Biliary Tract Cancer Management

Subjects: Oncology

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Biliary tract cancers (BTC) comprise a group of malignancies originating in the epithelium of the biliary tract. These include cholangiocarcinoma (CCA) and gallbladder carcinoma (GBC). Intrahepatic cholangiocarcinoma or iCCA refers to tumors proximal to the second-order ducts, while extrahepatic cholangiocarcinoma or eCCA refers to tumors arising more distally (perihilar CCA, between second-order ducts and cystic duct and distal CCA, distal to cystic duct). Perihilar CCA represents 50% of the total CCAs, with distal lesions comprising 40% and the final 10% being intrahepatic. BTC are often diagnosed at advanced stages and have a grave outcome due to limited systemic options. Gemcitabine and cisplatin combination (GC) has been the first-line standard for more than a decade. Second-line chemotherapy (CT) options are limited. Targeted therapy or TT (fibroblast growth factor 2 inhibitors or FGFR2, isocitrate dehydrogenase 1 or IDH-1, and neurotrophic tyrosine receptor kinase or NTRK gene fusions inhibitors) have had reasonable success, but <5% of total BTC patients are eligible for them. The use of immune checkpoint inhibitors (ICI) such as pembrolizumab is restricted to microsatellite instability high (MSI-H) patients in the first line. The success of the TOPAZ-1 trial (GC plus durvalumab) is promising, with numerous trials underway that might soon bring targeted therapy (pemigatinib and infrigatinib) and ICI combinations (with CT or TT in microsatellite stable cancers) in the first line.

cholangiocarcinoma | gall bladder cancer | FGFR2 | pemigatinib | infrigatinib | HER2 | durvalumab | gemcitabine | NTRK | IDH

1. Introduction

Biliary tract cancers (BTC) comprise a group of malignancies originating in the epithelium of the biliary tract [1]. These include cholangiocarcinoma (CCA) and gallbladder carcinoma (GBC). Intrahepatic cholangiocarcinoma or iCCA refers to tumors proximal to the second-order ducts, while extrahepatic cholangiocarcinoma or eCCA refers to tumors arising more distally (perihilar CCA, between second-order ducts and cystic duct and distal CCA, distal to cystic duct) [2]. Perihilar CCA represents 50% of the total CCAs, with distal lesions comprising 40% and the final 10% being intrahepatic [3]. BTCs are relatively rare in developed countries, comprising approximately 3% of gastrointestinal malignancies with an incidence of 0.35 to 2 in 100,000 [4]. In developing countries such as China and Thailand, the incidence can be as high as 14–80 in 100,000. GBCs are less common, with an incidence of 1 in 100,000 in the USA but increasing as high as 27 in 100,000 in Chile [5][6]. Risk factors for CCAs include primary sclerosing cholangitis, choledochal cysts, cholelithiasis, hepatolithiasis, chronic liver disease, genetic conditions such as Lynch syndrome, BRCA mutations, cystic fibrosis, biliary papillomatosis, and liver fluke infection in endemic regions [7][8]. Risk factors for GBC include cholelithiasis, chronic infection with pathogens such as

salmonella and Helicobacter pylori, obesity, and anatomical changes in the biliary tree [9]. The continued rise of CCAs, specifically iCCA, in the past four decades globally is concerning [10][11][12]. Its association with metabolic and infectious risk factors might be the primary reason for this dangerous trend.

A lack of robust screening measures, late diagnosis (unresectable to metastatic), challenging histology at presentations combined with limited systemic options, the high recurrence rate after surgery, and unreliable biomarkers to monitor the treatment response contribute to poor outcomes in BTCs [13]. Surgical management is curative in early-stage BTC, but it is feasible in only a small fraction of cases (≈30%) [14][15]. Therefore, the majority of the patients must be treated with systemic therapy and palliative intent. Even with resection, 3-year recurrence rates can be as high as 80% [16]. Liver transplant is approved for certain unresectable hilar or perihilar eCCA (≤3 cm, absent nodal and intra or extrahepatic metastatic disease and no biopsy) only [17].

2. Chemotherapy in Biliary Tract Cancers

2.1. Chemotherapy in the First Line

Over 70% BTCs present in advanced stages or aBTC (unresectable or metastatic) and are only eligible to receive palliative therapy. The combination of gemcitabine (Gem) and cisplatin (Cis), or GC, is the current approved first-line therapy [18]. There were no positive first-line trials for over a decade. The standard approach to BTCs is illustrated in **Figure 1**.

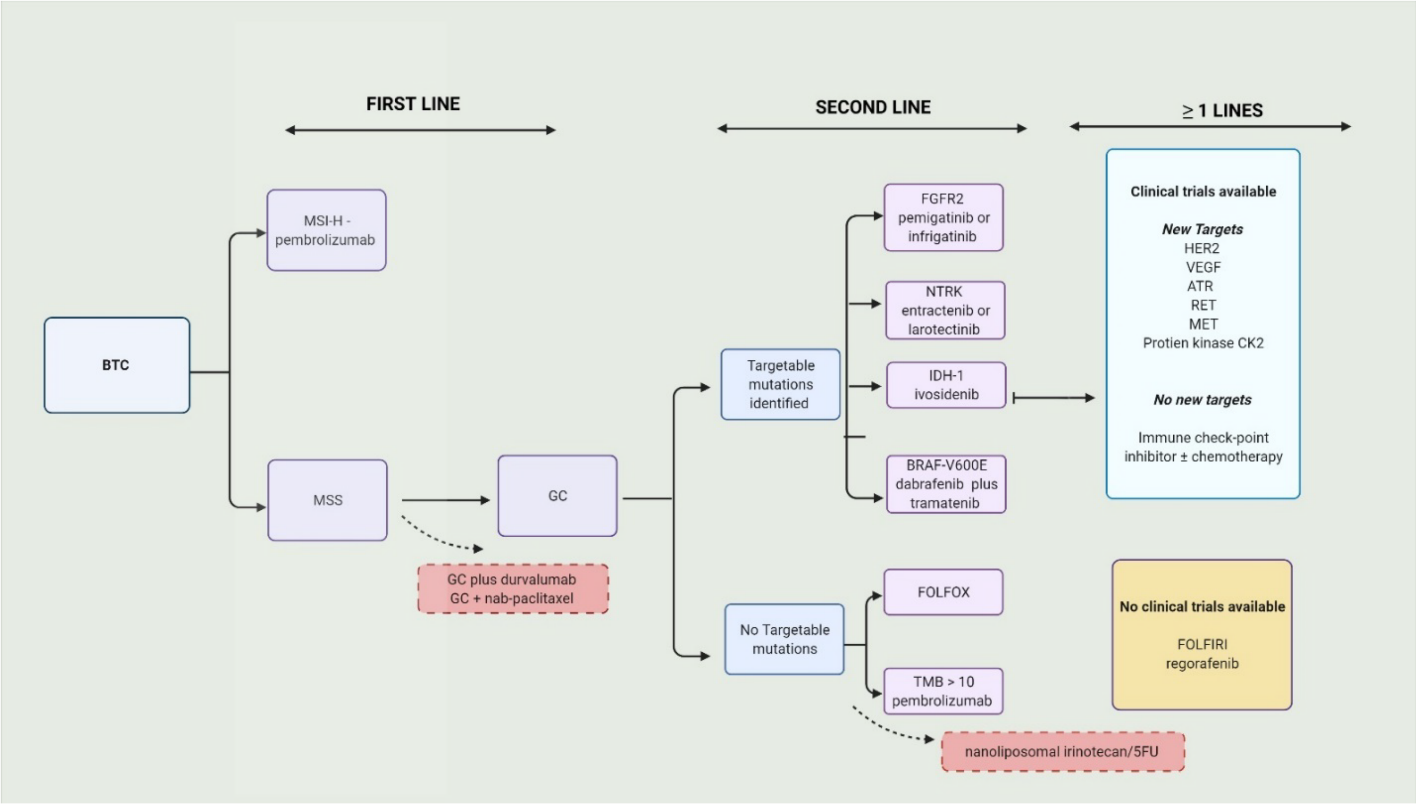

Figure 1. Current approach to biliary tract cancers. BTC—biliary tract cancers; MSI-H—microsatellite instability; MSS—microsatellite stable; GC—gemcitabine/cisplatin; FGFR2—fibroblast growth factor 2; IDH—isocitrate dehydrogenase-1; NTRK—neurotrophic tyrosine receptor kinase; HER2—human epidermal growth factor receptor 2 inhibitors; VEGF—vascular endothelial growth factor; TMB—tumor mutational burden; ATR—ataxia telangiectasia mutated and Rad3-related.

In ABC-01, a phase II randomized trial, GC combination was compared to Gem alone in treatment-naïve aBTC patients [19]. The tumor response rates (28% vs. 23%), time to progression (8 months vs. 4 months), and 6-month progression-free survival or PFS rate (57% vs. 46%) were higher in the combination group. GC approval in the first line was based on the ABC-02 trial, a phase III randomized control trial in which GC was compared to Gem alone. The median overall survival or OS (11.7 months vs. 8.1 months; hazard ratio or HR = 0.64; $p < 0.001$) and the median PFS (8 months vs. 5 months; HR = 0.63; $p < 0.001$) was higher in the GC group. The tumor control (complete response (CR) or partial response (PR) or stable disease (SD)) was also higher in the GC group (81% vs. 72%; $p = 0.04$). The tolerance profile was comparable between both groups, except for neutropenia (higher with GC).

The combination of oxaliplatin, irinotecan, and infusional fluorouracil (mFOLFIRINOX) was inferior to GC in the first-line setting, as evidenced by the PRODIGE 38 AMEBICA trial [20]. In this randomized phase II/III trial, the 6-month PFS rate (44.6% in mFOLFIRINOX vs. 47.3% in GC), PFS (6.2 m vs. 7.4 m), and OS (11.7 m vs. 13.8 m) were superior in the GC group. A partially activated monophosphorylated Gem compound, NUC-1031, that can overcome the resistance developed against Gem, was tested in the first line for aBTC [21]. This compound does not need a nucleoside transporter to enter the cell, has enzyme-mediated activation, and resists degradation by cytidine deaminase [22]. Although early trials with NUC-1031 plus Cis had a greater objective response rate or ORR over GC (44% vs. 26%), the phase III trial was discontinued as the interim analysis showed that it would be unlikely to meet its primary end-point of 2.2 months superiority in OS compared to GC [21]. In the BREGO trial, Regorafenib (Reg) and GEMOX (gemcitabine and oxaliplatin combination) were compared to GEMOX alone in aBTC [23]. The overall results were unsatisfactory (the Reg-GEMOX group was not superior to the GEMOX-only group for PFS or OS). Subgroup analysis showed a higher disease control rate (or DCR), PFS, and OS in patients who continued Reg beyond four cycles.

The addition of nab-paclitaxel (NP) to GC (GC/NP) in the first line had encouraging results in a single-arm phase II trial [24]. The hematological toxicity was very high in the first 32 (of 60) patients enrolled in the trial who received Gem (1000 mg/m^2), Cis (25 mg/m^2), and NP (125 mg/m^2) on days 1 and 8 of 21-day cycles. The doses of Gem and NP were dropped to 800 and 100 mg/m^2, respectively, for the next 28 patients. The median PFS was 11.8 months and the median OS was 19.2 months. DCR (PR plus SD) was superior in the high-dose group (90% vs. 78% in reduced dose). Comparing GC and GC/NP is not ideal (no head–head trials), but GC/NP seems to have a better OS and PFS, and worse neutropenia and anemia, based on observations from the respective published trial data [18][24].

In a Korean retrospective review from four medical centers, the safety and efficacy of GC/NP in treating aBTC was reported last year [25]. The authors looked at the outcomes (ORR, DCR, PFS, and OS) in two groups of patients based on when they received GC/NP: a) in the first line; b) NP was added to GC before or after disease progression (PD). The former group's ORR (48% vs. 31%) and DCR (90% vs. 75%) were superior. The ORR (40% vs. 16%) and DCR (86% vs. 60%) were greater when NP was added before PD in the latter group. The safety profile was acceptable in these patients and, as expected, Grade 3/4 events were lower in patients who received a reduced dose of GC/NP. A phase III randomized trial (SWOG1815, NCT03768414) is underway to examine the benefit of adding NP to GC in aBTC (GC/NP vs. GC). GC plus S-1 (an oral fluoropyrimidine derivative) combination has a survival benefit over GC in treating aBTCs [26]. The preliminary data of KHBO1401-MITSUBA, a phase III randomized trial, showed improved OS (13.5 months vs. 12.6 months), PFS (7.4 months vs. 5.5 months), and response rates (41% vs. 15%) in the triplet group compared to the GC group.

In the TOPAZ-1 trial, phase III randomized, double-blind, placebo-controlled GC plus durvalumab (ICI) or GC-D was compared to GC plus a placebo [27]. Patients received GC-D for eight cycles (days 1 and 8, Q3W) followed by durvalumab only or placebo Q4W. The mOS 12.8 months vs. 11.5 months (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.66–0.97; $p = 0.021$), mPFS 7.2 months vs. 5.7 months (HR, 0.75; 95% CI, 0.64–0.89; $p = 0.001$), and ORR (26.7% vs. 18.7%) was superior in GC-D compared to the GC group. G3/4 AEs were similar in both groups. While the results of the GC-D combination are promising, the researchers need to wait for the full study data to make reliable conclusions. The results of other clinical trials are discussed in **Table 1**.

2.2. Chemotherapy in the Second Line

In aBTC (and ampullary cancers), patients who progressed on GC with a preserved performance status (Eastern Cooperative Oncology Group or ECOG scale of 0–1), FOLFOX had a small OS benefit (6.2 months vs. 5.3 months; adjusted hazard ratio = 0.69 [95% CI 0.50–0.97]; $p = 0.031$) compared to supportive care [28]. The survival rate was higher in the FOLFOX group at 6 months (51% vs. 36%) and 1 year (26% vs. 11%). Subgroup analysis in this trial produced some interesting results. The OS (not PFS) was superior with FOLFOX among the platinum-sensitive (PD after 90 days of completion of first-line chemotherapy) and platinum-resistant/refractory (PD on the first line or in less than 90 days after completion of first-line chemotherapy). Expectedly, high-grade AE were more prevalent in the FOLFOX group (69% vs. 52%). A retrospective study in Italy examined the differences in outcomes after second-line chemotherapy (post-GC) between elderly (≥70 years) and younger (<70 years) patients. There were no significant differences in the outcomes (OS or PFS) between the two groups. The most-used second-line agents in the elderly population were Gem alone or capecitabine alone or a combination of both. Treatment-related toxicity was very high in the elderly population compared to the younger group (48.5% vs. 8.2%; OR 6.31; $p < 0.001$) [29].

A combination of nanoliposomal irinotecan (Nan-Iri) and 5FU was compared to 5FU alone in the NIFTY trial [30]. It was a multicenter, open-label, randomized, phase IIb trial in which patients progressed on GC. The combination group had a superior PFS (7.1 m vs. 1.4 m; HR = 0.56; 95% CI 0.39–0.81; $p = 0.0019$) and ORR (19.3% vs. 2.1%) compared to the 5FU group. G3-4 neutropenia (24% vs. 1%) and serious adverse events (42% vs. 24%) occurred more in the combination group than the 5FU-only group. It was concluded that Nan-Iri plus 5-FU could be

considered for second-line treatment in patients with BTC who formerly progressed on GC, especially in patients who cannot tolerate platinum agents. On the other hand, mFOLFIRINOX had reasonable efficacy and safety for patients who progressed on GC (≥3 cycles) and is an option for patients with no targetable mutations [31].

3. Targeted Therapy in Biliary Tract Cancers

Second-line options in patients who progressed on GC are limited. In the subset of patients with targetable mutations, fibroblast growth factor 2 (FGFR2) inhibitors such as those with pemigatinib and infrigatinib [32], neurotrophic tyrosine receptor kinase (NTRK) gene fusions such as larotrectinib and entrectinib [33][34], and isocitrate dehydrogenase 1 (IDH-1) with ivosidenib [35], are suitable agents which are preferred over chemotherapy in the second line (preferably after GC). Individual targeted therapy options will be discussed in the following text. The reported results of trials and ongoing trials with targeted therapy are summarized in **Table 1** and **Table 2**.

Table 1. Results of recent trials in biliary tract cancer.

Line	Phase (N)	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Target of the Drug (If Applicable)	Comparative Arm	Primary Outcome Studied in the Trial	Top 3 Treatment-Related Adverse Events	Notes
First line	III	NCT03875235 [27]	BTC	Durvalumab (D) + GC	PD-1	GC + placebo (Pbo)	OS—12.8 m vs. 11.5 m (D vs. Pbo, HR = 0.80; 95% CI, 0.66–0.97; *p* = 0.021)	Anemia Low neutrophil count Low platelet count	PFS-7.2 m vs. 5.7 m (D vs. Pbo, HR, 0.75; 95% CI, 0.64–0.89; *p* = 0.001); ORR—26.7% vs. 18.7% (D vs. Pbo); Grade 3/4—62.7% vs. 64.9% (D vs. Pbo)
	II	NCT03796429 [36]	BTC	Toripalimab + GC	PD-1	Single arm	PFS—6.7 m OS—NR	Leukopenia Anemia Rash	ORR—21 DCR—85% G3/4, non-hematological

Line	Phase (N)	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Target of the Drug (If Applicable)	Comparative Arm	Primary Outcome Studied in the Trial	Top 3 Treatment-Related Adverse Events	Notes
									in 20% and hematological—69%
	II	NCT03951597 [37]	iCCA	Toripalimab + lenvatinib + GemOx +	PD-1 + TKI	Single arm	ORR—80% (1CR and three patients obtained enough control to allow for resection)	Jaundice Rash Proteinuria	DCR—93.3%, PFS—10 m OS—NR DOR—9.8 m
	II	NCT04361331 [38]	iCCA	Lenvatinib + GemOx	TKI	Single arm	ORR—30% 1/30 was down staged to have resection	Fatigue Jaundice Vomiting	PFS and OS—NR DCRc—87% No G5, ≥G3 in 40%
	Ib II	NCT02992340	BTC	Varlitinib + GC	Pan-HER 2	Single arm	DLT—1/11 (200 mg); 1/12 (300 mg)	blood and lymphatic system disorders	PR = 8/23; SD = 12/23 ORR—35%, DCR—87%, DoR—4 m, PFS—6.8 m
	Ib II	NCT02128282 [39]	CCA	Silmitasertib (CX-4945) + GC	Casein kinase 2 (CK2)	Single arm	PFS 11 m	Diarrhea Neutropenia Nausea	Compared to GC—Better PFS

Line	Phase (N)	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Target of the Drug (If Applicable)	Comparative Arm	Primary Outcome Studied in the Trial	Top 3 Treatment-Related Adverse Events	Notes
									Lesser neutropenia
	I	NCT02375880 [40]	BTC	DKN-01 + GC	Dickkopf-1 (DKK1)	Single arm	Safety—no DLT	Neutropenia Thrombocytopenia Leukopenia	ORR—21.3% PFS—8.7 m
Subsequent lines	III	NCT02989857 (ClarIDHy) [41]	CCA	Ivosidenib (IVO)	IDH-1	IVO alone vs. placebo	PFS—2.7 m vs. 1.4 m (HR = 0.37; 95% CI 0.25–0.54; $p < 0.0001$).	Ascites Fatigue Anemia	OS in updated analysis 10.3 m IVO vs. 7.5 m (HR = 0.79; 95% CI 0.56–1.12; $p = 0.093$)
	II	NCT02966821 [42]	BTC	Surufatinib	VEGF	Single arm	PFS rate at 16 wks—46.33% (95%, 24.38–65.73)	Elevated bilirubin Hypertension Proteinuria	PFS—3.7 m OS—6.9 m
	II	ChiCTR1900022003 [43].	BTC	Anlotinib + sintlimab	TKI + PD-1	Single arm	OS—NR	Hypertension ** Diarrhea Hypothyroidism	PFS—6.5 m ORR—40% DCR—87%
	II	NCT02052778 [44].	iCCA #	Futibatinib	FGFR2	Single arm	ORR 37%	Hyperphosphatemia Diarrhea *	DoR—8.3 m and DCR = 82%

Line	Phase (N)	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Target of the Drug (If Applicable)	Comparative Arm	Primary Outcome Studied in the Trial	Top 3 Treatment-Related Adverse Events	Notes
								Dry mouth *	
	II	NCT03230318 [45]	iCCA	Derazantinib	FGFR2—mutations and amplifications	Single arm	3-month PFS rate—76%	Not specified	DCR = 80% PFS = 7.3 m 6-month PFS rate = 50%
	II	NCT03797326 [46]	BTC #	Pembrolizumab + lenvatinib	PD-1 + TKI	Single arm	ORR—10% Safety—TRAE in 97% (>G354%)	Hypertension Dysphonia Diarrhea	DCR—68% PFS—6.1 m OS—8.6 m
									CR = 0, PR—

Line	Phase	Clinical Trial Identifier	Target of the Drug	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
First line	III	NCT03773302	FGFR rearrangement	CCA	Pemigatinib	GC	PFS	OS, OR, DOR, DCR
	III	NCT03773302	FGFR2 fusion/translocation	CCA	Infrigatinib	GC	PFS	OS. DCR, DOR, BOR
	III	NCT04093362	iCCA with FGFR2	iCCA	Futibatinib	GC	PFS	ORR. DCR. OS. Safety/Tolerability
	II	NCT03768414	Not specific	BTC	GC/NP	GC	OS	PFS, ORR, DCR
	II	NCT03579771	High risk *	Resectable IHC	GC/NP	None	SR	RR, R0; OS; PFS
Subsequent lines	II	NCT04722133	HER 2	aBTC	Trastuzumab-pkrb + FOLFOX	None	ORR	PFS, OS, DCR, incidence of TRAE

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Line	Phase	Clinical Trial Identifier	Target of the Drug	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
	II	jRCT2031180150	HER 2	Advanced solid tumors [#]	Trastuzumab and pertuzumab	None	ORR	PFS, OS, DoR, safety
	II	NCT02091141 (My Pathway)	HER 2	BTC [#]	Trastuzumab and pertuzumab	None	ORR	DCR, PFS, OS, AE
	II	NCT04466891	HER 2	BTC	Zanidatamab monotherapy	None	ORR	DoR; DoR > 16 wks; DCR, PFS, OS; incidence of TRAE, PK
	II	NCT02999672	HER 2	CCA [#]	Trastuzumab emtansine	None	BOR	PFS, OS, TRAE, SAE, PK
	II	NCT04482309	HER2	BTC [#]	Trastuzumab deruxtecan	None	ORR	DOR, DCR, PFF, OS, AEs, PK and immunogenicity
	II	NCT03839342.	Non-V600E BRAF mutations	Advanced solid tumors [#]	Bimimetinib + encorafenib	None	ORR	Safety, DCR, PFS
	II	NCT02428855	IDH1 mutation	iCCA	Dasatinib	None	ORR	PFS, OS, TRAE
	II	NCT02675829	HER2 amplification	Advanced solid tumors [#]	Ado-Trastuzumab emtansine	None	ORR	None

Line	Phase	Clinical Trial Identifier	Target of the Drug	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
	II	NCT03207347	BAP1 and other DDR genes	CCA #	Niraparib	None	ORR	PFS, OS, TRAE
	II	NCT03212274	IDH1/2 mutation	CCA	Olaprib	None	ORR	PFS, OS, safety
	II	NCT04042831	DNA repair gene mutation	BTC	Olaparib	None	ORR	OS, PFS, TRAE, DoR
	II	NCT03207347	DNA repair gene mutation	CCA #	Niraparib	None	ORR	OS, PFS, TRAEs
	II	NCT02162914	VEGF mutation	CCA	Regorafenib	None	PFS	RR, OS
	II	NCT03339843	CDK 4/6 mutation	CCA #	Abemaciclib	None	Anti-tumor activity	PFS, OS, toxicity
	II	NCT04003896	CDK 4/6 mutation	BTC	Abemaciclib	None	ORR	PFS, DCR, OS, QoL
	II	NCT02232633	STAT3 inhibitor	CCA	BBI503	None	DCR	ORR, OS, PFS, PK TRAE
	II	NCT03878095	IDH1/2 mutation	CCA #	Ceralasertib + olaparib	None	ORR	PFS, OS, DoR, Safety
	I/II	NCT02273739	IDH2 mutation	Advanced solid tumors #	Enasidenib Enasidenib	None	DLT, ECOG	Plasma concentration metrics

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Line	Phase	Clinical Trial Identifier	Target of the Drug	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
	I	NCT04764084	HRR mutations	CCA #	Niraparib + anlotinib	None	DLT, MTD	ORR, PFS
	I	NCT04521686	IDH1 R132-mutant advanced solid tumor types or circulating tumor DNA IDH2 R140 or IDH2 R172 mutation (CCA)	CCA #	LY3410738 LY3410738 + GC		Maximum tolerated dose	ORR Safety and tolerability Efficacy PK properties
	I	NCT02381886	IDH1 mutation	BTC #	IDH305	None	DLT	TRAE, PK, delta 2-hydroxyglutarate, ORR, SAE
	I	NCT03272464	BRAF-V600E	BTC #	JSI-1187 + dabrafenib	None	TRAE	DOR, OS, PFS, TTP
	I	NCT04190628	BRAF-V600E	BTC #	ABM-1310 + cobimetinib	None	MTD	TRAE, PK, DOR, OS, PFS, TTP
	I	NCT02451553	No specific target	BTC #	Afatinib dimaleate + capecitabine	None	AE, DLT, MTD	DOR, OS, PFS, RR, TTP, biomarker profile
	I	NCT03507998	Wnt/β-catenin signaling inhibitors	BTC #	CGX1321	None	TRAE	PK

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Biliary tract cancers include gall bladder cancers and CCA; iCCA—intrahepatic cholangiocarcinoma; eCCA—extra-

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4. Immunotherapy in Biliary Tract Cancers

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In the current clinical practice, immunotherapy can be broadly divided into ICIs and less explored adoptive cell therapy (chimeric antigen receptor T cell therapy or CAR-T) and vaccines. Reported results and ongoing trials with immunotherapy are summarized in **Table 1** (above) and **Table 3** (below).

Table 3. Ongoing trials with immunotherapy in biliary tract cancer.

Line	Phase	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
First line	III	NCT04003636	BTC	Pembrolizumab + GC	GC + placebo	OS	PFS, ORR, DOR
	II/III	NCT04066491	BTC	Bintrafusp alfa	GC + placebo	OS DLT	PFS, DOR, ORR
	II	NCT04217954	BTC	HAIC (oxaliplatin + 5-FU) + toripalimab (T) + bevacizumab	None	PFS, ORR	OS, AE, CA 19-9, DCE-MRI signal change, DWI MRI signal change

21, 13, 175883592110359.

Line	Phase	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
	II	NCT04172402	BTC	TS-1 + gemcitabine + nivolumab	None	ORR	None specified
	II	NCT03898895	iCCA	Camrelizumab + radiotherapy	GC	PFS	OS, AE, tumor response
	III	NCT03478488	BTC	KN035 (PD-L1 antibody) + gemcitabine + oxaliplatin	GEMOX	OS	PFS, ORR, DCR, DOR, TTP
	II	NCT03796429	BTC	Gemcitabine/S-1 + toripalimab	None	PFS, OS	ORR, Safety
	II	NCT04027764	BTC	Toripalimab + S1 and albumin paclitaxel	None	ORR	PFS, DCR, OS
	II	NCT04191343	BTC	Toripalimab + GEMOX	None	ORR	None specified
	II	NCT04300959	BTC	Anlotinib hydrochloride + PD1 + gemcitabine + cisplatin	Gemcitabine Cisplatin	OS 1 yr	OS 2 yr, PFS, ORR, AE

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Line	Phase	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
Subsequent lines	II	NCT03482102	HCC, BTC	Tremelimumab + durvalumab + radiation	None	ORR	AE, OS, DCR, PFS, DOR, TTP
	II	NCT04238637	BTC	Durvalumab (D) vs. D + T	None	ORR	Safety, DoR, PFS, OS
	II	NCT02821754	HCC, BTC	D + T	D +T + TACE D + T + RFA D + T + Cryo	PFS	Safety
	II	NCT02703714	BTC	Pembrolizumab and sargramostim (GM-CSF)	None	ORR	AE, PD-L1 positivity, PFS, OS, DOR
	I/II	NCT03937895	BTC *	Allogeneic natural killer cells + pembrolizumab	None	Phase I—DLT Phase II—ORR	TTP, toxicity
	II	NCT04306367	BTC	Pembrolizumab and olaparib	mFOLFOX-historical control	ORR	DOR, PFS, OS, safety

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Line	Phase	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
	II	NCT04295317	iCCA—adjuvant	PD-1 blocking antibody SHR-1210 + capecitabine	None	PFS	OS, side effects
	II	NCT03250273	BTC, PDA	Entinostat + nivolumab	None	ORR	Toxicity, PFS, OS, DOR
	II	NCT02866383	BTC, PDA	Nivolumab + ipilimumab + radiotherapy	Nivolumab + radiotherapy	CBR	AE, ORR, PFS, OS, QOL
	II	NCT04057365	BTC	DKN-01 + nivolumab	None	ORR	PFS, OS
	II	NCT03639935	BTC	Rucaparib + nivolumab	None	4-month PFS rate	Response rate, PFS, OS
	II	NCT04299581	iCCA	Camrelizumab + cryo	None	ORR	DOR, PFS, OS, DCR, AE
	II	NCT03999658	BTC [#]	STI-3031 anti-PD-L1 antibody	None	ORR	DOR, CR, PFS, 1-year PFS rate, correlative studies

s with advanced refractory biliary tract cancer (BTC): An open-label, dose-escalating, and dose-expansion cohort of phase Ib trial. J. Clin. Oncol. 2021, 39, 292.

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Line	Phase	Clinical Trial Identifier	Treated Cancer Group	Experimental Arm	Comparative Arm	Primary Outcome	Secondary Outcome (Main)
	II	NCT03801083	BTC	Tumor infiltrating lymphocytes (TIL) + aldesleukin	None	ORR	CRR, DOR, DCR, PFS, OS, QOL
	I/II	NCT03684811	BTC #	FT-2102 vs. FT-2102 + nivolumab	None	DLT, Dose, ORR	ORR, AE, PFS, TTP, DOR, OS, TT
	I/II	NCT03475953	BTC #	Regorafenib + avelumab	None	I = dose II = antitumor activity	MTD, DLT, toxicity, AE, PK and correlative studies
	I/II	NCT03785873	BTC	Nal-Irinotecan + nivolumab + 5-Fluorouracil + leucovorin	None	I = DLT II = PFS	AE, ORR, OS
	I	NCT03849469	iCCA #	XmAb®22841 and pembrolizumab	XmAb®22841 Monotherapy	Safety and tolerability	None
	I	NCT03257761	BTC, PDA, HCC	Guadecitabine + durvalumab	None	AE, Tumor response	OS, PFS

64. Hashimot
Yoshida, T.; Ohnishi, T.; et al. A case of curatively resected advanced intrahepatic cholangiocellular carcinoma through effective response to neoadjuvant chemotherapy. Gan Kagaku Ryoho 2014, 41, 2083–2085.

BTC—biliary tract cancers, includes gall bladder cancer and CCA; iCCA—intrahepatic cholangiocarcinoma; eCCA—extrahepatic cholangiocarcinoma; CCA—cholangiocarcinoma includes iCCA and eCCA; PDAC—pancreatic cancer; HCC—hepatocellular carcinoma; FGFR2—fibroblast growth factor 2; IDH—isocitrate dehydrogenase-1; VEGF—vascular endothelial growth factor; HER2—human epidermal growth factor receptor 2 inhibitors; HHR—homologous recombination repair; GC—gemcitabine/cisplatin; GM-CSF—granulocyte-macrophage colony-stimulating factor; TACE—transcatheter arterial chemoembolization; RFA—radiofrequency ablation; Cryo—cryotherapy; HAIC—hepatic arterial infusion chemotherapy; CPS—combined positive score; MSI-H—microsatellite instability; DCE—dynamic contrast enhanced; DWI—diffusion weighted imaging; TTP—time to progression; CBR—clinical benefit rate; QOL—quality of life; TTR—time to response; * basket trials with BTC among them; ** at least 1% CPS PD-L1 or MSI-high or dMMR positive.

5. Systemic Therapy in Early-Stage Biliary Tract Cancers

Capecitabine is the preferred agent for AT in BTCs based on the BILCAP trial [54]. On the other hand, BCAT and PRODIGE 12 trials could not show the clinical benefit of gemcitabine or gemcitabine/oxaliplatin combination over observation [55][56][57]. A recently presented pooled analysis of these two trials further proved this point [58]. A total of 419 patients were included in the two studies, which showed no difference in PFS (2.9 years in gem-based vs. 2.1 years in observation; HR = 0.91; p = 0.45) or OS (5.1 years vs. 5 years; HR = 1.03; p = 0.83). Radiation alone (XRT) or chemoradiation (CRT) in the adjuvant setting is not a popular approach in managing BTC. CRT is offered to eCCA and GBC patients with positive margins, lymph nodes [59][60][61]. Retrospective studies showed benefits with chemotherapy only in resected BTCs, but it is difficult to compare the AT strategies as SBRT or XRT is offered to BTCs with high-risk factors (positive margins/lymph nodes) [62].

Neoadjuvant (NAT) systemic therapy is not a standard approach in resectable BTCs. Some case reports and retrospective studies show the benefit of NAT downstaging the locally advanced or unresectable BTCs enough to have resection [63][64][65]. The addition of pre-operative radiation can increase the probability of R0 resection in these tumors [66][67]. On the other hand, NAT did not result in any survival advantage in managing resectable BTCs in the reported studies [68]. Multiple trials investigating the role of neoadjuvant therapy in resectable (GC-D in NCT04308174 or DEBATE; GC in NCT03673072; GC/NP in NCT03579771) and unresectable/locally advanced BTCs (FOLOXIRI in NCT03603834; toripalimab + GEMOX + lenvatinib in NCT0450628) are underway that may give us a definite answer in the coming years. In the current practice, systemic options typically for NAT are similar to those used for treating aBTCs (such as GC).

Locoregional therapy (LRT) with high-dose XRT (58–67.5 Gy in 15 fractions) and SBRT (30–50 Gy in 3 to 5 fractions) improves local control and OS in unresectable iCCA, and can be an option for suitable patients [69][70]. Other LRTs such as transcatheter arterial chemoembolization (TACE) and transarterial radioembolization (TARE) are not typically employed in treating BTCs. SBRT plus capecitabine combination increased local control rates (≈80%) with minimal toxicity (no ≥ grade 3 toxicity) in unresectable perihilar CCA [71]. Other trials intended to see the benefit of SBRT and chemotherapy combinations were closed due to low accrual (NCT01151761 and NCT00983541). ICI with TACE or SBRT, or TARE trials, are underway (NCT03898895, NCT04866836,

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NCT03937830, NCT02821754, NCT04238637, and NCT04708067), which may open up more options in the near future.