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Adjuvant systemic treatment in resected biliary tract cancer: State of the art, controversies, and future directions

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ABSTRACT

Biliary tract cancer (BTC) includes a heterogeneous group of aggressive malignancies comprising gallbladder cancer (GBC), ampulla of Vater cancer (AVC), intrahepatic cholangiocarcinoma (iCCA), and extrahepatic cholangiocarcinoma (eCCA). Unfortunately, potentially curative resection is possible in approximately the 25% of presenting patients, and relapse rates are high, with a notable proportion of BTCs experiencing disease recurrence. Recent years have seen the publication of several prospective clinical trials evaluating the role of adjuvant systemic treatments, and among these, the phase III BILCAP study provided evidence supporting the use of capecitabine after radical surgery in BTC patients; in fact, although the study failed to meet its primary endpoint, the capecitabine arm showed improved clinical outcomes in terms of overall survival (pre-planned sensitivity analysis in the intention-to-treat population and in the per-protocol analysis) and relapse-free survival. However, the BILCAP has been widely criticized, with several authors that have not accepted adjuvant capecitabine as novel standard of care. In this review, we summarize current state of the art regarding adjuvant systemic treatment in BTC, highlighting advantages and disadvantages of recent clinical trials, and suggesting new research directions in this setting.

Introduction

Biliary tract cancer (BTC) includes a heterogeneous group of aggressive gastrointestinal malignancies, including ampulla of Vater cancer (AVC), gallbladder carcinoma (GBC), and cholangiocarcinoma (CCA) – which is further sub-classified into intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA) [1-3]. Overall, BTCs constitute the second most frequent hepatobiliary cancer, representing approximately the 3% of all gastrointestinal malignancies worldwide [4,5]. While eCCA and iCCA have been suggested to be more common in males, GBC is more frequent in females [6,7]. Traditionally, a notable incidence variation has been reported, with certain geographical areas showing high prevalence, such as South Korea, Thailand, Japan, India, and China [8,9]. However, despite historically considered rare tumors, in the past few decades BTC incidence has increased in Western Countries, as a result of improved imaging techniques, changes in tumor classification, and the growing burden of emerging risk factors [10,11]. Although radical surgical resection with negative tumor margins represents the only curative treatment option for BTCs, unfortunately only the 30–35% of patients are diagnosed with early-stage disease, and thus, surgery is not feasible for approximately the 70% of cases [12-14]. Additionally, a remarkable proportion of BTC patients deemed to have resectable disease at diagnosis, are subsequently found to be unresectable during surgery; moreover, even following radical surgical resection, recurrence rates are high [15,16].

For the front-line treatment of advanced BTCs, the standard of care has been established as cisplatin plus gemcitabine (CisGem), on the basis of the ABC-02 clinical trial [17,18]. In fact, according to the landmark results of this phase III study, median overall survival (mOS) was longer for CisGem compared with gemcitabine monotherapy (11.7 months versus 8.1 months; Hazard Ratio [HR] 0.64, 95% Confidence Intervals [CI] 0.52–0.8; $p<0.001$). Although recent years have seen the emerging of novel therapeutic options in this setting, the modest survival benefit gained from first-line CisGem has not yet been surpassed, and unfortunately, the 5-year survival for BTC patients with metastatic disease is less than 5% [19-22]. In view of the high relapse rate and the limited survival of advanced disease, adjuvant treatment has been explored in this setting, with therapeutic approaches including chemotherapy, radiotherapy, and chemo-radiotherapy [23,24]. Until few years ago, available data regarding adjuvant treatment in BTC were limited, with

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Table 1
Recent randomized phase III clinical trials evaluating adjuvant chemotherapy in resected biliary tract cancer.

Name	Author	Experimental Arm	Control Arm	Country (number of sites)	Number of patients	BTC subtypes	Nodal involvement	Margin involvement	Ref
BCAT	Ebata	Gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 4 weeks for 6 cycles)	Observation	Japan (48)	Experimental arm: 117 Control arm: 108	Only eCCAs: 102 pCCAs 123 dCCAs	N0: 64% N1: 36%	R0: 91% R1: 9%	[48]
PRODIGE-12 / ACCORD-18	Edeline	Gemcitabine (1000 mg/m^2 on day 1) plus oxaliplatin (85 mg/m^2 on day 2) every 2 weeks for 12 cycles	Observation	France (33)	Experimental arm: 73 Control arm: 82	GBCs + CCAs: predominance of iCCA (43% in Arm A, 46% in Arm B)	N0: 65% N1: 35%	R0: 86% R1: 14%	[47]
BILCAP	Primrose	Capecitabine (1250 mg/m^2 orally on days 1–14 of a 21-day cycle, for 8 cycles)	Observation	United Kingdom (44)	Experimental arm: 210 Control arm: 220	GBCs + CCAs: predominance of pCCA (29% in Arm A, 28% in Arm B)	N0: 52% N1: 48%	R0: 62% R1: 38%	[49]

Abbreviations: BTC: biliary tract cancer; CCA: cholangiocarcinoma; dCCA: distal cholangiocarcinoma; eCCA: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; pCCA: perihilar cholangiocarcinoma; Ref: reference.

lack of randomized trials exploring systemic therapies in this setting; in addition, due to the relative rarity of BTCs and the notable heterogeneity of anatomical subtypes, few randomized prospective clinical trials were conducted [25-27]. In fact, the use of adjuvant treatment – as chemotherapy or chemoradiotherapy – was supported by the pivotal meta-analysis by Horgan and colleagues [28]. According to the results of this analysis including 20 clinical trials (17 retrospective studies, 2 registry studies, and one randomized trial), adjuvant therapy reported a benefit in the two BTC high risk populations of patients with lymph node metastases (N1) and microscopically involved margins (R1 resection) [28]. However, this meta-analysis presented several issues, such as the inclusion of trials with heterogeneous schedules and small sample size.

Since 2017, data from three phase III randomized trials have been published, reporting conflicting results [29,30]; however, although the interpretation of some studies remains controversial, these results changed clinical practice. In this review, we will provide an overview of the current scenario of adjuvant systemic treatment in BTC, discussing recent trials in this setting.

Resected biliary tract cancer: factors associated with disease relapse

As previously stated, disease relapse is an extremely frequent event in resected BTC, with anatomical subgroups presenting distinct relapse patterns [31]. In fact, GBC relapse frequently occurs with distant metastases, while CCAs have been associated with widely varied types of recurrences [32,33]. In the last decades, several clinicopathological factors have been associated with increased risk of relapse in BTCs, including high serum carbohydrate antigen (CA) 19–9, the involvement of lymph nodes, and the presence of R1 surgery [34]. In analogy with recurrence patterns, distinct anatomical subgroups have shown slightly different risk factors. For example, increased risk of disease relapse and worse clinical outcomes have been described in resected iCCAs presenting risk factors such as vascular invasion, lymphatic invasion, periductal infiltrating disease, and R1 resection. In these patients, several nomograms have been proposed [35]; in particular, a prognostic nomogram by Wang and colleagues - including direct invasion, local extra-hepatic metastasis, vascular invasion, lymph node metastasis, tumor diameter, and serum CA19–9 and carcinoembryonic antigen (CEA) – showed a superior prognostic discrimination compared to other five systems previously used in this setting [36]. Similarly, a recent study by Kim and colleagues suggested that lymph node involvement and postoperative CA19–9 were associated with increased relapse rate in eCCA patients undergoing radical surgery [37]; in particular, eCCAs with high serum CA 19–9 before and after surgery presented worse outcomes – in terms of disease-free survival and distant metastasis rate. In the same setting of eCCA, high grade disease, perineural invasion and local invasion have been factors associated with poor prognosis. Lastly, perineural invasion, R1 surgery, lymph node involvement and extramural invasion have been associated with lower survival in resected GBCs, as suggested by several retrospective studies [36-38].

Before 2017: evidence supporting adjuvant therapy

The role of adjuvant chemotherapy and radiotherapy has been explored in small prospective and retrospective trials before 2017 [39]. As regards adjuvant radiotherapy, some retrospective and phase II clinical trials seemed to show a benefit compared to surgery alone in resected BTC, predominantly for patients with R1 resection [40,41]. A large retrospective series assessed the role of adjuvant radiotherapy in 3839 patients with iCCA [42]; median OS was 11 months (95% CI, 9–13) and 6 months (95% CI, 5–6) for patients receiving surgery followed by adjuvant radiotherapy or surgery alone, respectively. When the authors adjusted for other prognostic factors in the multivariable analysis, differences were significant [42].

Of note, international guidelines supported the use of adjuvant therapy on the basis of a pivotal meta-analysis by Horgan and colleagues [28]. In particular, this quantitative analysis included 20 clinical trials – 17 retrospective studies, one randomized trial, and 2 Surveillance, Epidemiology, and End Results (SEER) registry studies – for a total of more than 6700 BTC patients [28]. The results of this study supported adjuvant chemotherapy or chemoradiotherapy in resected BTCs with R1 resection (Odds Ratio [OR] 0.36, 95% CI 0.19–0.68) or with lymph node-positive disease (OR 0.49, 95% CI 0.30–0.80). Conversely, the meta-analysis highlighted a lack of benefit of radiotherapy alone in BTC patients with negative surgical margins. Nonetheless, the analysis raised several issues, including the presence of studies with different study design, the variable data quality, and the high level of heterogeneity of treatments – in terms of both chemotherapy and chemoradiotherapy schedules and fractions, also suggesting that therapeutic choices in this setting varied greatly worldwide.

Prior to 2017, the results of two randomized trials were available, and of note, these studies enrolled widely different pancreato-biliary malignancies [43,44]. In particular, a study by Takada et al. compared adjuvant mitomycin-C plus 5-fluorouracil (MF regimen) versus surgery alone in 508 resected bilio-pancreatic cancers – including GBCs and CCAs [43]. According to the results of this phase III trial conducted in Japan, adjuvant MF provided a survival benefit in 69 GBC patients compared to surgery alone ($n = 43$), with 5-year OS rate of 26.0% and 14.4%, respectively ($p = 0.021$). Additionally, a relapse-free survival (RFS) advantage was observed in the experimental arm (20.3% versus 11.6%, $p = 0.8892$); relapse rate was 79.7% in GBC patients treated with MF and 88.4% in the observation group. Conversely, this study showed no benefit in CCAs.

Similarly, the phase III ESPAC-3 study compared adjuvant 5-fluorouracil monotherapy versus gemcitabine single-agent versus observation in resected pancreato-biliary malignancies [44]; interestingly, almost 100 CCAs were included in this trial, where adjuvant chemotherapy failed to improve survival compared to observation alone [44].

2017, three randomized phase III trials: so similar, so different

Certainly, the remarkable rates of locoregional and distant recurrence following surgical resection justified the further exploration of adjuvant treatment – especially considering that the two randomized clinical trials available prior to 2017 presented important selection bias and heterogeneous treatment schedules [45,46]. On the basis of these premises, the last three years have seen the publication of three randomized phase III studies selectively focused on the patient population of resected BTCs and comparing systemic chemotherapy versus observation alone: the PRODIGE-12/ACCORD-18, the BCAT, and the BILCAP trials (Table 1) [47-49].

In the PRODIGE-12/ACCORD-18 trial conducted in 33 French sites, 196 BTC patients were randomized to gemcitabine plus oxaliplatin (GEMOX regimen; gemcitabine 1000 mg/m^2 on day 1 and oxaliplatin 85 mg/m^2 on day 2 - every 2 weeks for 12 cycles) versus surgery alone [47]. After a median follow-up of 46.5 months, no differences in RFS were observed between the two arms (HR 0.83, 95% CI 0.58–1.19; p = 0.31); moreover, no statistically significant differences in mOS were highlighted between the experimental and the control arm (75.8 versus 50.8 month; HR 1.08, 95% CI 0.70–1.66; p = 0.74) [47]. In terms of patient population, the PRODIGE-12/ACCORD-18 study included a predominance of iCCAs, representing the 44% of all patients. Additionally, the 36% of subjects had lymph node metastases (N1 disease) and only 13% had microscopically involved margins (R1), with all these features being balanced between the two study arms. Another interesting point to consider concerns post-relapse survival in the experimental and the control arm, with this outcome resulting worse in patients receiving GEMOX (mOS 8.0 months versus 15.2 months; HR 1.55, 95% CI 0.98–2.47; p = 0.06) [47].

In the Japanese phase III BCAT trial, 226 eCCA patients were randomized to gemcitabine (n = 117) or observation alone (n = 109) [48]. Of note, the study included only perihilar and distal CCA; the R1 resection rate was 9.4% and 13.0% in the gemcitabine and observation arms, respectively, while the 35.9% and the 33.3% of eCCA patients in the two arms had N1 disease [48]. According to the results of this study, there was no significant difference in mOS between the experimental and the control arm (mOS 62.3 months versus 63.8 months; HR 1.01, 95% CI 0.70–1.45; p = 0.964). In addition, no statistically significant differences were observed in terms of median RFS in patients receiving gemcitabine or observation alone (36.0 months versus 39.9 months respectively; HR 0.93, 95% CI 0.66–1.32; p = 0.693) [48].

The BILCAP trial, conducted in the United Kingdom over a time period of 9 years, randomized patients to capecitabine or observation [49]. The study enrolled 447 BTC patients, thus representing the largest trial so far assessing adjuvant therapy in this setting. In terms of patient population, the BILCAP trial had a high proportion of eCCA patients, that were more than 60% of the overall BTCs; in fact, in contrast to the PRODIGE-12/ACCORD-18 study, iCCAs represent only the 19% and the 18% of the capecitabine and the observation arms, respectively [49]. In terms of factors associated to disease recurrence, the 48% of patients treated with capecitabine had nodal involvement, while the 46% of the observation arm were N1; R1 disease was observed in the 38% of BTCs in each arm. Unfortunately, the BILCAP trial did not meet its primary endpoint in terms of OS in the intention-to-treat (ITT) population, with mOS in the experimental and the control arm of 51.1 months and 36.4 months, respectively (HR 0.81, 95% CI 0.63–1.04; p = 0.097). Nonetheless, the pre-specified ITT sensitivity analysis adjusted for gender, nodal status and grade of disease (HR 0.71, 95% CI 0.55–0.92; p-value 0.010), and the per protocol population analysis reported a survival benefit in patients receiving adjuvant capecitabine (53 months versus 36 months, HR 0.75, 95% CI 0.58–0.97; p = 0.028). In addition, a statistically significant benefit in terms of RFS was observed in the experimental arm compared to observation alone (median 24.4 months versus 17.5 months, HR 0.75, 95% CI 0.58–0.98; p-value 0.033). Lastly, adjuvant capecitabine was associated with a manageable safety profile, with no treatment-related grade 5 adverse events [49]. Importantly, the 55% of enrolled patients in the capecitabine arm completed the 8 planned cycles of adjuvant treatment, with 46% of BTCs requiring at least one dose adjustment.

Controversies in recent studies and the emerging of a standard of care

Modern studies on adjuvant chemotherapy in resected BTC marked a new era due to several reasons, including important novelties in terms of study design.

First, the time interval between surgery and start of adjuvant therapy represents an important difference with studies prior to 2017. For example, in the trial conducted by Takada and colleagues [43], adjuvant chemotherapy was administered at the time of surgical resection, and it was continued 1 week after. Conversely, recent trials allowed a maximum of 12 to 16 weeks before starting adjuvant therapy, a time interval which could help in improving treatment tolerance, and thus having an impact on the compliance [47-49]. Moreover, if previous trials continued adjuvant treatment indefinitely, until disease progression, recent studies support the inclusion of a determined period of time – usually 6 months of treatment [47-49].

As regards the statistical design, some “modern” studies aimed to provide an ambitious, and probably even too optimistic, benefit. The PRODIGE-12/ACCORD-18 is a shining example, since the planned HR for RFS was 0.6 [47]. Thus, this study cannot exclude a role for GEMOX, although the trial itself was not powered enough to detect small but potentially meaningful differences; in fact, the planned HR would have probably required a longer, more expensive, and larger study.

As previously mentioned, although the PRODIGE-12/ACCORD-18, the BCAT, and the BILCAP trials presented several analogies, important differences could have produced an impact on results of these studies [47-49]. The patient population of each study widely differed in terms of BTC subtype. For example, the BCAT trial included only eCCAs, while the French trial presented a predominance of iCCA, and eCCA was the most frequent BTC subtype in the BILCAP trial. Since each anatomical subgroup presents enormous differences in terms of etiology, molecular features, prognosis, treatment options, and natural history, these elements could have played a role in orienting the results of this trial. In fact, iCCAs have been suggested to present better clinical outcomes compared to GBCs and eCCAs.

Another key point to consider is relapse rate in recent trials. For example, this is even more relevant if we look at the absolute reduction of relapse rate in the BILCAP study between the capcitabine and the observation am. In fact, relapse rate was 65% and 60% in the experimental and the control arm, respectively, a result which is further corroborated by the lack of RFS superiority beyond 24 months for capecitabine. In addition, the maturity of the data is another important aspect, with the 5-year survival data of the BILCAP that are highly awaited and will probably clarify the real role of adjuvant capecitabine on survival [49]. In other terms, the confirmation of an OS benefit following 5 years of follow-up will probably be the moment of truth for capecitabine in this setting.

Although the recently published trials widely differ in median follow-up time, maturity of data, patient population, sample size and statistical design, thus making complex any kind of comparison, the results of the BILCAP trial have changed clinical practice [49]. In fact, this statistically negative but clinically meaningful study has led to the novel standard of care of adjuvant capecitabine in resected BTCs. Despite several international guidelines on BTC management have not

Table 2
Ongoing clinical trials evaluating adjuvant systemic treatment in resected biliary tract cancer.

NCT name	Phase	BTC subtypes	Arm A	Arm B	Compounds description	Estimated enrolment	Primary outcomes
NCT02170090 (ACTICCA-1)	3	GBC, eCCA, iCCA	Gemcitabine plus cisplatin	Observation	Chemotherapy	781	DFS
NCT03079427	2	eCCA	Gemcitabine plus cisplatin	Capecitabine	Chemotherapy	100	2-year DFS
NCT02548195	3	iCCA	Gemcitabine plus oxaliplatin	Capecitabine	Chemotherapy	286	RFS
NCT04077983	2	iCCA	Gemcitabine plus nab-paclitaxel		Chemotherapy	40	DFS
NCT03779035 (AdBTC-1)	3	GBC, eCCA, iCCA	Gemcitabine plus capecitabine	Capecitabine	Chemotherapy	460	DFS
NCT03702491	2	GBC	Apatinib plus SOX (tegafur, oxaliplatin)	SOX (tegafur, oxaliplatin)	VEGFR inhibitor plus chemotherapy	138	PFS
NCT03609489	2	GBC, eCCA, iCCA	Apatinib plus capecitabine	Capecitabine	VEGFR inhibitor plus chemotherapy	40	PFS
NCT04295317	2	iCCA	SHR-1210 plus capecitabine		PD-1 inhibitor plus chemotherapy	65	RFS
NCT04608786	1	GBC, eCCA, iCCA	ZKAB001 plus capecitabine		PD-L1 inhibitor plus chemotherapy	10	DLTs RP2D

Abbreviations: DFS: disease-free survival; DLTs: dose-limiting toxicities; eCCA: extrahepatic cholangiocarcinoma; GBC: gallbladder cancer; iCCA: intrahepatic cholangiocarcinoma; PFS: progression-free survival; RFS: relapse-free survival; RP2D: recommended phase II dose.

yet been updated, the recently updated and published ASCO guidelines recommend adjuvant capecitabine for six months following radical resection of CCA or GBC [50-52]. Of note, the ASCO guidelines authors also stated that the role of adjuvant chemoradiotherapy remains unclear in this setting, suggesting the use of this approach for patients with R1 resection and eCCA – based on the results of the SWOG SO809 phase II trial conducted by Ben-Josef and colleagues [53].

Ongoing clinical trials

Despite all the criticisms regarding the results of the BILCAP study, this trial has undoubtedly changed the treatment landscape of adjuvant therapy in BTC, by establishing capecitabine as novel standard of care. However, several unanswered questions remain, since relapse rate remains sadly high, and further studies are needed to explore novel and more effective treatment strategies [54,55]. In fact, a plethora of clinical trials is currently ongoing, aimed at further assessing the role of adjuvant therapy in BTC (Table 2). Of note, different therapeutic approaches are under evaluation, including the use of targeted therapies and immune checkpoint inhibitors (ICIs) in combination with other anticancer agents.

The phase III ACTICCA-1 trial (NCT02170090) is randomizing resected BTC patients to CisGem (the reference doublet in first-line setting) or to capecitabine (the current standard regiment in the adjuvant setting); the aim of this study is to assess the superiority of the doublet regimen over the oral monotherapy, with RFS as primary endpoint [56]. The study has a planned enrollment of 781 patients with an estimated primary completion date in April 2021; the patient population of this trial includes GBCs and CCAs.

A South Korean randomized phase II trial (NCT03079427) is performing a similar analysis, comparing CisGem versus capecitabine in patients with resected lymph node-positive eCCA. The schedules of the two treatment arms derive from ABC-02 and BILCAP studies: gemcitabine 1000 mg/m^2 plus cisplatin 25 mg/m^2 day 1 and 8, every three weeks, and capecitabine 1250 mg/m^2 day 1 to 14, every 3 weeks, respectively. The 2-year disease-free survival (DFS) is the primary endpoint of the study, which has DFS, toxicities, and OS as secondary endpoints. The study has been planned to enroll 100 eCCA patients.

The GEMOX regimen is currently being assessed in comparison with capecitabine in a randomized Chinese phase III trial (NCT02548195) on resected iCCAs. The study has a planned enrollment of 286 patients with RFS as primary endpoint, and OS and toxicities as secondary endpoints. In the same patient population of iCCAs, an open-label phase II trial (NCT04077983) is evaluating the role of adjuvant nab-paclitaxel combined with gemcitabine after radical resection. The study has a planned enrollment of 40 patients with an estimated study completion date in September 2022.

Another chemotherapeutic doublet, the combination of gemcitabine with capecitabine is being compared versus capecitabine monotherapy in the open-label, randomized phase III AdBTC-1 trial (NCT03779035)

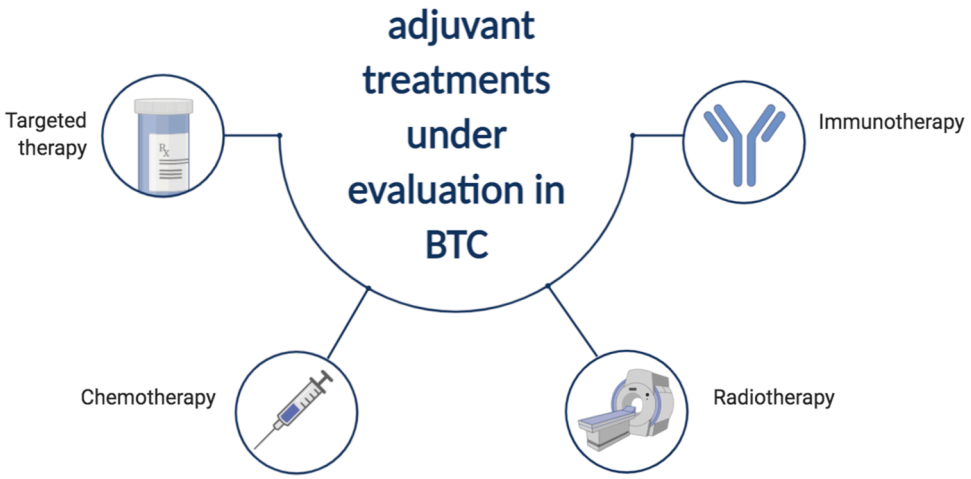

Fig. 1. Schematic representation of the main adjuvant therapies under evaluation in resected biliary tract cancer. *Abbreviations: BTC, biliary tract cancer.*

including GBC and CCA patients. RFS represents the primary outcome of the study, having a planned enrollment of 460 participants.

Recent years have witnessed the emerging of the molecular landscape of BTCs, with novel molecularly targeted therapies entering in clinical practice, such as fibroblast growth factor receptors (FGFR) and isocitrate dehydrogenase (IDH) inhibitors [57-65]. Thus, the role of targeted agents is under evaluation also in the adjuvant setting, trying to translate the evidence observed in metastatic disease (Fig. 1). A single-center Chinese phase II study (NCT03702491) is randomizing resected GBC patients to apatinib combined with SOX regimen (tegafur plus oxaliplatin) versus SOX alone; PFS is the primary endpoint of this trial, which has a planned enrollment of 138 patients. The same tyrosine kinase inhibitor, apatinib, is currently being evaluated in a randomized, open-label, phase II trial (NCT03609489) comparing the combination of apatinib plus capecitabine versus capecitabine monotherapy as adjuvant treatment; PFS is the primary endpoint of this study.

Since immunotherapy has radically changed previous treatment paradigms in several hematological and solid tumors, the role of ICIs is under assessment also in BTC, in the advanced as well as in the adjuvant setting [66-73]. With regard to the latter, an ongoing phase II trial (NCT04295317) is enrolling resected iCCA patients to receive the programmed cell death protein 1 (PD-1) inhibitor SHR-1210 plus capecitabine as adjuvant treatment. The study presents a planned enrollment of 65 patients with an estimated study completion date in February 2024. Lastly, a phase I study (NCT04608786) is evaluating the role of the experimental PD-L1 inhibitor ZKAB001 combined with capecitabine as adjuvant therapeutic approach for BTCs after radical resection.

Conclusions

In the last three years, the results of three multicenter, randomized phase III trials on adjuvant systemic treatment in resected BTCs have been published, with the BILCAP trial representing a novel standard of care in this setting. Although we are witnessing a new era in BTC management, several issues remain, and future efforts in designing clinical trials evaluating adjuvant therapies in BTC should be focused on specific patient and tumor characteristics [74-80]. Results of ongoing prospective clinical trials are awaited and will provide further information regarding the role of adjuvant systemic treatment, in the hope of improving RFS and OS of resected BTC patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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