# How We Treat Advanced Biliary Tract Cancers in the Second-Line Setting

Haley Ellis, MD,[1,2] Srivatsan Raghavan, MD, PhD,[1,2] Brian M. Wolpin, MD, MPH,[1,2] and James M. Cleary, MD, PhD[1,2]

[1]Dana-Farber Cancer Institute, Boston, Massachusetts

[2]Harvard Medical School, Boston, Massachusetts

**Overview**

- Advanced biliary tract cancers are a group of rare and aggressive malignancies with a poor prognosis.
- The effectiveness of cytotoxic chemotherapy is modest in the second-line setting. Given this limited efficacy, molecularly matched therapies and clinical trials are preferred when available.
- Up to 50% of intrahepatic cholangiocarcinomas have potentially actionable molecular alterations. Multiple targeted therapies have been approved for biliary tract cancers with *FGFR2* rearrangements, *IDH1* mutations, *BRAF* V600E mutations, *NTRK* fusions, and *RET* fusions, as well as immunotherapy for tumors that are mismatch repair–deficient/microsatellite instability–high.

## Introduction

Biliary tract cancers (BTC), classified as intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC) according to their anatomic origin, are a group of rare and aggressive malignancies.[1] Although they currently account for just 3% of gastrointestinal cancers, their incidence is rising, particularly driven by an increase in cases of ICC.[2] Approximately 10% to 40% of patients are eligible for surgical resection; however, even in this potentially curative setting, the risk for recurrence remains high.[3] Unfortunately, most patients are diagnosed with unresectable or metastatic disease, where the cornerstone of treatment is palliative systemic therapy. For more than a decade, combination chemotherapy with gemcitabine and cisplatin was the standard-of-care first-line regimen.[4] The addition of durvalumab (Imfinzi, AstraZeneca) to gemcitabine/cisplatin improved overall survival (OS) by 20% in comparison with gemcitabine/cisplatin alone in the phase 3 TOPAZ-1 trial, representing a possible new first-line standard of care in untreated metastatic BTC.[5] Additionally, early-phase data from the ongoing phase 3 SWOG S1815 trial demonstrated improvements in median progression-free survival (PFS) and OS when nanoparticle albumin–bound paclitaxel, also known as nab-paclitaxel (Abraxane, Bristol Myers Squibb), is combined with gemcitabine/cisplatin.[6] Despite these treatment advances, disease inevitably progresses during first-line therapy. The overall prognosis of patients with BTC remains poor, with a median OS of approximately 12 months.[7] In this review, we discuss the current landscape of second-line therapies, including cytotoxic chemotherapy, targeted therapy, and immunotherapy (Figure).

## Cytotoxic Chemotherapy

### *5-Fluorouracil and Oxaliplatin*

Until recently, the benefit of second-line systemic therapy was unclear for patients with advanced BTC as much of the evidence was limited to small retrospective studies. The multicenter, open-label, randomized phase 3 ABC-06 trial compared leucovorin, 5-fluorouracil (5-FU), and oxaliplatin (FOLFOX) plus active symptom control vs active symptom control alone in patients with metastatic or locally advanced BTC after progression on first-line gemcitabine/cisplatin (N=162). After a median follow-up of 21.7 months, the addition of FOLFOX to active symptom control led to a statistically significant, although modest, improvement in the primary endpoint of OS vs active symptom control alone (median OS, 6.2 vs 5.3 months; adjusted hazard ratio [HR], 0.69; 95% CI, 0.50-0.97; *P*=.031). The 6-month OS rates (51% vs 36%) and 12-month OS rates (26% vs 11%) also were improved with the addition of FOLFOX to active symptom control. Of note, objective radiologic responses were observed in only 5% of the patients treated with FOLFOX. As expected, grade 3 adverse events occurred more often in the chemotherapy arm than in the control

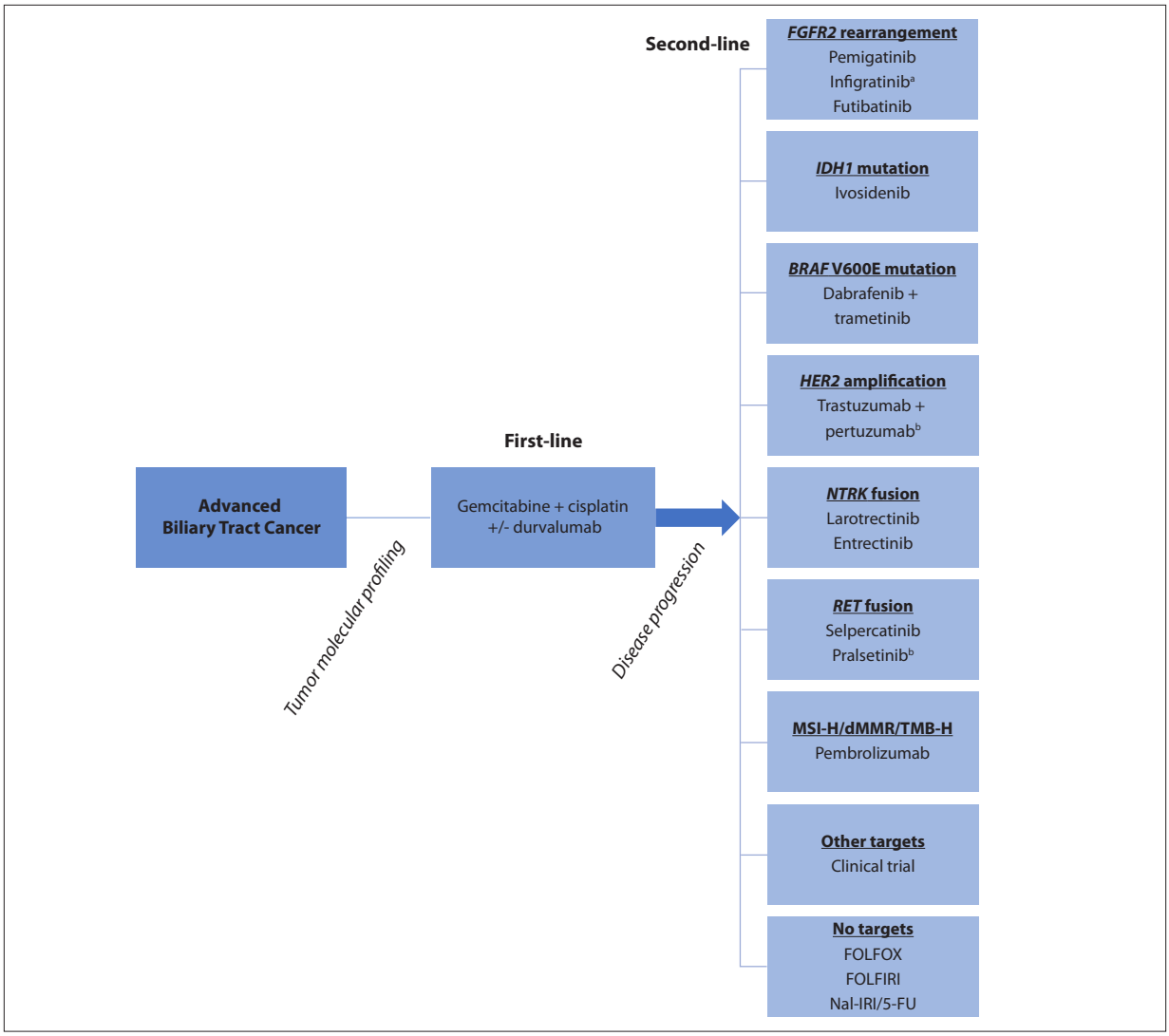


**Figure.** Algorithm for the systemic treatment of advanced biliary tract cancers.

[a]Infigratinib will be withdrawn from the market in the first quarter of 2023.
[b]Recommended in the NCCN guidelines; not yet FDA-approved for advanced biliary tract cancer.

dMMR, mismatch repair–deficient; FOLFIRI, leucovorin, 5-FU, and irinotecan; FOLFOX, leucovorin, 5-FU, and oxaliplatin; 5-FU, 5-fluorouracil; MSI-H, microsatellite instability–high; nal-IRI, liposomal irinotecan; TMB-H, tumor mutational burden–high.

arm (69% vs 52%), with the most common side effects being neutropenia, fatigue, and infection.[8] Importantly, the addition of chemotherapy was not detrimental to patients' quality of life (QOL). Some QOL scores were worse at 4 months than at baseline in the active symptom control–alone arm, whereas the scores were similar at 4 months and at baseline in the FOLFOX arm, suggesting that the addition of chemotherapy helped in maintaining QOL.[9]

### *Liposomal Irinotecan/5-FU and FOLFIRI*

Alternatives to FOLFOX are regimens containing liposomal or conventional irinotecan. The multicenter, randomized phase 2b NIFTY trial, conducted in South Korea, compared second-line liposomal irinotecan (nal-IRI) plus 5-FU vs 5-FU alone in patients with metastatic BTC that had progressed after the use of gemcitabine/cisplatin (N=174). The study met its primary endpoint of median PFS as assessed by blinded independent central review (BICR), which was longer in the combination arm than in the 5-FU–alone arm (7.1 vs 1.4 months; HR, 0.56; 95% CI, 0.39-0.81; *P*=.0019). Notably, a discrepancy was found between the BICR-assessed median PFS and the investigator-reviewed median PFS, at 7.1 vs 3.9 months,

respectively.[10] In an updated analysis of this study that was presented at the European Society for Medical Oncology (ESMO) Congress 2022, the survival benefit with nal-IRI/5-FU vs 5-FU alone was maintained, with a median OS of 8.6 vs 5.3 months, respectively (HR, 0.68; 95% CI, 0.48-0.95; *P*=.02). However, because of the inconsistency between the BICR-assessed and investigator-reviewed median PFS in the initial NIFTY analysis, an updated analysis was performed by a different BICR team. The PFS results of the new BICR team were similar to the investigator-reviewed PFS results, at 4.2 vs 3.9 months, respectively.[11] In contrast, the randomized phase 2 NALIRICC trial of nal-IRI/5-FU vs 5-FU monotherapy did not meet its primary endpoint of improving PFS in patients with metastatic BTC previously treated with gemcitabine-based therapies (N=100).[12] The disparate PFS outcomes in these 2 trials of nal-IRI/5-FU in the second-line setting have several possible explanations. First, the NIFTY trial enrolled only Asian patients. Second, the NALIRICC trial enrolled predominantly patients with ICC, whereas the NIFTY trial had more patients with ECC or GBC. Third, the dose of nal-IRI was higher in the NALIRICC trial than in the NIFTY study (80 vs 70 mg/m$^2$), which likely explains the higher level of toxicity seen in the NALIRICC study. Also, it is important to note that unlike the ABC-06 trial of FOLFOX, the nal-IRI–based studies compared these regimens with an active treatment arm of 5-FU.

In reviewing the role of second-line leucovorin, 5-FU, and irinotecan (FOLFIRI), a randomized phase 2 study of patients with advanced BTC conducted in South Korea (N=118) evaluated FOLFIRI vs FOLFOX. Although the study failed to show that FOLFIRI significantly improved survival outcomes in comparison with FOLFOX, data from the trial suggest that second-line FOLFIRI and FOLFOX have comparable efficacy. Like other studies of FOLFOX and nal-IRI/5-FU, the trial confirmed that chemotherapy has only modest efficacy in the second-line setting. Trial outcomes comparing FOLFOX vs FOLFIRI included similar median OS results (6.3 vs 5.7 months), median PFS results (2.8 vs 2.1 months), and overall response rates (ORR; 5.9% vs 3.9%).[13] On the basis of data from this collection of nal-IRI/5-FU and FOLFIRI studies, both regimens have received National Comprehensive Cancer Network (NCCN) category 2B recommendations for second-line therapy.[14]

## Targeted Therapy

The advent of tumor molecular profiling has facilitated the characterization of multiple recurrent genomic alterations in cholangiocarcinoma, including *FGFR2* rearrangements and *IDH1* mutations.[1,15-17] Numerous groups have demonstrated that approximately 40% to 50% of ICC harbor actionable oncogenic alterations. Highlighting the importance of incorporating comprehensive genomic profiling into the clinical care of patients with advanced BTC, the survival of patients in the BTC subgroup of the MOSCATO-01 trial (n=43) who were treated with molecularly matched therapies had improved survival compared with those who received unmatched therapies (median OS, 17.0 vs 5.0 months; HR, 0.29; 95% CI, 0.11-0.76; *P*=.008).[18,19]

If feasible, we recommend biopsies for comprehensive genomic profiling at the time of advanced disease diagnosis to identify patients who are potential candidates for targeted therapies. Tissue-based testing is the most sensitive method, particularly in detecting alterations like translocations, although sometimes it may be difficult to obtain sufficient tumor tissue for analysis in BTC. Blood-based testing with cell-free DNA has the advantage of being a less invasive method for the serial monitoring of tumor heterogeneity and genomic evolution with selective therapeutic pressure.[20] Cell-free DNA can be helpful at the time of progression to investigate the mechanism of resistance to targeted therapy.

Mutational profiles in BTC are distinct depending on the anatomic location of the tumor. Although actionable genomic alterations are frequently seen in patients with ICC, targetable genomic alterations currently are only rarely observed in ECC and GBC. ICC is enriched with *FGFR2* fusions/rearrangements and *IDH1/2* mutations. ECC has an increased frequency of *KRAS*, *TP53*, *PIK3CA*, *SMAD4,* and *ARID1A* mutations and *HER2/3* amplifications. Finally, GBC also has *HER2* amplification/overexpression and a lower frequency of *TP53*, *KRAS*, *ARID1A*, and *PIK3CA* mutations.[16,21,22]

### FGFR2 *Fusions or Rearrangements*

Fibroblast growth factor receptor (FGFR) is a receptor tyrosine kinase that normally functions to regulate cellular growth, differentiation, proliferation, and survival via the activation of downstream cascades, including RAS/RAF/MEK, PI3K/AKT, JAK/STAT, and other pathways.[23] FGFR2 signalling is aberrantly activated in approximately 15% of cholangiocarcinomas, almost exclusively ICC, and is most commonly caused by oncogenic gene fusions or rearrangements in *FGFR2*.[24] Other targetable *FGFR2* alterations include *FGFR2* extracellular domain in-frame deletions, which occur in approximately 3.5% of ICC.[17] Targeting FGFR has therapeutic potential for patients with these genomic aberrations, and numerous agents have been approved or are under investigation.

Pemigatinib (Pemazyre, Incyte) is an oral small-molecule pan-FGFR inhibitor. FIGHT-202 was a global, open-label, single-arm phase 2 study of pemigatinib

in patients with previously treated locally advanced or metastatic cholangiocarcinoma (N=147). Final analysis demonstrated a 37% ORR, a 9.1-month median duration of response (DOR), a 7.0-month median PFS, and a 17.5-month median OS in patients with *FGFR2* fusions/rearrangements (n=108) treated with pemigatinib.[25,26] Patients with other *FGF/FGFR* alterations (n=20), primarily *FGFR* mutations or amplifications, failed to show a response to pemigatinib.[25] Post hoc analysis of the FIGHT-202 trial verified that the median PFS in patients with *FGFR2* fusions/rearrangements who received second-line pemigatinib was better than that of patients with *FGFR2* fusions/rearrangements who had received second-line systemic therapy before enrolling in this study (PFS, 7.0 vs 4.2 months).[27] These results led to US Food and Drug Administration (FDA) approval of pemigatinib in April 2020 for patients with advanced *FGFR2* fusion–positive cholangiocarcinoma that had progressed on at least one line of systemic treatment, making it the first approved targeted therapy in cholangiocarcinoma.

Infigratinib (Truseltiq, Helsinn) is another oral pan-FGFR inhibitor. Preliminary results of a single-arm phase 2 trial showed a BICR ORR of 23% and a median DOR of 5.0 months in patients with previously treated *FGFR2* fusion–positive advanced cholangiocarcinoma (n=108). Median PFS was similar to that with pemigatinib, at 7.3 months. Responses were more likely in patients treated in the second-line setting (ORR, 34%) than in the third-line or later setting (ORR, 13%) according to prespecified subgroup analyses.[28] This FGFR-targeted therapy was also granted accelerated approval by the FDA for cholangiocarcinoma with *FGFR2* fusions in May 2021. However, infigratinib will be withdrawn from the market in the first quarter of 2023. A press release states the infigratinib is being discontinued for business reasons rather than for safety or efficacy concerns.[29]

The approved first-generation small-molecule inhibitors, pemigatinib and infigratinib, are considered pan-FGFR inhibitors because they non-selectively block FGFR1, 2, and 3. This characteristic leads to a spectrum of on- and off-target toxicities, limiting their dose intensity. Hyperphosphatemia is the most common adverse event with pan-FGFR inhibitors, related to inhibition of FGFR1 in the renal tubules, and was seen in 60% (Common Terminology Criteria for Adverse Events [CTCAE] all grades; 0% grade ≥3) of patients in the FIGHT-202 trial. Patients with an increase in phosphate levels of more than 25% above baseline should follow a low-phosphorus diet. In addition to dietary changes, phosphate-lowering therapy should be considered in the setting of an elevated phosphate level of 7 mg/dL or greater. Adherence to these agents is a challenge; therefore, starting at the lowest possible dose and titrating upward as needed is recommended. Lanthanum carbonate is preferred over magnesium-based regimens or sevelamer because the latter exacerbates diarrhea, which can also be seen as an FGFR inhibitor–associated toxicity. Dose interruptions and reductions may be required if hyperphosphatemia persists despite dietary changes and phosphate binders. Other adverse events include ocular toxicities (eg, dry eyes, central serous retinopathy, retinal detachment) and dermatologic/mucosal side effects (eg, alopecia, stomatitis, palmar-plantar erythrodysesthesia).[30] Patients should have a baseline ophthalmologic examination before FGFR inhibition is initiated and undergo an immediate ophthalmologic evaluation in the event of vision changes. Central serous retinopathy is often reversible with discontinuation. For skin protection, patients should keep their skin moist, should use emollients, and may employ topical corticosteroids. Good oral hygiene, avoidance of spicy foods, and the use of mouthwash containing dexamethasone or lidocaine are helpful for stomatitis.

As with other targeted therapies, acquired resistance inevitably develops after treatment with reversible ATP-competitive FGFR kinase inhibitors such as pemigatinib and infigratinib. Molecular analysis has revealed that most ICC that initially respond to FGFR inhibitors ultimately acquire resistance via polyclonal *FGFR2* kinase domain mutations. Circulating tumor DNA is a potentially less invasive approach for monitoring these heterogeneous resistance mechanisms and capturing tumor evolution.[31,32] Notably, the irreversible, covalent pan-FGFR inhibitor futibatinib (Lytgobi, Taiho Oncology) can overcome some cases of acquired resistance due to *FGFR2* kinase domain mutations.[32] In addition to overcoming acquired resistance, futibatinib achieved an ORR of 42%, a median PFS of 8.9 months, and a median DOR of 9.7 months in patients with FGFR inhibitor–naive cholangiocarcinoma in the phase 2b FOENIX-CCA2 trial. This agent was the third FGFR inhibitor to be granted FDA approval, in September 2022.[33]

Other pan-FGFR agents are currently under study. In interim results from the phase 2 FIDES-01 study of derazantinib in patients who had ICC with *FGFR2* mutations (78%), *FGFR2* short variants (11%), and *FGFR2* amplifications (11%)—molecular events not addressed by other FGFR inhibitors—the ORR was 8.7% and the median PFS was 7.3 months.[34] Erdafitinib (Balversa, Janssen) is a small-molecule tyrosine kinase inhibitor with activity against all four FGFR members and is FDA-approved in bladder cancer. Interim analysis of the RAGNAR study of erdafitinib in *FGFR*-positive (mutations or fusions) advanced refractory solid tumors confirmed an investigator-assessed ORR of 42% in

cholangiocarcinoma.[35]

Finally, clinical trial data from next-generation FGFR inhibitors are beginning to emerge. RLY-4008 is an irreversible inhibitor that is highly selective for FGFR2. Because it has minimal activity against FGFR1, unlike the pan-FGFR inhibitors, hyperphosphatemia is much less common. Preliminary data from the phase 1/2 REFOCUS study of RLY-4008 demonstrated an ORR of 88% in patients with FGFR inhibitor–naive cholangiocarcinoma with *FGFR2* fusions or rearrangements treated at the recommended phase 2 dose of 70 mg daily. Long-term efficacy and safety data are still pending.[36]

Current data suggest that in comparison with *FGFR2* fusions, *FGFR2* mutations are not very responsive to FGFR inhibitors, although ongoing studies are evaluating other targetable *FGFR2* alterations. Some trials are testing the combination of FGFR2 inhibitors with cytotoxic chemotherapy in the first-line setting. The challenge with testing targeted therapies in patients with newly diagnosed disease is that molecular profiling is slow to produce results; however, this limitation may be overcome with blood-based genomic testing.

### IDH1/2 *Mutations*

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes that are mutated in approximately 20% and 4% of ICC, respectively. Gain-of-function mutations in *IDH1* and *IDH2* lead to the production of the oncometabolite 2-hydroxyglutarate (2-HG), which results in epigenetic dysregulation, aberrant metabolism, and immune evasion.[37] Ivosidenib (AG-120; Tibsovo, Agios Pharmaceuticals) is an oral small-molecule inhibitor of mutant *IDH1* that is FDA-approved in *IDH1*-mutant acute myeloid leukemia. Final data from the multicenter, randomized phase 3 ClarIDHy trial displayed statistically significant improvement in PFS in a comparison of ivosidenib with placebo (median PFS, 2.7 vs 1.4 months; HR, 0.37; 95% CI, 0.25-0.54; *P*<.0001) in patients with previously treated unresectable or metastatic *IDH1*-mutant cholangiocarcinoma (N=185). Median OS was 10.3 months for ivosidenib vs 7.5 months for placebo (HR, 0.79; 95% CI, 0.56-1.12; *P*=.09). After adjustment for the high rate of crossover to ivosidenib among patients in the placebo group at disease progression (71%), median OS with placebo was assessed as 5.1 months, indicating a statistically significant improvement in OS for ivosidenib in comparison with placebo (HR, 0.49; 95% CI, 0.34-0.70; *P*<.0001).[38,39] Notably, although objective radiologic responses are rare with ivosidenib, several patients in the phase 1 and 3 trials had long-term stable disease, suggesting that this agent may be cytostatic in some cases. In terms of the side effect profile, ivosidenib can cause prolongation of the QTc interval but overall is well tolerated. On the basis of the ClarIDHy trial data, ivosidenib was approved by the FDA in August 2021 for cholangiocarcinoma with *IDH1* mutations. Although ivosidenib improves outcomes for this subset of patients, resistance invariably develops. Resistance to ivosidenib can be acquired through the development of genomic alterations such as oncogenic *IDH2* mutations or secondary *IDH1* mutations, which can restore the production of 2-HG.[40] New IDH-directed therapies with the potential to overcome these resistance mechanisms, including IDH305, LY3410738, and olutasidenib, are under investigation in early-phase trials in cholangiocarcinoma.[41]

Given the excellent toxicity profile of ivosidenib, it may be possible to combine it with other therapies. Trials combining ivosidenib with nivolumab (Opdivo, Bristol Myers Squibb; NCT04056910) and with first-line standard-of-care chemotherapy (NCT04088188) are currently underway.

### BRAF *V600E Mutations*

*BRAF* mutations, mostly commonly at p.V600E, are a strong activator of the RAS/RAF/MEK/ERK or MAPK pathway. The incidence of this mutation in BTC is low, at less than 5%, and the mutation is most often seen in ICC. Like *BRAF* V600E–mutated colorectal cancers, cholangiocarcinomas harboring *BRAF* V600E mutations have an aggressive biology, and the OS of these patients is decreased.[17] The multicenter phase 2 ROAR basket trial evaluated the combination of dabrafenib (Tafinlar, Novartis; BRAF inhibitor) and trametinib (Mekinist, Novartis; MEK1/2 inhibitor) in advanced *BRAF* V600E–mutated cancers, including BTC. The ORR was 51% and the median DOR and PFS were 9.0 months in patients with heavily pretreated BTC (n=43).[42,43] The FDA granted dabrafenib/trametinib tissue-agnostic accelerated approval in July 2022 for refractory advanced solid tumors, including BTC, with *BRAF* p.V600E mutations.

### HER2 *Amplification and Overexpression*

Human epidermal growth factor receptor 2 (*HER2*) gene amplification and/or overexpression is seen in 5% to 20% of cases of GBC and ECC, with a relatively low incidence in non–liver fluke-associated cholangiocarcinoma.[44,45] In the open-label phase 2 MyPathway basket study of 39 patients with previously treated *HER2*-positive metastatic BTC (amplification, overexpression, or both), the combination of pertuzumab (Perjeta, Genentech) and trastuzumab (Enhertu, AstraZeneca) showed an ORR of 23%, a median PFS of 4.0 months, and a median OS of 10.9 months. This combination treatment was overall well tolerated and is now included in the NCCN guidelines as

a category 2A recommendation.[46]

Other HER2-targeting therapies are currently under investigation. Zanidatamab, a bispecific HER2-targeted antibody, is being studied in the HERIZON-BTC-01 trial and received FDA breakthrough therapy designation in November 2020. The HER2 antibody-drug conjugate (ADC) trastuzumab deruxtecan, also known as T-DXd, demonstrated a 36% ORR and a 5.1-month median PFS in the single-arm phase 2 HERB trial in Japanese patients with *HER2*-positive unresectable or recurrent BTC. A signal of response also occurred in *HER2* low expressors, with 1 of these 8 patients having a partial response.[47] Neratinib (Nerlynx, Puma), a tyrosine kinase inhibitor targeting HER2 and endothelial growth factor receptor (EGFR), produced an ORR of 16% in *HER2*-mutant BTC (most commonly p.S310F and p.V777L) in the phase 2 SUMMIT basket trial. The PFS and OS of 2.8 and 5.4 months, respectively, are comparable with those of standard-of-care cytotoxic chemotherapy.[48] Other efforts to target *HER2* amplification in BTC include a study combining trastuzumab with FOLFOX in gemcitabine/cisplatin-refractory *HER2*-amplified BTC tumors. Notably, FOLFOX/trastuzumab had an ORR of 29% and a median PFS of 5.1 months in this population.[49]

### NTRK *Fusions*

Neurotrophic receptor tyrosine kinase (*NTRK*) fusions are overall rare driver mutations, accounting for fewer than 1% of BTC cases. Like many other targetable alterations in BTC, they are most often seen in ICC. The landmark study assessing the role of the TRK inhibitor larotrectinib (Vitrakvi, Loxo Oncology) showed an ORR of 75% with an acceptable safety profile in 55 *NTRK*-positive cancers, including 2 cases of cholangiocarcinoma.[50] Analysis of three phase 1/2 trials (ALKA-372-001, STARTRK-1, STARTRK-2) of entrectinib (Rozlytrek, Genentech) in advanced *NTRK*-positive solid tumors, including 1 cholangiocarcinoma, revealed an ORR of 57%.[51] In 2018, larotrectinib and entrectinib were among the first agents to receive tissue-agnostic FDA approval—in this case, for previously treated locally advanced or metastatic solid tumors with *NTRK* fusions.

### RET *Fusions*

Another rare oncogenic fusion, usually seen in ICC, involves the RET receptor tyrosine kinase. The LIBRETTO-001 multicohort trial of the RET-specific inhibitor selpercatinib (Retevmo, Lilly) in patients previously treated or without satisfactory alternatives (2 with cholangiocarcinoma) confirmed an ORR of 44% with a 25-month DOR.[52] On the basis of these results, selpercatinib was FDA-approved in September 2022 for locally advanced or metastatic solid tumors harboring *RET* fusions, representing another step forward in precision oncology. Another highly potent and selective RET inhibitor, pralsetinib (Gavreto, Blueprint Medicines/Genentech), was evaluated in the phase 1/2 ARROW study of advanced *RET*-altered solid tumors refractory to standard therapies. This trial demonstrated clinical responses in 2 of 3 patients who had cholangiocarcinoma, with an ORR of 57% and a median DOR of 12 months in all patients.[53] Pralsetinib is currently approved only in *RET*-positive non–small cell lung cancer and thyroid cancer.

## Immunotherapy

Immunotherapy agents, including immune checkpoint inhibitors, have revolutionized the treatment of many cancers over the last decade. Programmed death ligand 1 (PD-L1) overexpression, mismatch repair deficiency, high microsatellite instability, and high tumor mutational burden (TMB-H) are considered to be important biomarkers of response to immunotherapy, although fewer than 5% of patients with BTC have these phenotypes.[54,55] The phase 2 KEYNOTE-158 study enrolled patients with mismatch repair–deficient (dMMR)/microsatellite instability–high (MSI-H) treatment-refractory noncolorectal advanced tumors, including 22 with dMMR cholangiocarcinoma. The ORR was 41% and the median DOR was not reached with the anti–PD-1 monoclonal antibody pembrolizumab (Keytruda, Merck).[56] Pembrolizumab is FDA-approved for advanced solid tumors, including BTC, that are dMMR/MSI-H or have a TMB of 10 mutations per megabase or higher. Of note, we do not recommend giving anti–PD-1 monotherapy after progression on gemcitabine/cisplatin/durvalumab.

Efforts to find novel immunotherapeutic strategies include future trials exploring combination immunotherapy regimens, including PD-1–directed therapy plus targeted therapies such as FGFR and IDH1 inhibitors.

## Liver-Directed Therapies

Liver-directed therapies, including radiation therapy and trans-arterial radio-embolization (TARE), can play a role in the management of a subset of patients who have unresectable cholangiocarcinoma without extrahepatic disease. Although no randomized data are available, emerging data suggest that TARE has activity in unresectable, chemotherapy-refractory ICC.[57] A cohort study of 2201 patients with metastatic ICC noted improved OS in the patients treated with chemotherapy plus liver-directed radiation or surgery.[58] In the first-line setting, TARE in combination with chemotherapy is being studied in a phase 3 trial.[59]

## Conclusion

The advancement of genomic sequencing has made it possible to identify multiple recurrent molecular targets in cholangiocarcinoma, particularly ICC. Although cytotoxic chemotherapy has only modest efficacy in the second-line treatment of BTC, some patients can significantly benefit from targeted therapies and immunotherapy. The list of approved therapies and potentially targetable alterations (eg, *KRAS* G12C mutations, *NRG1* fusions, *PIK3CA* mutations, and DNA damage repair gene mutations) is likely to continue to expand. We emphasize the importance of incorporating comprehensive tumor genotyping into routine clinical practice to identify patients with BTC who would benefit from molecularly matched therapies.

### *Disclosures*

*Dr Ellis has no conflicts to disclose. Dr Raghavan holds equity in Amgen. Dr Wolpin receives research funding from Celgene, Eli Lilly, Novartis, and Revolution Medicines and reports consulting for Celgene, GRAIL, and Mirati Therapeutics. Dr Cleary receives research funding to his institution from Merus, Roche, and Bristol Myers Squibb; receives research support from Merck, AstraZeneca, Esperas Pharma, Bayer, Tesaro, Arcus Biosciences, and Apexigen; and has received honoraria for serving on the advisory boards of Syros Pharmaceuticals, Incyte, and Blueprint Medicines.*

### *Funding*

*Dr Cleary is supported by the Haya Linde Memorial Fund, Team Evan Schumacher, and the Phyllis Cohen Fund for Bile Duct Cancer Research. The work was also supported by a grant from the National Institutes of Health (P50CA127003).*

## References

1. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New horizons for precision medicine in biliary tract cancers. *Cancer Discov*. 2017;7(9):943-962.

2. Bertuccio P, Malvezzi M, Carioli G, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. *J Hepatol*. 2019;71(1):104-114.

3. Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: ready for "prime time" in biliary tract cancer. *J Hepatol*. 2020;73(1):170-185.

4. Valle J, Wasan H, Palmer DH, et al; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273-1281.

5. Oh D-Y, He AR, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evid*. 2022;1(8).

6. Shroff RT, Javle MM, Xiao L, et al. Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: a phase 2 clinical trial. *JAMA Oncol*. 2019;5(6):824-830.

7. Marin JJG, Prete MG, Lamarca A, et al; working group 6 of the COST-action 18122 (Euro-Cholangio-NET) as part of the European Network for the study of Cholangiocarcinoma (ENSCCA). Current and novel therapeutic opportunities for systemic therapy in biliary cancer. *Br J Cancer*. 2020;123(7):1047-1059.

8. Lamarca A, Palmer DH, Wasan HS, et al; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol*. 2021;22(5):690-701.

9. Lamarca A, Palmer D, Wasan HS, et al. Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial [ESMO abstract 54MO]. *Ann Oncol*. 2022;33(7)(suppl).

10. Yoo C, Kim KP, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *Lancet Oncol*. 2021;22(11):1560-1572.

11. YooC, Kim K, Kang MJ, et al. Final analysis results from the NIFTY trial, a phase IIb, randomized, open-label study of liposomal irinotecan plus fluorouracil and leucovorin in patients with previously treated metastatic biliary tract cancer [ESMO abstract 55P]. *Ann Oncol*. 2022;33(7)(suppl).

12. Vogel A, Wenzel P, Folprecht G, et al. Nal-IRI and 5-FU/LV compared to 5-FU/LV in patients with cholangio- and gallbladder carcinoma previously treated with gemcitabine-based therapies (NALIRICC) [ESMO abstract 53MO]. *Ann Oncol*. 2022;33(7)(suppl).

13. Choi IS, Kim KH, Lee JH, et al. A randomised phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. *Eur J Cancer*. 2021;154:288-295.

14. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(5):541-565.

15. Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. *Clin Cancer Res*. 2018;24(17):4154-4161.

16. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: utility of next-generation sequencing for clinical management. *Cancer*. 2016;122(24):3838-3847.

17. Cleary JM, Raghavan S, Wu Q, et al. FGFR2 extracellular domain in-frame deletions are therapeutically targetable genomic alterations that function as oncogenic drivers in cholangiocarcinoma. *Cancer Discov*. 2021;11(10):2488-2505.

18. Verlingue L, Malka D, Allorant A, et al. Precision medicine for patients with advanced biliary tract cancers: an effective strategy within the prospective MOSCATO-01 trial. *Eur J Cancer*. 2017;87:122-130.

19. Mody K, Jain P, El-Refai SM, et al. Clinical, genomic, and transcriptomic data profiling of biliary tract cancer reveals subtype-specific immune signatures. *JCO Precis Oncol*. 2022;6:e2100510.

20. Mody K, Kasi PM, Yang J, et al. Circulating tumor DNA profiling of advanced biliary tract cancers. *JCO Precis Oncol*. 2019;3.

21. Churi CR, Shroff R, Wang Y, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One*. 2014;9(12):e115383.

22. Rimassa L, Personeni N, Aghemo A, Lleo A. The immune milieu of cholangiocarcinoma: from molecular pathogenesis to precision medicine. *J Autoimmun*. 2019;100:17-26.

23. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer*. 2017;17(5):318-332.

24. Wu YM, Su F, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov*. 2013;3(6):636-647.

25. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671-684.

26. Vogel A, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated locally advanced or metastatic cholangiocarcinoma: final results from FIGHT-202 [ESMO GI abstract O-2]. *Ann Oncol*. 2022;33(4)(suppl).

27. Bibeau K, Féliz L, Lihou CF, Ren H, Abou-Alfa GK. Progression-free survival in patients with cholangiocarcinoma with or without FGF/FGFR alterations: a FIGHT-202 post hoc analysis of prior systemic therapy response. *JCO Precis Oncol*. 2022;6:e2100414.

28. Javle M, Roychowdhury S, Kelley RK, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol*. 2021;6(10):803-815.

29. Truseltiq (infigratinib) capsules notice of permanent discontinuation of distribution. Helsinn. https://www.truseltiq.com/hcp. Posted October 2022. Accessed December 1, 2022.

30. Mahipal A, Tella SH, Kommalapati A, Yu J, Kim R. Prevention and treatment of FGFR inhibitor-associated toxicities. *Crit Rev Oncol Hematol*. 2020;155:103091.

31. Varghese AM, Patel J, Janjigian YY, et al. Noninvasive detection of polyclonal acquired resistance to FGFR inhibition in patients with cholangiocarcinoma harboring FGFR2 alterations. *JCO Precis Oncol*. 2021;5:44-50.

32. Goyal L, Shi L, Liu LY, et al. TAS-120 overcomes resistance to ATP-competitive FGFR inhibitors in patients with FGFR2 fusion-positive intrahepatic cholangiocarcinoma. *Cancer Discov*. 2019;9(8):1064-1079.

33. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Primary results of phase 2 FOENIX-CCA2: the irreversible FGFR1-4 inhibitor futibatinib in intrahepatic cholangiocarcinoma with FGFR2 fusions/rearrangements [AACR abstract CT010]. *Cancer Res*. 2021;81(13)(suppl).

34. Javle MM, Abou-Alfa GK, Macarulla T, et al. Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: interim results from the phase 2 study FIDES-01 [ASCO GI abstract 427]. *J Clin Oncol*. 2022;40(4)(suppl).

35. Loriot Y, Schuler MH, Iyer G, et al. Tumor agnostic efficacy and safety of erdafitinib in patients (pts) with advanced solid tumors with prespecified fibroblast growth factor receptor alterations (FGFRalt) in RAGNAR: interim analysis (IA) results [ASCO abstract 3007]. *J Clin Oncol*. 2022;40(16)(suppl).

36. Hollebecque A, Borad M, Goyal L, et al. Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients with an FGFR2-fusion or rearrangement, FGFR inhibitor-naive cholangiocarcinoma: ReFocus trial [ESMO abstract LBA12]. *Ann Oncol*. 2022;33(7)(suppl).

37. Wu MJ, Shi L, Dubrot J, et al. Mutant IDH inhibits IFNg-TET2 signaling to promote immunoevasion and tumor maintenance in cholangiocarcinoma. *Cancer Discov*. 2022;12(3):812-835.

38. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(6):796-807.

39. Zhu AX, Macarulla T, Javle MM, et al. 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(11):1669-1677.

40. Cleary JM, Rouaisnel B, Daina A, et al. Secondary IDH1 resistance mutations and oncogenic IDH2 mutations cause acquired resistance to ivosidenib in cholangiocarcinoma. *NPJ Precis Oncol*. 2022;6(1):61.

41. Adeva J. Current development and future perspective of IDH1 inhibitors in cholangiocarcinoma. *Liver Cancer Int*. 2022;3(1):17-31.

42. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with $BRAF^{V600E}$-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol*. 2020;21(9):1234-1243.

43. Wainberg ZA, Lassen UN, Elez E, et al. Efficacy and safety of dabrafenib and trametinib in patients with BRAF V600E-mutated biliary tract cancer: a cohort of the ROAR basket trial [ASCO GI abstract 187]. *J Clin Oncol*. 2019;37(4)(suppl).

44. Weinberg BA, Xiu J, Lindberg MR, et al. Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets. *J Gastrointest Oncol*. 2019;10(4):652-662.

45. Albrecht T, Rausch M, Rössler S, et al. HER2 gene (ERBB2) amplification is a rare event in non-liver-fluke associated cholangiocarcinogenesis. *BMC Cancer*. 2019;19(1):1191.

46. Javle M, Borad MJ, Azad NS, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2021;22(9):1290-1300.

47. Ohba A, Morizane C, Kawamoto Y, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-expressing unresectable or recurrent biliary tract cancer: an investigator-initiated multicenter phase 2 study (HERB trial) [ASCO abstract 4006]. *J Clin Oncol*. 2022;40(16)(suppl).

48. Harding J, Targeting HER2 (ERBB2) mutation-positive advanced biliary tract cancers with neratinib: results from the phase II SUMMIT 'basket' trial [ASCO abstract 320]. *J Clin Oncol,* 2021;39(3)(suppl).

49. Lee CK, Chon HJ, Cheon J, et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14) [published online October 31, 2022]. *Lancet Gastroenterol Hepatol*. doi:10.1016/S2468-1253(22)00335-1.

50. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion–positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739.

51. Doebele RC, Drilon A, Paz-Ares L, et al; 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(2):271-282.

52. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol*. 2022;23(10):1261-1273.

53. Subbiah V, Cassier PA, Siena S, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. *Nat Med*. 2022;28(8):1640-1645.

54. Silva VW, Askan G, Daniel TD, et al. Biliary carcinomas: pathology and the role of DNA mismatch repair deficiency. *Chin Clin Oncol*. 2016;5(5):62.

55. Shao C, Li G, Huang L, et al. Prevalence of high tumor mutational burden and association with survival in patients with less common solid tumors. *JAMA Netw Open*. 2020;3(10):e2025109.

56. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(1):1-10.

57. White J, Carolan-Rees G, Dale M, et al. Yttrium-90 transarterial radioembolization for chemotherapy-refractory intrahepatic cholangiocarcinoma: a prospective, observational study. *J Vasc Interv Radiol*. 2019;30(8):1185-1192.

58. Sebastian NT, Tan Y, Miller ED, et al. Association of liver-directed local therapy with overall survival in adults with metastatic intrahepatic cholangiocarcinoma. *JAMA Netw Open*. 2019;2(9):e1911154.

59. Edeline J, Touchefeu Y, Guiu B, et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocaricnoma: a phase 2 clinical trial. *JAMA Oncol*. 2020;6(1):51-59.