



First-line Chemotherapy in Advanced Biliary Tract Cancer Ten Years After the ABC-02 Trial: “And Yet It Moves!”

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ABSTRACT

Biliary tract cancers (BTCs) include a heterogeneous group of highly aggressive hepatobiliary malignancies, representing the 3% of all gastrointestinal cancers and the second most frequent type of primary liver cancer after hepatocellular carcinoma. Ten years after the publication of the phase III, randomized, ABC-02 trial, the combination of cisplatin plus gemcitabine remains the standard first-line treatment for patients with advanced BTC. In the last decade, a large number of attempts has been made to improve the efficacy of the reference doublet by using novel drugs or adding a third agent to cisplatin-gemcitabine. Unfortunately, despite the addition of different cytotoxic drugs failed to improve clinical outcomes in several studies, recently published clinical trials have provided interesting results, and other first-line chemotherapy options are currently under investigation in randomized phase III studies. Moreover, recent years have witnessed the parallel emergence of molecularly targeted therapies and immune checkpoint inhibitors, with these novel agents having the potential to revolutionize the therapeutic algorithm of advanced BTC. In this review, we will provide an overview on first-line therapeutic opportunities currently available in the management of advanced BTCs, especially focusing on recently published data and ongoing clinical trials in this setting.

Introduction

Biliary tract cancers (BTCs) constitute a heterogeneous group of aggressive malignancies, including the following: ampulla of Vater cancer (AVC), gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (iCCA), and extrahepatic cholangiocarcinoma (eCCA) (Fig. 1) [1-3]. BTCs account for approximately the 3% of all gastrointestinal adult malignancies, representing the most frequent hepatobiliary cancer following hepatocellular carcinoma (HCC) [4, 5]. Of note, despite a huge variation in incidence has been classically depicted, with certain areas showing high prevalence (e.g., South Korea, Japan, China, Thailand), the incidence and mortality rate of BTCs are rising in most western countries [6-10].

Surgery remains the mainstay of cure in early stages of BTC, but unfortunately, only a minority of patients is diagnosed with resectable disease, ranging from 10 to 40% [11-13]. Even following curative surgery, recurrence rate is extremely high, with a median 5-year survival of less than 50% in completely resected BTC patients [14, 15]. Recent results of the BILCAP phase III trial support the use of adjuvant

capecitabine following surgical resection, on the basis of an improvement in median overall survival (OS) from 36 months to 53 months (in the observation and the capecitabine arms, respectively; Hazard Ratio [HR] 0.75, $p = 0.028$ in the sensitivity analysis) [16, 17]. However, the BILCAP did not meet its primary endpoint, and the results of this trial are highly discussed. For patients with locoregional disease, local treatments including radiofrequency ablation, chemoembolization and radio-embolization may be considered, although few data are available regarding the role of these techniques in BTCs [18-20].

Conversely, for patients with metastatic BTC systemic therapies are the only potential treatment option, and the combination of cisplatin plus gemcitabine (CisGem) represents the current standard of care, on the basis of the results of the pivotal ABC-02 trial [21]. Ten years after the publication of this study in 2010, the therapeutic landscape of BTC has seen important changes, with the identification of novel treatment options [22-27]. First, the molecular features of BTC have begun to emerge over the last decade, providing researchers the basis for developing targeted treatments, which are currently being assessed as monotherapy or in combination with other anticancer agents [28-34].

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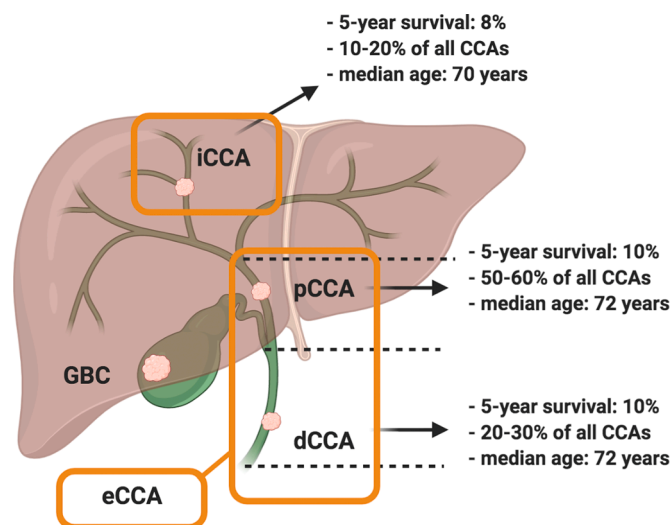


Fig. 1. Schematic figure of the anatomical site and main clinical features of each cholangiocarcinoma subtype. Biliary tract cancer comprises cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer. Cholangiocarcinoma includes the intrahepatic, perihilar and distal subtypes; moreover, perihilar and distal cholangiocarcinomas are grouped together in the category of extrahepatic cholangiocarcinoma. Abbreviations: CCA: cholangiocarcinoma; dCCA: distal cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; iCCA: intrahepatic cholangiocarcinoma; pCCA: perihilar cholangiocarcinoma.

Second, immune checkpoint inhibitors (ICIs) have provided remarkable results, revolutionizing the therapeutic algorithm of several hematological and solid malignancies [35-40]; nonetheless, immunotherapy is still trying to find its niche in advanced BTC, and a wide range of trials is currently evaluating the role of ICIs in front-line setting, mainly in combination with cytotoxic chemotherapy [41-47]. Third, several cytotoxic agents have been assessed or are under investigation as first-line treatment, including S1, nab-paclitaxel, and nanoliposomal-irinotecan [48, 49]. In this review, we critically discuss research progress in first-line chemotherapy for advanced BTC, ten years after the publication of the landmark ABC-02 trial. We provide a comprehensive review of recent trials and the current state of ongoing active and recruiting studies according to Clinicaltrials.gov.

We performed a research on PubMed/Medline, Cochrane library, and Scopus using the keyword “biliary tract cancer” OR “cholangiocarcinoma” OR “intrahepatic cholangiocarcinoma” OR “gallbladder cancer” OR “extrahepatic cholangiocarcinoma” AND “first-line treatment” OR “front-line chemotherapy” OR “first-line chemotherapy”. We selected the most relevant and pertinent studies considering how the studies were conducted, their applicability, statistical analysis, number of patients enrolled, outcomes. For ongoing clinical trials, we searched in the Clinicaltrials.gov database for recruiting and active, not recruiting trials, using the following keywords: “biliary tract cancer” OR “cholangiocarcinoma” OR “intrahepatic cholangiocarcinoma” OR “gallbladder cancer” OR “extrahepatic cholangiocarcinoma” AND “first-line treatment” OR “front-line chemotherapy” OR “first-line chemotherapy”. We restricted our research to clinical trials focused on the front-line setting.

The birth of a standard of care: the ABC-02 trial

Prior to 2010, several chemotherapeutic regimens have been explored either alone or in combination with other cytotoxic agents in a range of studies which were mainly nonrandomized phase II trials with small sample size [50]. A pooled analysis by Eckel and colleagues - including 2810 patients and 104 clinical trials - suggested better clinical outcomes in BTCs receiving doublet chemotherapy compared to

single-agent chemotherapy [50]. In particular, response rate (RR), disease control rate (DCR), and time to progression (TTP) in the two groups were 28% versus 15.3% ($p = 0.000$), 61% versus 50.4% ($p = 0.000$), and 4.4 months versus 3.4 months ($p = 0.015$), respectively. In addition, a non-statistically significant trend for higher mOS was observed in the doublet arm (9.3 months and 7.5 months respectively, $p = 0.061$) [50]. Lastly, this analysis highlighted that the combination of gemcitabine plus platinum (cisplatin or oxaliplatin) appeared as the most active regimen in terms of DCR and RR, when these two doublets were compared with other regimens. In fact, the results of this study signaled the urgent need for more effective therapies, providing a benchmark for subsequent trials exploring the association of platinum-compounds with gemcitabine in advanced disease [50].

Firstly, the combination of cisplatin plus gemcitabine was assessed in the Advanced Biliary Cancer (ABC)-01 trial [51]. In this randomized phase II trial, an improvement in terms of progression-free survival (PFS) was observed among patients treated with CisGem compared to BTCs receiving gemcitabine single-agent [51]. These results led to the phase III randomized ABC-02 trial, where 410 patients with advanced BTC were randomly allocated to receive CisGem or gemcitabine alone, with OS assessed as primary endpoint [21]. According to the design of this study, BTC patients were stratified according to Eastern Cooperative Oncology Group Performance Status (ECOG-PS), primary tumor site, and extent of disease [21]. After a median follow-up of 8.2 months, the mOS was 11.7 months in the CisGem arm and 8.1 months in the gemcitabine monotherapy group ($p < 0.001$); moreover, median PFS in the two arms were 8.0 and 5.0 months, respectively ($p < 0.001$). In addition, the benefit conferred by the doublet was consistent across the anatomical subgroups of BTC. Lastly, in terms of safety, CisGem showed a non-significant increase in neutropenia, although these results were not mirrored into higher infection rates [21].

Similarly, the randomized phase II BT22 on Japanese patients confirmed these findings, with CisGem showing superior mOS compared to gemcitabine monotherapy (11.2 months versus 7.7 months), and the survival benefit provided by the doublet was further corroborated by a meta-analysis by Valle and colleagues [52, 53]. Thus, the ABC-02 and the BT22 trials changed the paradigm of first-line treatment, establishing CisGem as the new standard of care for treatment-naïve BTC patients with advanced disease [54, 55].

Prognostic factors in advanced BTC receiving first-line chemotherapy

Certainly, the ABC-02 and the BT22 trials showed that systemic chemotherapy has the potential to extend survival in BTC [21, 52-55]. But at the same time, the poor prognosis of these patients clearly suggests that the identification of factors which could help in the process of treatment selection is mandatory [56-58]. An important number of parameters and factors have been proposed to play a prognostic role in advanced BTC patients receiving front-line chemotherapy [59-61]. Among these, disease status, liver metastasis, gender, ECOG-PS, number of metastatic sites, and several biochemical parameters (such as bilirubin, white blood count, neutrophils, hemoglobin, and neutrophil-lymphocyte ratio) have been suggested as independent prognostic factors for survival in BTC patients treated with first-line chemotherapy [62]. More specifically, the most relevant independent prognostic factor for patients with advanced disease receiving first-line chemotherapy is ECOG-PS, a simple clinical parameter which may help to guide therapeutical choices. For example, all international guidelines suggest that monotherapy should be preferred in BTC patients with ECOG-PS 2, also on the basis of a meta-analysis including the ABC-02 and the BT-22 trials, showing that BTCs with poor ECOG-PS do not seem to derive benefit from the reference doublet, and thus suggesting that gemcitabine monotherapy is a feasible treatment in this patient population [14, 17].

A multicenter Italian experience conducted by the G.I.Co. (Italian

Group of Cholangiocarcinoma) including 940 BTC patients, suggested that prior resection, tumor grading, baseline CEA, baseline CA 19.9, and ECOG-PS could be factors independently associated with survival [63].

However, despite several factors and scores have been proposed, all these tools have shown limited accuracy in determining survival and clinical outcomes in advanced BTC, highlighting the need for novel reliable biomarkers which could help to predict treatment outcomes in this setting [64-66].

Novel chemotherapeutic regimens or the addition of a third agent: trying to raise the bar

Despite CisGem still represents the current standard of care, the modest survival benefit conferred by the reference doublet highlights that new first-line strategies for management of metastatic BTC represent an urgent need [67]. In fact, in the last ten years, an impressive number of attempts have been made to improve the efficacy of CisGem, including the addition of a third agent or the use of novel anticancer drugs. Traditionally, the combination of gemcitabine plus oxaliplatin (GEMOX regimen) has been widely used, representing a valuable alternative strategy as front-line treatment in cisplatin-unfit patients, although its use is based on results of a nonrandomized phase II trial [68].

More recently, an important question has been whether more intensive strategies including triplets could be superior to the reference doublet. A phase II trial conducted by Shroff and colleagues assessed the role of the combination of CisGem plus nab-paclitaxel, reporting interesting results [69]. In fact, this single-arm, open-label study has shown that the triplet was associated with a RR of 32.2% and a DCR of 82.3% in treatment-naïve patients with advanced BTC [69]. Additionally, median PFS was 11.4 months while mOS 19.2 months, a remarkable result in the front-line setting of BTC [69]. The 58% of the enrolled patients presented grade 3 or higher adverse events, with neutropenia as the most common grade 3–4 toxicity, occurring in the 33% of BTCs [69]. The triplet is currently undergoing prospective evaluation in a phase III randomized trial which is allocating advanced BTC patients to CisGem plus nab-paclitaxel versus CisGem alone (NCT03768414); OS is the primary endpoint of this study.

Following the notable results of a phase II trial on Japanese patients reporting a mOS of 16.2 months in treatment-naïve BTC, another triplet - the combination of CisGem plus the oral fluoropyrimidine S1 - has been evaluated in a randomized phase III trial [70]. In this study, this experimental treatment was compared to the standard doublet. Although the study was formally positive, with a HR of 0.791 ($p = 0.046$, 95% CI 0.628–0.996), the differences between the two arms were extremely limited, with mOS in the triplet arm and the doublet arm of 13.5 months and 12.6 months, respectively, suggesting an overall limited clinical impact of the trial [70].

Another strategy assessed in a phase III Japanese trial included the combination of gemcitabine plus the fluoropyrimidine S-1 [67]. In this study, efficacy and safety of the reference doublet CisGem was compared with gemcitabine – S-1 (GEM/S1) in 354 treatment naïve BTC patients [67]. The overall response rate (ORR) was 29.8% in patients receiving GEM/S1 and 32.4% in the CisGem group; conversely, median PFS was 6.8 months and 5.8 months in the first and the second arm, respectively. Lastly, patients treated with GEM/S1 showed a median OS of 15.1 months, versus 13.4 months in the CisGem arm [67]. Both treatments were altogether well-tolerated. Clinically significant AEs were observed in 35.1% of patients in the GC arm and 29.9% in the GS arm [67]. Of note, the authors stated that GEM/S1 could represent a new and convenient standard of care option for treatment-naïve patients; however, the characteristics of this study (including the patient population and the type of treatment, the use of which is limited to Asia) make hard to translate these results in clinical practice in Western Countries.

In an attempt to translate the experience of advanced pancreatic cancer, the FOLFIRINOX regimen has been tested in a phase I trial

including 28 patients with advanced BTC [71]. However, only the 21% (6/28) showed partial response (PR), with clinical outcomes which did not overcome the benefit provided by the reference doublet [71]. However, the AMEBICA French III trial is ongoing, with the aim of comparing FOLFIRINOX versus CisGem in this setting (NCT02591030). The primary outcomes of this study include OS and the percentage of BTC patients who are alive without radiological progression at 6 months; the study has a planned enrollment of 316 participants, with an estimated primary completion date in September 2023.

An interesting and novel approach in front-line setting is certainly the application of ProTide technology to design the NUC-1031, a new agent aimed to overcome the key resistance mechanisms associated with gemcitabine – in terms of transport, activation, and catabolism [72]. In addition, NUC-1031 (or acelarin) differs from gemcitabine since this molecule is not subject to metabolism by cytidine deaminase, and thus, its mechanism of action reduces toxic metabolites. Recently, McNamara and colleagues published the results of the ABC-08 phase Ib study reporting a favorable safety profile for CisGem plus NUC-1031 [73]. According to the results of this trial, in combination with CisGem for the front-line treatment of patients with advanced BTC, 725 mg/m² NUC-1031 was recommended for phase III trial evaluation. In fact, the phase III randomized NuTide trial is currently ongoing, with the aim of comparing the combination of the reference first-line doublet plus NUC-1031 versus CisGem alone (NCT04163900) [74]. Lastly, several other first-line regimens are under investigation in advanced BTC, including the combination of nanoliposomal-irinotecan (Nal-IRI) plus 5-fluorouracil (5-FU) / leucovorin [75]. More specifically, the phase II, open-label, NIFE trial is comparing the combination of Nal-IRI plus 5-FU / leucovorin versus CisGem in treatment-naïve BTC patients with advanced disease (NCT03044587). PFS is the primary outcome of this study, which has a planned enrollment of 92 participants.

Checkpoint point inhibitors and targeted therapies plus chemotherapy: promises and failures

In the last decade, immunotherapy has changed treatment paradigms of a wide range of solid tumors, improving clinical outcomes and reporting unprecedented response rates [76, 77]. However, ICIs have shown controversial and highly discussed results in several malignancies [78-80]; among these, ICIs as monotherapy have been disappointing in unselected BTC patients [81]. In an attempt to increase the antitumor efficacy of immunotherapy as first-line treatment, and on the basis of a strong biological rationale, ICIs are being tested in combination with chemotherapy [82]. In fact, chemoimmunotherapy could play a synergistic effect, since several chemotherapeutic agents are able to upregulate checkpoint expression [83].

A phase I trial on 30 treatment-naïve Japanese patients treated with first-line CisGem plus nivolumab was conducted by Ueno and colleagues [84]. Of note, this triplet reported an unprecedented RR of 37% in advanced BTC patients, with a median PFS and OS of 4.2 months and 15.4 months, respectively. Several other trials are currently ongoing, including the phase III TOPAZ-1 and KEYNOTE-966 trials, which will provide further information regarding the role of chemoimmunotherapy as first-line treatment (Table 1). The phase III, double-blind, TOPAZ-1 study is randomly allocating treatment-naïve patients to CisGem plus placebo versus CisGem in combination with the anti-PD-L1 agent durvalumab. Similarly, the KEYNOTE-966 is currently evaluating the role of the PD-1 inhibitor pembrolizumab combined with the reference doublet versus CisGem plus placebo. The primary outcomes of this study are PFS and OS, with an estimated primary completion date in August 2023 and a planned enrollment of 788 patients. In addition, a wide number and type of immune-based combinations is being assessed as front-line treatment, and further results from several studies are expected soon (Table 1). Among these trials, a multicenter, randomized, placebo-controlled study is evaluating the role of CisGem in combination with bintrafusp alfa (M7824), an innovative first-in-class

Table 1

Ongoing trials evaluating immunotherapy plus systemic chemotherapy as first-line treatment in advanced biliary tract cancer. Abbreviations: CisGem: cisplatin plus gemcitabine combination; CTLA-4: Cytotoxic T-Lymphocyte Antigen 4; DLTs: dose-limiting toxicities; FGFR: fibroblast growth factor receptor; GEMOX: gemcitabine plus oxaliplatin; ORR: overall response rate; OS: overall survival; PDGFR: platelet-derived growth factor receptor; PD-1: programmed death 1; PFS: progression-free survival; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor.

NCT name	Phase	Setting	Arm A	Arm B	Compounds description	Estimated enrolment	Primary outcomes
NCT04066491	2/3	First-line	Bintrafusp alfa (M7824) plus CisGem	Placebo plus CisGem	Bintrafusp alfa: first-in-class bifunctional fusion protein composed of PD-L1 antibody fused with 2 extracellular domains of TGF- β receptor	512	DLTs OS
NCT03260712	2	First-line	Pembrolizumab plus CisGem		Pembrolizumab: PD-1 antibody	50	PFS at 6 months OS
NCT03875235 (TOPAZ-1)	3	First-line	Durvalumab plus CisGem	Placebo plus CisGem	Durvalumab: PD-L1 inhibitor	757	OS
NCT03046862	2	First-line	Durvalumab plus tremelimumab plus CisGem		Durvalumab: PD-L1 inhibitor Tremelimumab: anti-CTLA-4 agent	31	ORR
NCT03796429	2	First-line	Toripalimab plus S-1 plus gemcitabine		Toripalimab: PD-1 antibody	40	PFS OS
NCT04172402	2	First-line	Nivolumab plus S-1 plus gemcitabine		Nivolumab: PD-1 antibody	48	ORR
NCT04027764	2	First-line	Toripalimab plus S-1 plus albumin paclitaxel		Toripalimab: PD-1 antibody	30	ORR
NCT04300959	2	First-line	Anlotinib plus sintilimab plus CisGem	CisGem	Anlotinib: TKI inhibiting VEGFR, FGFR, PDGFR and c-KIT kinase Sintilimab: PD-1 antibody	80	12-month OS rate
NCT03478488	3	First-line	KN035 plus GEMOX	GEMOX	KN035: PD-L1 inhibitor	390	OS
NCT04191343	2	First-line	Toripalimab plus GEMOX		Toripalimab: PD-1 antibody	20	ORR
NCT04003636 (KEYNOTE-966)	3	First-line	Pembrolizumab plus CisGem	Placebo plus CisGem	Pembrolizumab: PD-1 antibody	788	PFS OS
NCT03937895	1/2A	First- or later-line	Pembrolizumab plus allogenic NK cell (SMT-NK)		Pembrolizumab: PD-1 antibody SMT-NK: allogenic natural killer cell	40	DLTs ORR

bifunctional fusion protein composed of a human IgG1 monoclonal antibody against PD-L1 fused with 2 extracellular domains of TGF- β receptor (NCT04066491). This study testing the TGF- β “trap” has a planned enrollment of 512 patients, with an estimated primary completion date in November 2022.

Among the currently ongoing trials, it is worth mentioning a phase II open-label study which is evaluating the role of the combination of CisGem plus durvalumab plus tremelimumab in treatment-naïve patients with advanced disease (NCT03046862). Response rate represents the primary endpoint of this trial. Several other combinations are being assessed in the front-line setting, including toripalimab plus GEMOX (NCT04191343), toripalimab plus S1-gemcitabine (NCT03796429), and the PD-1 monoclonal antibody SH2-1210 combined with GEMOX regimen (NCT03486678). In an “immunologically” cold group of malignancies such as BTCs, the identification of specific molecular and histological biomarkers which could predict response to ICIs – as monotherapy or in combination with chemotherapy - represents a high unmet need [85].

As regards targeted therapies, the massive advent of improved technologies has recently led to the identification of several actionable alterations in BTC, which are estimated to be present in the 50% of patients [86-90]. As previously stated, molecular profiling of BTC has gained great importance during the last ten years due to the development of targeted therapies against druggable molecular alterations, such as fibroblast growth factor receptor (FGFR)–2 fusions and isocitrate dehydrogenase (IDH)–1 mutations, as witnessed by the recently published FIGHT-202 and ClarIDHy trials. [91, 92]. In addition to these aberrations, several other alterations have been observed, with the hope of providing novel molecules to the therapeutic landscape of BTCs [93-95]. In analogy with ICIs, targeted agents have been tested in combination with chemotherapy in treatment-naïve patients, reporting disappointing results so far. For example, Epithelial Growth Factor Receptor (EGFR) inhibitors have been assessed in combination with

first-line chemotherapy in several phase II and III clinical trials, failing to result in improved clinical outcomes [96-100]. In addition, the recently published phase II PICCA trial conducted by Vogel and colleagues further confirmed these findings, with panitumumab in combination with front-line CisGem reporting no improvement in terms of ORR, PFS, and OS in BTC patients compared to CisGem alone [101]. Similarly, previous attempts to improve clinical outcomes adding other anticancer drugs to the reference doublet – such as sorafenib, cediranib, veliparib, and other anti-angiogenic agents – in advanced BTCs failed to produce promising results [102-105].

Although genomic sequence technologies have shed light on a previously unknown landscape, unfortunately this knowledge has only marginally been translated into improved clinical outcomes, and further studies are needed to detect if novel targeted agents could be added to the reference doublet - or could even replace CisGem in patients harboring druggable mutations [106-108]. For example, the FIGHT-302 (NCT03656536) is evaluating the efficacy and safety of pemigatinib – the only approved targeted therapy in cholangiocarcinoma so far – versus CisGem chemotherapy in first-line treatment of patients with FGFR2 rearrangement [109].

The FGFR1, FGFR2, and FGFR3 inhibitor pemigatinib has reported notable results in the phase II FIGHT-202 study, which investigated the role of this agent in previously treated cholangiocarcinoma patients, showing an ORR of 35.5% and median PFS of 6.9 months in those patients harboring FGFR2 fusion or other rearrangements [31]. Based on these results, in April 2020 the Food and Drug Administration (FDA) granted accelerated approval for this agent, something that represented the first molecularly targeted therapy to be approved for the treatment of cholangiocarcinoma patients [31]. However, several questions remain unanswered, including the emergence of polyclonal mutations determining resistance to FGFR inhibition, the identification of biomarkers predictive of response, and the knowledge gaps regarding the role of other FGFR gene aberrations. The results of the FIGHT-302 are highly

awaited and will clarify if pemigatinib could be superior to the doublet in this setting. However, it is worth noting that a large cohort of patients (approximately the 50% of BTCs) has no currently actionable mutations, something which further suggests that novel strategies are needed and that only a minority and very specific population of BTC patients could benefit from “precision medicine” [110, 111].

Conclusions

Although we are witnessing a new era in BTC management, 10 years after the publication of the ABC-02 trial, the combination of CisGem in the first-line setting remains the standard treatment for patients without targetable alterations. The development of novel molecules and the identification of novel targets represent urgent needs in this setting, and results of ongoing clinical trials are awaited, with the hope of providing better clinical outcomes in patients with advanced BTC.

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