 fusions/rearrangement</td>
<td>57%</td>
<td>Not reported</td>
<td>Not reported</td>
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<tr>
<td>Zanidatamab</td>
<td>Her2 inhibitor</td>
<td>NCT0446891</td>
<td>47%</td>
<td>65%</td>
<td>HER2-amplification</td>
<td>18%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dabrafenib + Trametinib</td>
<td>BRAFV600E inhibitor</td>
<td>NCT02034110</td>
<td>51%</td>
<td>81.3%</td>
<td>BRAFV600E-mutation</td>
<td>40%</td>
<td>9.1 months</td>
<td>13.5 months</td>
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<tr>
<td>Adagrasib</td>
<td>KRASG12C inhibitor</td>
<td>NCT03785249</td>
<td>41.7%</td>
<td>50%</td>
<td>KRASG12C inhibitor</td>
<td>27%</td>
<td>7.4 months</td>
<td>Not reported</td>
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</tbody>
</table>

py. FGFR2 inhibitors, including erdafitinib, infigratnib, pemigatinib, derazantinib, and futibatinib, can be considered as a second-line option for patients with unresectable or metastatic CCA with FGFR2 fusion/rearrangements who have not responded well to chemotherapy. The combination of dabrafenib and trametinib may be used for patients with BRAFV600E-mutated CCA. Trastuzumab plus pertuzumab is recommended as first-line therapy for patients with HER2-positive CCA. Olaparib is the primary PARP inhibitor for BRCA-mutated pancreatic cancer or biliary tract cancers. For patients with Kars G12C mutation CCA, adagrasib has shown promising clinical activity. Pembrolizumab in combination with gemcitabine and cisplatin may be considered as a first-line option for patients with previously untreated metastatic or unresectable biliary tract cancer with dMMR, MSI-high, and high TMB. Table 1 presents relevant clinical studies for targeted therapies with FDA approval for CCA.

However, it is important to note that precision medicine in cholangiocarcinoma is still relatively new, and more research is needed to fully understand the molecular drivers of the disease and develop effective targeted therapies. Moreover, these targeted therapies may only be the second-line choice for patients with CCA, highlighting the need for further clinical trials in combination with chemotherapy or immunotherapy to prove their efficacy. Overall, precision medicine holds promise for improving outcomes in patients with cholangiocarcinoma by identifying specific genomic alterations and tailoring treatment approaches accordingly. It has the potential to revolutionize the management of this challenging cancer and provide more personalized and effective therapies to patients.

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Abbreviations

CCA, Cholangiocarcinoma; iCCA, Intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA, distal extrahepatic cholangiocarcinoma; eCCA, extrahepatic cholangiocarcinoma; FDA, Food and Drug Administration; PFS, progression-free survival; OS, overall survival; TEAE, treatment-emergent adverse events; PR, partial response; BTC, biliary tract cancer; MSI, microsatellite instability; MMR, mismatch repair; TMB, tumor mutational burden.

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