



**HAL**  
open science

## The choice for the optimal therapy in advanced biliary tract cancers: Chemotherapy, targeted therapies or immunotherapy

L.-J. Palmieri, J. Lavolé, S. Dermine, C. Brezault, M. Dhooge, A. Barré, S. Chaussade, R. Coriat

### ► To cite this version:

L.-J. Palmieri, J. Lavolé, S. Dermine, C. Brezault, M. Dhooge, et al.. The choice for the optimal therapy in advanced biliary tract cancers: Chemotherapy, targeted therapies or immunotherapy. *Pharmacology and Therapeutics*, 2020, 210, pp.107517 -. 10.1016/j.pharmthera.2020.107517 . hal-03490320

**HAL Id: hal-03490320**

**<https://hal.science/hal-03490320>**

Submitted on 22 Aug 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

P&T #23647

**The choice for the optimal therapy in advanced biliary tract cancers:  
chemotherapy, targeted therapies or immunotherapy**

L.-J. Palmieri<sup>1,2</sup>, J. Lavolé<sup>1</sup>, S. Dermine<sup>1,2</sup>, C. Brezault<sup>1</sup>, M. Dhooge<sup>1</sup>, A. Barré<sup>1,2</sup>, S.  
Chaussade<sup>1,2</sup>, R. Coriat<sup>1,2</sup>

**List of affiliations :**

<sup>1</sup>: *Gastroenterology and Digestive Oncology Department, Cochin Hospital,  
Assistance Publique-Hôpitaux de Paris, Paris, 75014, France.*

<sup>2</sup>: *Unité INSERM U1016, University of Paris, France.*

**Corresponding author:**

Lola-Jade Palmieri, MD, MSc

Gastroenterology and Digestive Oncology Department

Cochin Hospital

27 rue du faubourg St Jacques, 75014 Paris, France

e-mail: lolajade.palmieri@aphp.fr

Phone: +33(1) 58 41 17 17 Fax: +33(1) 79 73 17 05

**Word count: 5074**

**Abstract word count: 140**

**Figure: 1**

**Table: 2**

## **Abstract**

Biliary tract cancers (BTCs) represent a heterogeneous group that includes intrahepatic cholangiocarcinomas (CCAs), perihilar-CCAs or Klatskin tumors, extrahepatic-CCAs, and gallbladder adenocarcinoma. These entities have distinct demographics, risk factors, clinical presentation, and molecular characteristics.

In advanced BTCs, the recommendations are mainly supporting a doublet chemotherapy regimen using cisplatin/gemcitabine (CisGem) with a 5-year overall survival rate close to 5% and median overall survival (mOS) of less than a year. The lack of overall efficacy stresses the need for personalized therapies.

Recently, whole-genome and transcriptome sequencing highlighted the diversity of BTCs' subtypes. Distinct genetic alterations were retrieved according to the localization, with a high rate of potentially actionable alterations. Targeted therapies and immunotherapy have since then been tested for BTCs, trying to propose a more personalized treatment.

This review describes the different therapeutic options, validated and in development, for patients with advanced BTCs.

**Keywords:** Biliary tract cancers; cholangiocarcinoma; targeted therapy; immunotherapy; genome sequencing

## **Table of contents**

1. Introduction
2. Epidemiology and molecular pathogenesis of BTCs
3. Chemotherapy
4. Targeted therapy
5. Immunotherapy
6. Conclusion

## **List of abbreviations**

**ALK** Anaplastic Lymphoma Kinase

**BRAF** Rapidly accelerated Fibrosarcoma B

**BSC** Best Supportive Care

**BTCs** Biliary tract cancers

**CCA** cholangiocarcinoma

**CisGem** cisplatin/gemcitabine

**ECOG-PS** ECOG performance status

**EGFR** Epidermal Growth Factor Receptor

**ERK** extracellular signal–regulated kinases

**FGFR** Fibroblast Growth Factor Receptor

**FOLFIRI** Folinic acid/5-Fluorouracil/Irinotecan

**GEMOX** gemcitabine/oxaliplatin

**HGF** hepatocyte growth factor

**IDH** Isocitrate dehydrogenase

**KRAS** Kirsten rat sarcoma viral oncogene homolog

**m-FOLFOX** modified Folinic acid/5-Fluorouracil/Oxaliplatin

**MAPK** mitogen-activated protein kinase

**mTOR** mammalian target of rapamycin

**mTORC** mTOR complex

**n** number

**NCT** ClinicalTrials.gov identifier number

**NTRK** Neurotrophic Tyrosine Receptor Kinase

**ORR** Overall Response Rate

**OS** overall survival

**PARP** poly ADP-ribose polymerase

**PFS** Progression free survival

**PI3K** phosphatidylinositol 3-kinase

**Ras** rat sarcoma

**TDM-1** trastuzumab emtansine

**TKIs** tyrosine kinase inhibitors

**TRKs** tropomyosin kinase receptors

**VEGFR** Vascular Endothelial Growth Factor Receptor

## **1. Introduction**

Biliary tract cancers (BTCs) represent a heterogeneous group that includes intrahepatic cholangiocarcinoma (CCA), perihilar-CCA or Klatskin tumors, extrahepatic-CCA, and gallbladder adenocarcinoma. These entities have distinct demographics, risk factors, clinical presentation, molecular characteristics and treatment options. The incidence in South-East Asia is up to ten times superior to the incidence in Europe (Banales et al., 2016). The overall incidence in the United States is 12,360 new cases and 3,960 estimated deaths per year (Siegel et al., 2019).

Only 30 to 40% of patients undergo surgery (J. W. Valle et al., 2016). The rate of recurrence after surgery is high and the 5-year overall survival rate is below 40% (Lim et al., 2013). In advanced BTCs, the recommendations are mainly supporting a doublet chemotherapy regimen using cisplatin/gemcitabine (CisGem) with a 5-year overall survival rate close to 5% and median overall survival (mOS) of less than a year (Juan W. Valle, Lamarca, Goyal, Barriuso, & Zhu, 2017).

The lack of overall efficacy stresses the need for personalized therapies. Recently, whole-genome and transcriptome sequencing highlighted the diversity of BTCs' subtypes. Distinct genetic alterations were retrieved according to the localization, with a high rate of potentially actionable alterations. Targeted therapies and immunotherapy have since then been tested for BTCs, trying to propose a more personalized treatment. In the present review, we highlighted the different therapeutic options for patients with advanced BTCs.

## **2. Epidemiology and molecular pathogenesis of BTCs**

BTCs represent a heterogeneous group of cancers with distinct demographics, risk factors, clinical presentation, and molecular characteristics.

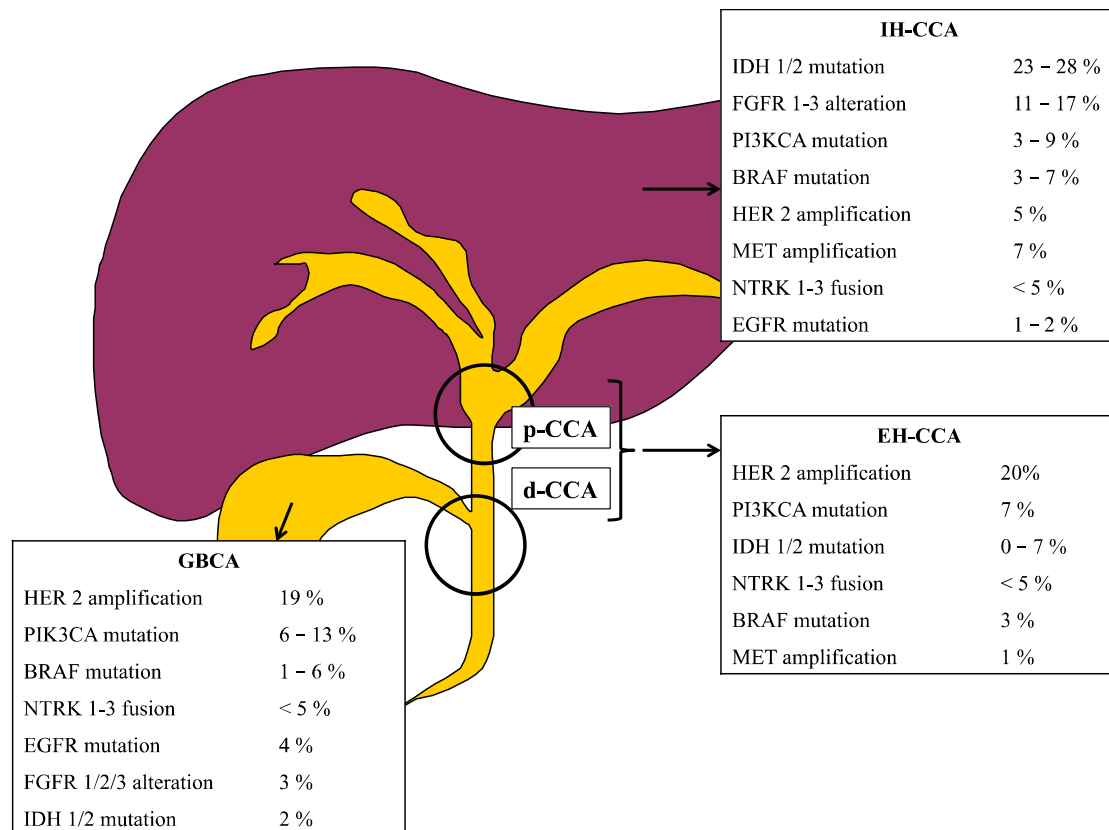
The prevalence of the anatomical subtypes of BTCs is different according to geographical origin. CCAs are more common in Asia (Japan, South Korea, north-east Thailand, China), where there is liver fluke infestation (*Opisthorchis viverrini*) (Parkin et al., 1991). Gallbladder adenocarcinomas are more common in India and Chile, where there is a high prevalence of cholelithiasis (Randi et al., 2009). Other risk factors for BTCs are primary sclerosing cholangitis, primary biliary cirrhosis, cirrhosis due to other causes, hepatitis C and congenital malformations such as choledochal cysts and multiple biliary papillomatosis (Khan, Toledano, & Taylor-Robinson, 2008). There is also an increased risk of BTCs in Lynch syndrome and BRCA 1 / 2 aberrations (Shigeyasu et al., 2014; Golan et al., 2017).

Whole-genome and transcriptome sequencing recently highlighted the diversity of BTCs' subtypes (**Figure 1**). Nakamura et al. analyzed, using whole-exome and transcriptome sequencing techniques, a large cohort of patients with BTCs including intra-hepatic (n=145), perihilar or distal (n=86) or gallbladder (n=29) BTCs (Nakamura et al., 2015). They identified potential targetable alterations in up to 39% of BTCs. The rate of genetics alterations was different in BTCs subtypes: intra-hepatic CCAs harbored especially recurrent mutations in Isocitrate dehydrogenase 1/2 (IDH 1/2) and Fibroblast growth factors receptors (FGFR) 1/2/3 in 28% and 14% of cases, respectively. FGFR2 alterations were associated with a better response to FGFR inhibitors and better mOS. Extra-hepatic CCAs harbored recurrent mutations in HER genes (up to 25% for epidermal growth factor receptor [EGFR] in peri-hilar CCAs and 14% for ERBB2/3 in distal CCAs). Confirming these data, sequencing of 28 intrahepatic-CCAs revealed potentially actionable alterations in IDH 1/2, FGFR2, Kirsten rat sarcoma viral oncogene homolog (KRAS), PTEN, and CDKN2A (Ross et

al., 2014). These data were in line with the integrated genomic analysis from The Cancer Genome Atlas (Farshidfar et al., 2017).

Besides, different etiologies of BTCs might induce different somatic alterations. Whole-exome sequencing data from 108 liver-fluke-related and 101 non-liver-fluke-related tumors highlighted that non-liver-fluke-related intra-hepatic CCAs had a higher prevalence of mutations in IDH1/2 and loss-of-function mutations in the tumor-suppressor gene BAP1 (Chan-On et al., 2013). Mutations in the tumor-suppressor gene TP53 were more frequent in liver-fluke-related CCAs. Altogether, those molecular alterations led to targeted therapies evaluation as indicated below.

**Figure 1. Genetic alterations according to the different anatomic subtypes of biliary tract cancers.**



**BRAF**: Rapidly accelerated Fibrosarcoma B; **d-CCA**: distal cholangiocarcinoma ; **EGFR**: Epidermal Growth Factor Receptor; **EH-CCA**: extrahepatic cholangiocarcinoma; **FGFR**: Fibroblasts Growth Factor Receptor;



**GBCA:** Gall Bladder Carcinoma; **HER:** Human epidermal growth factor receptor; **IDH:** Isocitrate Dehydrogenase; **IH-CCA:** intrahepatic cholangiocarcinoma; **MET:** Mesenchymal-Epithelial Transition factor; **NTRK:** Neurotrophic tyrosine kinase; **p-CCA:** perihilar cholangiocarcinoma; **PI3K:** phosphoinositide-3-kinase

### **3. Chemotherapy**

Best supportive care (BSC) offers to patients with advanced BTCs a mOS of 2.5 months. The chemotherapy 5-fluorouracil/leucovorin +/- etoposide was evaluated versus BSC in 37 patients with advanced BTCs, with a gain in term of mOS of 3.5 months (6 months versus 2.5 months,  $p > 0.01$ ) and an improvement in the quality of life (Glimelius et al., 1996).

The ABC-02 study set the CisGem regimen (gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> at D1 and D8, every 21 days) as the standard of care in first-line setting. Four hundred and ten patients with BTCs were randomly assigned to receive either CisGem or gemcitabine. mOS was 11.7 versus 8.1 months and median progression-free survival (mPFS) was 8.0 versus 5.0 months, in CisGem and gemcitabine arms respectively (J. Valle et al., 2010). These results were confirmed by a Japanese study on 83 patients. mOS was 11.2 vs 7.7 months, the mPFS 5.8 vs 3.7 months and overall response rate (ORR) was 19.5 vs 11.9%, in CisGem and gemcitabine arms respectively (Okusaka et al., 2010).

Sharma et al evaluated a different option in first-line for BTCs, the gemcitabine + oxaliplatin (GEMOX) regimen compared to BSC. They identified an overall gain in terms of mPFS and mOS in unresectable BTCs of 8.5 months and 9.5 months, respectively (OS: 9.5 versus 4.5 months,  $p=0.039$ ; PFS: 8.5 versus 2.8 months,  $p<0.001$ ) (Sharma et al., 2010). André et al. highlighted that GEMOX (gemcitabine 1000 mg/m<sup>2</sup> and oxaliplatin 100 mg/m<sup>2</sup> every 14 days) for patients with

an ECOG performance status (ECOG-PS) 0–2 and a bilirubin  $<2.5N$  showed an ORR, a mPFS and a mOS of 36%, 5.7 months and 15.4 months, respectively (André et al., 2004). Patients with an ECOG-PS  $>2$  and/or bilirubin  $>2.5N$  and/or prior chemotherapy had an ORR, a PFS and a mOS of 22%, 3.9 months and 7.6 months (André et al., 2004). A systematic review of 104 first-line chemotherapy trials including 2,810 patients identified superior ORR and tumor control rates with gemcitabine plus platinum (cisplatin or oxaliplatin) (Eckel & Schmid, 2007). Therefore, the recommended therapy in first-line is the CisGem regimen (J. W. Valle et al., 2016).

The ABC-06 trial recently identified the best therapy in second-line after disease progression with CisGem. The authors evaluated the modified Folinic acid/5-Fluorouracil/Oxaliplatin (mFOLFOX) regimen versus BSC in patients previously treated with CisGem. Second-line with mFOLFOX significantly improved the mOS versus the BSC alone (6.2 versus 5.3 months;  $p=0.031$ ) (Lamarca et al., 2019, p. 06). In second-line treatment, the Folinic acid/5-Fluorouracil/Irinotecan (FOLFIRI) regimen was evaluated in a retrospective study ( $n=52$ ) in patients who experienced disease progression with the GEMOX regimen (Sebbagh et al., 2016). mPFS and mOS were 3.2 months and 8.4 months, respectively. Fluoropyrimidine-based doublet chemotherapy in second-line setting was identified as none superior to fluoropyrimidine alone in terms of mOS and mPFS in a large retrospective study (mPFS: 3.3 vs 3 months,  $p=0.91$ ; mOS: 6.3 months vs 5.6 months,  $p=0.93$ ) (Brieau et al., 2015). Four parameters were identified as independent prognostic factors for starting second-line therapy: ECOG-PS, the reason for first-line discontinuation, a prior resection of primary tumor and peritoneal carcinomatosis (Neuzillet et al., 2019).

## 4. Targeted therapy

Targeted therapies have been evaluated for BTCs, mainly in phase 1 or 2, some with interesting or promising results. Selected ongoing studies on targeted therapies for advanced BTCs are reported in **Table 1**.

### 4.1. VEGF inhibitors

Vascular Epidermal Growth factors (VEGF) is overexpressed in ~ 42% to 76% of BTCs and its expression correlates with metastases (both hematologic and lymphatic), positive surgical margins and poor survival rates, suggesting the potential for anti-angiogenic agents in the treatment of these cancers (Yoshikawa et al., 2008). Intra-hepatic CCAs are associated with high VEGF-A expression and increased microvessel density in comparison to other BTCs (Guedj et al., 2009), prompting the evaluation of antiangiogenics in this specific subgroup.

**Bevacizumab** is a recombinant humanized monoclonal antibody against vascular epidermal growth factor (VEGFR). A non-randomized phase 2 trial evaluated the combination of bevacizumab with GEMOX in advanced BTCs and showed an ORR, a mPFS and a mOS of 40%, 7 months and 12.7 months, respectively (Zhu et al., 2010). The addition of bevacizumab to gemcitabine/capecitabine was tested in a phase 2 study for patients with advanced BTCs. The mPFS and the mOS were of 8.1 months and 10.2 months, respectively. The study failed to improve the mOS compared to historical controls (Iyer et al., 2018). On the other hand, a large retrospective study evaluated the addition of bevacizumab to GEMOX regimen in the first-line setting in patients with advanced or metastatic BTCs. The addition of bevacizumab to chemotherapy compared to chemotherapy alone showed a significant

increase of mPFS (6.48 months versus 3.72 months;  $p= 0.049$ ) but without any benefit in terms of mOS (11.31 months versus 10.34 months;  $p= 0.044$ ) (Bréchon et al., 2018). Also, a small retrospective ( $n= 13$ ) study with intra-hepatic CCAs treated with FOLFIRI plus bevacizumab in second-line after GEMOX showed interesting results with a mPFS and a mOS of 8 months and 20 months, respectively (Guion-Dusserre, Lorgis, Vincent, Bengrine, & Ghiringhelli, 2015).

**Sunitinib** is a tyrosine kinase inhibitor (TKI) that inhibits VEGFR 1, 2, 3, platelet-derived growth factor receptor, colony-stimulating factor receptor and the stem cell factor receptor c-KIT. A phase 2 study of sunitinib as a second-line treatment demonstrated marginal efficacy with a median time to progression of 1.7 months (Yi et al., 2012). A prospective phase 2 multicenter trial evaluated sunitinib in advanced intra-hepatic CCAs, with promising preliminary results with a mPFS and a mOS of 5.2 months or 9.6 months, respectively (Neuzillet et al., 2015).

**Sorafenib** is a multitargeted TKI that inhibits VEGF signaling but also the protein RAF-1. Sorafenib was tested as monotherapy in a phase 2 that reported a mPFS and a mOS of 2.3 months and 4.4 months, respectively (Bengala et al., 2010). Limited antitumor activity was also reported in another phase 2 trial, with a mPFS and a mOS of 3 months and 9 months, respectively (El-Khoueiry et al., 2012). The addition of sorafenib to gemcitabine and cisplatin was also tested but did not improve efficacy over historical data (J. K. Lee et al., 2013).

**Cediranib**, a TKI targeting VEGFR 1/2/3, has also been tested in combination with CisGem in the ABC-03 trial but did not meet its primary endpoint of improvement of the mPFS (Juan W. Valle et al., 2015).

**Axitinib**, a TKI targeting VEGFR 1/2/3, was tested in a phase 2 study for patients with advanced BTCs refractory to gemcitabine-based regimen (Okano et al., 2019). It showed modest activity, with a mPFS of 2.8 months, a mOS of 5.8 months and an ORR of 5.3%.

#### **4.2. HER-family inhibitors**

HER family receptors (EGFR/HER1, HER2neu, HER3 and HER4) triggers multiple signaling cascades, including the mitogen-activated protein kinase (MAPK) cascade phosphatidylinositol 3-kinase (PI3K) / AKT pathway and STAT transcription factor, leading to a multitude of effects including cell proliferation, cell differentiation, angiogenesis, metastasis, and inhibition of apoptosis, participating in the development of several carcinomas.

**The epidermal growth factor receptor (EGFR/HER1)** signaling pathway regulates biliary epithelial cell growth and proliferation. In BTCs, EGFR is overexpressed in 67–100% of cases (Nakazawa et al., 2005). KRAS mutations in BTCs were identified only in 10 to 30% of cases, which support the idea of adding an EGFR inhibitor to the chemotherapy. EGFR expression is associated with a poor outcome in BTCs (Yoshikawa et al., 2008).

**Cetuximab** is an EGFR chimeric human-murine monoclonal antibody. Three small non-randomized phase 2 studies showed the efficiency of cetuximab for unresectable locally advanced or metastatic BTCs in addition to GEMOX (Gruenberger et al., 2010), to gemcitabine and capecitabine (Rubovszky et al., 2013) or in addition to gemcitabine alone (Borbath et al., 2013). Three larger randomized phase 2 trials did not find any efficiency of cetuximab with GEMOX regimen (Malka

et al., 2014), even when stratified on KRAS mutation status (Chen et al., 2015), and neither with gemcitabine and oxaliplatin and capecitabine (Ole Larsen, Taksony Solyom Hoegdall, Hoegdall, & Nielsen, 2016).

**Panitumumab**, a fully human antibody against EGFR, was also tested in non-randomized phase 2 studies in KRAS wild-type BTCs (Jensen, Lindebjerg, Ploen, Hansen, & Jakobsen, 2012; Hezel et al., 2014) or without rat sarcoma (RAS) stratification, with a positive signal (Sohal et al., 2013). Meantime, two randomized phase 2 studies evaluated panitumumab in combination with CisGem (Arndt Vogel et al., 2015) or with GEMOX (Leone et al., 2016) in KRAS wild-type BTCs and both were negative. As for example, in the Vecti-BIL trial, panitumumab failed to improve mPFS (5.3 vs 4.4 months;  $p=0.27$ ) and mOS (10.2 versus 9.9 months;  $p=0.42$ ) (Leone et al., 2016).

**Erlotinib** is a reversible TKI inhibiting EGFR. Erlotinib administered with docetaxel in a phase 2 randomized study showed a benefit in terms of mPFS but not mOS (Chiorean et al., 2012). The addition of erlotinib to GEMOX in first-line setting didn't show any benefit in a phase 3 study in term of mPFS (4.2 versus 5.8 months;  $p=0.087$ ) and mOS (9.5 versus 9.5 months;  $p=0.611$ ) (J. Lee et al., 2012). However, a subgroup analysis identified a benefit in mPFS for CCA versus gallbladder cancer: 5.9 vs 3.0 months.

**Afatinib**, an irreversible panErbB TKI, has also been tested in a phase 1 study but failed to show survival benefits in combination with CisGem in chemotherapy-naive patients (Moehler et al., 2019).

**Vandetanib** a TKI targeting VEGFR2, EGFR, and RET kinase, was tested in a randomized phase 2 study, alone or in combination with gemcitabine, versus

gemcitabine in patients with advanced BTCs and showed no improvement in mPFS (Santoro et al., 2015).

**Amplification of HER2 is an oncogenic driver alteration.** Protein dimers of HER2 with HER family receptors, such as EGFR, HER2, HER3, or HER4, accelerate cell proliferation and prolong cell survival. Binding of EGF to EGFR at the plasma membrane initiates the activation of various signaling pathways. Well-defined pathways include the RAS- ERK pathway, PI3K-Akt pathway, PLC- $\gamma$ 1 pathway, STAT pathway, and Src pathway.

In BTCs, HER2 overexpression is observed in ~ 5% of intra-hepatic CCA, ~20% of extra-hepatic CCA and ~19% of gallbladder carcinoma (Galdy et al., 2017). The prognostic value of positive HER2 has not been clarified in BTCs (Roa et al., 2014; Yoshida, Shimada, Kosuge, & Hiraoka, 2016). Two phase 2 studies with **lapatinib**, a dual tyrosine kinase EGFR and HER2 inhibitor, were conducted and failed to show activity of lapatinib as a single agent in first and second-line of patients with BTCs (Peck et al., 2012; Ramanathan et al., 2009). Alternative anti-HER2 therapies such as monoclonal antibodies **trastuzumab** and **pertuzumab** seem to be more promising. Three case reports were reported with dramatic and durable responses for BTCs with HER2 amplification treated with trastuzumab alone (Sorscher, 2013), trastuzumab and paclitaxel (Law, 2012) or with dual HER2 blockade with trastuzumab and pertuzumab (Czink et al., 2016). Nam et al. reported that trastuzumab inhibited cell proliferation in HER2-overexpressing BTC cell lines in vitro but the response of HER2-positive BTC patients to trastuzumab combined with chemotherapy was limited (Nam et al., 2016). Trastuzumab is being evaluated in HER2-positive BTC in a phase 2 trial (ClinicalTrials.gov identifier number (NCT)

03613168). The results of a phase 2 trial on trastuzumab emtansine (**TDM-1**) in BTCs are awaited (NCT02999672).

The SUMMIT cohort, an ongoing phase 2 basket trial, is examining the efficacy of **neratinib**, TKI of EGFR, HER2, and HER4 in HER2-mutated BTCs. Updated interim results were presented at the European Society for Medical Oncology 21st World Congress on Gastrointestinal Cancer 2019. Twenty patients with HER2 – mutated BTC with a median of 2 prior systemic regimens were included. The ORR and the mPFS were 10% and 1.8 months, respectively.

The results of a randomized phase 2/3 randomized controlled trial (NCT03093870) of capecitabine plus **varletinib** (EGFR/Her2 co-inhibitor) or placebo in the second-line setting in BTCs are awaited. It is also being evaluated in combination with CisGem for treatment naïve advanced or metastatic BTCs (NCT02992340).

#### ***4.3. PI3K/PTEN/AKT/mTOR pathway inhibitors***

Everolimus is a derivative of rapamycin that selectively inhibits mammalian target of rapamycin complex 1 (mTORC1), a key protein kinase complex that regulates cell growth, proliferation, and survival. Activation of mTORC1 is mediated by the PI3K pathway through activation of AKT/PKB and subsequent inhibition of the tuberous sclerosis complex 1/2.

Constitutive activation of the PI3K/AKT/ mTOR pathway occurs in ~10–20% BTCs. In addition, immunohistochemistry staining of PI3K pathway suggests that up to 50% of BTCs may harbor activation of this pathway (Simbolo et al., 2014) which is associated with worse survival outcomes (Herberger et al., 2007). Biomarker studies in a panel of BTC cell lines revealed mutations and/or amplification of KRAS to be



associated with resistance, and high basal p-AKT levels to be associated with response to everolimus (Yeung et al., 2017). In 2014, a phase 2 Italian trial assessed **everolimus** activity in first or second-line in patients (n=39) with locally advanced, metastatic or recurrent BTCs. The mPFS and the mOS were 3.2 months and 7.7 months, respectively (Buzzoni et al., 2014). Another phase 2 study evaluated everolimus in patients with PIK3CA amplification/mutation and/or PTEN loss metastatic BTCs and in  $\geq 2$  lines and observed no objective response (Kim et al., 2017). Everolimus, tested in monotherapy and in first-line (27 patients with metastatic BTCs) showed a mPFS and a mOS of 5.5 months, and 9.5 months (Lau et al., 2018).

**Copanlisib** is a PI3K inhibitor. A phase 2 trial evaluating copanlisib in combination with gemcitabine and cisplatin in patients with advanced BTC, in a first-line setting, is ongoing (BAY 80-6946).

#### ***4.4. RAF/MEK/ERK mitogen-activated protein (MAP) kinase inhibitors***

The RAS/RAF/MEK/ERK MAPK pathway regulates cellular proliferation, survival, and migration, and is aberrantly activated in the majority of solid tumors, including BTCs. Alterations in this pathway have been reported in intra-hepatic CCAs (35%) and extra-hepatic CCAs (55%) (Churi et al., 2014).

**MEK inhibitors** have shown modest signs of activity in BTCs. **Selumetinib** has shown clinical activity as monotherapy in a phase 2 study on 28 patients, with a mPFS and a mOS of 3.7 months and 9.8 months, respectively (Bekaii-Saab et al., 2011). The ABC-04 study, a phase 1b evaluating selumetinib in combination with cisplatin and gemcitabine in first-line, showed a mPFS of 6.4 months (Bridgewater et al., 2016). It is being evaluated with CisGem in a phase 2 study (NCT02151084).

**Trametinib** was tested in a Japanese phase 2, single-arm study in patients with advanced BTCs refractory to gemcitabine-based therapy. On 20 patients, the mPFS was 10.6 weeks and 1-year OS was 20.0%. Only one patient had confirmed partial response (Ikeda et al., 2018). Trametinib has also been tested in combination with pazopanib (TKI inhibiting VEGFR) on 25 patients with advanced BTCs who received a median of 2 prior systemic therapies. The study did not achieve a statistically significant improvement in the 4-month PFS, with a mPFS of 6.4 months (Shroff et al., 2017).

**Binimetinib** was evaluated in a phase 1b study in combination with capecitabine in second-line (Bendell et al., 2017). The mPFS and mOS were 3.9 months and 8.0 months, respectively. Additional evaluations of binimetinib in combination with gemcitabine and cisplatin in phase 1/2 studies (NCT01828034, NCT02151084) are ongoing. Intermediate analysis of NCT01828034 study showed that six patients experienced partial responses and four experienced stable diseases among the 12 patients (Lowery et al., 2017).

Activating mutations of the Rapidly accelerated Fibrosarcoma B (BRAF) oncogene are present in approximately 5-10% of all human malignancies and lead to constitutive activation of the MAPK pathway. The most common BRAF mutation results in a single amino acid substitution of valine for glutamic acid at residue 600 (V600E). BRAF V600E mutation is a rare event in BTCs, accounting for only 1% of all subtypes, and mainly in intra-hepatic CCAs (Goepfert et al., 2014). Both genetic and epigenetic alterations play a major role in resistance to BRAF inhibitors by reactivation of the MAPK and/or the PI3K–Akt pathways. **Dual inhibition with BRAF and MEK inhibition** is one of the strategies to overcome this acquired resistance.

**Dabrafenib and vemurafenib** are inhibitors of the mutated BRAF kinase. Several case reports of dual BRAF and MEK inhibition in patients with BRAF mutant BTCs have shown important objective responses (Kocsis et al., 2017; Lavingia & Fakih, 2016; Loaiza-Bonilla, Clayton, Furth, O'Hara, & Morrissette, 2014). Vemurafenib in addition with an anti-EGFR and chemotherapy has been tested in a phase 2 basket trial for BRAF mutated non-melanoma cancers: on the 8 patients with BTCs included, one had a sustained partial response over a year (Hyman et al., 2015).

#### ***4.5. FGFR alterations***

Fibroblast growth factors (FGFs) and FGFRs drive crucial developmental signaling pathways, which are responsible for many functions, including cell proliferation, survival (through the activation of PI3K–AKT or STAT signaling), migration and angiogenesis. As such, they are susceptible to be hijacked by cancer cells and have oncogenic roles in many cancers. FGFR genetic alterations (fusions, mutations, amplifications) occur mainly in intra-hepatic CCAs, in 10 to 15% of cases (Graham et al., 2014). FGFR2 gene fusions have been identified as an oncogenic driver in 10–20% of intra-hepatic CCAs. FGFR2 translocations are usually mutually exclusive of KRAS, IDH1/2, and BRAF mutations. BTCs with FGFR alterations seem to have a relatively indolent disease course (Churi et al., 2014).

**Infigratinib (BGJ398)**, a pan-FGFR kinase inhibitor, was evaluated in a multicenter, open-label, phase 2 study for patients with advanced BTCs with FGFR alterations, in progression after prior therapy. The Disease control rate was 83.3% in patients with FGFR2 fusions. The mPFS was 5.8 months (Javle et al., 2018). It is currently being evaluated in a phase 3 study (NCT03773302).

**Pemigatinib (INCB054828)** is a potent, selective, oral inhibitor of FGFR isoforms 1, 2 and 3. The updated interim results of phase 2 study FIGHT-202 presented at European society of medical oncology in 2019 showed an ORR of 35.5% on 146 patients with advanced intra-hepatic CCAs with FGFR2 translocations (A. Vogel et al., 2019). The mPFS and mOS were 6.9 months and 21.1 months, respectively. A phase 3 study is currently recruiting to evaluate pemigatinib versus chemotherapy (NCT03656536).

**TAS-120** is an irreversible FGFR1–4 inhibitor. A phase 1 trial demonstrated tolerability and preliminary evidence of clinical efficacy for patients with intra-hepatic CCAs (Goyal, Arkenau, et al., 2017). A phase 2 study (NCT02052778) is ongoing.

**Erdafitinib** a pan-FGFR kinase inhibitor has been evaluated in an Asian phase 2 study on 14 patients with BTCs with FGFR alterations. The disease control rate was 83.3% the mPFS was 5.59 months. In 10 evaluable FGFR2+ patients, the disease control rate and the mPFS were 100% and 12.4 months, respectively (Park et al., 2019).

**Rogaratinib**, a pan-FGFR inhibitor, has been tested in vivo with good efficacy (Grünewald et al., 2019) and clinical trials are currently ongoing (NCT01976741, NCT03410693, NCT03473756).

**Derazantinib (ARQ 087)** has been tested in a phase 1/2 study, with patients with unresectable intra-hepatic CCAs with FGFR2 fusion (n=29). The disease control rate and the mPFS were 82.8% was 5.7 months, respectively (Mazzaferro et al., 2019). Derazantinib is currently being tested in a phase 2 study (NCT03230318).

#### ***4.6. IDH inhibitors***

The normal function of IDH enzymes is to catalyze the conversion of isocitrate to  $\alpha$ -ketoglutarate in the citric acid cycle. Mutated IDH enzymes acquire gain-of-function activity, converting  $\alpha$ KG to the oncometabolite D-2-hydroxyglutarate. The resulting D-2-hydroxyglutarate accumulation competitively inhibits  $\alpha$ -ketoglutarate-dependent enzymes, causing cellular metabolism alterations, epigenetic regulation, redox states, and DNA repair, all of which may contribute to carcinogenesis. Mutations in the genes encoding for these enzymes occur in various types of malignancies, including >80% of low-grade gliomas and secondary glioblastomas, ~60% of chondrosarcomas and ~10% of acute myeloid leukemias. For BTCs, it occurs mainly in intra-hepatic CCAs (25%) and IDH1 mutations are more common than IDH2 mutations (Borger et al., 2012; Goyal et al., 2015). The prognosis associated with IDH mutations remains controversial.

Concerning BTCs, **Ivosidenib (AG-120)** has been evaluated versus placebo in ClarIDHY, a phase 3 study on 185 patients with mutant IDH1 CCAs progressing after 1 or 2 prior therapies (Abou-Alfa et al., 2019). Ivosidenib improved mPFS: 2.7 vs 1.4 months ( $p < 0.001$ ). By intention-to-treat analysis, mOS was 10.8 vs 9.7 months ( $p = 0.06$ ) with 57% of placebo patient crossed over to ivosidenib. After statistical adjustment taking into account cross-over, hazard ratio was 0.46 ( $p < 0.001$ ).

#### ***4.7. Tropomyosin receptor kinases inhibitors***

Genomic translocations with chromosomal fusion lead to the constitutive activation of tropomyosin receptor kinases (TRKs). Tyrosine kinases receptors fusions lead to overexpression of the chimeric protein, resulting in constitutively active, ligand-independent downstream signaling. Most common and studied tyrosine kinase fusions

involve Anaplastic Lymphoma Kinase (ALK), ROS1, and Neurotrophic Tyrosine Receptor Kinase (NTRK) 1-2-3.

In BTCs, a Chinese study reported overexpression of TRKs in 20.5% of intra-hepatic CCAs (Yang et al., 2014) and it is estimated that less than 5% CCAs harbor NTRK gene fusions (Hsiao, Zehir, Sireci, & Aisner, 2019). However, a recent European study retrospectively analyzed 106 patients with BTCs, with a confirmation cohort of 254 cases. TRKs were not expressed in the population, questioning the applicability of TRK inhibitors to European populations (Westphalen et al., 2019). Sporadic fusions of ROS1 (up to 8.7%) and ALK (2.6%) were also described (K.-H. Lee et al., 2015).

**Larotrectinib**, a highly selective TRK inhibitor, was evaluated in a phase 1/2 study for tumors with TRK fusions (A. Drilon et al., 2018). Larotrectinib induced an ORR of 75% with 71% of responses ongoing at 1 year. More than half of the patients remained progression-free at 1 year. Two patients with BTCs were included in the study, one achieving nearly 80% decrease of its initial tumor size. Therefore, larotrectinib (Vitrakvi) received an FDA – approval for use in patients with metastatic or unresectable solid tumors with an *NTRK* gene fusion and no satisfactory alternative treatment.

**Entrectinib**, an inhibitor of TRK, ROS1, and ALK, has also demonstrated impressive ORR (57 to 86%) in a phase 1 study in a selected population of solid tumors including BTCs (Alexander Drilon et al., 2017). A basket study of entrectinib for patients with tumors with NTRK 1/2/3, ROS1 or ALK fusions is ongoing (NCT02568267).

The results of a phase 2 trial evaluating **Crizotinib**, an ALK and c-Met inhibitor, for patients harboring an ALK, MET, or ROS1 alteration are awaited

(NCT02034981).

#### **4.8. PARP inhibitors**

IDH1/2 mutations induce a homologous recombination defect that renders tumor cells sensitive to poly ADP-ribose polymerase (PARP) inhibitors. This «BRCAness» phenotype of IDH mutant cells can be completely reversed by treatment with small molecule inhibitors of the mutant IDH1 enzyme. A multicenter retrospective analyzed 18 patients with BTCs with germline or somatic variants in BRCA1/2: 6 were extra-hepatic CCAs and the rest intra-hepatic CCAs. Thirteen patients received platinum-based therapy and four were treated with PARP inhibitors, of whom 1 experienced sustained disease response with a PFS of 42.6 months (Golan et al., 2017). Starting from these observations, a basket phase 2 trial of **olaparib** for patients with metastatic solid tumors with *IDH1* or *IDH2* mutations including BTCs has been undertaken (NCT03212274).

#### **4.9. c-met inhibitors**

The binding of hepatocyte growth factor (HGF) to the receptor tyrosine kinase c-Met initiates a series of intracellular signals, that mediate embryogenesis and wound healing. However, in cancer cells, aberrant HGF/c-Met axis activation promotes tumor development and progression by stimulating the PI3K/AKT/ mTOR pathway, the MAPK pathway and the STAT pathway. In BTCs, c-MET overexpression is associated with poor prognosis and is detected in 12-25% of intra-hepatic CCAs and 0-16% of extra-hepatic CCAs (Terada, Nakanuma, & Sirica, 1998). c-MET amplification is detected in 7% of intra-hepatic CCAs (Ross et al., 2014). To inhibit c-

MET signaling, small kinase inhibitors, biological antagonists and monoclonal antibodies targeting either c-MET or HGF can be used.

In 2017 Goyal et al. tested **cabozantinib**, a TKI targeting VEGFR2 and MET, for previously treated patients with advanced BTCs. Cabozantinib demonstrated limited activity and significant toxicity. One patient with a MET-high tumor had a prolonged benefit from treatment, but patients were not selected depending on their MET expression (Goyal, Zheng, et al., 2017). A phase 2 study with **merestinib** (LY2801653) in addition to CisGem in first-line is ongoing (NCT02711553).



**Table 1. Selected ongoing studies on targeted therapies in advanced BTCs**

	Drug	Target	Phase	Population	Status	Recruiting countries	NCT references
Anti-angiogenics	Ramucirumab	VEGFR2, MET	I/II	Advanced BTC, L1	Active, not recruiting	International	NCT02711553
			II	Advanced BTC, ≥L2	Recruiting	USA	NCT02520141
	Apatinib	VEGFR2	II	Advanced BTC, ≥L2	Recruiting	China	NCT03427242
			II	Advanced IH-CCA, ≥L2	Recruiting	China	NCT03521219
	Regorafenib	VEGFR, FGFR, BRAF, PDGFR	II	Advanced BTC, ≥L1	Active, non recruiting	USA	NCT02115542
Anti-EGFR and anti-HER	Varlitinib	EGFR, HER2, HER4	II/III	Advanced BTC, L2	Active, non recruiting	International	NCT03093870
			I/II	Advanced BTC, ≥L1	Recruiting	South Korea / Singapore / Taiwan	NCT02992340
			II/III	Advanced BTC, L2	Active, non recruiting	China	NCT03231176
	Trastuzumab	HER2	II	Advanced BTC, ≥L1, HER2+	Recruiting	South Korea	NCT03613168
						China	NCT03185988

	Erlotinib	HER1	II	Advanced BTC, $\geq$ L2	Not yet recruiting	South Korea	NCT03110484
	TAS0728	HER2/3	I/II	Advanced BTC, $\geq$ L2, HER2/3+	Active, non recruiting	International	NCT03410927
	Afatinib	EGFR	I	Advanced BTC, $\geq$ L1	Recruiting	USA	NCT02451553
PI3K	Copanlisib	PI3K	II	Advanced BTC, L1	Active, non recruiting	USA	NCT02631590
	Selumetinib	MEK	II	Advanced BTC, L1	Active, non recruiting	Canada	NCT02151084
TRK inhibitors	Merestinib	NTRK, MET, ROS1,	IIR	Advanced BTC, $\geq$ L1	Active, non recruiting	International	NCT02711553
	Entrectinib	NTRK, ROS1, ALK	II	Advanced BTC, $\geq$ L1, NTRK 1/2/3, ROS1 or ALK fusion positive	Recruiting	International	NCT02568267
FGFR inhibitors	Derazantinib	Pan-FGFR	II	Advanced IH-CCA, FGFR2 fusion +, $\geq$ L2	Recruiting	International	NCT03230318
	Infigratinib	FGFR 2	III	Advanced BTC, FGFR2 rearrangement, $\geq$ L1	Recruiting	International	NCT03773302
	Pemigatinib	FGFR 1/2/3	III	Advanced BTC, FGFR2 rearrangement, $\geq$ L1	Recruiting	International	NCT03656536
			III	Advanced BTC, FGFR2 rearrangement, $\geq$ L1	Active, non recruiting	International	NCT02924376

PARP inhibitors	Olaparib	PARP	II	Advanced BTC, ≥L1	Not yet recruiting	USA	NCT04042831
			II	Advanced BTC, ≥L2, IDH2 mutation	Recruiting	USA	NCT03212274
	Niraparib	PARP	II	Advanced BTC, ≥L2	Recruiting	USA	NCT03207347
	ABC294640	Sphingosine kinase	II	Advanced BTC, ≥L1	Recruiting	USA	NCT03377179
	Abémaciclib	CDK4/6	II	Advanced BTC, ≥L2	Recruiting	Belgium	NCT03339843
	Bortezomib	Proteasome	III	Advanced IH-CCA, ≥L2, PTEN mutation/ deletion	Recruiting	China	NCT03345303
	Amcasertib	Cell stemness	II	Advanced BTC, ≥L2	Active, non recruiting	Canada	NCT02232633

**Abbreviations:** **IIR:** randomized phase II; **ALK:** anaplastic lymphoma kinase ; Rapidly accelerated Fibrosarcoma B ; **BTC:** biliary tract cancer; **CDK:** cyclin-dependent kinase; **EGFR:** Epidermal Growth Factor Receptor; **FGFR:** Fibroblasts Growth Factor Receptor; **HER:** Human epidermal growth factor receptor; **IDH:** Isocitrate Dehydrogenase; **IH-CCA:** intrahepatic cholangiocarcinoma; **L1:** first-line treatment; **L2:** second-line treatment; **MET:** Mesenchymal-Epithelial Transition factor ; **NTRK:** Neurotrophic tyrosine kinase; **PARP:** poly-ADP-ribose-polymerase; **PI3K:** phosphoinositide-3-kinase; **PDGFR:** Platelet-derived growth factor receptors; **VEGFR:** Vascular Growth Factor Receptor.

## 5. Immunotherapy

*Check-point inhibitors* have had a major impact on the clinical course of various types of malignancies in the last decade. However, their efficacy is limited to a few amount of patients. BTCs have a high mutational load, which could be predictive of the efficacy of immunotherapy (Nakamura et al., 2015). High level MSI has been found in about 10% of intrahepatic and extrahepatic CCAs and in 5% of gallbladder carcinoma (Silva et al., 2016). Expression of PD-L1 has been found in intra-hepatic CCAs in up to ~30 to 40% (Sabbatino et al., 2016).

The KEYNOTE-028 phase 1b basket trial evaluated **pembrolizumab**, an anti-PD1 antibody, for advanced BTCs with prior progression on standard therapy and enrolled 104 patients (M. Ueno et al., 2018). The mPFS and mOS were 2.0 months and 9.1 months, respectively. In patients with PD-L1 CPS  $\geq 1$  compared to those with a CPS  $< 1$ , the mPFS and mOS were 1.9 months vs 2.1 months and 7.2 months vs 9.6 months, respectively. The KEYNOTE-158, a phase 2 basket trial of pembrolizumab in patients with advanced solid tumors -including BTCs- progressing on standard of care therapy is currently ongoing (NCT02628067).

**Nivolumab**, another anti-PD1 antibody, alone or in combination with cisplatin plus gemcitabine was tested in a phase 1 study (Makoto Ueno et al., 2019). Patients with advanced BTCs refractory to gemcitabine-based treatment regimen received nivolumab as monotherapy. Chemotherapy-naive patients with advanced BTCs received nivolumab and cisplatin plus gemcitabine chemotherapy (n=30). In the monotherapy cohort, mPFS and mOS were 1.4 months and 5.2 months, respectively. In the combined therapy cohort, mPFS and mOS were 4.2 months and 15.4 months, respectively. Phases 2 are ongoing, studying in BTCs either nivolumab in

monotherapy, (NCT02829918), either in combination with chemotherapy (gemcitabine/cisplatin) or with another immunotherapy (ipilimumab; NCT03101566).

A Chinese study reported the preliminary results of the use of **lenvatinib plus nivolumab and pembrolizumab** in 14 patients with intra-hepatic CCAs in an observational study. All patients had received previously  $\geq 2$  anticancer therapies. The disease control rate was 92.9%. The mPFS was 5.9 months. High tumor mutational burden from 450-gene NGS panel was strongly associated with a better therapeutic response (Lin et al., 2018).

Selected ongoing studies on immunotherapy for advanced BTCs are reported in **Table 2**.

**Table 2. Selected ongoing studies on immunotherapies in advanced BTCs**

	Drug	Target	Phase	Population	Status	Recruiting countries	NCT references
In monotherapy or combotherapy	Nivolumab plus ipilimumab	PD-1, CTLA-4	II	Advanced BTC, $\geq$ L1	Active, non recruiting	USA	NCT03101566
					Recruiting	International	NCT02834013
	Pembrolizumab	PD-1	II	Advanced BTC, $\geq$ L2	Recruiting	International	NCT02628067
				Advanced BTC, L2	Recruiting	South Korea	NCT03110328
	Nivolumab	PD-1	II	Advanced BTC, $\geq$ L2	Active, non recruiting	USA	NCT02829918
	M7824	PD-L1	II	Advanced BTC, $\geq$ L2	Recruiting	USA	NCT03833661
Adoptive transfer of tumor infiltrating lymphocytes	TIL	II	Advanced BTC, $\geq$ L2	Recruiting	USA	NCT03801083	
With chemotherapy	KN035	PD-L1	III	Advanced BTC, L1	Recruiting	China	NCT03478488
	Durvalumab	PD-L1	III	Advanced BTC, L1	Recruiting	International	NCT03875235
	Durvalumab plus tremelimumab	PDL-1, CTLA-4	IIR	Advanced BTC, $\geq$ L1	Recruiting	Germany	NCT03473574
			II	Advanced BTC, L1	Recruiting	South Korea	NCT03046862
			II	Advanced BTC, L2	Recruiting	France	NCT03704480
	Pembrolizumab	PD-1	II	Advanced BTC, $\geq$ L1	Recruiting	Europe	NCT03260712
			II	Advanced BTC, $\geq$ L2	Recruiting	USA	NCT03111732
			III	Advanced BTC, L1	Recruiting	USA	NCT04003636
	Nivolumab	PD-1	Ib/II	Advanced BTC, L2	Recruiting	USA	NCT03785873
	Toripalimab	PD-1	II	Advanced BTC, $\geq$ L1	Recruiting	China	NCT03796429
SHR-1210	PD-1	II	Advanced BTC, $\geq$ L1	Recruiting	China	NCT03486678	
With other	SHR-1210 + apatinib	PD-1	IIR	Advanced BTC, $\geq$ L2	Recruiting	China	NCT03092895
	Nivolumab + DKN-01	PD-1	II	Advanced BTC, $\geq$ L2	Recruiting	USA	NCT04057365

	Nivolumab + rucaparib	PD-1	II	Advanced BTC, ≥L2	Recruiting	USA	NCT03639935
	Nivolumab + entinostat (HDAC inhibitor)	PD-1	II	Advanced BTC, ≥L2	Recruiting	USA	NCT03250273
	Pembrolizumab + lenvatinib	PD-1	II	Advanced BTC, ≥L2	Recruiting	International	NCT03797326
	Pembrolizumab + Ramucirumab	PD-1	I	Advanced BTC, L2	Active, non recruiting	International	NCT02443324
	Pembrolizumab + sargramostim	PD-1	II	Advanced BTC, ≥L1	Active, non recruiting	USA	NCT02703714
	Avelumab + Regorafenib	PD-L1	I/II	Advanced BTC, ≥L2	Recruiting	France	NCT03475953
	Atezolizumab + cometinib	PD-L1	IIR	Advanced BTC, ≥L2	Active, non recruiting	USA	NCT03201458
locoregional treatments	Durvalumab and Tremelimumab	PDL-1, CTLA-4	II	Advanced BTC, ≥L2	Recruiting	USA	NCT03482102
			II	Advanced BTC, ≥L2	Recruiting	USA	NCT02821754
	Nivolumab +/- ipilimumab	PDL-1, CTLA-4	IIR	Advanced BTC, ≥L2	Recruiting	Denmark	NCT02866383

**Abbreviations:** **IIR:** randomized phase II; **BTC:** biliary tract cancer; **CTLA-4:** cytotoxic T-lymphocyte-associated antigen 4; **GM-CSF:** granulocyte-macrophage colony stimulating factor; **HDAC:** histone deacetylase; **L1:** first-line treatment; **L2:** second-line treatment; **PD-1:** programmed death 1; **PD-L1:** programmed death ligand-1

## 6. Conclusions

Advanced BTCs harbor a poor prognosis, with a poor chemosensitivity. Genome sequencing and comprehensive transcriptomic highlighted the diversity of BTCs' subtypes and appear essential in order to propose a precision medicine. FGFR inhibitors and IDH inhibitors are promising emerging targeted therapies, mainly for intra-hepatic CCAs. Other targeted therapies such as anti-HER2 therapies or BRAF inhibitors need further evaluation, with combination strategies. Immunotherapy, either alone or in addition to chemotherapy or other treatments, is still under evaluation in

several ongoing studies. The multiples interactions between signaling pathways of BTCs carcinogenesis make combination therapies interesting.

### **Conflicts of Interest statement**

Dr. Palmieri and Dr. Lavole received honoraria from Servier outside the submitted work. Pr. Coriat received honoraria from AAA, Ipsen, Novartis, Merck, Amgen, Roche, Pfizer, Biogen and Bayer outside the submitted work. The remaining authors disclose no conflicts. We wish to confirm that there has been no significant financial support for this work that could have influenced its outcome.

### **Financial Disclaimers**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### **Author contributions**

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.



## Bibliography

- Abou-Alfa, G. K., Macarulla Mercade, T., Javle, M., Kelley, R. K., Lubner, S., Adeva, J., Cleary, J. M., Catenacci, D. V., Borad, M. J., Bridgewater, J. A., Harris, W. P., Murphy, A. G., Oh, D.-Y., Whisenant, J., Wu, B., Jiang, L., Gliser, C., Pandya, S. S., Valle, J. W., & Zhu, A. X. (2019). LBA10\_PRClarIDHy: A global, phase III, randomized, double-blind study of ivosidenib (IVO) vs placebo in patients with advanced cholangiocarcinoma (CC) with an isocitrate dehydrogenase 1 (IDH1) mutation. *Annals of Oncology*, *30*(Supplement\_5). <https://doi.org/10.1093/annonc/mdz394.027>
- André, T., Tournigand, C., Rosmorduc, O., Provent, S., Maindrault-Goebel, F., Avenin, D., Selle, F., Paye, F., Hannoun, L., Houry, S., Gayet, B., Lotz, J. P., de Gramont, A., Louvet, C., & GERCOR Group. (2004). Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Annals of Oncology*, *15*(9), 1339–1343. <https://doi.org/10.1093/annonc/mdh351>
- Banales, J. M., Cardinale, V., Carpino, G., Marzioni, M., Andersen, J. B., Invernizzi, P., Lind, G. E., Folseraas, T., Forbes, S. J., Fouassier, L., Geier, A., Calvisi, D. F., Mertens, J. C., Trauner, M., Benedetti, A., Maroni, L., Vaquero, J., Macias, R. I. R., Raggi, C., ... Alvaro, D. (2016). Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nature Reviews. Gastroenterology & Hepatology*, *13*(5), 261–280. <https://doi.org/10.1038/nrgastro.2016.51>

- Bekaii-Saab, T., Phelps, M. A., Li, X., Saji, M., Goff, L., Kauh, J. S. W., O'Neil, B. H., Balsom, S., Balint, C., Liersemann, R., Vasko, V. V., Bloomston, M., Marsh, W., Doyle, L. A., Ellison, G., Grever, M., Ringel, M. D., & Villalona-Calero, M. A. (2011). Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. *Journal of Clinical Oncology*, *29*(17), 2357–2363. <https://doi.org/10.1200/JCO.2010.33.9473>
- Bendell, J. C., Javle, M., Bekaii-Saab, T. S., Finn, R. S., Wainberg, Z. A., Laheru, D. A., Weekes, C. D., Tan, B. R., Khan, G. N., Zalupski, M. M., Infante, J. R., Jones, S., Papadopoulos, K. P., Tolcher, A. W., Chavira, R. E., Christy-Bittel, J. L., Barrett, E., & Patnaik, A. (2017). A phase 1 dose-escalation and expansion study of binimetinib (MEK162), a potent and selective oral MEK1/2 inhibitor. *British Journal of Cancer*, *116*(5), 575–583. <https://doi.org/10.1038/bjc.2017.10>
- Bengala, C., Bertolini, F., Malavasi, N., Boni, C., Aitini, E., Dealis, C., Zironi, S., Depenni, R., Fontana, A., Del Giovane, C., Luppi, G., & Conte, P. (2010). Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. *British Journal of Cancer*, *102*(1), 68–72. <https://doi.org/10.1038/sj.bjc.6605458>
- Borbath, I., Ceratti, A., Verslype, C., Demols, A., Delaunoit, T., Laurent, S., Deleporte, A., Vergauwe, P., Van Maanen, A., Sempoux, C., Van Cutsem, E., Van Laethem, J. L., & Belgian Group of Digestive Oncology. (2013). Combination of gemcitabine and cetuximab in patients with advanced cholangiocarcinoma: a phase II study of the Belgian Group of Digestive Oncology. *Annals of Oncology*, *24*(11), 2824–2829. <https://doi.org/10.1093/annonc/mdt337>

- Borger, D. R., Tanabe, K. K., Fan, K. C., Lopez, H. U., Fantin, V. R., Straley, K. S., Schenkein, D. P., Hezel, A. F., Ancukiewicz, M., Liebman, H. M., Kwak, E. L., Clark, J. W., Ryan, D. P., Deshpande, V., Dias-Santagata, D., Ellisen, L. W., Zhu, A. X., & Iafrate, A. J. (2012). Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. *The Oncologist*, *17*(1), 72–79. <https://doi.org/10.1634/theoncologist.2011-0386>
- Bréchon, M., Dior, M., Dréanic, J., Brieu, B., Guillaumot, M.-A., Brezault, C., Mir, O., Goldwasser, F., & Coriat, R. (2018). Addition of an antiangiogenic therapy, bevacizumab, to gemcitabine plus oxaliplatin improves survival in advanced biliary tract cancers. *Investigational New Drugs*, *36*(1), 156–162. <https://doi.org/10.1007/s10637-017-0492-6>
- Bridgewater, J., Lopes, A., Beare, S., Duggan, M., Lee, D., Ricamara, M., McEntee, D., Sukumaran, A., Wasan, H., & Valle, J. W. (2016). 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*, *16*, 153. <https://doi.org/10.1186/s12885-016-2174-8>
- Brieu, B., Dahan, L., Rycke, Y. D., Boussaha, T., Vasseur, P., Tougeron, D., Lecomte, T., Coriat, R., Bachet, J.-B., Claudez, P., Zaan, A., Soibinet, P., Desrame, J., Thiot - Bidault, A., Trouilloud, I., Mary, F., Marthey, L., Taieb, J., Cacheux, W., & Lièvre, A. (2015). Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the Association des Gastro-

Entérologues Oncologues. *Cancer*, 121(18), 3290–3297.

<https://doi.org/10.1002/cncr.29471>

Buzzoni, R., Pusceddu, S., Bajetta, E., De Braud, F., Platania, M., Iannacone, C., Cantore, M., Mambrini, A., Bertolini, A., Alabiso, O., Ciarlo, A., Turco, C., & Mazzaferro, V. (2014). Activity and safety of RAD001 (everolimus) in patients affected by biliary tract cancer progressing after prior chemotherapy: a phase II ITMO study. *Annals of Oncology*, 25(8), 1597–1603. <https://doi.org/10.1093/annonc/mdu175>

Chan-On, W., Nairismägi, M.-L., Ong, C. K., Lim, W. K., Dima, S., Pairojkul, C., Lim, K. H., McPherson, J. R., Cutcutache, I., Heng, H. L., Ooi, L., Chung, A., Chow, P., Cheow, P. C., Lee, S. Y., Choo, S. P., Tan, I. B. H., Duda, D., Nastase, A., ... Teh, B. T. (2013). Exome sequencing identifies distinct mutational patterns in liver fluke-related and non-infection-related bile duct cancers. *Nature Genetics*, 45(12), 1474–1478. <https://doi.org/10.1038/ng.2806>

Chen, J. S., Hsu, C., Chiang, N. J., Tsai, C. S., Tsou, H. H., Huang, S. F., Bai, L. Y., Chang, I. C., Shiah, H. S., Ho, C. L., Yen, C. J., Lee, K. D., Chiu, C. F., Rau, K. M., Yu, M. S., Yang, Y., Hsieh, R. K., Chang, J. Y., Shan, Y. S., ... Taiwan Cooperative Oncology Group. (2015). A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in combination with cetuximab in advanced biliary tract cancer. *Annals of Oncology*, 26(5), 943–949. <https://doi.org/10.1093/annonc/mdv035>

Chiorean, E. G., Ramasubbaiah, R., Yu, M., Picus, J., Bufill, J. A., Tong, Y., Coleman, N., Johnston, E. L., Currie, C., & Loehrer, P. J. (2012). Phase II trial of erlotinib and docetaxel in advanced and refractory hepatocellular and

- biliary cancers: Hoosier Oncology Group GI06-101. *The Oncologist*, 17(1), 13. <https://doi.org/10.1634/theoncologist.2011-0253>
- Churi, C. R., Shroff, R., Wang, Y., Rashid, A., Kang, H. C., Weatherly, J., Zuo, M., Zinner, R., Hong, D., Meric-Bernstam, F., Janku, F., Crane, C. H., Mishra, L., Vauthey, J.-N., Wolff, R. A., Mills, G., & Javle, M. (2014). Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PloS One*, 9(12), e115383. <https://doi.org/10.1371/journal.pone.0115383>
- Czink, E., Heining, C., Weber, T. F., Lasitschka, F., Schemmer, P., Schirmacher, P., Weiss, K. H., Glimm, H., Brors, B., Weichert, W., Jäger, D., Fröhling, S., & Springfield, C. (2016). [Durable remission under dual HER2 blockade with Trastuzumab and Pertuzumab in a patient with metastatic gallbladder cancer]. *Zeitschrift Fur Gastroenterologie*, 54(5), 426–430. <https://doi.org/10.1055/s-0042-103498>
- Drilon, A., Laetsch, T. W., Kummar, S., DuBois, S. G., Lassen, U. N., Demetri, G. D., Nathenson, M., Doebele, R. C., Farago, A. F., Pappo, A. S., Turpin, B., Dowlati, A., Brose, M. S., Mascarenhas, L., Federman, N., Berlin, J., El-Deiry, W. S., Baik, C., Deeken, J., ... Hyman, D. M. (2018). Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *The New England Journal of Medicine*, 378(8), 731–739. <https://doi.org/10.1056/NEJMoa1714448>
- Drilon, Alexander, Siena, S., Ou, S.-H. I., Patel, M., Ahn, M. J., Lee, J., Bauer, T. M., Farago, A. F., Wheler, J. J., Liu, S. V., Doebele, R., Giannetta, L., Cerea, G., Marrapese, G., Schirru, M., Amatu, A., Bencardino, K., Palmeri, L., Sartore-Bianchi, A., ... De Braud, F. G. (2017). Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined

- Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). *Cancer Discovery*, 7(4), 400–409. <https://doi.org/10.1158/2159-8290.CD-16-1237>
- Eckel, F., & Schmid, R. M. (2007). Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *British Journal of Cancer*, 96(6), 896–902. <https://doi.org/10.1038/sj.bjc.6603648>
- El-Khoueiry, A. B., Rankin, C. J., Ben-Josef, E., Lenz, H.-J., Gold, P. J., Hamilton, R. D., Govindarajan, R., Eng, C., & Blanke, C. D. (2012). SWOG 0514: a phase II study of sorafenib in patients with unresectable or metastatic gallbladder carcinoma and cholangiocarcinoma. *Investigational New Drugs*, 30(4), 1646–1651. <https://doi.org/10.1007/s10637-011-9719-0>
- Farshidfar, F., Zheng, S., Gingras, M.-C., Newton, Y., Shih, J., Robertson, A. G., Hinoue, T., Hoadley, K. A., Gibb, E. A., Roszik, J., Covington, K. R., Wu, C.-C., Shinbrot, E., Stransky, N., Hegde, A., Yang, J. D., Reznik, E., Sadeghi, S., Pedamallu, C. S., ... Kwong, L. N. (2017). Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH-Mutant Molecular Profiles. *Cell Reports*, 18(11), 2780–2794. <https://doi.org/10.1016/j.celrep.2017.02.033>
- Galdy, S., Lamarca, A., McNamara, M. G., Hubner, R. A., Cella, C. A., Fazio, N., & Valle, J. W. (2017). HER2/HER3 pathway in biliary tract malignancies; systematic review and meta-analysis: a potential therapeutic target? *Cancer Metastasis Reviews*, 36(1), 141–157. <https://doi.org/10.1007/s10555-016-9645-x>
- Glimelius, B., Hoffman, K., Sjöden, P. O., Jacobsson, G., Sellström, H., Enander, L. K., Linné, T., & Svensson, C. (1996). Chemotherapy improves survival and

quality of life in advanced pancreatic and biliary cancer. *Annals of Oncology*, 7(6), 593–600.

Goeppert, B., Frauenschuh, L., Renner, M., Roessler, S., Stenzinger, A., Klauschen, F., Warth, A., Vogel, M. N., Mehrabi, A., Hafezi, M., Boehmer, K., von Deimling, A., Schirmacher, P., Weichert, W., & Capper, D. (2014). BRAF V600E-specific immunohistochemistry reveals low mutation rates in biliary tract cancer and restriction to intrahepatic cholangiocarcinoma. *Modern Pathology*, 27(7), 1028–1034.

<https://doi.org/10.1038/modpathol.2013.206>

Golan, T., Raitses-Gurevich, M., Kelley, R. K., Bocobo, A. G., Borgida, A., Shroff, R. T., Holter, S., Gallinger, S., Ahn, D. H., Aderka, D., Apurva, J., Bekaii-Saab, T., Friedman, E., & Javle, M. (2017). Overall Survival and Clinical Characteristics of BRCA-Associated Cholangiocarcinoma: A Multicenter Retrospective Study. *The Oncologist*, 22(7), 804–810.

<https://doi.org/10.1634/theoncologist.2016-0415>

Goyal, L., Arkenau, H.-T., Tran, B., Soria, J.-C., Bahleda, R., Mak, G., Zhu, A., Javle, M., Hiroshi, H., Benedetti, F., Huang, J., Winkler, R., & Meric-Bernstam, F. (2017). O-020 Early clinical efficacy of TAS-120, a covalently bound FGFR inhibitor, in patients with cholangiocarcinoma. *Annals of Oncology*, 28(suppl\_3). <https://doi.org/10.1093/annonc/mdx262.019>

Goyal, L., Govindan, A., Sheth, R. A., Nardi, V., Blaszkowsky, L. S., Faris, J. E., Clark, J. W., Ryan, D. P., Kwak, E. L., Allen, J. N., Murphy, J. E., Saha, S. K., Hong, T. S., Wo, J. Y., Ferrone, C. R., Tanabe, K. K., Chong, D. Q., Deshpande, V., Borger, D. R., ... Zhu, A. X. (2015). Prognosis and Clinicopathologic Features of Patients With Advanced Stage Isocitrate Dehydrogenase (IDH)

Mutant and IDH Wild-Type Intrahepatic Cholangiocarcinoma. *The Oncologist*, 20(9), 1019–1027.

<https://doi.org/10.1634/theoncologist.2015-0210>

- Goyal, L., Zheng, H., Yurgelun, M. B., Abrams, T. A., Allen, J. N., Cleary, J. M., Knowles, M., Regan, E., Reardon, A., Khachatryan, A., Jain, R. K., Nardi, V., Borger, D. R., Duda, D. G., & Zhu, A. X. (2017). A phase 2 and biomarker study of cabozantinib in patients with advanced cholangiocarcinoma. *Cancer*, 123(11), 1979–1988. <https://doi.org/10.1002/cncr.30571>
- Graham, R. P., Barr Fritcher, E. G., Pestova, E., Schulz, J., Sitailo, L. A., Vasmatazis, G., Murphy, S. J., McWilliams, R. R., Hart, S. N., Halling, K. C., Roberts, L. R., Gores, G. J., Couch, F. J., Zhang, L., Borad, M. J., & Kipp, B. R. (2014). Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. *Human Pathology*, 45(8), 1630–1638. <https://doi.org/10.1016/j.humpath.2014.03.014>
- Gruenberger, B., Schueller, J., Heubrandtner, U., Wrba, F., Tamandl, D., Kaczirek, K., Roka, R., Freimann-Pircher, S., & Gruenberger, T. (2010). Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *The Lancet. Oncology*, 11(12), 1142–1148. [https://doi.org/10.1016/S1470-2045\(10\)70247-3](https://doi.org/10.1016/S1470-2045(10)70247-3)
- Grünewald, S., Politz, O., Bender, S., Héroult, M., Lustig, K., Thuss, U., Kneip, C., Kopitz, C., Zopf, D., Collin, M.-P., Boemer, U., Ince, S., Ellinghaus, P., Mumberg, D., Hess-Stumpp, H., & Ziegelbauer, K. (2019). Rogaratinib: A potent and selective pan-FGFR inhibitor with broad antitumor activity in FGFR-overexpressing preclinical cancer models. *International Journal of Cancer*, 145(5), 1346–1357. <https://doi.org/10.1002/ijc.32224>



- Guedj, N., Zhan, Q., Perigny, M., Rautou, P.-E., Degos, F., Belghiti, J., Farges, O., Bedossa, P., & Paradis, V. (2009). Comparative protein expression profiles of hilar and peripheral hepatic cholangiocarcinomas. *Journal of Hepatology*, *51*(1), 93–101. <https://doi.org/10.1016/j.jhep.2009.03.017>
- Guion-Dusserre, J.-F., Lorgis, V., Vincent, J., Bengrine, L., & Ghiringhelli, F. (2015). FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma. *World Journal of Gastroenterology*, *21*(7), 2096–2101. <https://doi.org/10.3748/wjg.v21.i7.2096>
- Herberger, B., Puhalla, H., Lehnert, M., Wrba, F., Novak, S., Brandstetter, A., Gruenberger, B., Gruenberger, T., Pirker, R., & Filipits, M. (2007). Activated mammalian target of rapamycin is an adverse prognostic factor in patients with biliary tract adenocarcinoma. *Clinical Cancer Research*, *13*(16), 4795–4799. <https://doi.org/10.1158/1078-0432.CCR-07-0738>
- Hezel, A. F., Noel, M. S., Allen, J. N., Abrams, T. A., Yurgelun, M., Faris, J. E., Goyal, L., Clark, J. W., Blaszkowsky, L. S., Murphy, J. E., Zheng, H., Khorana, A. A., Connolly, G. C., Hyrien, O., Baran, A., Herr, M., Ng, K., Sheehan, S., Harris, D. J., ... Zhu, A. X. (2014). Phase II study of gemcitabine, oxaliplatin in combination with panitumumab in KRAS wild-type unresectable or metastatic biliary tract and gallbladder cancer. *British Journal of Cancer*, *111*(3), 430–436. <https://doi.org/10.1038/bjc.2014.343>
- Hsiao, S. J., Zehir, A., Sireci, A. N., & Aisner, D. L. (2019). Detection of Tumor NTRK Gene Fusions to Identify Patients Who May Benefit from Tyrosine Kinase (TRK) Inhibitor Therapy. *The Journal of Molecular Diagnostics*, *21*(4), 553–571. <https://doi.org/10.1016/j.jmoldx.2019.03.008>

Hyman, D. M., Puzanov, I., Subbiah, V., Faris, J. E., Chau, I., Blay, J.-Y., Wolf, J., Raje, N. S., Diamond, E. L., Hollebecque, A., Gervais, R., Elez-Fernandez, M. E., Italiano, A., Hofheinz, R.-D., Hidalgo, M., Chan, E., Schuler, M., Lasserre, S. F., Makrutzki, M., ... Baselga, J. (2015). Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *The New England Journal of Medicine*, *373*(8), 726–736.

<https://doi.org/10.1056/NEJMoa1502309>

Ikeda, M., Ioka, T., Fukutomi, A., Morizane, C., Kasuga, A., Takahashi, H., Todaka, A., Okusaka, T., Creasy, C. L., Gorman, S., Felitsky, D. J., Kobayashi, M., Zhang, F., & Furuse, J. (2018). Efficacy and safety of trametinib in Japanese patients with advanced biliary tract cancers refractory to gemcitabine. *Cancer Science*, *109*(1), 215–224. <https://doi.org/10.1111/cas.13438>

Iyer, R. V., Pokuri, V. K., Groman, A., Ma, W. W., Malhotra, U., Iancu, D. M., Grande, C., & Saab, T. B. (2018). A Multicenter Phase II Study of Gemcitabine, Capecitabine, and Bevacizumab for Locally Advanced or Metastatic Biliary Tract Cancer. *American Journal of Clinical Oncology*, *41*(7), 649–655. <https://doi.org/10.1097/COC.0000000000000347>

Javle, M., Lowery, M., Shroff, R. T., Weiss, K. H., Springfield, C., Borad, M. J., Ramanathan, R. K., Goyal, L., Sadeghi, S., Macarulla, T., El-Khoueiry, A., Kelley, R. K., Borbath, I., Choo, S. P., Oh, D.-Y., Philip, P. A., Chen, L.-T., Reungwetwattana, T., Van Cutsem, E., ... Bekaii-Saab, T. (2018). Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. *Journal of Clinical Oncology*, *36*(3), 276–282. <https://doi.org/10.1200/JCO.2017.75.5009>

- Jensen, L. H., Lindebjerg, J., Ploen, J., Hansen, T. F., & Jakobsen, A. (2012). Phase II marker-driven trial of panitumumab and chemotherapy in KRAS wild-type biliary tract cancer. *Annals of Oncology*, *23*(9), 2341–2346.  
<https://doi.org/10.1093/annonc/mds008>
- Khan, S. A., Toledano, M. B., & Taylor-Robinson, S. D. (2008). Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB*, *10*(2), 77–82.  
<https://doi.org/10.1080/13651820801992641>
- Kim, S. T., Lee, J., Park, S. H., Park, J. O., Park, Y. S., Kang, W. K., & Lim, H. Y. (2017). Prospective phase II trial of everolimus in PIK3CA amplification/mutation and/or PTEN loss patients with advanced solid tumors refractory to standard therapy. *BMC Cancer*, *17*(1), 211.  
<https://doi.org/10.1186/s12885-017-3196-6>
- Kocsis, J., Árokszállási, A., András, C., Balogh, I., Béres, E., Déri, J., Peták, I., Jánváry, L., & Horváth, Z. (2017). Combined dabrafenib and trametinib treatment in a case of chemotherapy-refractory extrahepatic BRAF V600E mutant cholangiocarcinoma: dramatic clinical and radiological response with a confusing synchronic new liver lesion. *Journal of Gastrointestinal Oncology*, *8*(2), E32–E38. <https://doi.org/10.21037/jgo.2017.01.06>
- Lamarca, A., Palmer, D. H., Wasan, H. S., Ross, P. J., Ma, Y. T., Arora, A., Falk, S., Gillmore, R., Wadsley, J., Patel, K., Anthoney, A., Maraveyas, A., Waters, J. S., Hobbs, C., Barber, S., Ryder, D., Ramage, J., Davies, L. M., Bridgewater, J. A., & Valle, J. W. (2019). ABC-06 | A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with

cisplatin/gemcitabine (CisGem) chemotherapy. *Journal of Clinical Oncology*, 37(15\_suppl), 4003–4003.

[https://doi.org/10.1200/JCO.2019.37.15\\_suppl.4003](https://doi.org/10.1200/JCO.2019.37.15_suppl.4003)

Lau, D. K., Tay, R. Y., Yeung, Y. H., Chionh, F., Mooi, J., Murone, C., Skrinos, E., Price, T. J., Mariadason, J. M., & Tebbutt, N. C. (2018). Phase II study of everolimus (RAD001) monotherapy as first-line treatment in advanced biliary tract cancer with biomarker exploration: the RADiChol Study. *British Journal of Cancer*, 118(7), 966–971.

<https://doi.org/10.1038/s41416-018-0021-1>

Lavingia, V., & Fakih, M. (2016). Impressive response to dual BRAF and MEK inhibition in patients with BRAF mutant intrahepatic cholangiocarcinoma-2 case reports and a brief review. *Journal of Gastrointestinal Oncology*, 7(6), E98–E102.

<https://doi.org/10.21037/jgo.2016.09.13>

Law, L. Y. (2012). Dramatic response to trastuzumab and paclitaxel in a patient with human epidermal growth factor receptor 2-positive metastatic cholangiocarcinoma. *Journal of Clinical Oncology*, 30(27), e271-273.

<https://doi.org/10.1200/JCO.2012.42.3061>

Lee, J. K., Capanu, M., O'Reilly, E. M., Ma, J., Chou, J. F., Shia, J., Katz, S. S., Gansukh, B., Reidy-Lagunes, D., Segal, N. H., Yu, K. H., Chung, K.-Y., Saltz, L. B., & Abou-Alfa, G. K. (2013). A phase II study of gemcitabine and cisplatin plus sorafenib in patients with advanced biliary adenocarcinomas. *British Journal of Cancer*, 109(4), 915–919.

<https://doi.org/10.1038/bjc.2013.432>

- Lee, J., Park, S. H., Chang, H.-M., Kim, J. S., Choi, H. J., Lee, M. A., Jang, J. S., Chang, J. S., Jeung, H. C., Kang, J. H., Lee, H. W., Shin, D. B., Kang, H. J., Sun, J.-M., Park, J. O., Park, Y. S., Kang, W. K., & Lim, H. Y. (2012). Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. *The Lancet. Oncology*, *13*(2), 181–188. [https://doi.org/10.1016/S1470-2045\(11\)70301-1](https://doi.org/10.1016/S1470-2045(11)70301-1)
- Lee, K.-H., Lee, K.-B., Kim, T.-Y., Han, S.-W., Oh, D.-Y., Im, S.-A., Kim, T.-Y., Yi, N.-J., Lee, K.-W., Suh, K.-S., Jang, J.-J., & Bang, Y.-J. (2015). Clinical and pathological significance of ROS1 expression in intrahepatic cholangiocarcinoma. *BMC Cancer*, *15*, 721. <https://doi.org/10.1186/s12885-015-1737-4>
- Leone, F., Marino, D., Cereda, S., Filippi, R., Belli, C., Spadi, R., Nasti, G., Montano, M., Amatu, A., Aprile, G., Cagnazzo, C., Fasola, G., Siena, S., Ciuffreda, L., Reni, M., & Aglietta, M. (2016). Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type KRAS advanced biliary tract cancer: A randomized phase 2 trial (Vecti-BIL study). *Cancer*, *122*(4), 574–581. <https://doi.org/10.1002/cncr.29778>
- Lim, H., Seo, D. W., Park, D. H., Lee, S. S., Lee, S. K., Kim, M.-H., & Hwang, S. (2013). Prognostic factors in patients with gallbladder cancer after surgical resection: analysis of 279 operated patients. *Journal of Clinical Gastroenterology*, *47*(5), 443–448. <https://doi.org/10.1097/MCG.0b013e3182703409>
- Lin, J., Shi, W., Zhao, S., Hu, J., Hou, Z., Yao, M., Chrin, G., Pan, J., Hu, K., Zhao, L., Javle, M., Wang, K., & Zhao, H. (2018). Lenvatinib plus checkpoint inhibitors in patients (pts) with advanced intrahepatic

cholangiocarcinoma (ICC): Preliminary data and correlation with next-generation sequencing. *Journal of Clinical Oncology*, 36(4\_suppl), 500–500.

[https://doi.org/10.1200/JCO.2018.36.4\\_suppl.500](https://doi.org/10.1200/JCO.2018.36.4_suppl.500)

Loaiza-Bonilla, A., Clayton, E., Furth, E., O'Hara, M., & Morrissette, J. (2014).

Dramatic response to dabrafenib and trametinib combination in a BRAF V600E-mutated cholangiocarcinoma: implementation of a molecular tumour board and next-generation sequencing for personalized medicine.

*Ecancermedicalscience*, 8, 479.

<https://doi.org/10.3332/ecancer.2014.479>

Lowery, M. A., O'Reilly, E. M., Harding, J. J., Yu, K. H., Cercek, A., Hollywood, E.,

Salehi, E., Margona, E., Bradley, M., Witter, T., Gerst, S. R., Capanu, M., Saltz, L., & Abou-Alfa, G. K. (2017). A phase I/II trial of MEK162 in combination with gemcitabine (G) and cisplatin (C) for patients (pts) with untreated advanced biliary cancer (ABC).

*Journal of Clinical Oncology*, 35(4\_suppl),

290–290. [https://doi.org/10.1200/JCO.2017.35.4\\_suppl.290](https://doi.org/10.1200/JCO.2017.35.4_suppl.290)

Malka, D., Cervera, P., Foulon, S., Trarbach, T., de la Fouchardière, C., Boucher, E.,

Fartoux, L., Faivre, S., Blanc, J.-F., Viret, F., Assenat, E., Seufferlein, T.,

Herrmann, T., Grenier, J., Hammel, P., Dollinger, M., André, T., Hahn, P.,

Heinemann, V., ... BINGO investigators. (2014). Gemcitabine and

oxaliplatin with or without cetuximab in advanced biliary-tract cancer

(BINGO): a randomised, open-label, non-comparative phase 2 trial. *The*

*Lancet. Oncology*, 15(8), 819–828. [https://doi.org/10.1016/S1470-](https://doi.org/10.1016/S1470-2045(14)70212-8)

[2045\(14\)70212-8](https://doi.org/10.1016/S1470-2045(14)70212-8)

Mazzaferro, V., El-Rayes, B. F., Busset, M. D. dit, Cotsoglou, C., Harris, W. P.,

Damjanov, N., Masi, G., Rimassa, L., Personeni, N., Braiteh, F., Zagonel, V.,

Papadopoulos, K. P., Hall, T., Wang, Y., Schwartz, B., Kazakin, J., Bhoori, S., Braud, F. de, & Shaib, W. L. (2019). Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. *British Journal of Cancer*, *120*(2), 165.  
<https://doi.org/10.1038/s41416-018-0334-0>

Moehler, M., Maderer, A., Ehrlich, A., Foerster, F., Schad, A., Nickolay, T., Ruckes, C., Weinmann, A., Sivanathan, V., Marquardt, J. U., Galle, P. R., Woerns, M., & Thomaidis, T. (2019). Safety and efficacy of afatinib as add-on to standard therapy of gemcitabine/cisplatin in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, phase I trial with an extensive biomarker program. *BMC Cancer*, *19*(1), 55.  
<https://doi.org/10.1186/s12885-018-5223-7>

Nakamura, H., Arai, Y., Totoki, Y., Shiota, 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., & Shibata, T. (2015). Genomic spectra of biliary tract cancer. *Nature Genetics*, *47*(9), 1003–1010.  
<https://doi.org/10.1038/ng.3375>

Nakazawa, K., Dobashi, Y., Suzuki, S., Fujii, H., Takeda, Y., & Ooi, A. (2005). Amplification and overexpression of c-erbB-2, epidermal growth factor receptor, and c-met in biliary tract cancers. *The Journal of Pathology*, *206*(3), 356–365. <https://doi.org/10.1002/path.1779>

Nam, A.-R., Kim, J.-W., Cha, Y., Ha, H., Park, J. E., Bang, J.-H., Jin, M. H., Lee, K.-H., Kim, T.-Y., Han, S.-W., Im, S.-A., Kim, T.-Y., Oh, D.-Y., & Bang, Y.-J. (2016). Therapeutic implication of HER2 in advanced biliary tract cancer.

*Oncotarget*, 7(36), 58007–58021.

<https://doi.org/10.18632/oncotarget.11157>

Neuzillet, C., Casadei Gardini, A., Brieu, B., Vivaldi, C., Smolenschi, C., Brandi, G., Tougeron, D., Filippi, R., Vienot, A., Silvestris, N., Pointet, A.-L., Lonardi, S., Rousseau, B., Scartozzi, M., Dahan, L., Aprile, G., Boussaha, T., Malka, D., Crusz, S. M., ... Barts Cancer Institute Cohort. (2019). Prediction of survival with second-line therapy in biliary tract cancer: Actualisation of the AGEO CT2BIL cohort and European multicentre validations. *European Journal of Cancer (Oxford, England: 1990)*, 111, 94–106.

<https://doi.org/10.1016/j.ejca.2019.01.019>

Neuzillet, C., Seitz, J.-F., Fartoux, L., Malka, D., Lledo, G., Tijeras-Raballand, A., De Gramont, A., Ronot, M., Bouattour, M., Dreyer, C., Amin, A., Brunisholz - Bourget, P., Hadengue, A., Roldan, N., Chibaudel, B., Raymond, E., & Faivre, S. J. (2015). Sunitinib as second-line treatment in patients with advanced intrahepatic cholangiocarcinoma (SUN-CK phase II trial): Safety, efficacy, and updated translational results. *Journal of Clinical Oncology*, 33(3\_suppl), 343–343. [https://doi.org/10.1200/jco.2015.33.3\\_suppl.343](https://doi.org/10.1200/jco.2015.33.3_suppl.343)

Okano, N., Ueno, M., Morizane, C., Yamanaka, T., Ojima, H., Ozaka, M., Sasaki, M., Takahara, N., Kobayashi, S., Morimoto, M., Hosoi, H., Nakai, Y., Ikeda, M., Maeno, S., Nagashima, F., Okusaka, T., & Furuse, J. (2019). 737PMulticenter phase II trial of axitinib monotherapy for advanced biliary tract cancer refractory to gemcitabine-based chemotherapy. *Annals of Oncology*, 30(Supplement\_5).

<https://doi.org/10.1093/annonc/mdz247.064>



- Okusaka, T., Nakachi, K., Fukutomi, A., Mizuno, N., Ohkawa, S., Funakoshi, A., Nagino, M., Kondo, S., Nagaoka, S., Funai, J., Koshiji, M., Nambu, Y., Furuse, J., Miyazaki, M., & Nimura, Y. (2010). Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *British Journal of Cancer*, *103*(4), 469–474. <https://doi.org/10.1038/sj.bjc.6605779>
- Ole Larsen, F., Taksony Solyom Hoegdall, D., Hoegdall, E., & Nielsen, D. (2016). Gemcitabine, capecitabine and oxaliplatin with or without cetuximab in advanced biliary tract carcinoma. *Acta Oncologica (Stockholm, Sweden)*, *55*(3), 382–385. <https://doi.org/10.3109/0284186X.2015.1080858>
- Park, J. O., Feng, Y.-H., Chen, Y.-Y., Su, W.-C., Oh, D.-Y., Shen, L., Kim, K.-P., Liu, X., Bai, Y., Liao, H., Nie, J., Qing, M., Ji, Q., Li, J., Zhao, M., De Porre, P., & Monga, M. (2019). Updated results of a phase IIa study to evaluate the clinical efficacy and safety of erdafitinib in Asian advanced cholangiocarcinoma (CCA) patients with FGFR alterations. *Journal of Clinical Oncology*, *37*(15\_suppl), 4117–4117. [https://doi.org/10.1200/JCO.2019.37.15\\_suppl.4117](https://doi.org/10.1200/JCO.2019.37.15_suppl.4117)
- Parkin, D. M., Srivatanakul, P., Khlatt, M., Chenvidhya, D., Chotiwan, P., Insiripong, S., L'Abbé, K. A., & Wild, C. P. (1991). Liver cancer in Thailand. I. A case-control study of cholangiocarcinoma. *International Journal of Cancer*, *48*(3), 323–328. <https://doi.org/10.1002/ijc.2910480302>
- Peck, J., Wei, L., Zalupski, M., O'Neil, B., Villalona Calero, M., & Bekaii-Saab, T. (2012). HER2/neu may not be an interesting target in biliary cancers: results of an early phase II study with lapatinib. *Oncology*, *82*(3), 175–179. <https://doi.org/10.1159/000336488>

- Ramanathan, R. K., Belani, C. P., Singh, D. A., Tanaka, M., Lenz, H.-J., Yen, Y., Kindler, H. L., Iqbal, S., Longmate, J., Mack, P. C., Lurje, G., Gandour-Edwards, R., Dancey, J., & Gandara, D. R. (2009). A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. *Cancer Chemotherapy and Pharmacology*, *64*(4), 777–783.  
<https://doi.org/10.1007/s00280-009-0927-7>
- Randi, G., Malvezzi, M., Levi, F., Ferlay, J., Negri, E., Franceschi, S., & La Vecchia, C. (2009). Epidemiology of biliary tract cancers: an update. *Annals of Oncology*, *20*(1), 146–159. <https://doi.org/10.1093/annonc/mdn533>
- Roa, I., de Toro, G., Schalper, K., de Aretxabala, X., Churi, C., & Javle, M. (2014). Overexpression of the HER2/neu Gene: A New Therapeutic Possibility for Patients With Advanced Gallbladder Cancer. *Gastrointestinal Cancer Research: GCR*, *7*(2), 42–48.
- Ross, J. S., Wang, K., Gay, L., Al-Rohil, R., Rand, J. V., Jones, D. M., Lee, H. J., Sheehan, C. E., Otto, G. A., Palmer, G., Yelensky, R., Lipson, D., Morosini, D., Hawryluk, M., Catenacci, D. V. T., Miller, V. A., Churi, C., Ali, S., & Stephens, P. J. (2014). New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. *The Oncologist*, *19*(3), 235–242.  
<https://doi.org/10.1634/theoncologist.2013-0352>
- Rubovszky, G., Láng, I., Ganofszy, E., Horváth, Z., Juhos, É., Nagy, T., Szabó, E., Szentirmay, Z., Budai, B., & Hitre, E. (2013). Cetuximab, gemcitabine and capecitabine in patients with inoperable biliary tract cancer: A phase 2 study. *European Journal of Cancer*, *49*(18), 3806–3812.  
<https://doi.org/10.1016/j.ejca.2013.07.143>

- Sabbatino, F., Villani, V., Yearley, J. H., Deshpande, V., Cai, L., Konstantinidis, I. T., Moon, C., Nota, S., Wang, Y., Al-Sukaini, A., Zhu, A. X., Goyal, L., Ting, D. T., Bardeesy, N., Hong, T. S., Fernandez-del Castillo, C., Tanabe, K. K., Lillemoe, K. D., Ferrone, S., & Ferrone, C. R. (2016). PD-L1 and HLA Class I Antigen Expression and Clinical Course of the Disease in Intrahepatic Cholangiocarcinoma. *Clinical Cancer Research*, *22*(2), 470–478. <https://doi.org/10.1158/1078-0432.CCR-15-0715>
- Santoro, A., Gebbia, V., Pressiani, T., Testa, A., Personeni, N., Arrivas Bajardi, E., Foa, P., Buonadonna, A., Bencardino, K., Barone, C., Ferrari, D., Zaniboni, A., Tronconi, M. C., Carteni, G., Milella, M., Comandone, A., Ferrari, S., & Rimassa, L. (2015). A randomized, multicenter, phase II study of vandetanib monotherapy versus vandetanib in combination with gemcitabine versus gemcitabine plus placebo in subjects with advanced biliary tract cancer: the VanGogh study. *Annals of Oncology*, *26*(3), 542–547. <https://doi.org/10.1093/annonc/mdu576>
- Sebbagh, S., Roux, J., Dreyer, C., Neuzillet, C., de Gramont, A., Orbegoso, C., Hentic, O., Hammel, P., de Gramont, A., Raymond, E., André, T., Chibaudel, B., & Faivre, S. (2016). Efficacy of a sequential treatment strategy with GEMOX-based followed by FOLFIRI-based chemotherapy in advanced biliary tract cancers. *Acta Oncologica (Stockholm, Sweden)*, *55*(9–10), 1168–1174. <https://doi.org/10.1080/0284186X.2016.1191670>
- Sharma, A., Dwary, A. D., Mohanti, B. K., Deo, S. V., Pal, S., Sreenivas, V., Raina, V., Shukla, N. K., Thulkar, S., Garg, P., & Chaudhary, S. P. (2010). Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. *Journal of Clinical*

*Oncology*, 28(30), 4581–4586.

<https://doi.org/10.1200/JCO.2010.29.3605>

Shigeyasu, K., Tanakaya, K., Nagasaka, T., Aoki, H., Fujiwara, T., Sugano, K., Ishikawa, H., Yoshida, T., Moriya, Y., Furukawa, Y., Goel, A., & Takeuchi, H. (2014). Early detection of metachronous bile duct cancer in Lynch syndrome: report of a case. *Surgery Today*, 44(10), 1975–1981.

<https://doi.org/10.1007/s00595-013-0669-3>

Shroff, R. T., Yarchoan, M., O'Connor, A., Gallagher, D., Zahurak, M. L., Rosner, G., Ohaji, C., Sartorius-Mergenthaler, S., Parkinson, R., Subbiah, V., Zinner, R., & Azad, N. S. (2017). The oral VEGF receptor tyrosine kinase inhibitor pazopanib in combination with the MEK inhibitor trametinib in advanced cholangiocarcinoma. *British Journal of Cancer*, 116(11), 1402–1407.

<https://doi.org/10.1038/bjc.2017.119>

Siegel, R. L., Miller, K. D., & Jemal, A. (2019). Cancer statistics, 2019. *CA: A Cancer Journal for Clinicians*, 69(1), 7–34. <https://doi.org/10.3322/caac.21551>

Silva, V. W. K., Askan, G., Daniel, T. D., Lowery, M., Klimstra, D. S., Abou-Alfa, G. K., & Shia, J. (2016). Biliary carcinomas: pathology and the role of DNA mismatch repair deficiency. *Chinese Clinical Oncology*, 5(5), 62.

<https://doi.org/10.21037/cco.2016.10.04>

Simbolo, M., Fassan, M., Ruzzenente, A., Mafficini, A., Wood, L. D., Corbo, V., Melisi, D., Malleo, G., Vicentini, C., Malpeli, G., Antonello, D., Sperandio, N., Capelli, P., Tomezzoli, A., Iacono, C., Lawlor, R. T., Bassi, C., Hruban, R. H., Guglielmi, A., ... Scarpa, A. (2014). Multigene mutational profiling of cholangiocarcinomas identifies actionable molecular subgroups.

*Oncotarget*, 5(9), 2839–2852. <https://doi.org/10.18632/oncotarget.1943>

- Sohal, D. P. S., Mykulowycz, K., Uehara, T., Teitelbaum, U. R., Damjanov, N., Giantonio, B. J., Carberry, M., Wissel, P., Jacobs-Small, M., O'Dwyer, P. J., Sepulveda, A., & Sun, W. (2013). A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. *Annals of Oncology*, 24(12), 3061–3065. <https://doi.org/10.1093/annonc/mdt416>
- Sorscher, S. (2013). Marked radiographic response of a HER-2-overexpressing biliary cancer to trastuzumab. *Cancer Management and Research*, 9, 1–3. <https://doi.org/10.2147/CMAR.S55091>
- Terada, T., Nakanuma, Y., & Sirica, A. E. (1998). Immunohistochemical demonstration of MET overexpression in human intrahepatic cholangiocarcinoma and in hepatolithiasis. *Human Pathology*, 29(2), 175–180.
- Ueno, M., Chung, H. C., Nagrial, A., Marabelle, A., Kelley, R. K., Xu, L., Mahoney, J., Pruitt, S. K., & Oh, D.-Y. (2018). 625PDPembrolizumab for advanced biliary adenocarcinoma: Results from the multicohort, phase II KEYNOTE-158 study. *Annals of Oncology*, 29(suppl\_8). <https://doi.org/10.1093/annonc/mdy282.009>
- Ueno, Makoto, Ikeda, M., Morizane, C., Kobayashi, S., Ohno, I., Kondo, S., Okano, N., Kimura, K., Asada, S., Namba, Y., Okusaka, T., & Furuse, J. (2019). Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. *The Lancet. Gastroenterology & Hepatology*, 4(8), 611–621. [https://doi.org/10.1016/S2468-1253\(19\)30086-X](https://doi.org/10.1016/S2468-1253(19)30086-X)

- Valle, J. W., Borbath, I., Khan, S. A., Huguet, F., Gruenberger, T., Arnold, D., & ESMO Guidelines Committee. (2016). Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 27(suppl 5), v28–v37. <https://doi.org/10.1093/annonc/mdw324>
- Valle, J., Wasan, H., Palmer, D. H., Cunningham, D., Anthoney, A., Maraveyas, A., Madhusudan, S., Iveson, T., Hughes, S., Pereira, S. P., Roughton, M., Bridgewater, J., & ABC-02 Trial Investigators. (2010). Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *The New England Journal of Medicine*, 362(14), 1273–1281. <https://doi.org/10.1056/NEJMoa0908721>
- Valle, Juan W., Lamarca, A., Goyal, L., Barriuso, J., & Zhu, A. X. (2017). New Horizons for Precision Medicine in Biliary Tract Cancers. *Cancer Discovery*, 7(9), 943–962. <https://doi.org/10.1158/2159-8290.CD-17-0245>
- Valle, Juan W., Wasan, H., Lopes, A., Backen, A. C., Palmer, D. H., Morris, K., Duggan, M., Cunningham, D., Anthoney, D. A., Corrie, P., Madhusudan, S., Maraveyas, A., Ross, P. J., Waters, J. S., Steward, W. P., Rees, C., Beare, S., Dive, C., & Bridgewater, J. A. (2015). Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. *The Lancet Oncology*, 16(8), 967–978. [https://doi.org/10.1016/S1470-2045\(15\)00139-4](https://doi.org/10.1016/S1470-2045(15)00139-4)
- Vogel, A., Sahai, V., Hollebecque, A., Vaccaro, G., Melisi, D., Al-Rajabi, R., Paulson, A. S., Borad, M. J., Gallinson, D., Murphy, A. G., Oh, D.-Y., Dotan, E., Catenacci, D. V., Van Cutsem, E., Lihou, C. F., Zhen, H., Féliz, L., & Abou-Alfa,

G. K. (2019). LBA40FIGHT-202: A phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA). *Annals of Oncology*, 30(Supplement\_5).  
<https://doi.org/10.1093/annonc/mdz394.031>

Vogel, Arndt, Kasper, S., Weichert, W., Bitzer, M., Block, A., Riess, H., Schulze-Bergkamen, H., Moehler, M. H., Merx, K. E., Endris, V., Schnoy, E., Siveke, J. T., Michl, P., Waldschmidt, D., Kuhlmann, J., Geissler, M., Kahl, C., & Kubicka, S. (2015). Panitumumab in combination with gemcitabine/cisplatin (GemCis) for patients with advanced kRAS WT biliary tract cancer: A randomized phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Journal of Clinical Oncology*, 33(15\_suppl), 4082–4082.  
[https://doi.org/10.1200/jco.2015.33.15\\_suppl.4082](https://doi.org/10.1200/jco.2015.33.15_suppl.4082)

Westphalen, C. B., Preinfalk, A., Kruger, S., Haas, M., Renz, B. W., Riener, M.-O., Weber, A., Kirchner, T., Werner, J., Heinemann, V., von Bergwelt-Baildon, M., Baba, H. A., Siveke, J. T., Ormanns, S., & Boeck, S. (2019). Neurotrophic tropomyosin receptor kinase (NTRK) and nerve growth factor (NGF) are not expressed in Caucasian patients with biliary tract cancers: pooled data from three independent cohorts. *Clinical & Translational Oncology*, 21(8), 1108–1111. <https://doi.org/10.1007/s12094-018-02030-6>

Yang, X.-Q., Xu, Y.-F., Guo, S., Liu, Y., Ning, S.-L., Lu, X.-F., Yang, H., & Chen, Y.-X. (2014). Clinical significance of nerve growth factor and tropomyosin-receptor-kinase signaling pathway in intrahepatic cholangiocarcinoma. *World Journal of Gastroenterology*, 20(14), 4076–4084.  
<https://doi.org/10.3748/wjg.v20.i14.4076>

- Yeung, Y., Lau, D. K., Chionh, F., Tran, H., Tse, J. W. T., Weickhardt, A. J., Nikfarjam, M., Scott, A. M., Tebbutt, N. C., & Mariadason, J. M. (2017). K-Ras mutation and amplification status is predictive of resistance and high basal pAKT is predictive of sensitivity to everolimus in biliary tract cancer cell lines. *Molecular Oncology*, *11*(9), 1130–1142. <https://doi.org/10.1002/1878-0261.12078>
- Yi, J. H., Thongprasert, S., Lee, J., Doval, D. C., Park, S. H., Park, J. O., Park, Y. S., Kang, W. K., & Lim, H. Y. (2012). A phase II study of sunitinib as a second-line treatment in advanced biliary tract carcinoma: a multicentre, multinational study. *European Journal of Cancer (Oxford, England: 1990)*, *48*(2), 196–201. <https://doi.org/10.1016/j.ejca.2011.11.017>
- Yoshida, H., Shimada, K., Kosuge, T., & Hiraoka, N. (2016). A significant subgroup of resectable gallbladder cancer patients has an HER2 positive status. *Virchows Archiv*, *468*(4), 431–439. <https://doi.org/10.1007/s00428-015-1898-1>
- Yoshikawa, D., Ojima, H., Iwasaki, M., Hiraoka, N., Kosuge, T., Kasai, S., Hirohashi, S., & Shibata, T. (2008). Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. *British Journal of Cancer*, *98*(2), 418–425. <https://doi.org/10.1038/sj.bjc.6604129>
- Zhu, A. X., Meyerhardt, J. A., Blazzkowsky, L. S., Kambadakone, A. R., Muzikansky, A., Zheng, H., Clark, J. W., Abrams, T. A., Chan, J. A., Enzinger, P. C., Bhargava, P., Kwak, E. L., Allen, J. N., Jain, S. R., Stuart, K., Horgan, K., Sheehan, S., Fuchs, C. S., Ryan, D. P., & Sahani, D. V. (2010). 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. *The Lancet. Oncology*, 11(1), 48–54. [https://doi.org/10.1016/S1470-2045\(09\)70333-X](https://doi.org/10.1016/S1470-2045(09)70333-X)