

Washington University School of Medicine

Digital Commons@Becker

---

Open Access Publications

---

6-1-2017

## Current biologics for treatment of biliary tract cancers

Diana Y. Zhao

*Washington University School of Medicine in St. Louis*

Kian-Huat Lim

*Washington University School of Medicine in St. Louis*

Follow this and additional works at: [https://digitalcommons.wustl.edu/open\\_access\\_pubs](https://digitalcommons.wustl.edu/open_access_pubs)

Please let us know how this document benefits you.

---

### Recommended Citation

Zhao, Diana Y. and Lim, Kian-Huat, "Current biologics for treatment of biliary tract cancers." *Journal of Gastrointestinal Oncology*. 8, 3. 430 - 440. (2017).

[https://digitalcommons.wustl.edu/open\\_access\\_pubs/9936](https://digitalcommons.wustl.edu/open_access_pubs/9936)

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact [vanam@wustl.edu](mailto:vanam@wustl.edu).

# Current biologics for treatment of biliary tract cancers

Diana Y. Zhao<sup>1</sup>, Kian-Huat Lim<sup>2</sup>

<sup>1</sup>Medical Scientist Training Program, <sup>2</sup>Division of Oncology, Department of Internal Medicine, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

**Contributions:** (I) Conception and design: All authors; (II) Administrative support: KH Lim; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Kian-Huat Lim, MD, PhD. Assistant Professor, Division of Oncology, Washington University in Saint Louis, St. Louis, MO, USA. Email: [kian-huat.lim@wustl.edu](mailto:kian-huat.lim@wustl.edu).

**Abstract:** Biliary tract cancers (BTC) is a group of malignancies that arise from the epithelial cells of the biliary tree. These cancers are typically classified by anatomic site of origin: intrahepatic cholangiocarcinoma (IHCC) and extrahepatic cholangiocarcinoma (EHCC), and gallbladder cancer (GBC). To date, complete surgical resection remains the mainstay of treatment especially for earlier stage disease. Unfortunately, most patients present with advanced or metastatic disease, when systemic chemotherapy is the only treatment option. Due to the paucity of effective treatments, BTCs have a dismal prognosis. There is a tremendous need to better understand the disease biology, discover new therapies, and improve clinical outcomes for this challenging disease. Next-generation sequencing has produced a more accurate and detailed picture of the molecular signatures in BTCs. The three BTC histologic subtypes are, in fact, quite molecularly distinct. IHCC commonly contain FGFR2 fusions and IDH 1 and 2 mutations, whereas EHCC and GBC tend to carry mutations in EGFR, HER2, and MAPK pathway. In light of this emerging knowledge, clinical trials have become more biomarker-driven, which allows capturing of subsets of patients that are most likely to respond to certain therapies. Many new and promising targeted therapeutics are currently in the pipeline. Here we review the genetic landscape of BTCs while focusing on new molecular targets and targeted therapeutics currently being investigated in biomarker-driven clinical trials.

**Keywords:** Biliary tract cancer (BTC); cholangiocarcinoma; gallbladder cancer (GBC); biologics

Submitted Feb 26, 2017. Accepted for publication Apr 26, 2017.

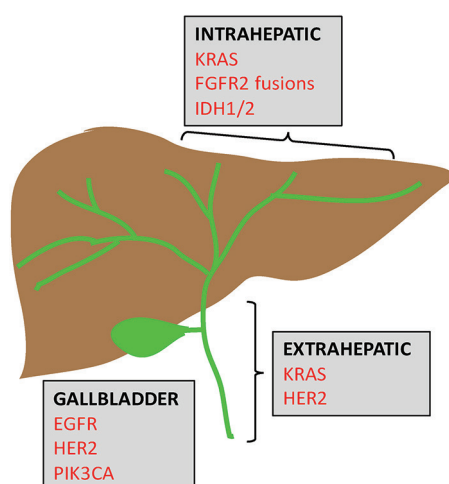
doi: 10.21037/jgo.2017.05.04

**View this article at:** <http://dx.doi.org/10.21037/jgo.2017.05.04>

## Introduction

Biliary tract cancers (BTC) is a group of rare and aggressive malignancies arising from the epithelium of the biliary duct system. They are classified based on their anatomical site in the biliary tree [intrahepatic cholangiocarcinoma (IHCC) or extrahepatic cholangiocarcinoma (EHCC)] or gallbladder cancer (GBC) (*Figure 1*). IHCC is the most common BTC and the second most common hepatic malignancy, accounting for 10–20% of all primary hepatic malignancies (1,2). Owing to the insidious nature of this group of cancers, they are usually diagnosed at an advanced stage and carry a dismal

prognosis. Surgery is potentially curative in early stage disease. In cases of advanced and metastatic disease, the current standard of care is systemic chemotherapy with gemcitabine and cisplatin. Clinical response rates to these cytotoxic chemotherapies are low, with a 5-year survival of less than 10% for all three BTC subtypes. In recent years, we have made strides in our understanding of the disease biology, as well as advancements in diagnostic techniques and novel therapeutic strategies. Notably, the genomic revolution has ushered in an era of high-throughput and deep molecular profiling, which has provided invaluable insight into actionable molecular alterations, as well as their prognostic significance. We have also developed



**Figure 1** Distinct molecular signatures of BTCs. Shown is a schematic of the biliary tract and gallbladder, along with common genetic aberrations seen in intrahepatic and extrahepatic cholangiocarcinoma, and GBC. Red font indicates targetable genes.

a greater appreciation for the molecular heterogeneity across the BTC subtypes, realizing that these anatomically classified subgroups exhibit distinct molecular architectures. Considering this emerging knowledge, clinical trial design has steered away from the “one-size-fits-all” mentality and has become more biomarker-driven. Currently there are several ongoing clinical studies investigating the efficacy of targeted therapies aimed at populations that underwent biomarker selection. In this review, we will highlight actionable molecular targets and their novel targeted therapeutics in current clinical trials.

## Epidemiology

The incidence of BTC varies by geography and demographics, likely due to distinct environmental risk factors and genetic predisposition. Though BTCs are traditionally more common in Asian countries, their incidence has been rising in Western countries in recent decades (3). Though it is a rare disease, the global incidence is rising. Chronic inflammation and bile stasis in the biliary tract are thought to be major risk factors underlying the pathogenesis of these cancers. Specific risk factors include primary sclerosing cholangitis, liver fluke (*Clonorchis*, *Opisthorchis*) infection, hepatitis B and C infections, cholelithiasis or choledocholithiasis, cirrhosis, alcohol, smoking, and fatty liver disease (3,4).

## Current management

Overall, the 5-year survival rate of BTCs is extremely low (10% for CCAs and less than 5% for GBC) (5,6). Surgery is the only potentially curative modality but most patients are asymptomatic until late in the disease course and present with locally advanced or metastatic disease. Thus, only 10–15% of BTCs are amenable to surgery at initial presentation (7). Even though improved surgical techniques and better patient selection based on more advanced radiologic techniques have resulted in better tumor resection rates, the recurrence rates of these aggressive cancers remain high at 50–60% (7,8). The role of adjuvant therapy is poorly-defined and standard regimen is unclear due to the relative rarity of this disease which hinders large scale prospective studies (9,10). Therefore, the benefit of adjuvant treatment is commonly appraised from meta-analyses of multiple small retrospective studies that usually include more than one, if not all, subtypes of BTC. To more clearly determine the role of adjuvant treatment, two phase III randomized controlled trials are currently ongoing in the Europe to determine the role of adjuvant gemcitabine plus cisplatin (ACTICCA-1 trial, NCT02170090) or oxaliplatin (NCT01313377) versus observation for patients with resected BTC. Before results from these trials are available, current NCCN guidelines recommend adjuvant fluoropyrimidine or gemcitabine-based chemotherapy with consideration of radiation for patients with node-positive disease or R1/R2 resections.

For patients presenting with unresectable BTCs (locally advanced, recurrent, or metastatic), the current standard first-line therapy is a combination of gemcitabine and cisplatin. This regimen was established by the ABC-02 trial, the largest randomized phase III study to date, which showed a survival benefit of the combination as opposed to gemcitabine alone (11.7 vs. 9 months) (11). Other chemotherapy combinations (e.g., oxaliplatin, 5-FU, capecitabine, irinotecan) have demonstrated only marginal improvements in survival (12). Targeted therapies such as anti-EGFR or anti-VEGF antibodies have so far struggled to succeed in phase I or II clinical trials. Performing randomized control trials (RCT) for advanced BTCs has proven challenging due to the rarity of these malignancies, lack of effective agents, potential high heterogeneity within this diagnostic entity, and possibly fundamental differences among the three BTC subtypes (IHCC, EHCC, and GBC). In fact, next generation sequencing (NGS) and transcriptomic analyses have revealed that these BTC

**Table 1** Prevalence of key genetic alterations in biliary tract cancers

Variables	IHCC (%)	EHCC (%)	GBC (%)	References
Tyrosine kinase signaling				
<i>EGFR</i>	4	3	4–18	(16,17)
<i>HER2</i>	1.5–3	11–18	10–16	(16,18–20)
<i>KRAS</i>	17–30	12–40	0–13	(16,17,19–21)
<i>BRAF</i>	4–7	3	1–6	(16,19,22,23)
<i>PIK3CA</i>	5–6	7–9	8–14	(19,21,24,25)
<i>FGFR2</i> fusions	6–50	0–5	0–3	(17,19,26–29)
<i>IDH</i> pathway	10–28	0–7	0	(19,21,27,30–32)
Chromatin-remodeling genes				
<i>ARID1A</i>	17	12	13	(19,27)
<i>BAP1</i>	11	8	0	(17,27)
<i>PBRM1</i>	8	5	7	(17,27)

subtypes are molecularly distinct from one another, and therefore may respond differently to the same treatment strategy and should not be approached as a single entity for clinical trial design (13,14). To improve patient outcome, future clinical trial design must better stratify patients based on considerations of histologic and molecular subtypes, and allocate patients to the appropriate targeted agents driven by biomarkers that could predict treatment response.

## Genetic landscape

Before the advent of NGS, our knowledge of genetic aberrations in BTCs was limited because older methodologies restricted mutational profiling to a few select oncogenes or hotspots (15). That technology previously allowed us to identify key signaling pathways altered in BTCs, such as the EGFR and vascular endothelial growth factor receptor (VEGFR) pathways. Thus, many of the first generation BTC trials targeted EGFR and VEGFR, but these targeted agents ultimately proved ineffective at improving clinical outcome (12). NGS, which allows for characterization of an entire genetic landscape through gene panels, whole exome, or transcriptome sequencing, has led to the discovery of many novel actionable mutations in BTCs (15). Thus, pre-clinical and clinical studies have expanded from targeting well-established pathways like EGFR and VEGFR to promising, novel alterations.

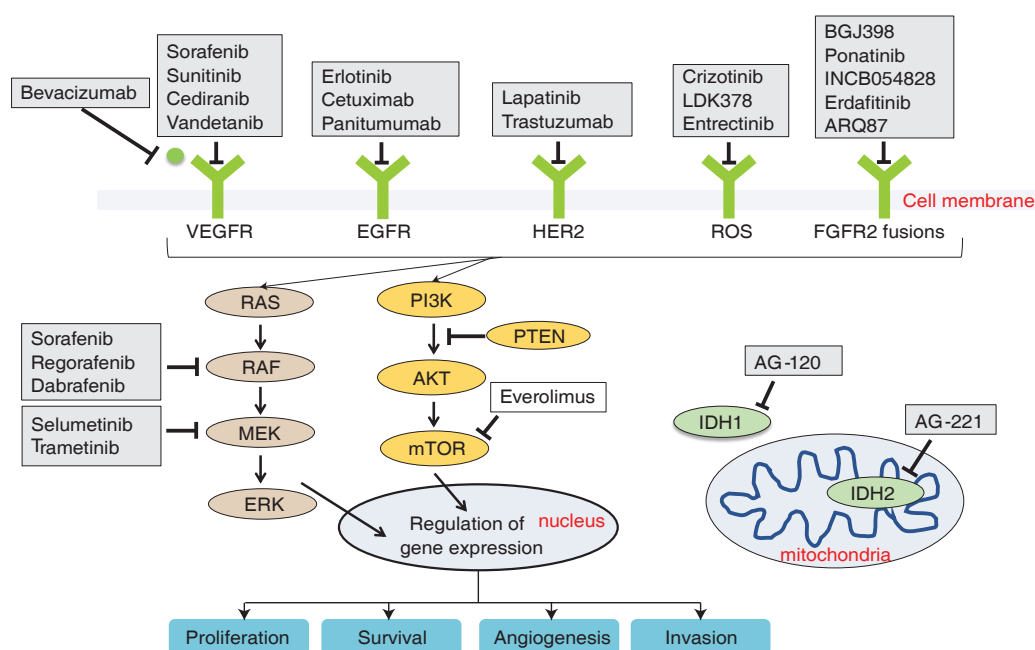
Recent studies employing NGS have shed light on

distinctive molecular spectra across the BTC subtypes (13,14). *FGFR2* gene fusions and mutations in *IDH1/2* are predominantly observed in IHCC. *KRAS* and *HER2* mutations are preferentially found in EHCC. Lastly, GBCs are enriched for mutations in *EGFR*, *HER2*, and *PIK3CA*. *Figure 1* and *Table 1* highlight these key genomic alterations along the biliary tract and gallbladder. Next, we will discuss key actionable aberrations in BTCs and the novel agents that target them in biomarker-driven clinical trials.

## Tyrosine kinase signaling

### EGFR

The EGFR family comprises four tyrosine kinase receptors (ERBB1–4) that regulate cell proliferation, survival, angiogenesis, and invasion through ligand binding and subsequent activation of signal transduction cascades involving the MAPK pathway (Ras-Raf-MEK-ERK) and the PI3K/AKT pathway (33) (*Figure 2*). Aberrant activation of the EGFR pathway is a common oncogenic event in BTCs and is associated with tumor recurrence and worsened outcome (16,18,26,34). Of the *EGFR* family members, *EGFR* (*ERBB1*) and *HER2* (*ERBB2*) are most commonly altered in BTCs. Overexpression of EGFR occurs in 11–27% of IHCC, 5–19% of EHCC (26), and 12% in GBCs (35), whereas activating *EGFR* mutations are preferentially seen in GBC (4–18%), but rarely in CCAs (*Table 1*) (16,17).



**Figure 2** Key signaling pathways and current targeted therapies. Molecular targeted therapies including drugs currently assessed in phase II/III trials are highlighted.

Given that EGFR activation regulates several cellular functions important for carcinogenesis and is one of the most altered pathways in BTCs, there was strong rationale to evaluate it as a therapeutic target. However, extensive clinical testing with EGFR inhibitors has failed to show a survival benefit in advanced BTCs. Although earlier single arm phase II trials suggested possible benefits of EGFR antagonists cetuximab and panitumumab either as single agents or in combination with chemotherapy (36-39), larger RCTs of erlotinib, cetuximab or panitumumab in combination with gemcitabine plus oxaliplatin failed to show a progression-free survival (PFS) or overall survival (OS) benefit over chemotherapy alone in advanced BTCs (40,41).

Of note, almost all of these trials have been performed without stratifying patients by molecular signatures that could predict response to anti-EGFR agents. In fact, none has used *EGFR* genomic alterations as a biomarker. Additionally, lessons from the colorectal cancer world have informed us that *KRAS* mutations negate response to anti-EGFR therapy (42-44). However, only a few of the BTC trials have used *KRAS* status to stratify patients. A recent phase II trial stratified BTC patients based on *KRAS* status, but failed to demonstrate that *KRAS* status predicted the population most likely to benefit from anti-EGFR therapy (45). Furthermore, two biomarker-driven

trials that was restricted to *KRAS* wild-type patients failed to show a clinically significant improvement in PFS or OS using panitumumab combined with chemotherapy (46,47). These studies call into question the utility of *KRAS* status as a clinically relevant biomarker predictive of EGFR therapy response in BTC, as opposed to colon cancer. The relative importance of mutations in other EGFR pathway genes, such as *BRAF*, are being investigated as mechanisms of resistance to anti-EGFR agents (47,48).

## HER2

*HER2* overexpression and amplification are predominantly seen in EHCC and GBCs (10-18% for both) and rarely in IHCC (Table 1) (16,19,20,26,34,35). Like EGFR-directed agents, similarly disappointing results came out of trials with HER2 antagonists (including trastuzumab, lapatinib, afatinib) combined with chemotherapy in advanced BTC (49-51). Currently, there is an ongoing phase II trial with trastuzumab aimed at a selected group of HER2-positive BTC patients (Table 2).

## VEGF

VEGF is the ligand that binds VEGFR, which initiates

**Table 2** Biomarker-driven clinical trials of biliary tract cancers

Drug(s)	Target	Biomarker selection	Phase	NCT number
Trastuzumab	HER2	HER2	II	NCT02999672
Dabrafenib + trametinib	BRAF, MEK	BRAF V600E	II	NCT02034110
BGJ398	FGFR2	FGFR alterations	II	NCT02150967
BGJ398	FGFR2	FGFR alterations	II	NCT02160041
Ponatinib	FGFR2	FGFR2 fusion	II	NCT02265341
Ponatinib	FGFR2	FGFR alteration	II	NCT02272998
INCB054828	FGFR2	FGFR2 translocation	II	NCT02924376
Erdafitinib	FGFR2	FGFR alteration	II	NCT02699606
ARQ087	FGFR2	FGFR alteration	I/II	NCT01752920
INCB054828	FGFR2	FGFR alteration	I	NCT02393248
AG-120	IDH1	IDH1 mutation	III	NCT02989857
AG-221	IDH2	IDH2 mutation	I/II	NCT02273739
Dasatinib	Multiple kinases	IDH1/2 mutation	II	NCT02428855
AG-120	IDH1	IDH1 mutation	I	NCT02073994

signals to promote cancer growth and metastasis through stimulating angiogenesis. VEGF is overexpressed in BTCs and associated with enhanced metastasis, increased tumor recurrence, and worsened prognosis (34). Studies with antagonists of the VEGF pathway, including bevacizumab, cediranib, sorafenib have not yielded encouraging results (52-56).

### MAPK pathway

Aberrations in cell-surface receptors and their ligands (e.g., EGFR, VEGF) can lead to constitutive activation of downstream cascades, including the MAPK arm (RAS-RAF-MEK-ERK, *Figure 2*). KRAS is a member of the RAS family and gain of function mutations in *KRAS* are one of the most common events in BTCs, with highest rates seen in EHCC, followed by IHCC, and lowest in GBC (16,17,19,20,57). KRAS is associated with lower median survival and perineural invasion (58). Its frequency also increases with disease stage (22). BRAF belongs to the RAF family of kinases that lie directly downstream of RAS (*Figure 2*). *BRAF* mutations are less frequent in BTCs (less than 10% across all subtypes) and are considered mutually exclusive with *KRAS* mutations (16,19,22,59). The most common *BRAF* mutation is V600E, but the mutational frequency is highly varied in BTCs ranging from 0-33% (60).

The clinical significance of *BRAF* mutations is less well-established, with one study demonstrated an association with advanced tumor stage, higher likelihood of lymph node involvement, and worsened survival (22).

Targeting the MAPK pathway has remained a challenge. Recently, the phase I ABC-04 study of selumetinib, a MEK inhibitor, in combination with gemcitabine and cisplatin failed to show clinical benefit in advanced or metastatic BTC (61). Even attempts to block multiple components of the MAPK pathway using multikinase inhibitors like sorafenib have not proved fruitful (62-65). These disappointing results are in stark contrast to melanomas, which frequently harbor the *BRAF* V600 mutations, where use of the *BRAF* inhibitors vemurafenib or dabrafenib has achieved a striking survival benefit (66-68). Recently, dual inhibition of *BRAF* with vemurafenib or dabrafenib and MEK with trametinib in *BRAF* V600-mutated melanoma patients has led to further survival improvements (69-71). Currently, there is an ongoing phase II trial with dabrafenib combined with trametinib for *BRAF* V600-mutated rare cancers including BTCs (*Table 2*).

Multiple signaling pathways seem to be involved in the pathogenesis of BTCs, rendering the decision of which pathways to target challenging. Moreover, no oncogene addiction pathway has been pinpointed. Targeting single pathways either as monotherapy or in combination with



chemotherapy has shown varying degrees of improvements in response rates, but these have not translated to clinically significant increases in PFS or OS. Currently, some clinical trials are using a multi-target approach by using multikinase inhibitors or a combinatorial approach with multiple agents aimed at different pathways (12,72). Results from studies using multikinase inhibitors regorafenib and pazopanib are anxiously awaited.

## Novel targets

Over the recent years, genomic profiling using NGS has revealed the presence of novel alterations in BTCs such as recurrent fusion events (*FGFR2* and *ROS1* fusions), somatic mutations in metabolic enzymes (*IDH1* and 2) (17-19,21,23,26-31,57,73,74), and chromatin-remodeling genes (*ARID1A*, *BAP1*, *PBRM1*) (17,19,27).

### *FGFR2* fusions

*FGFR2* is a member of the fibroblast growth factor family of receptor tyrosine kinases that regulate cell proliferation, differentiation, apoptosis (75). Alterations in this pathway through activating mutations, amplifications, or chromosomal translocation have been implicated in malignant transformation (76). Chromosomal fusions occur between exons 1–19 of *FGFR2* and various genomic partners (e.g., *AHCYL1*, *BICC1*, *PARK2*, *KCTD1*, *MGEA5*, *TACC3*, *TXLNA*) in BTCs (17,19,26-29). The resulting fusion protein undergoes ligand-independent dimerization and subsequent autophosphorylation, which leads to constitutive activation of downstream signaling pathways, such as MAPK (76) (Figure 2). The oncogenic potential of *FGFR2* fusions has been demonstrated *in vitro* (23,28,77,78) and *in vivo* (28). Screening for fusions by massive parallel sequencing or FISH-based assays has revealed a wide range of IHCC (6–50%) containing *FGFR2* fusions, whereas EHCC and GBC rarely do (Table 1).

In preclinical studies, the presence of *FGFR2* fusions seems to predict high sensitivity to *FGFR2* inhibitors (23,28,73,77,78). This provided the catalyst to target the *FGFR* pathway specifically in tumors harboring these fusions. FGF pathway antagonists include small molecule tyrosine kinase inhibitors that act at the receptor level to suppress oncogenic signaling (28). Clinical efficacy of *FGFR2* inhibitors is being investigated in biomarker-driven clinical trials aimed at patients harboring *FGFR2* pathway alterations (Table 2). The pan-*FGFR* inhibitor BGJ398 has

potent activity against *FGFR1–3* and is under evaluation in advanced CCAs with *FGFR* genetic alterations in two phase II studies (Table 2). Preliminary results from one of the studies (NCT02150967) was recently reported. Amongst the 26 patients with advanced or metastatic CCA harboring *FGFR2* fusions or other alterations, the disease control rate was 82% (79). The drug was well tolerated except for hyperphosphatemia.

Ponatinib is an example of a non-selective pan-*FGFR* inhibitor that is far along in clinical development. In a preclinical study, treatment with ponatinib resulted in biochemical CA 19-9 response with tumor shrinkage in a patient with the *FGFR-MGEA5* fusion (73). Another patient in the study with *FGFR-TACC3I* fusion whose disease had progressed on pazopanib (another non-selective *FGFR* inhibitor) was treated with ponatinib therapy, resulting in stabilization of disease (73). This preliminary evidence supported assessing the anti-tumor activity of ponatinib in clinical trials. Ponatinib is being investigated in a phase II trial of advanced BTCs harboring *FGFR2* gene fusions detected by either NGS or FISH (NCT02265341, Table 2). Another ongoing phase II trial is assessing the efficacy of ponatinib in advanced malignancies including CCA with any *FGFR* aberrations (mutations, fusions, amplifications) (NCT02272998, Table 2).

Other ongoing phase II studies include oral pan-*FGFR* selective small molecular inhibitors INCB054828, erdafitinib (JNJ-42756493), ARQ087 (Table 2). Preclinical and phase I studies have suggested that these compounds have potent and selective anti-tumor activity against *FGFR*-mutated cancers (80-83). A recently developed monoclonal antibody against *FGFR2* (BAY1179470) showed tumor suppressive potential in tumors with high *FGFR2* expression (84). Phase I testing of this antibody just recently completed (NCT01881217). Another phase I trial with oral pan-*FGFR* inhibitor AZD4547 also just completed (NCT00979134).

### *IDH1/2*

*IDH1* and *IDH2* encode metabolic enzymes that participate in the Krebs cycle. Mutations in *IDH1* and *IDH2* result in the accumulation of the oncometabolite 2-hydroxyglutarate, which affects cell differentiation, survival, as well as DNA methylation. The epigenetic alterations caused by mutations in *IDH1/2* lead to a blockade of hepatocyte differentiation, causing an increase in hepatic progenitor cells, which eventually results in tumorigenesis (85). *IDH* mutations

have been seen in solid tumors, including gliomas, and recently identified in BTCs. They occur primarily in IHCC (10–28%) and rarely in EHCC and GBCs (19,21,27,30,31) (Table 1). The most common *IDH1* and *IDH2* mutations cluster at the hotspot codons 132 and 172, respectively (86). The prognostic significance of these mutations remains to be fully elucidated, as there is some conflicting data. Two studies have correlated *IDH* mutations with decreased survival in IHCC compared to wild-type cases (27,31). Another study failed to demonstrate an association between *IDH* mutation status and survival (32). In contrast, a large cohort of IHCC samples (n=326) showed *IDH* mutations were associated with longer time to recurrence (30).

The efficacy of pharmacologically targeting the mutant *IDH* enzymes has been demonstrated in other types of tumors. *IDH1* inhibitor AGI-5198 slowed the growth of *IDH*-mutant glioma cells (87) and *IDH2* inhibitor AGI-6780 selectively inhibited the growth of leukemic cells carrying mutant *IDH2/R140Q* (30). The role of *IDH* inhibitors in IHCC is currently being investigated. AG-120, an *IDH1* inhibitor, has been shown to transiently stabilize disease progression in patients with *IDH1*-mutant IHCC. The expansion phase is currently underway (NCT02073994, Table 2). AG-120 is also being tested in the ongoing phase III RCT “ClarIDHy” in patients with advanced or metastatic CCA carrying an *IDH1* mutation (Table 2). A phase I/II trial with AG-221 (*IDH2* inhibitor) has just completed. A recent study showed that a subset of IHCC tumors with *IDH* mutations are exquisitely sensitive to the multikinase inhibitor dasatinib (88). This evidence paved the way for designing a phase II trial using dasatinib in IHCC cases harboring mutations in *IDH1* or 2 (Table 2). Other agents that have demonstrated preclinical efficacy and are now in phase I testing include BAY1436032 (*IDH1* inhibitor), *IDH305* (*IDH1* inhibitor), and AG-881 (*IDH1/2* inhibitor) (89).

## ROS1

*ROS1* kinase fusions between kinase domain of *ROS* and *FIG* have been found in 8.7% of CCAs (74). The resultant *FIG-ROS1* fusion protein has oncogenic potential *in vitro* and *in vivo* and can be inhibited by pharmacological targeting (74,90). A phase II trial of crizotinib (*ALK/ROS1* inhibitor) in patients with *ALK*, *MET*, or *ROS1* alterations is underway (Table 2). LDK378, a *ALK/ROS1* inhibitor, is being investigated in *ROS1*-overexpressing advanced CCAs (Table 2). Entrectinib, another *ALK/ROS1* inhibitor, is

being tested in CCAs carrying *ROS1* gene fusions.

## Conclusions

BTCs are highly aggressive tumors that carry a dismal prognosis. Historically, the BTC subtypes have been studied as a single entity. Application of NGS technologies has allowed for enhanced characterization of the distinct genetic landscapes in the various BTC subtypes. FGF and *IDH* pathway alterations are commonly seen in IHCC, whereas alterations in the *EGFR-MAPK-PI3K* pathway occur more frequently in EHCC and GBC. The molecular heterogeneity across these subtypes likely confers differential responses to various treatments. Thus, therapy should be customized based on mutational spectra. To optimize clinical trial design, targeted therapies should be matched to specific molecular alterations through patient biomarker selection. Past investigations into agents targeting receptor tyrosine kinase and *MAPK* pathways have not shown significant benefit over standard chemotherapy regimen. However, improvements in genetic profiling have unveiled novel actionable mutations, such as *FGFR2* fusion proteins and mutated *IDH1/2*. Agents targeted against these newly discovered aberrations are being actively investigated in clinical trials and hold the promise of improving clinical outcomes in this devastating orphan disease.

## Acknowledgements

**Funding:** This work is supported by 5T32 GM07200 National Research Science Award-Medical Scientist (DY Zhao).

## Footnote

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

## References

1. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology* 2009;136:1134-44.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7-30.
3. Tyson GL, Ilyas JA, Duan Z, et al. Secular trends in the incidence of cholangiocarcinoma in the USA and the impact of misclassification. *Dig Dis Sci* 2014;59:3103-10.



4. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford)* 2008;10:77-82.
5. Razumilava N, Gores GJ. Cholangiocarcinoma. *Lancet* 2014;383:2168-79.
6. Misra S, Chaturvedi A, Misra NC, et al. Carcinoma of the gallbladder. *Lancet Oncol* 2003;4:167-76.
7. Nathan H, Pawlik TM, Wolfgang CL, et al. Trends in survival after surgery for cholangiocarcinoma: a 30-year population-based SEER database analysis. *J Gastrointest Surg* 2007;11:1488-96; discussion 96-7.
8. Mavros MN, Economopoulos KP, Alexiou VG, et al. Treatment and Prognosis for Patients With Intrahepatic Cholangiocarcinoma: Systematic Review and Meta-analysis. *JAMA Surg* 2014;149:565-74.
9. Horgan AM, Amir E, Walter T, et al. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:1934-40.
10. McNamara MG, Walter T, Horgan AM, et al. Outcome of adjuvant therapy in biliary tract cancers. *Am J Clin Oncol* 2015;38:382-7.
11. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273-81.
12. Chong DQ, Zhu AX. The landscape of targeted therapies for cholangiocarcinoma: current status and emerging targets. *Oncotarget* 2016;7:46750-67.
13. Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. *J Gastrointest Oncol* 2016;7:797-803.
14. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: Utility of next-generation sequencing for clinical management. *Cancer* 2016;122:3838-47.
15. Jain A, Kwong LN, Javle M. Genomic Profiling of Biliary Tract Cancers and Implications for Clinical Practice. *Curr Treat Options Oncol* 2016;17:58.
16. Li M, Zhang Z, Li X, et al. Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway. *Nat Genet* 2014;46:872-6.
17. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. *Nat Genet* 2015;47:1003-10.
18. Ross JS, Wang K, Gay L, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. *Oncologist* 2014;19:235-42.
19. Ross JS, Wang K, Thomas Catenacci DV, et al. Comprehensive genomic profiling of biliary tract cancers to reveal tumor-specific differences and genomic alterations. *J Clin Oncol* 2015;33:abstr 231.
20. Holcombe RF, Xiu J, Pishvaian MJ, et al. Tumor profiling of biliary tract carcinomas to reveal distinct molecular alterations and potential therapeutic targets. *J Clin Oncol* 2015;33:abstr 285.
21. Borger DR, Tanabe KK, Fan KC, et al. Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. *Oncologist* 2012;17:72-9.
22. Robertson S, Hyder O, Dodson R, et al. The frequency of KRAS and BRAF mutations in intrahepatic cholangiocarcinomas and their correlation with clinical outcome. *Hum Pathol* 2013;44:2768-73.
23. Sia D, Losic B, Moeini A, et al. Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma. *Nat Commun* 2015;6:6087.
24. Deshpande V, Nduaguba A, Zimmerman SM, et al. Mutational profiling reveals PIK3CA mutations in gallbladder carcinoma. *BMC Cancer* 2011;11:60.
25. Simbolo M, Fassan M, Ruzzenente A, et al. Multigene mutational profiling of cholangiocarcinomas identifies actionable molecular subgroups. *Oncotarget* 2014;5:2839-52.
26. Churi CR, Shroff R, Wang Y, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One* 2014;9:e115383.
27. Jiao Y, Pawlik TM, Anders RA, et al. Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat Genet* 2013;45:1470-3.
28. Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology* 2014;59:1427-34.
29. Graham RP, Barr Fritcher EG, Pestova E, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. *Hum Pathol* 2014;45:1630-8.
30. Wang P, Dong Q, Zhang C, et al. Mutations in isocitrate dehydrogenase 1 and 2 occur frequently in intrahepatic cholangiocarcinomas and share hypermethylation targets with glioblastomas. *Oncogene* 2013;32:3091-100.
31. Javle M, Rashid A, Churi C, et al. Molecular characterization of gallbladder cancer using somatic mutation profiling. *Hum Pathol* 2014;45:701-8.
32. Kipp BR, Voss JS, Kerr SE, et al. Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. *Hum Pathol* 2012;43:1552-8.
33. Scaltriti M, Baselga J. The epidermal growth factor

- receptor pathway: a model for targeted therapy. *Clin Cancer Res* 2006;12:5268-72.
34. Yoshikawa D, Ojima H, Iwasaki M, et al. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. *Br J Cancer* 2008;98:418-25.
  35. Nakazawa K, Dobashi Y, Suzuki S, et al. Amplification and overexpression of c-erbB-2, epidermal growth factor receptor, and c-met in biliary tract cancers. *J Pathol* 2005;206:356-65.
  36. Gruenberger B, Schueller J, Heubrandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* 2010;11:1142-8.
  37. Rubovszky G, Lang I, Ganofszy E, et al. Cetuximab, gemcitabine and capecitabine in patients with inoperable biliary tract cancer: a phase 2 study. *Eur J Cancer* 2013;49:3806-12.
  38. Hezel AF, Noel MS, Allen JN, et al. Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *Br J Cancer* 2014;111:430-6.
  39. Sohal DP, Mykulowycz K, Uehara T, et al. A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. *Ann Oncol* 2013;24:3061-5.
  40. Lee J, Park SH, Chang HM, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2012;13:181-8.
  41. Malka D, Cervera P, Foulon S, et al. Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. *Lancet Oncol* 2014;15:819-28.
  42. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757-65.
  43. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-34.
  44. Hecht JR, Douillard JY, Schwartzberg L, et al. Extended RAS analysis for anti-epidermal growth factor therapy in patients with metastatic colorectal cancer. *Cancer Treat Rev* 2015;41:653-9.
  45. Chen JS, Hsu C, Chiang NJ, et al. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. *Ann Oncol* 2015;26:943-9.
  46. Jensen LH, Lindebjerg J, Ploen J, et al. Phase II marker-driven trial of panitumumab and chemotherapy in KRAS wild-type biliary tract cancer. *Ann Oncol* 2012;23:2341-6.
  47. Ferraro D, Goldstein D, O'Connell RL, et al. TACTIC: a multicentre, open-label, single-arm phase II trial of panitumumab, cisplatin, and gemcitabine in biliary tract cancer. *Cancer Chemother Pharmacol* 2016;78:361-7.
  48. Berlin J. Beyond exon 2--the developing story of RAS mutations in colorectal cancer. *N Engl J Med* 2013;369:1059-60.
  49. Ramanathan RK, Belani CP, Singh DA, et al. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. *Cancer Chemother Pharmacol* 2009;64:777-83.
  50. Peck J, Wei L, Zalupski M, et al. HER2/neu may not be an interesting target in biliary cancers: results of an early phase II study with lapatinib. *Oncology* 2012;82:175-9.
  51. Kwak EL, Shapiro GI, Cohen SM, et al. Phase 2 trial of afatinib, an ErbB family blocker, in solid tumors genetically screened for target activation. *Cancer* 2013;119:3043-51.
  52. Zhu AX, Meyerhardt JA, Blaszkowsky LS, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. *Lancet Oncol* 2010;11:48-54.
  53. Lubner SJ, Mahoney MR, Kolesar JL, et al. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. *J Clin Oncol* 2010;28:3491-7.
  54. Iyer RV, Pokuri VK, Groman A, et al. A Multicenter Phase II Study of Gemcitabine, Capecitabine, and Bevacizumab for Locally Advanced or Metastatic Biliary Tract Cancer. *Am J Clin Oncol* 2016. [Epub ahead of print].
  55. Valle JW, Wasan H, Lopes A, et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *Lancet Oncol* 2015;16:967-78.
  56. Knox JJ, Qin R, Strosberg JR, et al. A phase II trial of bevacizumab plus temsirolimus in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2015;33:241-6.
  57. Borger DR, Zhu AX. IDH mutations: new genetic signatures in cholangiocarcinoma and therapeutic implications. *Expert Rev Anticancer Ther* 2012;12:543-6.
  58. Chen TC, Jan YY, Yeh TS. K-ras mutation is strongly associated with perineural invasion and represents

- an independent prognostic factor of intrahepatic cholangiocarcinoma after hepatectomy. *Ann Surg Oncol* 2012;19 Suppl 3:S675-81.
59. Sia D, Hoshida Y, Villanueva A, et al. Integrative molecular analysis of intrahepatic cholangiocarcinoma reveals 2 classes that have different outcomes. *Gastroenterology* 2013;144:829-40.
  60. Goepfert B, Frauenschuh L, Renner M, et al. BRAF V600E-specific immunohistochemistry reveals low mutation rates in biliary tract cancer and restriction to intrahepatic cholangiocarcinoma. *Mod Pathol* 2014;27:1028-34.
  61. Bridgewater J, Lopes A, Beare S, et al. A phase 1b study of Selumetinib in combination with Cisplatin and Gemcitabine in advanced or metastatic biliary tract cancer: the ABC-04 study. *BMC Cancer* 2016;16:153.
  62. El-Khoueiry AB, Rankin CJ, Ben-Josef E, et al. SWOG 0514: a phase II study of sorafenib in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. *Invest New Drugs* 2012;30:1646-51.
  63. Lee JK, Capanu M, O'Reilly EM, et al. A phase II study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. *Br J Cancer* 2013;109:915-9.
  64. Moehler M, Maderer A, Schimanski C, et al. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: a double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. *Eur J Cancer* 2014;50:3125-35.
  65. Bengala C, Bertolini F, Malavasi N, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *Br J Cancer* 2010;102:68-72.
  66. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012;366:707-14.
  67. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:1087-95.
  68. Ascierto PA, Minor D, Ribas A, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. *J Clin Oncol* 2013;31:3205-11.
  69. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30-9.
  70. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015;386:444-51.
  71. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014;371:1877-88.
  72. Moeini A, Sia D, Bardeesy N, et al. Molecular Pathogenesis and Targeted Therapies for Intrahepatic Cholangiocarcinoma. *Clin Cancer Res* 2016;22:291-300.
  73. Borad MJ, Champion MD, Egan JB, et al. Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma. *PLoS Genet* 2014;10:e1004135.
  74. Gu TL, Deng X, Huang F, et al. Survey of tyrosine kinase signaling reveals ROS kinase fusions in human cholangiocarcinoma. *PLoS One* 2011;6:e15640.
  75. Rizvi S, Borad MJ. The rise of the FGFR inhibitor in advanced biliary cancer: the next cover of time magazine? *J Gastrointest Oncol* 2016;7:789-96.
  76. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. *Nat Rev Cancer* 2010;10:116-29.
  77. Wu YM, Su F, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov* 2013;3:636-47.
  78. Tanizaki J, Ercan D, Capelletti M, et al. Identification of Oncogenic and Drug-Sensitizing Mutations in the Extracellular Domain of FGFR2. *Cancer Res* 2015;75:3139-46.
  79. Javle MM, Shroff RT, Zhu A, et al. A phase 2 study of BGJ398 in patients (pts) with advanced or metastatic FGFR-altered cholangiocarcinoma (CCA) who failed or are intolerant to platinum-based chemotherapy. *J Clin Oncol* 2016;34:abstr 335.
  80. Liu PC, Wu L, Koblish H, et al. Preclinical characterization of the selective FGFR inhibitor INCB054828. *Cancer Res* 2015;75:Abstract nr 771.
  81. Tabernero J, Bahleda R, Dienstmann R, et al. Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors. *J Clin Oncol* 2015;33:3401-8.
  82. Hall TG, Yu Y, Eathiraj S, et al. Preclinical Activity of ARQ 087, a Novel Inhibitor Targeting FGFR Dysregulation. *PLoS One* 2016;11:e0162594.
  83. Papadopoulos KP, Tolcher AW, Patnaik A, et al. Phase 1,

- first-in-human study of ARQ 087, an oral pan-Fibroblast Growth Factor Receptor (FGFR) inhibitor, in patients (pts) with advanced solid tumors. *J Clin Oncol* 2015;33:abstr 2545.
84. Schatz CA, Kopitz C, Wittemer-Rump S, et al. Pharmacodynamic and stratification biomarker for the anti-FGFR2 antibody (BAY1179470) and the FGFR2-ADC. *Cancer Res* 2014;74:Abstract nr 4766.
  85. Saha SK, Parachoniak CA, Ghanta KS, et al. Mutant IDH inhibits HNF-4alpha to block hepatocyte differentiation and promote biliary cancer. *Nature* 2014;513:110-4.
  86. Grassian AR, Pagliarini R, Chiang DY. Mutations of isocitrate dehydrogenase 1 and 2 in intrahepatic cholangiocarcinoma. *Curr Opin Gastroenterol* 2014;30:295-302.
  87. Rohle D, Popovici-Muller J, Palaskas N, et al. An inhibitor of mutant IDH1 delays growth and promotes differentiation of glioma cells. *Science* 2013;340:626-30.
  88. Saha SK, Gordan JD, Kleinstiver BP, et al. Isocitrate Dehydrogenase Mutations Confer Dasatinib Hypersensitivity and SRC Dependence in Intrahepatic Cholangiocarcinoma. *Cancer Discov* 2016;6:727-39.
  89. Panknin O, Pusch S, Herbst L, et al. BAY 1436032: A highly selective, potent and orally available inhibitor of mutant forms of IDH1. *Cancer Res* 2016;76:Abstract nr 2645.
  90. Saborowski A, Saborowski M, Davare MA, et al. Mouse model of intrahepatic cholangiocarcinoma validates FIG-ROS as a potent fusion oncogene and therapeutic target. *Proc Natl Acad Sci U S A* 2013;110:19513-8.

**Cite this article as:** Zhao DY, Lim KH. Current biologics for treatment of biliary tract cancers. *J Gastrointest Oncol* 2017;8(3):430-440. doi: 10.21037/jgo.2017.05.04