Am J Cancer Res 2024;14(5):2570-2583
www.ajcr.us /ISSN:2156-6976/ajcr0155812

Review Article

How to incorporate new agents into precise medicine for cholangiocarcinoma?

Yifan Li[1], Juying Kang[2], Xiaojuan Zhang[3]

[1]Department of Hepatobiliary, Pancreatic and Gastrointestinal Surgery, Shanxi Province Carcinoma Hospital, Shanxi Hospital Affiliated to Carcinoma Hospital, Chinese Academy of Medical Sciences, Carcinoma Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, Shanxi, PR China; [2]Department of Information, Shanxi Province Carcinoma Hospital, Shanxi Hospital Affiliated to Carcinoma Hospital, Chinese Academy of Medical Sciences, Carcinoma Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, Shanxi, PR China; [3]Department of Radiology, Shanxi Province Cancer Hospital, Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences, Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, Shanxi, PR China

Received February 6, 2024; Accepted May 15, 2024; Epub May 15, 2024; Published May 30, 2024

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

https://doi.org/10.62347/NFDL2398

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 hyponatremia (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

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, infigratinib, pemigatinib, derazantinib, and the non-ATP-competitive inhibitor futibatinib, have demonstrated therapeutic benefits [17].

Infigratinib 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 infigratinib 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 Infigratinib for patients with FGFR2 fusion-positive cholangiocarcinoma [20]. Currently, an ongoing phase III study (PROOF 301, NCT3773302) is assessing the use of Infigratinib 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 FGF/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 $BRAF^{V600E}$ 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 $BRAF^{V600E}$ 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 $BRAF^{V600E}$-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 KRYSTAL-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-

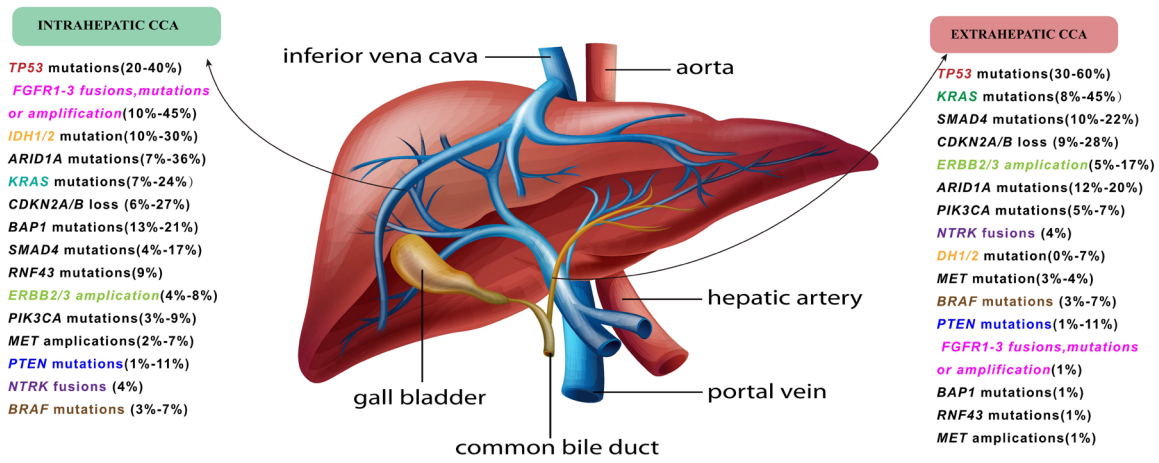

Figure 1. Genetic alterations in intrahepatic and extrahepatic cholangiocarcinoma (CCA).

teristics identify a subgroup of patients who may benefit from treatment with pembrolizumab, a PD-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 [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.

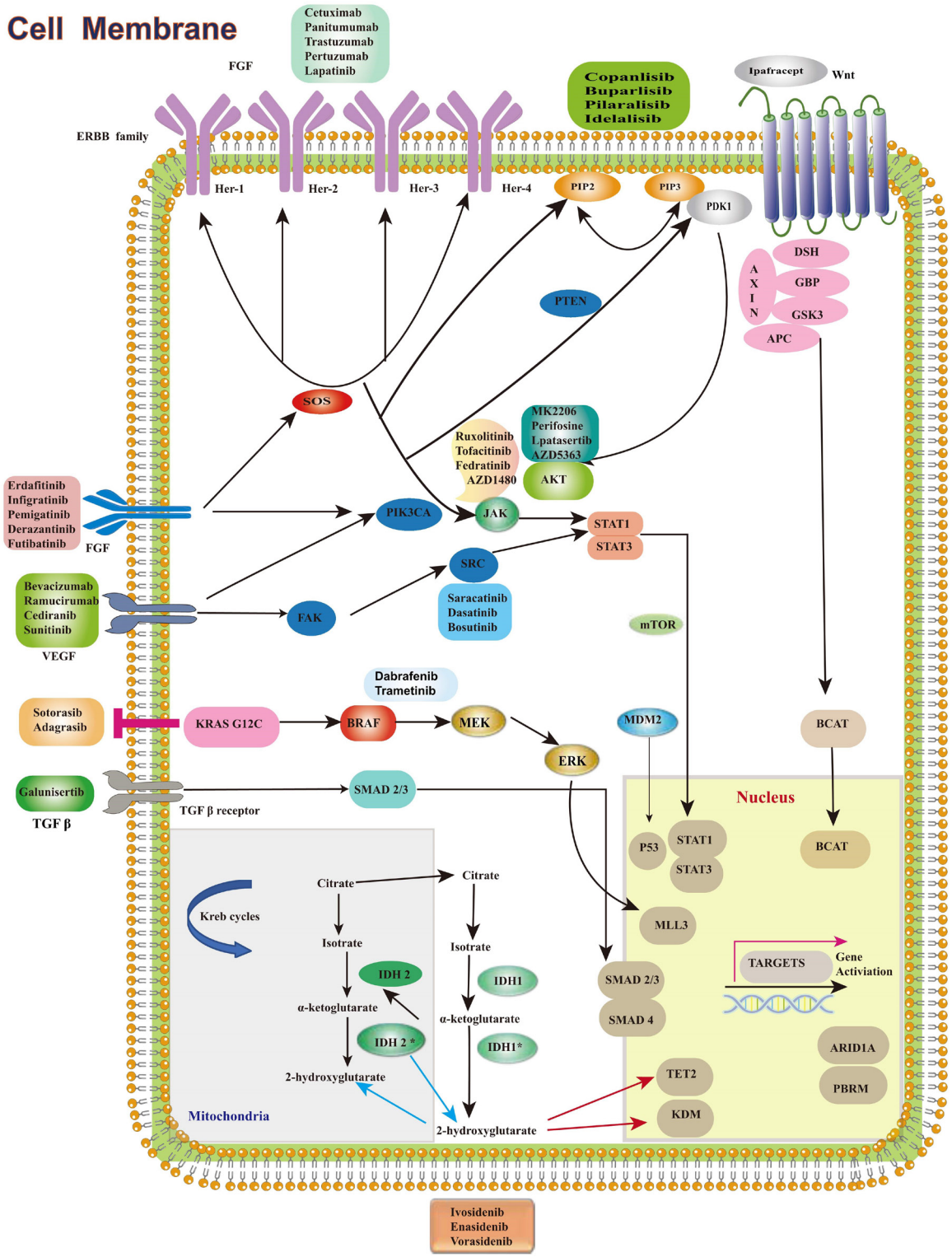

Figure 2. The alterations in tumor signaling pathways and targeted therapies for cholangiocarcinoma (CCA).

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-

Table 1. Relevant clinical studies for targeted therapies with FDA approval for CCA

Drug	Drug Class	Study	ORR	DCR	Clinical indication	Grade ≥ 3 TRAE	PFS	OS
Ivosidenib	IDH1 inhibitor	NCT02989857	2%	53%	IDH1 mutation	7%	2.7 months	10.3 months
Infigratinib	FGFR inhibitor	NCT02150967	14.8%	75.4%	FGFR2fusions/rearrangement	66.2%	5.8 months	Not reported
Pemigatinib	FGFR inhibitor	NCT02924376	35.5%	82%	FGFR2 fusions	68.7%	6.9 months	21.1 months
Derazantinib	FGFR inhibitor	NCT01752920	20.7%	82.8%	FGFR2 fusion	27.6%	Not reported	Not reported
Futibatinib	FGFR inhibitor	NCT02052778	15.6%	71.9%	FGFR2 fusions/rearrangement	57%	Not reported	Not reported
Zanidatamab	Her-2 inhibitor	NCT04466891	47%	65%	HER2-amplification	18%	Not reported	Not reported
Dabrafenib + Trametinib	$BRAF^{V600E}$ inhibitor	NCT02034110	51%	81.3%	$BRAF^{V600E}$-mutation	40%	9.1 months	13.5 months
Adagrasib	$KRAS^{G12C}$ inhibitor	NCT03785249	41.7%	50%	$KRAS^{G12C}$ inhibitor	27%	7.4 months	Not reported

py. FGFR2 inhibitors, including erdafitinib, infigratinib, 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 $BRAF^{V600E}$-mutated CCA. Trastuzumab plus pertuzumab is recommended as first-line treatment for patients with Her-2 positive CCA. Zanidatamab is another option for patients with HER2-amplified biliary tract cancer who have progressed after gemcitabine-based therapy. Entrectinib or larotrectinib can be used as first or later-line therapy for patients with NTRK gene fusion-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.

Acknowledgements

Special thanks were given to Suwen Ji and Chenjie Fan for proofreading the patient follow-up information.

Informed consent has been obtained from all patients.

Disclosure of conflict of interest

None.

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.

Address correspondence to: Juying Kang, Department of Hepatobiliary, Pancreatic and Gastrointestinal Surgery, Shanxi Province Carcinoma Hospital, Shanxi Hospital Affiliated to Carcinoma Hospital, Chinese Academy of Medical Sciences, Carcinoma Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, Shanxi, PR China. E-mail: mbk_mbk200087@126.com; Xiaojuan Zhang, Department of Radiology, Shanxi Province Cancer Hospital, Shanxi Hospital Affiliated to Cancer Hospital,

Chinese Academy of Medical Sciences, Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan 030013, Shanxi, PR China. E-mail: imagexj@163.com

References

[1] Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, Lind GE, Folseraas T, Forbes SJ, Fouassier L, Geier A, Calvisi DF, Mertens JC, Trauner M, Benedetti A, Maroni L, Vaquero J, Macias RI, Raggi C, Perugorria MJ, Gaudio E, Boberg KM, Marin JJ and Alvaro D. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European network for the study of cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 2016; 13: 261-80.

[2] Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM and Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014; 60: 1268-89.

[3] Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, La Vecchia C and Negri E. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol 2019; 71: 104-114.

[4] Valle JW. Targeted therapy for cholangiocarcinoma. Lancet Gastroenterol Hepatol 2019; 4: 661-662.

[5] Wu MJ, Shi L, Merritt J, Zhu AX and Bardeesy N. Biology of IDH mutant cholangiocarcinoma. Hepatology 2022; 75: 1322-1337.

[6] Farshidfar F, Zheng S, Gingras MC, Newton Y, Shih J, Robertson AG, Hinoue T, Hoadley KA, Gibb EA, Roszik J, Covington KR, Wu CC, Shinbrot E, Stransky N, Hegde A, Yang JD, Reznik E, Sadeghi S, Pedamallu CS, Ojesina AI, Hess JM, Auman JT, Rhie SK, Bowlby R, Borad MJ; Cancer Genome Atlas Network, Zhu AX, Stuart JM, Sander C, Akbani R, Cherniack AD, Deshpande V, Mounajjed T, Foo WC, Torbenson MS, Kleiner DE, Laird PW, Wheeler DA, McRee AJ, Bathe OF, Andersen JB, Bardeesy N, Roberts LR and Kwong LN. Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-Mutant molecular profiles. Cell Rep 2017; 19: 2878-2880.

[7] Wu MJ, Shi L, Dubrot J, Merritt J, Vijay V, Wei TY, Kessler E, Olander KE, Adil R, Pankaj A, Tummala KS, Weeresekara V, Zhen Y, Wu Q, Luo M, Shen W, García-Beccaria M, Fernández-Vaquero M, Hudson C, Ronseaux S, Sun Y, Saad-Berreta R, Jenkins RW, Wang T, Heikenwälder M, Ferrone CR, Goyal L, Nicolay B, Deshpande V, Kohli RM, Zheng H, Manguso RT and Bardeesy N. Mutant IDH inhibits IFNγ-TET2 signaling to promote immunoevasion and tumor maintenance in cholangiocarcinoma. Cancer Discov 2022; 12: 812-835.

[8] US Food and Drug Administration. Tibsovo® (ivosidenib tablets), for oral use. Prescribing information. 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211192s000lbl.pdf. Accessed February 4, 2022.

[9] Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DV, Borad MJ, Bridgewater J, Harris WP, Murphy AG, Oh DY, Whisenant J, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Fan B, Wu B, Chamberlain CX, Jiang L, Gliser C, Pandya SS, Valle JW and Zhu AX. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 2020; 21: 796-807.

[10] Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DVT, Borad MJ, Bridgewater JA, Harris WP, Murphy AG, Oh DY, Whisenant JR, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Chamberlain CX, Aguado-Fraile E, Choe S, Wu B, Liu H, Gliser C, Pandya SS, Valle JW and Abou-Alfa GK. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. JAMA Oncol 2021; 7: 1669-1677.

[11] Kim NI, Noh MG, Kim JH, Won EJ, Lee YJ, Hur Y, Moon KS, Lee KH and Lee JH. Frequency and prognostic value of IDH mutations in Korean patients with cholangiocarcinoma. Front Oncol 2020; 10: 1514.

[12] de Botton S, Montesinos P, Schuh A, Papayannidis C, Vyas P, Wei AH, Ommen HB, Semochkin S, Kim HJ, Larson RA, Koprivnikar J, Frankfurt O, Thol FR, Chromik J, Byrne JL, Pigneux A, Thomas X, Salamero O, Vidriales MB, Doronin VA, Döhner H, Fathi AT, Laille E, Yu X, Hasan M, Martín-Regueira P and DiNardo CD. Enasidenib vs conventional care in mutant-IDH2 relapsed/refractory acute myeloid leukemia: a randomized, phase 3 trial. Blood 2022; 141.

[13] Mellinghoff IK, van den Bent MJ, Blumenthal DT, Touat M, Peters KB, Clarke J, Mendez J, Yust-Katz S, Welsh L, Mason WP, Ducray F, Umemura Y, Nabors B, Holdhoff M, Hottinger AF, Arakawa Y, Sepulveda JM, Wick W, Soffietti R, Perry JR, Giglio P, de la Fuente M, Maher EA, Schoenfeld S, Zhao D, Pandya SS, Steelman L, Hassan I, Wen PY and Cloughesy TF; INDIGO Trial Investigators. Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. N Engl J Med 2023; 389: 589-601.

[14] Goyal L, Kongpetch S, Crolley VE and Bridgewater J. Targeting FGFR inhibition in

cholangiocarcinoma. Cancer Treat Rev 2021; 95: 102170.
[15] Lamarca A, Barriuso J, McNamara MG and Valle JW. Molecular targeted therapies: ready for "prime time" in biliary tract cancer. J Hepatol 2020; 73: 170-185.
[16] Goyal L, Shi L, Liu LY, Fece de la Cruz F, Lennerz JK, Raghavan S, Leschiner I, Elagina L, Siravegna G, Ng RWS, Vu P, Patra KC, Saha SK, Uppot RN, Arellano R, Reyes S, Sagara T, Otsuki S, Nadres B, Shahzade HA, Dey-Guha I, Fetter IJ, Baiev I, Van Seventer EE, Murphy JE, Ferrone CR, Tanabe KK, Deshpande V, Harding JJ, Yaeger R, Kelley RK, Bardelli A, Iafrate AJ, Hahn WC, Benes CH, Ting DT, Hirai H, Getz G, Juric D, Zhu AX, Corcoran RB and Bardeesy N. TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. Cancer Discov 2019; 9: 1064-1079.
[17] Zingg D, Bhin J, Yemelyanenko J, Kas SM, Rolfs F, Lutz C, Lee JK, Klarenbeek S, Silverman IM, Annunziato S, Chan CS, Piersma SR, Eijkman T, Badoux M, Gogola E, Siteur B, Sprengers J, de Klein B, de Goeij-de Haas RR, Riedlinger GM, Ke H, Madison R, Drenth AP, van der Burg E, Schut E, Henneman L, van Miltenburg MH, Proost N, Zhen H, Wientjens E, de Bruijn R, de Ruiter JR, Boon U, de Korte-Grimmerink R, van Gerwen B, Féliz L, Abou-Alfa GK, Ross JS, van de Ven M, Rottenberg S, Cuppen E, Chessex AV, Ali SM, Burn TC, Jimenez CR, Ganesan S, Wessels LFA and Jonkers J. Truncated FGFR2 is a clinically actionable oncogene in multiple cancers. Nature 2022; 608: 609-617.
[18] Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, Ramanathan RK, Goyal L, Sadeghi S, Macarulla T, El-Khoueiry A, Kelley RK, Borbath I, Choo SP, Oh DY, Philip PA, Chen LT, Reungwetwattana T, Van Cutsem E, Yeh KH, Ciombor K, Finn RS, Patel A, Sen S, Porter D, Isaacs R, Zhu AX, Abou-Alfa GK and Bekaii-Saab T. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. J Clin Oncol 2018; 36: 276-282.
[19] Neuzillet C. Infigratinib in pretreated cholangiocarcinoma with FGFR2 fusions or rearrangements. Lancet Gastroenterol Hepatol 2021; 6: 773-775.
[20] Infigratinib approved for cholangiocarcinoma. Cancer Discov 2021; 11: OF5.
[21] Makawita S, K Abou-Alfa G, Roychowdhury S, Sadeghi S, Borbath I, Goyal L, Cohn A, Lamarca A, Oh DY, Macarulla T, T Shroff R, Howland M, Li A, Cho T, Pande A and Javle M. Infigratinib in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF 301 trial. Future Oncol 2020; 16: 2375-2384.
[22] Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, Oh DY, Dotan E, Catenacci DV, Van Cutsem E, Ji T, Lihou CF, Zhen H, Féliz L and Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol 2020; 21: 671-684.
[23] Patel TH, Marcus L, Horiba MN, Donoghue M, Chatterjee S, Mishra-Kalyani PS, Schuck RN, Li Y, Zhang X, Fourie Zirkelbach J, Charlab R, Liu J, Yang Y, Lemery SJ, Pazdur R, Theoret MR and Fashoyin-Aje LA. FDA approval summary: pemigatinib for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangement. Clin Cancer Res 2022; 29: 838-842.
[24] Bekaii-Saab TS, Valle JW, Van Cutsem E, Rimassa L, Furuse J, Ioka T, Melisi D, Macarulla T, Bridgewater J, Wasan H, Borad MJ, Abou-Alfa GK, Jiang P, Lihou CF, Zhen H, Asatiani E, Féliz L and Vogel A. FIGHT-302: first-line pemigatinib vs gemcitabine plus cisplatin for advanced cholangiocarcinoma with FGFR2 rearrangements. Future Oncol 2020; 16: 2385-2399.
[25] Braun S, McSheehy P, Litherland K, McKernan P, Forster-Gross N, Bachmann F, El-Shemerly M, Dimova-Dobreva M, Polyakova I, Häckl M, Zhou P, Lane H, Kellenberger L and Engelhardt M. Derazantinib: an investigational drug for the treatment of cholangiocarcinoma. Expert Opin Investig Drugs 2021; 30: 1071-1080.
[26] Mazzaferro V, El-Rayes BF, Droz Dit Busset M, Cotsoglou C, Harris WP, Damjanov N, Masi G, Rimassa L, Personeni N, Braiteh F, Zagonel V, Papadopoulos KP, Hall T, Wang Y, Schwartz B, Kazakin J, Bhoori S, de Braud F and Shaib WL. Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. Br J Cancer 2019; 120: 165-171.
[27] Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, Fleming M, Rezazadeh A, Mellado B, Varlamov S, Joshi M, Duran I, Tagawa ST, Zakharia Y, Zhong B, Stuyckens K, Santiago-Walker A, De Porre P, O'Hagan A, Avadhani A and Siefker-Radtke AO; BLC2001 Study Group. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 2019; 381: 338-348.
[28] Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, Tran B, Kelley RK, Park JO, Javle M, He Y, Benhadji KA and Goyal L. Futibatinib, an irreversible FGFR1-4 inhibitor, in patients with advanced solid tumors harboring FGF/FGFR aberrations: a

phase I dose-expansion study. Cancer Discov 2022; 12: 402-415.
[29] Goyal L, Meric-Bernstam F, Hollebecque A, Morizane C, Valle JW, Karasic TB, Abrams TA, Kelley RK, Cassier P, Furuse J, Klümpen HJ, Chang HM, Chen LT, Komatsu Y, Masuda K, Ahn D, He Y, Soni N, Benhadji KA and Bridgewater JA. Primary results of phase 2 FOENIX-CCA2: the irreversible FGFR1-4 inhibitor futibatinib in intrahepatic cholangiocarcinoma (iCCA) with FGFR2 fusions/rearrangements. Cancer Res 2021; 81: CT010.
[30] Borad MJ, Bridgewater JA, Morizane C, Shroff RT, Oh DY, Moehler MH, Furuse J, Benhadji KA, He H and Valle JW. A phase III study of futibatinib (TAS-120) versus gemcitabine-cisplatin (gem-cis) chemotherapy as first-line (1L) treatment for patients (pts) with advanced (adv) cholangiocarcinoma (CCA) harboring fibroblast growth factor receptor 2 (FGFR2) gene rearrangements (FOENIX-CCA3). J Clin Oncol 2020; 38 Suppl 4: TPS600.
[31] Syed YY. Futibatinib: first approval. Drugs 2022; 82: 1737-1743.
[32] Rizzo A, Federico AD, Ricci AD, Frega G, Palloni A, Pagani R, Tavolari S, Marco MD and Brandi G. Targeting BRAF-mutant biliary tract cancer: recent advances and future challenges. Cancer Control 2020; 27: 1073274820983013.
[33] Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, Wolf J, Raje NS, Diamond EL, Hollebecque A, Gervais R, Elez-Fernandez ME, Italiano A, Hofheinz RD, Hidalgo M, Chan E, Schuler M, Lasserre SF, Makrutzki M, Sirzen F, Veronese ML, Tabernero J and Baselga J. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 2015; 373: 726-36.
[34] Subbiah V, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, de Braud F, Prager GW, Greil R, Stein A, Fasolo A, Schellens JHM, Wen PY, Viele K, Boran AD, Gasal E, Burgess P, Ilankumaran P and Wainberg ZA. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol 2020; 21: 1234-1243.
[35] Silipo M, Gautrey H, Satam S, Lennard T and Tyson-Capper A. How is Herstatin, a tumor suppressor splice variant of the oncogene HER2, regulated? RNA Biol 2017; 14: 536-543.
[36] Moasser MM. The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. Oncogene 2007; 26: 6469-87.
[37] Hori Y, Yoh T, Seo S, Minamiguchi S, Haga H and Taura K. Limited impact of HER2 expression on survival outcomes in patients with intrahepatic cholangiocarcinoma after surgical resection. Oncologist 2021; 26: e1893-e1894.
[38] Kim H, Kim R, Kim HR, Jo H, Kim H, Ha SY, Park JO, Park YS and Kim ST. HER2 aberrations as a novel marker in advanced biliary tract cancer. Front Oncol 2022; 12: 834104.
[39] Javle M, Borad MJ, Azad NS, Kurzrock R, Abou-Alfa GK, George B, Hainsworth J, Meric-Bernstam F, Swanton C, Sweeney CJ, Friedman CF, Bose R, Spigel DR, Wang Y, Levy J, Schulze K, Cuchelkar V, Patel A and Burris H. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol 2021; 22: 1290-1300.
[40] Harding JJ, Cleary JM, Quinn DI, Braña I, Moreno V, Borad MJ, Loi S, Spanggaard I, Park H, Ford JM, Arnedos M, Stemmer SM, De La Fouchardiere C, Viteri Ramirez S, Fountzilas C, Zhang J, Xu F and Lalani AS, Piha-Paul SA and Abou-Alfa GK. Targeting HER2 (ERBB2) mutation-positive advanced biliary tract cancers with neratinib: resultsfrom the phase II SUMMIT 'basket' trial. J Clin Oncol 2021; 39 Suppl 3: 320.
[41] Meric-Bernstam F, Beeram M, Hamilton E, Oh DY, Hanna DL, Kang YK, Elimova E, Chaves J, Goodwin R, Lee J, Nabell L, Rha SY, Mayordomo J, El-Khoueiry A, Pant S, Raghav K, Kim JW, Patnaik A, Gray T, Davies R, Ozog MA, Woolery J and Lee KW. Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. Lancet Oncol 2022; 23: 1558-1570.
[42] Okamura R, Boichard A, Kato S, Sicklick JK, Bazhenova L and Kurzrock R. Analysis of NTRK alterations in pan-cancer adult and pediatric malignancies: implications for NTRK-targeted therapeutics. JCO Precis Oncol 2018; 2018: PO.18.00183.
[43] Uren RT and Turnley AM. Regulation of neurotrophin receptor (Trk) signaling: suppressor of cytokine signaling 2 (SOCS2) is a new player. Front Mol Neurosci 2014; 7: 39.
[44] Amatu A, Sartore-Bianchi A, Bencardino K, Pizzutilo EG, Tosi F and Siena S. Tropomyosin receptor kinase (TRK) biology and the role of NTRK gene fusions in cancer. Ann Oncol 2019; 30: viii5-viii15.
[45] Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, Blakely CM, Seto T, Cho BC, Tosi D, Besse B, Chawla SP, Bazhenova L, Krauss JC, Chae YK, Barve M, Garrido-Laguna I, Liu SV, Conkling P, John T, Fakih M, Sigal D, Loong HH, Buchschacher GL Jr, Garrido P, Nieva J, Steuer C, Overbeck TR, Bowles DW,

Fox E, Riehl T, Chow-Maneval E, Simmons B, Cui N, Johnson A, Eng S, Wilson TR and Demetri GD; trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21: 271-282.

[46] Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, van Tilburg CM, Nagasubramanian R, Berlin JD, Federman N, Mascarenhas L, Geoerger B, Dowlati A, Pappo AS, Bielack S, Doz F, McDermott R, Patel JD, Schilder RJ, Tahara M, Pfister SM, Witt O, Ladanyi M, Rudzinski ER, Nanda S, Childs BH, Laetsch TW, Hyman DM and Drilon A. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020; 21: 531-540.

[47] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: hepatobiliary cancer, version 5.2021 September 21, 2021. NCCN Clinical Practice Guidelines in Oncology; 2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed March 18, 2022.

[48] Spizzo G, Puccini A, Xiu J, Goldberg RM, Grothey A, Shields AF, Arora SP, Khushman M, Salem ME, Battaglin F, Baca Y, El-Deiry WS, Philip PA, Nassem M, Hall M, Marshall JL, Kocher F, Amann A, Wolf D, Korn WM, Lenz HJ and Seeber A. Molecular profile of BRCA-mutated biliary tract cancers. ESMO Open 2020; 5: e000682.

[49] Costa BA, Tallón de Lara P, Park W, Keane F, Harding JJ and Khalil DN. Durable response after olaparib treatment for perihilar cholangiocarcinoma with germline BRCA2 mutation. Oncol Res Treat 2023; 46: 211-215.

[50] Li W, Ma Z, Fu X, Hao Z, Shang H, Shi J, Lei M, Xu M, Ning S and Hua X. Olaparib effectively treats local recurrence of extrahepatic cholangiocarcinoma in a patient harboring a BRCA2-inactivating mutation: a case report. Ann Transl Med 2021; 9: 1487.

[51] Cheng Y, Zhang J, Qin SK and Hua HQ. Treatment with olaparib monotherapy for BRCA2-mutated refractory intrahepatic cholangiocarcinoma: a case report. Onco Targets Ther 2018; 11: 5957-5962.

[52] Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, Chiorean EG, Chung V, Czito B, Del Chiaro M, Dillhoff M, Donahue TR, Dotan E, Ferrone CR, Fountzilas C, Hardacre J, Hawkins WG, Klute K, Ko AH, Kunstman JW, LoConte N, Lowy AM, Moravek C, Nakakura EK, Narang AK, Obando J, Polanco PM, Reddy S, Reyngold M, Scaife C, Shen J, Vollmer C, Wolff RA, Wolpin BM, Lynn B and George GV. Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021; 19: 439-457.

[53] Reiss KA, Mick R, O'Hara MH, Teitelbaum U, Karasic TB, Schneider C, Cowden S, Southwell T, Romeo J, Izgur N, Hannan ZM, Tondon R, Nathanson K, Vonderheide RH, Wattenberg MM, Beatty G and Domchek SM. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2, or PALB2. J Clin Oncol 2021; 39: 2497-2505.

[54] Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, DiSilvestro PA, Morgan MA, Nam JH, Leath CA 3rd, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak CK, Ansell PJ, Dinh MH, Aghajanian C and Bookman MA. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 2019; 381: 2403-2415.

[55] Gupta M, Iyer R and Fountzilas C. Poly(ADP-Ribose) polymerase inhibitors in pancreatic cancer: a new treatment paradigms and future implications. Cancers (Basel) 2019; 11: 1980.

[56] Wakai T, Nagahashi M, Shimada Y, Prasoon P and Sakata J. Genetic analysis in the clinical management of biliary tract cancer. Ann Gastroenterol Surg 2020; 4: 316-323.

[57] O'Dell MR, Huang JL, Whitney-Miller CL, Deshpande V, Rothberg P, Grose V, Rossi RM, Zhu AX, Land H, Bardeesy N and Hezel AF. Kras(G12D) and p53 mutation cause primary intrahepatic cholangiocarcinoma. Cancer Res 2012; 72: 1557-67.

[58] Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, Falchook GS, Price TJ, Sacher A, Denlinger CS, Bang YJ, Dy GK, Krauss JC, Kuboki Y, Kuo JC, Coveler AL, Park K, Kim TW, Barlesi F, Munster PN, Ramalingam SS, Burns TF, Meric-Bernstam F, Henary H, Ngang J, Ngarmchamnanrith G, Kim J, Houk BE, Canon J, Lipford JR, Friberg G, Lito P, Govindan R and Li BT. KRASG12C Inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020; 383: 1207-1217.

[59] Bekaii-Saab TS, Yaeger R, Spira AI, Pelster MS, Sabari JK, Hafez N, Barve M, Velastegui K, Yan X, Shetty A, Der-Torossian H and Pant S. Adagrasib in advanced solid tumors harboring a KRASG12C mutation. J Clin Oncol 2023; 41: 4097-4106.

[60] Wang X, Allen S, Blake JF, Bowcut V, Briere DM, Calinisan A, Dahlke JR, Fell JB, Fischer JP, Gunn RJ, Hallin J, Laguer J, Lawson JD, Medwid J, Newhouse B, Nguyen P, O'Leary JM, Olson P, Pajk S, Rahbaek L, Rodriguez M, Smith CR, Tang TP, Thomas NC, Vanderpool D, Vigers GP, Christensen JG and Marx MA. Identification of MRTX1133, a noncovalent, potent, and selective KRASG12D inhibitor. J Med Chem 2022; 65: 3123-3133.

[61] Ju JY, Dibbern ME, Mahadevan MS, Fan J, Kunk PR and Stelow EB. Mismatch repair protein deficiency/microsatellite instability is rare in cholangiocarcinomas and associated with distinctive morphologies. Am J Clin Pathol 2020; 153: 598-604.

[62] Goeppert B, Roessler S, Renner M, Singer S, Mehrabi A, Vogel MN, Pathil A, Czink E, Köhler B, Springfeld C, Pfeiffenberger J, Rupp C, Weiss KH, Schirmacher P, von Knebel Doeberitz M and Kloor M. Mismatch repair deficiency is a rare but putative therapeutically relevant finding in non-liver fluke associated cholangiocarcinoma. Br J Cancer 2019; 120: 109-114.

[63] Luchini C, Bibeau F, Ligtenberg MJL, Singh N, Nottegar A, Bosse T, Miller R, Riaz N, Douillard JY, Andre F and Scarpa A. ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach. Ann Oncol 2019; 30: 1232-1243.

[64] Maio M, Ascierto PA, Manzyuk L, Motola-Kuba D, Penel N, Cassier PA, Bariani GM, De Jesus Acosta A, Doi T, Longo F, Miller WH, Oh DY, Gottfried M, Xu L, Jin F, Norwood K and Marabelle A. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 2022; 33: 929-938.

[65] US Food and Drug Administration. Keytruda (pembrolizumab) injection, for intravenous use. Prescribing information. 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s120lbl.pdf. Accessed December 21, 2021.

[66] Zhao Z, Li W, Zhang X, Ge M and Song C. Correlation between TMB and MSI in patients with solid tumors. J Clin Oncol 2020; 38 Suppl 15: 265.

[67] Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K and Bang YJ. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020; 21: 1353-1365.

[68] Valle JW, Lamarca A, Goyal L, Barriuso J and Zhu AX. New horizons for precision medicine in biliary tract cancers. Cancer Discov 2017; 7: 943-962.

[69] Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, Hama N, Hosoda F, Urushidate T, Ohashi S, Hiraoka N, Ojima H, Shimada K, Okusaka T, Kosuge T, Miyagawa S and Shibata T. Genomic spectra of biliary tract cancer. Nat Genet 2015; 47: 1003-10.

[70] Bekaii-Saab TS, Bridgewater J and Normanno N. Practical considerations in screening for genetic alterations in cholangiocarcinoma. Ann Oncol 2021; 32: 1111-1126.

[71] Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, Yau T, Klümpen HJ, Chan SL, Ozaka M, Verslype C, Bouattour M, Park JO, Barajas O, Pelzer U, Valle JW, Yu L, Malhotra U, Siegel AB, Edeline J and Vogel A; KEYNOTE-966 Investigators. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023; 401: 1853-1865.