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REVIEW

Precision medicine for advanced biliary tract cancer in China: current status and future perspectives

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Abstract **Biliary tract cancer (BTC) is a rare group of malignancies that develop from the epithelial lining of the biliary tree and have a poor prognosis. Although chemotherapy is the standard of care for patients with advanced BTC in China, its clinical benefits are moderate. In recent years, the approval of targeted therapies and immunotherapies has provided new avenues for the management of advanced BTC. Nonetheless, the increasing number of personalized medicine approaches has created a challenge for clinicians choosing individualized treatment strategies based on tumor characteristics. In this article, we discuss recent progress in implementing precision medicine approaches for advanced BTC in China and examine genomic profiling studies in Chinese patients with advanced BTC. We also discuss the challenges and opportunities of using precision medicine approaches, as well as the importance of considering population-specific factors and tailoring treatment approaches to improve outcomes for patients with BTC. In addition to providing a comprehensive overview of current and emerging precision medicine approaches for the management of advanced BTC in China, this review article will support clinicians outside of China by serving as a reference regarding the role of patient- and population-specific factors in clinical decision-making for patients with this rare malignancy.**

Keywords biliary tract cancer; precision medicine; cholangiocarcinoma; China

Introduction

Biliary tract cancer (BTC) is a relatively rare group of malignancies encompassing a spectrum of tumors including cholangiocarcinoma, gallbladder cancer (GBC), and cancers of the ampulla of Vater [1].

Along with Chile, South Korea, and Japan, China is among the countries with the highest age-standardized incidence of BTC [2]. In 2019, the age-standardized incidence rate of BTC in China was 2.25 (95% confidence interval (CI), 1.52–2.79) per 100 000 men and 1.84 (95% CI, 1.10–2.41) per 100 000 women [3]. For comparison, the age-standardized incidence rate of BTC in the US between 2013 and 2017 ranged from 0.45 to 1.49 per 100 000 individuals [4]. In recent decades, the incidence of BTC has been increasing in China [5,6]. The age-standardized rates of incidence, prevalence, mortality, and disability-adjusted life years of BTC in China increased from 1990 to 2019, with an average annual percentage increase of 0.8% (95% CI, 0.6–1.0), 1.3% (95% CI, 1.1–1.5), 0.4% (95% CI, 0.2–0.6), and 0.2% (95% CI, 0.1–0.4), respectively [3].

Surgery is the first treatment option for 23%–65% of patients with newly diagnosed BTC in China [7]. However, tumor recurrence following surgery is common; relapse rates range from 42% for ampullary malignancies to 66%–68% for GBC and cholangiocarcinoma [8–10]. For many years, chemotherapy has been the standard of care for advanced BTC because of a lack of other effective therapies. Nevertheless, the clinical benefit of systemic chemotherapy in patients with non-resectable BTC is moderate. For example, the median overall survival (OS) of patients undergoing first-line

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treatment with gemcitabine and cisplatin-based chemotherapy is < 12 months [11]. Therefore, the prognosis for patients with BTC remains poor, and most patients have an OS of < 2 years from diagnosis [12,13]. Among Chinese patients with intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), and GBC, the latest estimates of 5-year survival rates are 13.8%–18.5%, 31.5%, and 16.4%, respectively [14].

In this article, we review recent progress in implementing precision medicine for advanced BTC in China and discuss future perspectives in this evolving field. This comprehensive review aims to improve the management of BTC in China by providing information to support clinicians in implementing personalized treatment decisions, as well as informing the tailoring of treatment strategies by considering population-specific factors to improve outcomes for patients with BTC in Western countries.

Etiology and pathogenesis

Although the etiology of BTC may vary among geographic regions and populations, risk factors identified in epidemiological studies involving large Chinese cohorts may help inform policies to prevent increases in the prevalence of BTC in other countries (Fig. 1).

Gallstones are the most important risk factor for BTC. A systematic review and meta-analysis of studies involving cohorts from Asia, Europe, and the US showed that, although gallstones were significantly associated with the risk of BTC in all geographic regions, the association was the strongest in Asia [15]. In addition, a population-based case-control study demonstrated that cholecystitis was the strongest risk factor for BTC in Chinese individuals [16], suggesting a role for inflammation in BTC development. In most Chinese patients with GBC, cholecystitis co-occurred with biliary stones, indicating that stones may play a crucial role in the link between cholecystitis and BTC [16]. Further supporting the role of the environment in BTC etiology, studies of cholangiocarcinoma indicated liver flukes as the main risk factor for BTC in East Asia, where parasitic infections with *Opisthorchis viverrini* and *Clonorchis sinensis* are endemic [17,18]. In contrast, primary sclerosing cholangitis is the most significant risk factor for cholangiocarcinoma development in Europe and the US [19,20]. Moreover, hepatitis B virus (HBV) infection and HBV-associated liver cirrhosis are significant risk factors for Chinese ICC in young patients but not in older individuals [21].

Metabolic syndrome, insulin resistance, and dyslipidemia have also been implicated as potential risk factors for BTC. A population-based case-control study conducted in Shanghai showed that metabolic syndrome was significantly associated with GBC (odds ratio (OR) = 2.75 (95% CI, 1.82–4.15)) [22]. Insulin resistance was also associated with GBC, although the association did not reach statistical significance (OR = 1.49 (95% CI, 0.95–2.34), P = 0.06). Serum lipids, including total triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol, have been identified as potential mediators of the association between diabetes and the risk of GBC [23].

Four types of precancerous lesions are well-known in

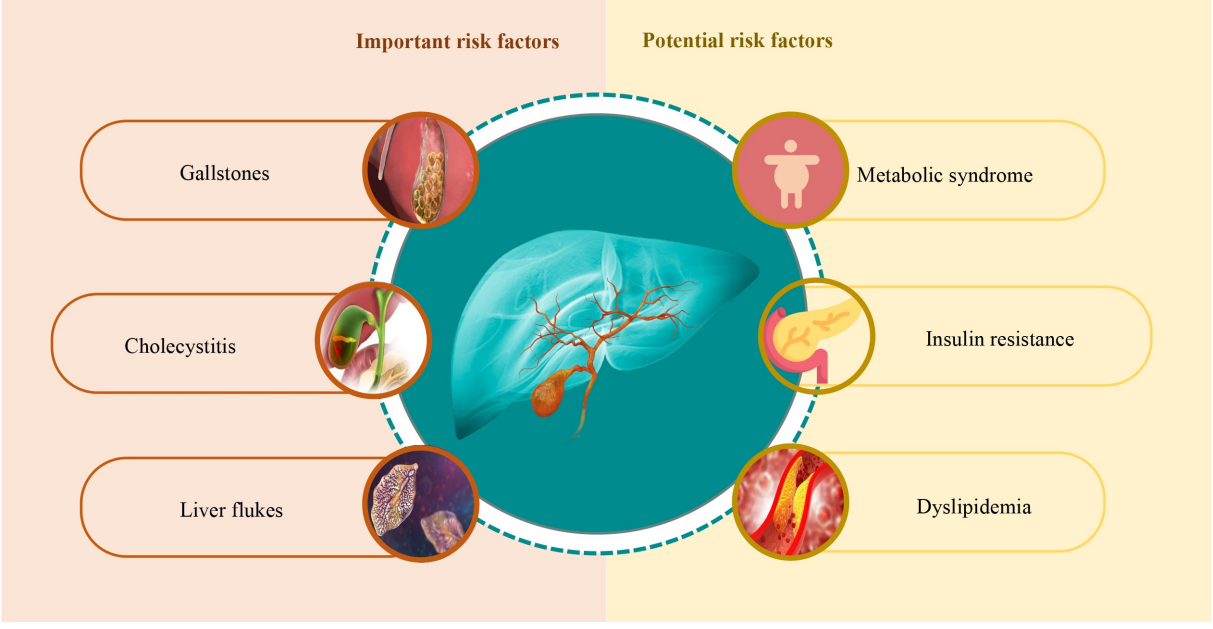

Fig. 1 The risk factors identified in Chinese BTC patients.

cholangiocarcinoma: the flat type (biliary intraepithelial neoplasia, BilIN), the papillary type (intraductal papillary neoplasm of the bile duct, IPNB), the cystic type (mucinous cystic neoplasm, MCN), and intraductal tubular neoplasm of the bile duct (ITNB) [24]. While for GBC, the premalignant lesions include adenoma, BilIN, and intracystic papillary neoplasm (ICPN) [24]. There is currently a lack of specific, high-quality analyses of disease occurrence and development in Chinese patients with BTC.

Chemotherapy

Chemotherapy is the traditional mainstay of treatment for unresectable or metastatic BTC, and the clinical guidelines for the management of unresectable or metastatic BTC in China are similar to those in the US and Europe. The combination of gemcitabine and cisplatin chemotherapy is the standard first-line treatment for advanced or metastatic cholangiocarcinoma and BTC, according to the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and Chinese Society of Clinical Oncology (CSCO) guidelines [1,25,26].

Only a small number of clinical studies have explored the role of new chemotherapy regimens in the first-line treatment of Chinese patients with advanced BTC (Table 1). The safety and efficacy of nab-paclitaxel plus gemcitabine and cisplatin were evaluated in a recent single-arm phase 2 study involving Chinese treatment-naïve patients with advanced or metastatic BTC [27]. After a median follow-up of 25 months, the median progression-free survival (PFS) was 7.1 months and median OS was 16.4 months. In another phase 2 study in Chinese patients with advanced or metastatic BTC, albumin-paclitaxel plus cisplatin was non-inferior to gemcitabine plus cisplatin in terms of objective response rate (ORR), OS, and PFS [28]. The efficacy and safety of these chemotherapy regimens warrant further investigation in phase 3 studies.

A new combination of nab-paclitaxel plus tegafur gimeracil oteracil potassium capsules (S-1) as a first-line treatment for patients with advanced BTC was investigated in a recent phase 2 trial [29]. The ORR in 51 patients was 27.5%, and 14 patients achieved a partial response. The ORR was higher in patients with GBC (53.8%) versus cholangiocarcinoma (18.4%). The median OS was 13.2 months (95% CI, 10.3–16.0), and median PFS was 6.0 months (95% CI, 4.2–7.7) [29]. The promising antitumor activity and favorable safety profile of nab-paclitaxel in combination with S-1 as first-line treatment for advanced BTC warrants further investigation in phase 3 studies.

A randomized open-label clinical trial showed that, compared with S-1 monotherapy, cisplatin and gemcitabine plus S-1 (GEM-S-1) provided a better OS, PFS, and response rate in Chinese patients with unresectable hilar cholangiocarcinoma [30]. Nevertheless, treatment outcomes were similar in the GEM-S-1 and GEM (cisplatin combined with gemcitabine) groups. The most common chemotherapy-related toxicities in the GEM-S-1 group were neutropenia (56%) and leukopenia (40%) [30].

The efficacy of modified FOLFIRINOX (mFOLFIRINOX) was compared with that of gemcitabine plus oxaliplatin in 49 Chinese patients with locally advanced or metastatic cholangiocarcinoma [31]. The median PFS was significantly longer in the mFOLFIRINOX group than in the gemcitabine plus oxaliplatin group. The frequency of grade 3–4 vomiting was higher in the mFOLFIRINOX than in the gemcitabine plus oxaliplatin group [31].

Targeted therapy for Chinese patients with advanced BTC

Genomic alterations and molecular characteristics of BTC in Chinese populations

BTC is characterized by genetic changes in cellular signaling pathways involved in cell proliferation and survival. Importantly, several of these alterations are clinically relevant and provide potential targets for precision treatments, which is especially relevant as next-generation signaling becomes more accessible. Differences in genomic alterations and molecular characteristics have been reported between Chinese and Western patients with BTC, with Chinese patients exhibiting a higher frequency of actionable genetic alterations [32,33]. These racial differences in tumor characteristics and patient outcomes highlight the importance of considering population-specific factors and tailoring treatment approaches to improve outcomes for patients with BTC. Meanwhile, shared/common oncodrivers are also found in Chinese and Caucasian patients with BTC [32,33], and clinical data on treatment responses in Chinese patients may be clinically relevant for Caucasian cohorts with tumors harboring similar genetic profiles.

The large population of China and the relatively high prevalence of BTC allow for the identification of onco-drivers that may also play a role in BTC development and progression in other populations. Moreover, the relatively high frequency of actionable alterations in Chinese patients with BTC suggests that a high proportion of Chinese patients may benefit from targeted therapy. An analysis of germline and somatic mutations in Chinese patients with BTC demonstrated actionable alterations in 57.1% of patients [33]. In addition, somatic alterations in the DNA damage repair (DDR) pathway were present in

Table 1 Summary of recent clinical studies with chemotherapy of first or second-line treatment of Chinese patients with advanced biliary tract cancer

Chemotherapy										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Nab-paclitaxel + gemcitabine + cisplatin [27]	First	2	34	Locally advanced or metastatic BTC	32.4	7.1 (5.4–13.7)	16.4 (10.9–23.6)	85.3	61.8	NA
Albumin-paclitaxel + cisplatin vs. gemcitabine + cisplatin [27,28]	First	2	67 (48 evaluated for efficacy)	Advanced or metastatic BTC	39.4 vs. 35.3	7.7 vs. 7.5 HR = 1.33 (0.61–2.91; $P = 0.469$)	12.1 vs. 12.9 HR = 1.62 (0.67–4.17; $P = 0.271$	NA	NA	NA
Nab-paclitaxel (125 mg/m^2) on days 1 and 8 + S-1 (80–120 mg/day) on days 1–14 [29]	First	2	54 (51 evaluated for efficacy)	Advanced BTC (gallbladder cancer or cholangiocarcinoma)	Overall: 27.5 Gallbladder carcinoma: 53.8 Cholangiocarcinoma: 18.4 (18.2 for iCCA, 20.0 for Ecca)	Overall: 6.0 (4.2–7.7) Gallbladder carcinoma: 4.5 (2.1–6.8) Cholangiocarcinoma: 6.0 (3.9–8.0)	Overall: 13.2 (10.3–16.0) Gallbladder carcinoma: 9.9 (3.7–16.0) Cholangiocarcinoma: 13.8 (10.0–17.5)	70.6	64.8	NA
GEM vs. S-1 vs. GEM + S-1 [30]*	First	NA	75	Unresectable hilar cholangiocarcinoma	GEM-S-1: 36 GEM: 24 S-1: 8	GEM-S-1: 4.90 (1.30–8.77) GEM: 3.70 (1.03–7.17) S-1: 1.60 (0.66–5.41)	GEM-S-1: 11 (9.80–12.20) GEM: 10 (8.38–11.62) S-1: 6 (5.51–6.49)	NA	NA	0.0
Modified FOLFIRINOX vs. gemcitabine + oxaliplatin [31]	First	NA	49	Locally advanced or metastatic cholangiocarcinoma	33.3 vs. 22.7	9.9 (7.3–12.4) vs. 6.4 (3.6–9.2)[a] HR = 0.353 (0.180–0.694); $P = 0.003$	15.7 (12.5–19.0) vs. 12.0 (9.3–14.8) HR = 0.547 (0.264–1.131); $P = 0.103$	77.8 vs. 63.5	NA	NA
FOLFOX-4 [132]	Second	2	37	Advanced BTC refractory to Gem/Cis	21.6	NA	6.9 (4.8–7.9)	62.2	37.8	NA

BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; Ecca, extrahepatic cholangiocarcinoma; FOLFOX-4, oxaliplatin, 5-fluorouracil, and leucovorin; GEM, cisplatin and gemcitabine; GEM-S-1, GEM plus S-1; HR, hazard ratio; iCCa, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitor; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-emergent adverse event; Q3W, every 3 weeks.

*Registered with the Chinese Clinical Trial Registry (ChiCTR); the remaining studies were registered with ClinicalTrials.gov.

[a]Significant difference at $P < 0.05$.

half (192/382) of the patients, and 23% of patients had a high tumor mutational burden (TMB-H). The most frequently mutated genes were *TP53* (51.6%), *ARID1A* (25.9%), *KMT2C* (24.6%), *NCOR1* (17%), *SMAD4* (15.2%), *KRAS* (14.9%), *KMT2D* (14.9%), *ATM* (14.1%), and *APC* (13.9%) [33]. The prevalence of mutations in *TP53*, *KRAS*, *IDH1*, *KMT2C*, and *SMAD4*, as well as the frequency of deleterious mutations in DDR genes, were significantly higher in Chinese patients than in US patients [33]. Another sequencing study of tumors from 803 Chinese patients with BTC showed that 25% of patients had at least one potentially actionable mutation (Fig. 2) [34]. In this study, potentially actionable mutations originating from single nucleotide variations or indels were relatively rare. However, in a recent sequencing analysis of 59 formalin-fixed paraffin-embedded tissue samples from Chinese patients with BTC, nearly 90% of samples had at least one single nucleotide variation (SNV) or copy number variation (CNV) [35]. In addition, *TP53*, *KRAS*, *ARID1A*, *VEGFA*, cyclin family-related genes, and cyclin-dependent kinases were the most frequently mutated genes; overall, actionable mutations were present in 59.3% of the patients. Germline mutations were less frequent than somatic mutations in Chinese patients with BTC. The frequency of germline mutations in the DDR pathway was also relatively low (6.7%) compared to the frequency of somatic alterations (~50%) [33,36]. Consistent with the findings of sequencing analyses of tumors, genomic profiling of circulating tumor DNA (ctDNA) from 154 Chinese patients with advanced BTC showed that *P53* was the most frequently mutated gene (35.1%), followed by *KRAS* (20.1%) [37]. The study also showed that P53, PI3K-Akt, ErbB, and Ras were the most commonly altered signaling pathways and mutations in *LRP1B*, *P53*, and *ErbB* were associated with higher tumor mutational burden (TMB).

Among Chinese patients with GBC, around 30% harbor potentially actionable mutations [34]. Genomic profiling of paraffin-embedded tumors from 108 Chinese and 107 US patients with GBC showed that the average number of genomic alterations was higher in Chinese than in US patients (6.4 vs. 3.8 genomic alterations per patient) [32]. However, the proportion of tumors with TMB-H was similar in Chinese and US patients (17.6% and 17.0%, respectively). The most frequently mutated genes in Chinese patients were *TP53* (69.4%), *CDKN2A/B* (26.0%), *ERBB2* (18.5%), *PIK3CA* (17.0%), and *CCNE1* (13.0%). Although the frequency of alterations in the PI3K/mTOR pathway was similar in the two cohorts (37.0% in Chinese patients vs. 33.0% in US patients; P = 0.5), mutations in *ERBB* genes were significantly more frequent in Chinese versus US patients (30.6% vs. 19.0%, P = 0.04). Rearrangements in chromatic structure and functional alterations in distinct genomic components have also been identified in Chinese patients with GBC [38]. Evidence suggests that cancer-specific chromatin remodeling and enhancer-promoter loops may contribute to GBC development and progression by promoting aberrant gene expression.

Molecular analyses of tumors from Chinese patients with BTC have shown differences in commonly mutated genes between ECC and ICC. Potentially actionable

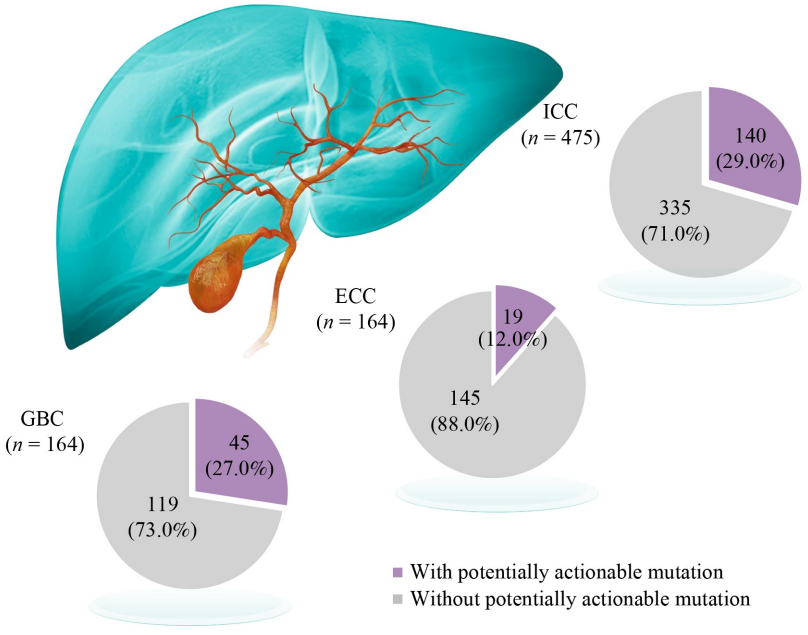

Fig. 2 Estimates of the proportion of Chinese patients with biliary tract cancer harboring at least one potentially actionable mutation by biliary tract cancer subtype among 803 Chinese patients [34].

mutations are found in 12% of Chinese patients with ECC [34]. *SMAD4* is the most frequently altered gene in Chinese patients with ECC [33], and the most common actionable mutations are in *CDKN2A*, *BRAF*, and *ERBB2* [39]. In addition, mutations in *RBM10* are common in ECC but not in ICC [40]. Mutations in *LRP2* are significantly associated with patient age and TMB in patients with ECC [41]. In contrast, among Chinese patients with ICC, approximately 30% harbor potentially actionable mutations [34]. *APC* is the most frequently altered gene in Chinese patients with ICC [33]. The most common actionable alterations in Chinese patients with ICC are in *KRAS*, *CDKN2A*, *PIK3CA*, and *FGFR2* [42]. Mutations in *STK11*, *CCND1*, and *FGF19* have been found in ICC but not in ECC [40]. A comparison of genomic alterations between Chinese and US patients with ICC showed a higher number of driver genes in Chinese patients (36 vs. 12 driver genes, respectively) [42]. However, mutations in seven oncogenes (*ARID1A*, *BAP1*, *IDH1*, *KRAS*, *NRAS*, *PBRM1*, and *TP53*) were present in both cohorts. Despite this, while most actionable mutations were shared between the two cohorts, their frequency differed considerably [42]. *TP53* deficiency in Chinese patients with ICC is associated with HBV seropositivity; in contrast, *KRAS* mutations are associated with HBV seronegativity [43]. Mutations in *LRP2* are significantly associated with patient age and TMB in patients with ICC [41].

A number of studies have shown associations between genetic/molecular characteristics, prognosis, and treatment outcomes in BTC. For example, high epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) expression were found to have a negligible impact on the prognosis of Chinese patients with BTC, while high c-MET expression was associated with longer survival [44]. One study found a relatively low prevalence of *IDH1/2* mutations, *FGFR2* translocations, *NTRK1* amplification, *MDM2* amplification, *HER2* amplification and *MET* amplification in Chinese patients with ICC compared with a Spanish patient population, suggesting that treatments targeting these alterations may be effective in limited Chinese patients [45]. Similarly, high heterogeneity in *BRAF* variant subtypes was observed among Chinese patients with ICC, which was associated with differential responses to BRAF or MEK inhibitors [46]. *KRAS* variant subtypes were also associated with survival and recurrence following surgical resection in patients with ICC [47]. As our understanding of the molecular landscape in different patient populations with BTC improves, and with molecular omics techniques identifying additional druggable targets [48], clinical trials investigating the efficacy of targeted therapies for BTC management will be especially important to establish clinically relevant biomarkers.

Tyrosine kinase inhibitors

Targeted therapy is recommended by the NCCN, ESMO, and CSCO guidelines as a second-line or subsequent-line treatment for patients with advanced BTC harboring actionable mutations [1,25,26]. The efficacy of second-line treatment with pemigatinib in Chinese patients with locally advanced or metastatic cholangiocarcinoma carrying *FGFR2* fusions or rearrangements was evaluated in a recent phase 2 study (Table 2) [49]. Among 30 patients treated with pemigatinib, 15 had a partial response, and 15 had stable disease. Grade 3–4 adverse events occurred in 8/31 (25.8%) patients [49]. Pemigatinib is the only targeted therapy specifically approved for the treatment of advanced cholangiocarcinoma in China [49]. A phase 3 study is warranted to confirm the antitumor activity of pemigatinib in previously-treated Chinese patients with cholangiocarcinoma harboring *FGFR2* rearrangements. It should also be noted that a phase 3 study of pemigatinib in the first-line setting for cholangiocarcinoma is currently in progress (NCT03656536) and will include Chinese study centers. Therefore, the use of targeted therapy in this setting in China is not widespread. However, various other treatment targets have been explored in Chinese patient populations, including HER2, IDH-1, and fibroblast growth factor receptor (FGFR).

Clinical data suggest that multi-targeted kinase inhibitors provide moderate clinical benefit in patients with advanced BTC when administered as monotherapy. *In vitro* data suggest that lenvatinib, a TKI widely used for the treatment of hepatocellular carcinoma in China, may play a potential anticancer role in GBC by inhibiting the PI3K/AKT pathway [50]. Specifically, treatment of human GBC cells with lenvatinib inhibited cell proliferation and migration and induced apoptosis and cell cycle arrest. However, the clinical efficacy of lenvatinib monotherapy in Chinese patients with advanced BTC remains unclear. In an open-label phase 2 trial, treatment with the vascular endothelial growth factor receptor (VEGFR) inhibitor surufatinib in unselected patients with unresectable BTC provided moderate clinical efficacy with expected tolerability and safety profiles [51]. The median PFS was 3.7 months, median OS was 6.9 months, and disease control rate (DCR) was 81.5% (Table 2).

Tyrosine kinase inhibitors plus chemotherapy

Currently, there is insufficient evidence to support the use of TKIs in combination with chemotherapy for the treatment of advanced BTC. A meta-analysis of seven

Table 2 Summary of recent clinical studies with targeted therapy of first or second-line treatment of Chinese patients with advanced biliary tract cancer

TKIs										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Surufatinib (300 mg) once daily [51]	Second	2	39	Unresectable or metastatic intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer	0.0	3.7 (2.4–6.0)	6.9 (5.1–8.1)	81.5 (61.92–93.70)	69.2	28.2
Pemigatinib (13.5 mg) once daily [49]	Second	2	30	Locally advanced or metastatic cholangiocarcinoma carrying *FGFR2* fusions or rearrangements	50.0 (31.3–68.7)	6.3 (4.9–not estimable)	NA	100 (88.4–100)	25.8	0.0
TKI plus chemotherapy										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
GEMOX + cetuximab vs. GEMOX alone [133]	First	2	122	Advanced BTC	27 (17–40) vs. 15 (7–27)	6.7 (5.0–8.1) vs. 4.1 (2.3–6.1)[a]	10.6 (8.8–13.1) vs. 9.8 (6.7–12.8)	58 vs. 37	NA	0.0

BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; GEMOX, gemcitabine plus oxaliplatin; NA, not available; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TRAE, treatment-emergent adverse event.
[a]Significant difference at $P < 0.05$.

randomized controlled trials demonstrated that chemotherapy plus agents targeting EGFR and VEGFR was significantly superior to chemotherapy alone in improving ORR [52]. However, targeted therapy plus chemotherapy and chemotherapy alone provided a similar benefit in terms of PFS and OS [52]. When different TKIs were considered separately in a sub-analysis, the addition of VEGFR inhibitors to chemotherapy was superior to adding EGFR inhibitors in terms of ORR, while addition of EGFR inhibitors significantly improved PFS. The addition of EGFR or VEGFR inhibitors to chemotherapy did not lead to increased unacceptable toxicities [52]. Nonetheless, an umbrella review of 14 trials in patients with advanced BTC demonstrated a higher incidence of skin rash and diarrhea in patients receiving gemcitabine-based chemotherapy plus targeted therapy than in those receiving gemcitabine monotherapy [53]. Although further clinical studies are needed to determine the optimal TKI plus chemotherapy regimen for Chinese patients with advanced BTC, the increased rate of adverse effects of combined treatment with TKIs and chemotherapy may limit the clinical usefulness of this combination treatment approach.

Immunotherapy for Chinese patients with advanced BTC

Immune landscape in Chinese patients with advanced BTC

There are currently limited data on the relationship between the immune landscape of the tumor microenvironment (TME) and prognosis in Chinese patients with BTC (Table 3). However, it is well established that chronic inflammation is a hallmark of BTC oncogenesis [54]. Furthermore, the systemic immune-inflammation index (SII), derived from counts of platelets, neutrophils, and lymphocytes in the peripheral blood, has been shown in multiple studies and meta-analyses to be a significant prognostic factor in BTC, with an elevated SII associated with worse clinical outcomes including disease stage, metastatic potential, PFS, and OS, including in Chinese patients [55,56].

Recent studies involving stool sample sequencing from Chinese patients undergoing anti-PD-1 immunotherapy for advanced BTC revealed signatures enriched in responders to treatment that may serve as biomarkers to

Table 3 Summary of available published data on the immune landscape of biliary tract cancer

	ICC	ECC	Gallbladder cancer
PD-L1 expression	No data found	32.3% [58]	No data found
HLA class I expression	No data found	50.0% [58]	No data found
High numbers of M2 tumor-associated macrophages	No data found	74.2% [58]	No data found
dMMR	2% [59]	No data found	No data found
TP53 mutation	55% (ICC and ECC) [134]		72% [134]
KRAS mutation	31% (ICC and ECC) [134]		14% [134]

dMMR, deficient mismatch repair; ECC, extrahepatic cholangiocarcinoma; HLA, human leukocyte antigens; ICC, intrahepatic cholangiocarcinoma; PD-L1, programmed death-ligand 1.

predict response to immunotherapy. For example, Lachnospiraceae bacterium-GAM79 and *Alistipes* sp. Marseille-P5997 were significantly enriched in responders and were associated with longer PFS and OS [57]. In contrast, Veillonellaceae were enriched in non-responders and were associated with poor PFS and OS [57]. These findings open new avenues for the non-invasive prediction of immunotherapy response based on sequencing of stool samples from patients with advanced BTC.

Characterization of the TME in tumor tissues from 62 Chinese patients with ECC demonstrated that programmed death-ligand 1 (PD-L1) was expressed on tumor cells in 32.3% of patients and on tumor-associated macrophages in 74.2% of patients [58]. In this study, PD-L1 expression was significantly associated with the density of intra-tumoral $CD3^+$ T cells ($P = 0.002$) and $CD8^+$ T cells ($P < 0.001$), in addition to expression of human leukocyte antigen (HLA) class I molecules ($P < 0.001$). Moreover, PD-L1 expression was significantly associated with the absence of venous invasion ($P = 0.030$) and improved OS ($P = 0.020$) and PFS ($P = 0.011$). Loss of HLA class I expression was observed in 50% of patients and was associated with a decreased density of intra-tumoral $CD8^+$ T cells ($P = 0.028$). An immunologically active TME, characterized by PD-L1 expression, HLA class I expression, and T cell infiltration, was observed in only 32% of patients. High numbers of M2 tumor-associated macrophages (TAMs) were detected in 74% of patients, further supporting the idea that the TME of ECC in Chinese patients is immunosuppressive [58]. These findings suggest that approximately 30% of Chinese patients with ECC may benefit from programmed death-1 (PD-1)/PD-L1 inhibition. Although the mechanisms underlying differences in immunotherapy response between GBC, ICC, and ECC remain to be elucidated, the immunosuppressive TME [58], limited immune cell infiltration [58], and low TMB [34,39] of ECC may contribute to a weaker response to immunotherapy among patients with this BTC subtype. However, these results need to be verified in prospective clinical trials.

A small number of studies have been conducted to identify factors predicting response to immunotherapy in Chinese patients with ICC. Analysis of tumor tissues from 73 Chinese patients with ICC showed that deficient mismatch repair (dMMR) was associated with partial response to immunotherapy [59]. However, the prevalence of dMMR was very low (2/97 patients; 2%), precluding drawing conclusions regarding the ability of dMMR to predict the immunological state of the TME [59]. A recent single-cell transcriptomic analysis of 14 pairs of ICC and non-tumor liver tissues from Chinese patients revealed two molecularly distinct tumor subtypes [60]. Compared with $S100P^-/SPP1^+$ peripheral small duct-type ICC, $S100P^+/SPP1^-$ perihilar large duct-type ICC had decreased numbers of tumor-infiltrating $CD4^+$ T cells and $CD56^+$ natural killer (NK) cells and increased numbers of $CCL18^+$ macrophages and PD1-expressing $CD8^+$ T cells. In addition, $S100P^-/SPP1^+$ peripheral small duct-type ICC had a high density of $SPP1^+$ macrophages and were associated with improved prognosis [60]. These findings suggest that response to immunotherapy may differ between patients with $S100P^-/SPP1^+$ peripheral small duct-type ICC and those with $S100P^+/SPP1^-$ perihilar large duct-type ICC. Another genomic, transcriptomic, and proteomic characterization of tissues from ICC in Chinese patients reported high heterogeneity of immunogenomic traits between patients and identified potential immune subgroups: immune suppressive (25.1% of samples), immune exclusion (42.7%), and immune activated (32.2%) [61]. This exploratory result also requires further validation in prospective trials.

Immune checkpoint inhibitors plus chemotherapy

Since 2010, registered clinical trials for patients with BTC in China have shown a focus on immunotherapy (Fig. 3). The most recent guidelines from the ESMO, NCCN, and CSCO recommend the combination of immune checkpoint inhibitors (ICIs) and chemotherapy for the primary treatment of patients with locally advanced unresectable or metastatic BTC as a standard of care. In clinical trials, pembrolizumab monotherapy provided durable antitumor activity in 6% of patients with advanced BTC, regardless of PD-L1 expression [62].

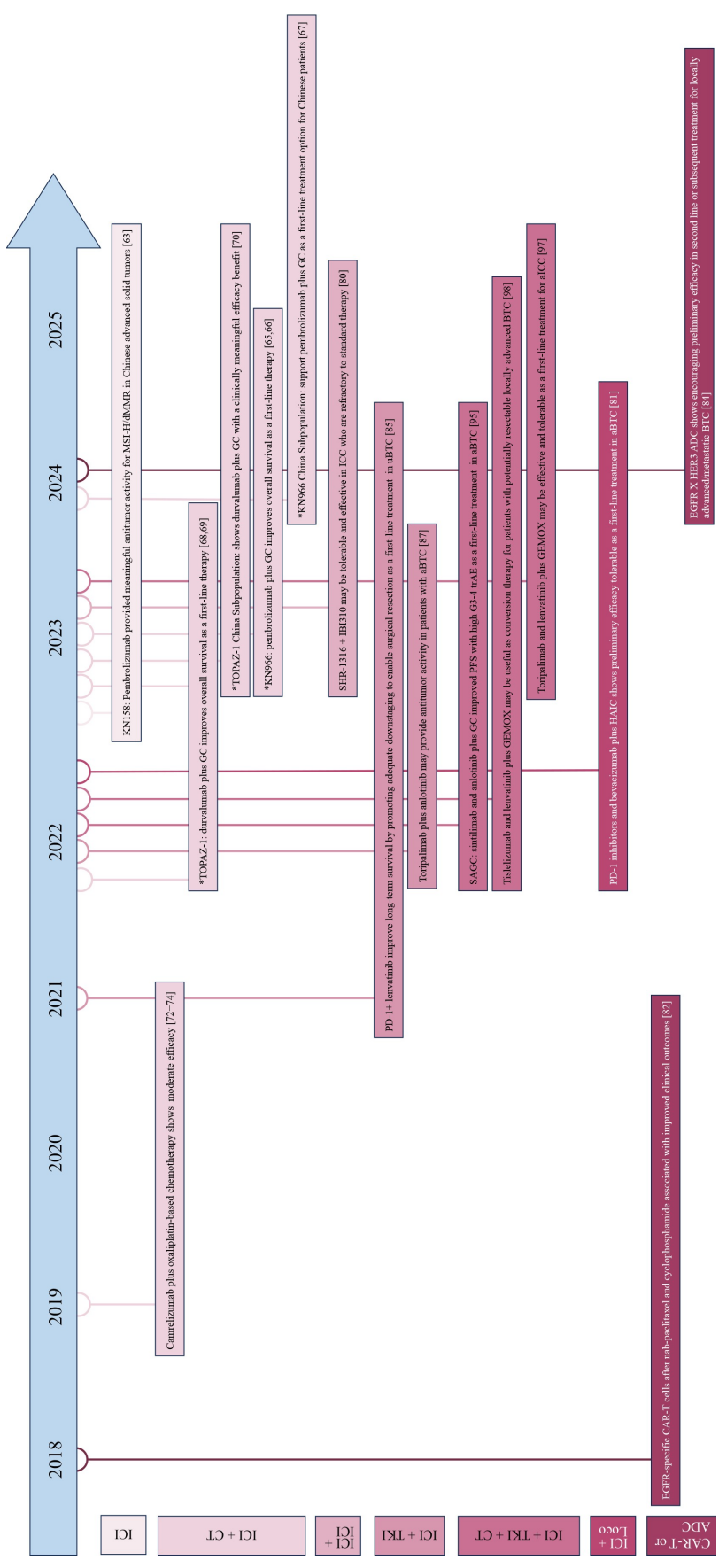

Fig. 3 Timeline of prospective clinical trials on immunotherapy in biliary tract cancer included Chinese patients. * indicates phase 3 trials, while the remaining are phase 2 trials. ICI, immune checkpoint inhibitors; TKI, tyrosine kinase inhibitor; Loco, locoregional therapy; ADC, antibody-drug conjugate; trAE, treatment related adverse event.

However, among cohort K of the KEYNOTE-158 trial, an ORR of 40.9% (95% CI, 20.7–63.6) was observed in 22 patients with cholangiocarcinoma/BTC with microsatellite instability high (MSI-H)/dMMR tumors [63]. Real-world data from China also suggest that MSI-H is associated with a clinical benefit and prolonged OS after treatment with anti-PD-1-based immunotherapy in patients with advanced cholangiocarcinoma [64]. Nevertheless, the prevalence of MSI-H/dMMR in Chinese patients with advanced BTC requires further confirmation.

Several studies have evaluated the efficacy and safety of the addition of ICIs to chemotherapy in the first-line treatment of patients with advanced BTC (Table 4). In the global phase 3 KEYNOTE-966 trial, first-line pembrolizumab in combination with gemcitabine and cisplatin provided a longer median OS (primary outcome) than chemotherapy alone in patients with advanced BTC: 12.7 months (95% CI, 11.5–13.6) with combination therapy versus 10.9 months (95% CI, 9.9–11.6) with chemotherapy alone; hazard ratio (HR), 0.83 (95% CI, 0.72–0.95); $P = 0.0034$ [65]. The incidence of grade 3–4 treatment-related adverse events (TRAEs) was similar between the two groups (70% vs. 69%), and the addition of pembrolizumab to chemotherapy did not compromise health-related quality of life [65,66]. A subgroup analysis of the data from both Asian (HRos = 0.88) and non-Asian patients (HRos = 0.80) in KEYNOTE-966 showed a similar trend toward an OS benefit [65]. In a subsequent subgroup analysis of Chinese patients who participated in the KEYNOTE-966 trial ($n = 158$), the median OS was 14.1 months (95% CI, 10.4–17.7) with combination therapy and 9.9 months (95% CI, 8.6–13.0) with chemotherapy alone (HR, 0.74 (95% CI, 0.51–1.08)), while the 12-month OS rate was 55% with combination therapy and 42% with chemotherapy alone [67]. Similarly, in the global phase 3 TOPAZ-1 trial of first-line durvalumab plus gemcitabine and cisplatin versus chemotherapy alone in patients with advanced BTC, data from the intention-to-treat population and Asian and Chinese subgroups showed a consistent survival benefit [68–70]. Secondary analyses of the KEYNOTE-966 and TOPAZ-1 trials have additionally revealed that the OS benefit observed with ICI-based combinations is retained regardless of hepatitis B virus (HBV) status, which is notable considering the high rate of HBV infection in Chinese populations [71]. However, first-line treatment with camrelizumab plus oxaliplatin-based chemotherapy in Chinese patients with advanced BTC showed moderate efficacy in phase 2 trials [72–74]. Preliminary data from phase 2 studies suggest that high expression of genes associated with interferon-γ signaling and T cell immune responses may be associated with response to first-line treatment with ICIs plus chemotherapy in patients with advanced BTC [75]. Several multinational and domestic phase 3 studies are ongoing to confirm the efficacy and tolerability of ICIs plus chemotherapy as first-line treatment for Chinese patients with advanced BTC (NCT03478488, CTR20232355, CTR20231590; Table S1).

Retrospective studies have also evaluated the efficacy of first-line treatment with ICIs plus chemotherapy in Chinese patients with advanced BTC (Table 4) [76,77]. Zhao *et al*. [76] showed that, in patients with metastatic or recurrent BTC, first-line chemotherapy plus an ICI (nivolumab, pembrolizumab, sintilimab, toripalimab, or camrelizumab) was superior to chemotherapy alone in prolonging PFS (HR, 0.62 (95% CI, 0.39–0.94); $P = 0.0306$). However, the median OS was similar in the two groups (HR, 0.93 (95% CI, 0.57–1.50); $P = 0.765$). The frequency of grade 3–4 TRAEs was also similar in the two groups (71.1% and 64.4%) [76]. Another retrospective study including 134 Chinese treatment-naïve patients with advanced BTC showed that the median PFS was significantly longer with ICI plus chemotherapy versus chemotherapy alone (5.8 months vs. 3.2 months; HR for progression, 0.47 (95% CI, 0.29–0.76); $P = 0.004$) [77]. However, the ORR and DCR did not differ significantly between the two groups [77]. Although these retrospective studies further support the efficacy of first-line ICI plus chemotherapy in Chinese patients with advanced BTC, showing prolonged PFS compared with chemotherapy alone, no benefits were observed for median OS. In contrast, clinical trials have shown an OS benefit in patients with BTC treated with first-line ICIs plus chemotherapy. The larger heterogeneity in patient populations in retrospective studies compared with clinical trials, in addition to small cohort sizes and delayed effects for OS, may have contributed to these observed differences in survival outcomes between clinical trials and real-world studies. On the other hand, results from both clinical trials and retrospective studies show limited improvements in ORR with the addition of immunotherapy. One reason for this observation is that biliary tumors have a desmoplastic stroma, which is also hard to measure. In addition, ECC, especially in the liver portal, is hard to measure. Another reason is that the benefit of adding immunotherapy to chemotherapy is usually not reflected in short-term responses but can still result in longer survival times.

Combination therapy with ICIs and chemotherapy has also been evaluated in the second-line setting in Chinese patients with advanced BTC, although evidence regarding the efficacy and safety of ICIs plus chemotherapy in this population is solely derived from retrospective studies (Table 4). A retrospective analysis of a case series involving 11 Chinese patients with advanced GBC who had progressed on previous treatment with gemcitabine-based chemotherapy showed that PD-1 inhibitors (pembrolizumab or sintilimab) plus nab-paclitaxel-

Table 4 Summary of recent clinical studies with immunotherapy of first or second-line treatment of Chinese patients with advanced biliary tract cancer

ICI monotherapy										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Pembrolizumab (200 mg) Q3W [62]	Second	2	104 (KEYNOTE-158) 24 (KEYNOTE-028)	Advanced BTC PD-L1 positive tumors in KEYNOTE-028 only	5.8 (2.1–12.1) 13 (2.8–33.6)	2.0 (1.9–2.1) 1.8 (1.4–3.1)	7.4 (5.5–9.6) 5.7 (3.1–9.8)	NA NA	13.5 16.7	5.8 4.2
ICI plus chemotherapy										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Pembrolizumab (200 mg Q3W) + gemcitabine and cisplatin vs. chemotherapy alone [65]	First	3	1069	Unresectable, locally advanced, or metastatic BTC	29 (25–33) vs. 29 (25–33)	6.5 (5.7–6.9) vs. 5.6 (5.1–6.6)	12.7 (11.5–13.6) vs. 10.9 (9.9–11.6)[a] HR = 0.83 (0.72–0.95); P = 0.0034	75 (71–79) vs. 76 (72–80)	70 vs. 69 (final analysis)	19 vs. 15 (final analysis)
Pembrolizumab (200 mg Q3W) + gemcitabine and cisplatin vs. chemotherapy alone [67]	First	3	158 (KN-966 China Extension Study)	Unresectable, locally advanced, or metastatic BTC	36.0 (25.2–47.9) vs. 28.9 (19.5–39.9)	5.6 (3.2–7.4) vs. 5.7 (4.4–6.9) HR = 0.83 (0.58–1.19)	14.1 (10.4–17.7) vs. 9.9 (8.6–13.0) HR = 0.74 (0.51–1.08)	NA	NA	24.3 vs. 17.1
Durvalumab + gemcitabine and cisplatin vs. chemotherapy alone [68,69]	First	3	685	Unresectable or metastatic BTC	26.7 vs. 18.7	7.2 (6.7–7.4) vs. 5.7 (5.6–6.7)[g] HR = 0.75 (0.63–0.89); P = 0.001	12.8 (11.1–14.0) vs. 11.5 (10.1–12.5) HR = 0.80 (0.66–0.97); P = 0.021 6m of additional follow-up: 12.9 (11.6–14.1) vs. 11.3 (10.1–12.5) HR = 0.76 (0.64–0.91)	85.3 vs. 82.6	62.7 vs. 64.9 6m of additional follow-up: 60.9 vs. 63.5	8.9 vs. 11.4 6m of additional follow-up: 8.9 vs. 11.4
Camrelizumab (3 mg/kg every 2 weeks) + FOLFOX-4 or GEMOX [72]	First	2	92	Advanced BTC	16.3 (9.4–25.5)	5.3 (3.7–5.7)	12.4 (8.9–16.1)	75.0 (64.9–83.4)	82.8 (Cam-FOLFOX4) 68.3 (Cam-GEMOX)	6.9 (Cam-FOLFOX4) 6.3 (Cam-GEMOX)
Chemotherapy[b] + ICI[c] vs. chemotherapy alone [76]	First	[d]	90	Metastatic or recurrent BTC	37.8 vs. 11.1	5.9 (4.3–7.5) vs. 4.2 (2.1–6.5) HR = 0.62 (0.39–0.94); P = 0.0306	14.7 (11.4–18.0) vs. 14.2 (12.5–15.9) HR = 0.93 (0.57–1.50); P = 0.765	82.2 vs. 51.1	71.1 vs 64.4	NA

(*Continued*)

Chemotherapy[e] + ICI[f] vs. chemotherapy alone [77]	First	[d]	134	Advanced BTC	21.7 vs. 15.2	5.8 vs. 3.2[a] HR = 0.47 (0.29–0.76); *P* = 0.004	NA	80.4 vs. 69.6	NA	NA
Pembrolizumab or sintilimab + nab-paclitaxel-containing chemotherapy [78]*	Second	[d]	11	Advanced gallbladder cancer	50.0	7.5 (2.5–12.5)	12.7 (5.5–19.9)	90.0	NA	NA
ICI[h] + chemotherapy vs. ICI alone vs. chemotherapy alone [79]	First or second	[d]	77	Advanced BTC	34.2 (21.6–48.8) vs. 0[a] vs. 5.3 (0.3–22.6)[a]	5.1 (3.59–6.61) vs. 2.2 (1.10–3.30)[a] vs. 2.4 (1.12–3.68)[a] HR = 0.59 (0.31–1.10); *P* = 0.014 for combination therapy vs. anti-PD-1 monotherapy HR = 0.61 (0.45–0.83); *P* = 0.003 for combination therapy vs. chemotherapy alone	14.9 (10.73–19.07) vs. 4.1 (2.79–5.42)[g] vs. 6.0 (3.66–8.34)[a] HR = 0.37 (0.17–0.80); *P* = 0.001 for combination therapy vs. anti-PD-1 monotherapy HR = 0.63 (0.42–0.94); *P* = 0.011) for combination therapy vs. chemotherapy alone	89.5 (77.5–96.3) vs. 65 (44.2–82.3)[a] vs. 47.4 (27.4–68.0)[a]	34.2 vs. 5.0 vs. 36.8	NA
Double-therapy with immune checkpoint inhibitors										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
SHR-1316 + IBI310 [80]	Second	2	39	Refractory ICC	20.0	NA	NR	60.0	41.0	NA
ICI plus targeted therapy										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Lenvatinib + ICI [85]*	First	2	38	Unresectable BTC	42.1 (25.7–58.6)	8.0	17.7	76.3 (62.2–90.5)	34.2	2.8
ICI + antiangiogenic therapy [86]	First or second	[d]	68	Unresectable BTC	13.2	5.5 (3.3–7.8)	10.7 (2.3–19.0)	75.0	36.8	NA
Pembrolizumab + olaparib [89]	Second	2	21 (13 evaluable for efficacy)	Advanced (metastatic or unresectable) BTC	15.3	5.5 (1.2–7.7)	11.9 (5.5–15.4)	NA	36	NA

(*Continued*)

Anlotinib + toripalimab [87]	Second	2	15	Advanced BTC	26.7	NA	NA	86.7	NA	NA
Lenvatinib (20 mg once daily) + pembrolizumab (200 mg Q3W) [88]	Second	2	31	Advanced (metastatic or unresectable) BTC	10 (2–26)	6.1 (2.1–6.4)	8.6 (5.6–NR)	68 (49–83)	48.4	6.5
Apatinib (250 mg once daily) + camrelizumab (200 mg Q3W) [90]	Second and beyond	1	22	Advanced BTC	19.0 (7–40)	4.4 (2.4–6.3)	13.1 (8.1–18.2)	71.4 (50–86.1)	63.6	13.6
Lenvatinib (12 or 8 mg once daily) + ICI[j] (Q3W) [91]	Second	[d]	74	Refractory advanced BTC	20.27 (10.89–29.65)	4.0 (3.5–5.0)	9.50 (9.0–11.0)	71.62 (61.11–82.14)	52.7	6.8
Lenvatinib (12 or 8 mg once daily) + pembrolizumab (200 mg Q3W) [92]	Second and beyond	[d]	32	Refractory BTC	25 (9.1–40.9)	4.9 (4.7–5.2)	11.0 (9.6–12.3)	78.1 (63–93.3)	62.4	25
Lenvatinib (8 mg daily) + ICI (200 mg Q3W) [93]	First or second	[d]	9	Advanced intrahepatic cholangiocarcinoma	44.44	8.63 (0–17.67)	NR	100	NA	NA
ICI + lenvatinib [94]	First and beyond	[d]	103	Advanced ICC	18.4	5.9 (5.1–6.7)	11.4 (10.1–12.7)	80.6	52.4	1.9
ICI plus chemo plus targeted therapy										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Sintilimab (200 mg Q3W) + anlotinib (10 mg Q3W) + gemcitabine/cisplat vs. gemcitabine/cisplat [95,96]	First	2	80	Advanced BTC	52.8 vs. 29.4	8.6 vs. 6.2 HR = 0.37; $P < 0.001$	NR	97.2 vs. 82.4	77.5 vs 40.0	NR
Toripalimab + GEMOX + lenvatinib [97]	First	2	30	Advanced ICC	80.0 (61.4–92.3)	10.2 (9.3–16.8)	22.5 (15.6–29.3)	93.3 (77.9–99.2)	NA	0.0
Toripalimab + gemcitabine + S1 [135]	First	2	50	Advanced BTC	30.6 (17.2–44.0)	7.0 (5.0–8.9)	15.0 (11.6–18.4)	87.8 (78.2–97.3)	NR	4.0

(*Continued*)

Tislelizumab + GEMOX + lenvatinib [98]	First	2	25	Potentially resectable locally advanced BTC	56.0	NA	NA	92.0	NA	NA
Anti-PD-1 + chemotherapy + TKI [99]	First	[d]	9	Advanced BTC	55.6	5.4	28.7	88.9	NA	NA
ICI + chemotherapy + anlotinib [100]	First	[d]	11	Advanced BTC	63.6 (30.8–89.1)	16.8 (7.0–NR)	16.8 (7.0–NR)	100 (71.5–100)	9.1	NA
Anti-PD-1 + chemotherapy + lenvatinib [101]	First	[d]	53	Advanced ICC	52.8 (39.7–65.6)	8.63 (7.17–11.6)	14.3 (11.3–not reached)	94.3 (84.6–98.1)	41.5	NA
Lenvatinib (12 or 8 mg once daily) + ICI + gemcitabine/oxaliplatin [102]	First or second	[d]	57	Advanced BTC	43.9 (31.8–56.7)	9.27 (7.1–11.6)	13.4 (10.0–NR)	91.2 (81.1–96.2)	45.6	NA
Immunotherapy plus locoregional treatment										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Toripalimab + bevacizumab + hepatic arterial infusion chemotherapy [81]	First	2	32	Advanced BTC	81.3	NR	NR	96.9	31.3	NA
ICI + TKI + HAIC vs. ICI + TKI + TACE [105]	First or second	2	58	Advanced ICC	48.7 vs. 15.8	NR vs. 11	NA	82.1 vs. 36.8	NA	NA
Local-regional chemotherapy + toripalimab + lenvatinib [106]	First or second	[d]	25	Advanced BTC	32.0 (12.3–51.7)	7.9 (2.8–13.1)	13.7 (10.4–17.0)	88 (74.3–101.7)	40.8	NA
ICI + lenvatinib + HAIC vs. lenvatinib + HAIC [107]	First or second	[d]	55	Advanced cholangiocarcinoma	28.6 vs. 20.0	6.5 vs. 3.5 HR = 0.390 (0.189–0.806); P = 0.001	16.0 vs. 11.0 HR = 0.461 (0.229–0.927); P = 0.01	80.0 vs. 65.0	NA	NA
Artery infusion chemotherapy + PD-1 immunotherapy [108]	First and beyond	2	41	Advanced BTC	11.5	3.7 (3.2–4.2)	8.8 (5.2–12.4)	76.9	44.4	NA

(*Continued*)

Toripalimab + lenvatinib + radiotherapy vs. Toripalimab + lenvatinib [81,105,108,111]	First	[d]	40	Advanced BTC	20.0 (0.8–39.2) vs. 35.0 (12.1–57.9)	10.8 (6.2–15.4) vs. 4.6 (3.3–5.8) HR = 0.21 (0.09–0.49); $P < 0.01$	13.7 (7.8–19.6) vs. 9.2 (6.5–11.8) HR = 0.36 (0.16–0.80); $P = 0.008$	75.0 (54.2–95.8) vs. 85% (67.9–102.1)	NA	NA
CAR-T cells										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS, month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
CART-EGFR cells after conditioning with nab-paclitaxel (100–250 mg/m^2) and cyclophosphamide (15–35 mg/kg) [82]	First or subsequent	1	19	*EGFR*-positive advanced unresectable, relapsed/metastatic BTC	NA	4 (2.5–22)	NA	NA	NA	NA
Antibody-drug conjugates										
Treatment	Treatment line	Study phase	No. of patients	Disease state	ORR, % (95% CI)	Median PFS, month (95% CI)	Median OS,month (95% CI)	DCR, % (95% CI)	TRAE grade 3–4, % (95% CI)	TRAE leading to discontinuation, % (95% CI)
Trastuzumab deruxtecan [136]	Second and beyond	1	60	Advanced, HER2-expressing solid tumors, including BTC	28.3	7.2 (4.8–11.1)	NA	90.9	62.7	8.5
Aprutumab ixadotin [137]	Second and beyond	1	20 (4 with cholangiocarcinoma)	Advanced FGFR2-positive solid tumors	NA	NA	NA	NA	45.0	25.0
BL-B01D1 [84]	Second and beyond	1a/1b	44	Advanced BTC	38.9 (23.1–56.5) Confirmed: 22.2 (10.1–39.2)	4.2 (2.8–7.1)	NA	88.9 (73.9–96.9)	NA	NA

BTC, biliary tract cancer; CAR-T, chimeric antigen receptor therapy; CI, confidence interval; DCR, disease control rate; EGFR, epithelial growth factor receptor; FOLFOX-4, oxaliplatin, 5-fluorouracil, and leucovorin; GEMOX, gemcitabine plus oxaliplatin; HAIC, hepatic arterial infusion; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitor; ICT, induction chemotherapy; NA, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PDL-1, programmed death ligand-1; PFS, progression-free survival; TACE, transartierial chemoembolization; TKI, tyrosine kinase inhibitor; TRAE, treatment-emergent adverse event; Q3W, every 3 weeks.

*Registered with the Chinese Clinical Trial Registry (ChiCTR); the remaining studies were registered with ClinicalTrials.gov.

[a]Significant difference at $P < 0.05$. [b]Gemcitabine-based or fluorouracil-based chemotherapy. [c]Nivolumab, pembrolizumab, sintilimab, toripalimab, or camrelizumab. [d]Retrospective study. [e]Nab-paclitaxel-based, gemcitabine-based, or platinum-based chemotherapy. [f]Pembrolizumab, nivolumab, sintilimab, or toripalimab; [g]Significant difference at $P = 0.001$. [h]Pembrolizumab or nivolumab. [i]Pembrolizumab, tislelizumab, sintilimab, camrelizumab, toripalimab every 3 weeks. [j]200 mg of sintilimab or tislelizumab or 240 mg of nivolumab or toripalimab.

containing chemotherapy provided an ORR of 50% and a DCR of 90% [78]. In addition, the median PFS was 7.5 months (95% CI, 2.5–12.5), and median OS was 12.7 months (95% CI, 5.5–19.9) and adverse events were manageable. Another retrospective study of ICIs plus chemotherapy in the first-line or second-line setting in Chinese patients with advanced BTC showed that the median OS was significantly longer with combination therapy than ICI monotherapy (HR, 0.37 (95% CI, 0.17–0.80); $P = 0.001$) or chemotherapy alone (HR, 0.63 (95% CI, 0.42–0.94); $P = 0.011$) [79]. The median PFS was also significantly longer with combination therapy than ICI monotherapy (HR, 0.59 (95% CI, 0.31–1.10); $P = 0.014$) or chemotherapy alone (HR, 0.61 (95% CI, 0.45–0.83); $P = 0.003$) [79]. The rate of grade 3–4 TRAEs was 34.2% with ICI plus chemotherapy, 36.8% with chemotherapy alone, and 5.0% with ICI monotherapy [79].

Immune checkpoint inhibitors plus targeted therapy

Clinical evidence for the efficacy of ICIs in combination with targeted therapy in the first-line treatment of Chinese patients with advanced BTC remains limited. Combination therapy with lenvatinib plus ICIs was evaluated as a first-line treatment in Chinese patients with initially unresectable BTC (ICC, ECC, or GBC) in an open-label phase 2 study [85]. Study participants had measurable initially unresectable BTC, defined as patients for whom R0 resection could not be achieved even with aggressive surgery. The goal of combined treatment with lenvatinib plus ICIs in this population was to improve long-term survival by promoting adequate downstaging to enable surgical resection (i.e., conversion resection). The ORR was 42.1%, DCR was 76.3%, and median OS was 17.7 months. A total of 34.2% of patients experienced a grade ⩾ 3 TRAE and no treatment-related deaths occurred. Mutations in *DNAH17*, *SSPO*, and *ARID1A* were significantly associated with poor treatment response [85]. Retrospective data also support the use of ICIs plus multi-targeted kinase inhibitors in the first-line treatment of patients with advanced BTC. A recent retrospective analysis of patients with unresectable BTC demonstrated that treatment with a PD-1 inhibitor combined with multi-targeted kinase inhibitors therapy (lenvatinib, apatinib, anlotinib, sorafenib, bevacizumab, or fruquintinib) was tolerated and provided an ORR of 13.2% [86].

Combination therapy with ICIs and targeted therapy has also been investigated in the second-line setting in Chinese patients with advanced BTC [87–89]. Apatinib combined with camrelizumab has shown promising results in various tumor types, and its efficacy and safety in Chinese patients with advanced BTC who have received previous treatments was investigated in a prospective phase 1 study [90]. Recent data from a phase 2 study suggest that treatment with anlotinib combined with toripalimab may provide promising antitumor activity in patients with advanced BTC, providing an ORR of 26.7% and DCR of 86.7% [87]. The multicohort phase 2 LEAP-005 study assessed the efficacy of second-line lenvatinib plus pembrolizumab in patients with advanced BTC, as recommended by CSCO guideline [88]. A preliminary analysis showed that combination therapy provided an ORR of 10% and DCR of 68%, the median PFS was 6.1 months and median OS was 8.6 months, grade 3–4 TRAEs occurred in 48.4% of the patients [88]. Retrospective studies have also evaluated the efficacy of lenvatinib plus pembrolizumab beyond first-line treatment in Chinese patients with advanced BTC, with ORRs of 18.4%–44.4% (Table 4) [91–94]. In a real-world analysis of the efficacy of lenvatinib plus ICIs in Chinese patients with advanced BTC who progressed after first-line cisplatin/gemcitabine chemotherapy, the ORR was 20.27%, DCR was 71.62%, median PFS was 4.0 months, and median OS was 9.50 months [91]. In addition, tumoral PD-L1 expression and high TMB were associated with prolonged PFS. Similar outcomes were observed in a retrospective analysis of data from Chinese patients with refractory BTC who were treated with lenvatinib plus pembrolizumab after progression following at least one prior line of systemic chemotherapy or targeted therapy [92].

In addition to improvements in survival outcomes and response rates, the most common types of adverse reactions with ICIs plus tyrosine kinase inhibitors (TKIs) are fatigue and hypertension [85–92]. This is different from immunotherapy plus chemotherapy, for which the most common types of adverse reactions are anemia, neutropenia, and nausea [65–70,72–74,76,77]. On balance, the moderate response rates and acceptable safety profiles of ICIs plus TKIs suggest this approach to be a favorable option, especially when tolerability to chemotherapy is of particular concern.

Combination therapy with immune checkpoint inhibitors, chemotherapy, and targeted therapy

The efficacy of first-line sintilimab and anlotinib in combination with gemcitabine plus cisplatin in Chinese patients with advanced BTC was evaluated in the phase 2 SAGC study (Table 4) [95,96]. Eighty patients were randomized 1:1 to receive sintilimab and anlotinib in combination with gemcitabine plus cisplatin, followed by sintilimab and anlotinib (SAGC group) or gemcitabine plus cisplatin (GC group) until disease progression or unacceptable toxicity. The median PFS was 8.6 months in the SAGC group and 6.2 months in the GC group (HR,

0.37; $P < 0.01$), and the ORR was 52.8% in the SAGC group and 29.4% in the GC group. Grade 3–4 TRAEs occurred in 77.5% and 40% of patients, respectively. Subgroup analysis showed that, compared with patients with low TMB, those with a high TBM were more likely to benefit from combination therapy [95]. Data from a single-arm phase 2 study suggest that first-line treatment with toripalimab combined with lenvatinib and GEMOX may be effective and tolerable in patients with advanced ICC, providing a median PFS of 10.2 months and OS of 22.5 months [97]. Furthermore, preliminary data from a phase 2 study ($n = 25$) suggest that first-line treatment with tislelizumab combined with lenvatinib and GEMOX may be useful as conversion therapy for patients with potentially resectable locally advanced BTC; the ORR and DCR were relatively high (56% and 92%, respectively) and 13 patients (52%) were able to undergo R0 resection [98]. The benefit of first-line triple therapy combining PD-1 inhibitors, chemotherapy, and targeted therapy in terms of OS and PFS was further supported by several recent retrospective analyses of Chinese patients with advanced BTC [99–101]. Nevertheless, these findings need to be confirmed in prospective randomized controlled trials.

The real-world effectiveness of lenvatinib combined with ICIs and GEMOX was retrospectively evaluated in 57 patients with BTC, 32 of whom had been previously treated with chemotherapy or targeted therapy [102]. The median OS was 13.4 months, median PFS was 9.27 months, ORR was 43.9%, and DCR was 91.2%. Treatment-naïve patients were more likely to benefit from lenvatinib combined with ICIs and oxaliplatin plus gemcitabine [102]. Moreover, recent real-world data from China suggest that first-line treatment with triple therapy (anti-PD-1 therapy in combination with targeted therapy and chemotherapy) may provide a clinical benefit in patients with advanced cholangiocarcinoma [103,104]. The most common treatment-emergent AEs associated with triple therapy regimens are similar to those observed with immunotherapy plus chemotherapy and include fever, neutropenia, and increased aspartate transaminase and alanine aminotransferase levels.

Both phase 2 trials and real-world data show that the ORR with first-line triple therapy (43.9%–79.6%) [95–98,102–104] is higher than the ORR reported in phase 3 clinical trials of first-line ICI plus chemotherapy (26.7%–29.0%) [68,69], suggesting that adding a TKI to the treatment regimen may improve treatment outcomes and inspiring the potential of conversion therapy. However, cohort sizes in these studies were small, and phase 3 randomized controlled trials are ongoing to confirm the benefit of first-line triple therapy in patients with advanced BTC (NCT05342194, NCT05823311; Table 3).

Double-therapy with immune checkpoint inhibitors

Emerging clinical data from one phase 2 study suggest that PD-L1 inhibitors in combination with CTLA-4 inhibitors may be tolerable and exert antitumor activity in Chinese patients with ICC who are refractory to standard therapy [80]. After a median follow-up of 6.1 months, the confirmed ORR and DCR among 25 evaluable patients were 20% and 60%, respectively. Interestingly, the ORR among patients who had previously received an anti-PD-1 antibody was 16.7% (2/13). Median PFS and OS had not been reached and the updated survival results are awaited.

Immunotherapy in combination with locoregional treatment

The combination of immunotherapy with locoregional treatment has shown promise in the treatment of advanced BTC. The first-line use of PD-1 inhibitors in combination with bevacizumab and hepatic arterial infusion chemotherapy (HAIC, oxaliplatin plus 5-fluorouracil) showed preliminary efficacy in a small phase 2 study involving 32 Chinese patients with advanced BTC, providing an ORR of 81.3% and 6-month OS of 89.9% [81]. Furthermore, the combination of TKIs and anti-PD-1 immunotherapy with HAIC as first- or second-line treatment has exhibited inspiring tolerability and antitumor effect in patients with advanced BTC, including those with unresectable ICC (Table 4) [105–109]. In these retrospective studies, the ORR (by RECIST v1.1), median PFS, and median OS values reported in these studies ranged from 11.5%–48.7%, 3.7–9.1 months, and 8.8–20.8 months, respectively. Systemic chemotherapy plus HAIC also appeared to be effective and well-tolerated in a small, single-arm, phase 2 study of patients with unresectable ICC [110]. Analysis of the optimal treatment timing in patients with advanced BTC receiving HAIC combined with PD-1 immunotherapy showed that early artery infusion chemotherapy (before progression on immunotherapy versus after progression) was associated with improved survival outcomes (median OS, 13.0 vs. 7.6 months; $P = 0.004$) [108]. Moreover, recent retrospective data suggest that use of toripalimab plus lenvatinib and radiotherapy for first-line treatment of patients with advanced BTC (75% with cholangiocarcinoma, including ICC and ECC, and 25% with GBC) is feasible and does not increase the risk of toxicity compared with treatment with toripalimab plus lenvatinib [111].

Taken together, these preliminary data suggest that adding locoregional therapy to regimens including immunotherapy plus TKIs is associated with relatively high response rates and potentially a survival benefit in patients with advanced BTC, with the majority of data in patients with ICC. Meanwhile, the ability of

combinatorial therapies involving immunotherapy and locoregional treatment to improve treatment outcomes while minimizing the adverse events associated with systemic treatment requires further investigation in large phase 3 studies.

Chimeric antigen receptor-T cell therapy and antibody-drug conjugates for Chinese patients with advanced BTC

The efficacy and safety of chimeric antigen receptor (CAR)-T cells have been evaluated in Chinese patients with advanced BTC. In a phase 1 study including 19 patients with *EGFR*-positive advanced unresectable, relapsed, or metastatic BTC, patients received one to three cycles of EGFR-specific CAR-T cells after conditioning treatment with nab-paclitaxel and cyclophosphamide [82]. Of the 17 patients evaluable for efficacy, one showed a complete response, and ten showed stable disease. The median PFS was 4 months (range, 2.5–22 months). Enrichment of central memory T cells (Tcm) in the infused CAR-T cells was associated with improved clinical outcomes. Although CAR-T cell infusion was generally well tolerated, some patients experienced grade 3 acute fever/chill and target-mediated toxicities. These toxicities included mucosal/cutaneous adverse events, acute pulmonary edema, lymphopenia, and thrombocytopenia [82]. Furthermore, the results of a recent early-phase clinical trial have provided evidence for future large, randomized trials comparing allogeneic NK cells and pembrolizumab to conventional chemotherapies for the treatment of chemotherapy-refractory advanced BTC [83]. Further studies are needed to confirm the usefulness of CAR-T cells and allogeneic NK cells in the treatment of patients with advanced BTC.

Currently, data regarding the efficacy and safety of antibody-drug conjugates in Chinese patients with advanced BTC are limited to phase 1 trials. Notably, a recent phase 1a/1b study of the first-in-class, bispecific EGFR x HER3 antibody-drug conjugate, BL-B01D1, which was developed in China, has shown encouraging preliminary efficacy in second line or subsequent treatment for locally advanced/metastatic BTC, with a confirmed ORR of 22.2% and median PFS of 4.2 months [84]. The safety profile was manageable, with the most common grade ⩾ 3 TRAEs being thrombocytopenia (31.8%), anemia (27.3%), leukopenia (20.5%), and neutropenia (18.2%) [84]. Further evaluation of BL-B01D1 in BTC is ongoing.

Future directions and conclusions

Despite recent progress in the treatment of advanced BTC in China and globally, the prognosis of patients with BTC remains poor, and several challenges remain, which indicates the future direction (Fig. 4). Although many clinical trials and retrospective studies have shown that

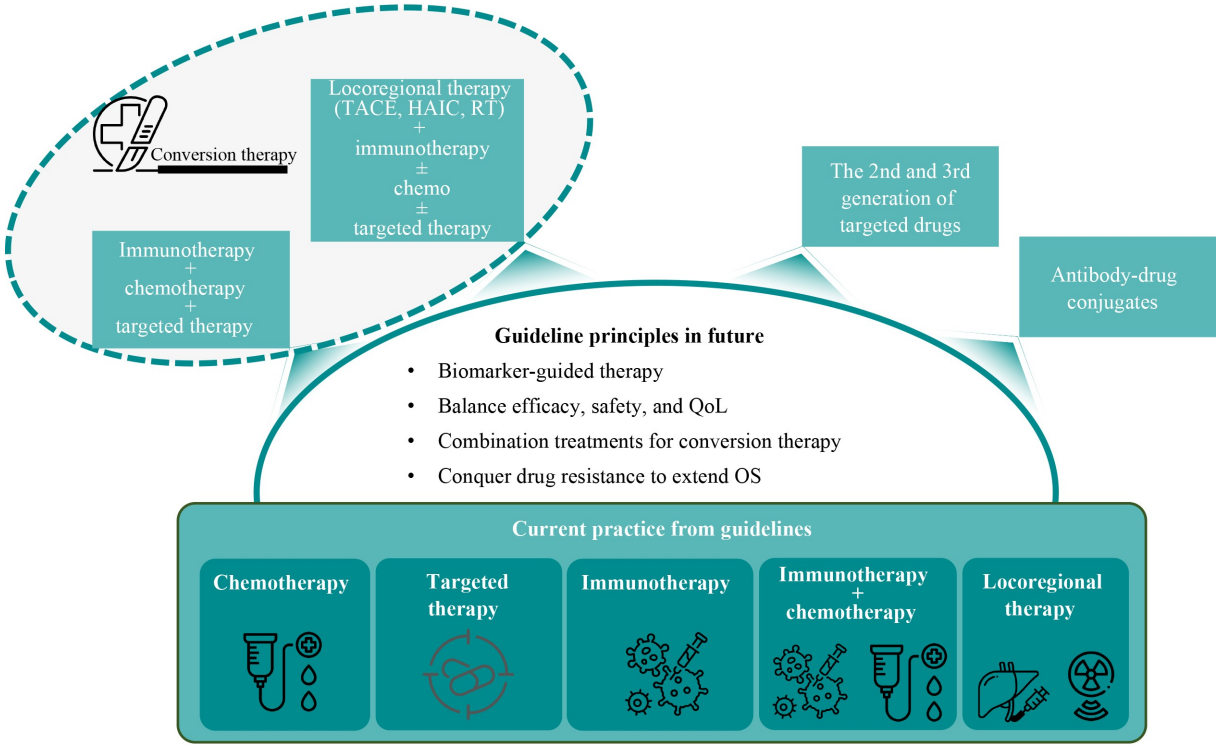

Fig. 4 Future directions in precision medicine for aBTC in China.

the benefit of targeted therapy and immunotherapy in patients with advanced BTC is statistically significant, the clinical significance of precision medicine remains unclear. In addition, the high heterogeneity of BTCs [112] poses a challenge in the identification of the most effective targeted therapies for individual patients. The identification of predictive biomarkers for response to targeted therapies and immunotherapy is crucial for optimizing treatment outcomes. Identification of bile biomarkers through metabolomic methods may provide additional novel biomarkers for the early detection of BTC and monitoring of treatment response [113]. Subanalyses of clinical data can help identify patients who may benefit the most from treatment with TKIs or immunotherapy. However, stratifying patients by tumor site, genotype, or immunological status of the TME is challenging because BTCs are rare malignancies. Biomarker-driven basket trials and umbrella studies encompassing a greater number of patients with advanced BTC could help to determine which patients are more likely to benefit from targeted therapy or immunotherapy.

Targeted therapies, ICIs, and various combination strategies can cause toxicity, leading to dose reduction, changes in medication plans, or even treatment discontinuation. These factors impact the evaluation of drug effectiveness and overall patient outcomes [114,115]. Therefore, guidelines are needed to help clinicians effectively manage treatment-related toxicities in patients with advanced BTC while minimizing treatment disruptions. In addition, underlying diseases are common in patients with advanced BTC, resulting in poor overall health and quality of life [16,116,117]. Thus, the effects of existing and emerging treatments on health-related quality of life should also be considered when deciding the best treatment approach.

Locoregional-combination therapy, chemotherapy/radiotherapy followed by curative surgical resection (i.e., conversion therapy), and novel combination therapies (including TKI, ICI, chemotherapy and antibody-drug conjugate combinations) are emerging as promising treatment approaches for various solid malignancies [118–121]. However, large phase 3 studies are needed to determine the usefulness of these novel combination therapies for the treatment of this rare malignancy.

Another tough problem is that drug resistance poses a significant challenge for chemotherapy, targeted therapy, and immunotherapy for BTC. Key mechanisms of chemotherapy resistance include altered drug metabolism and excretion, changes in the tumor microenvironment, and modifications in DNA repair processes [122–124]. To combat this, strategies such as optimizing drug delivery systems, adjusting the tumor environment, and personalizing chemotherapy doses are essential. To this end, a number of studies have applied various omics in an attempt to define resistance targets or pathways and further guide drug development to overcome chemotherapy resistance in Chinese patients with BTC. For example, in GBC, dysregulation of pathways such as the ELF3/PKMYT1/CDK1 axis, YTHDF2 mediated DAPK3 degradation and epigenetic activation of the elongator complex have been proposed as mechanisms of resistance to gemcitabine and potential treatment targets [125–127]. In ICC, heparinase-mediated activation of the AKT/β-catenin pathway, YBX1 upregulation, MAL2, and the saikosaponin-a/p-AKT/BCL-6/ABCA1 axis have been implicated in the development of treatment resistance and identified as potential treatment targets [128–131]. Our literature search did not identify any studies conducted in ECC. For targeted therapy, resistance mechanisms primarily involve genetic mutations, signaling pathway activation, and phenotypic conversion. Strategies to address these challenges include combining targeted agents, integrating therapies with chemotherapy and immunotherapy, and developing next-generation inhibitors aimed at specific resistance mutations. Immunotherapy also faces the challenge of treatment resistance, largely mediated through immune evasion and tumor microenvironment suppression. Addressing these issues requires combination immunotherapy, exploration of new immune targets, and the use of biomarkers to inform personalized treatment [122–124]. At present, research progress on ICI resistance in patients with BTC is relatively limited, and there is a lack of high-quality evidence to support treatment options following progression on first-line ICIs. This situation is reflected in the current treatment guidelines, which do not provide any specific recommendations. Further research to conquer resistance to the combination of immunotherapy and chemotherapy is especially urgent as it is becoming a new standard of care.

In conclusion, recent advances in precision medicine, particularly in targeted therapy and immunotherapy, have transformed the treatment landscape for advanced BTC in China. Targeted therapies and immunotherapy have shown promising results in clinical trials, providing new treatment options for patients with advanced disease. However, several challenges such as the high heterogeneity of BTCs, and lack of clinical data from large randomized trials to support the use of targeted therapies, and management of toxicity from combination treatment regimens, need to be addressed to fully realize the potential of precision medicine for BTC. China's growing precision medicine landscape also presents important opportunities for the treatment of advanced BTC. The high BTC incidence in China provides a sizable patient population for large-scale genomic analysis and clinical trials. Future research should focus on identifying predictive biomarkers, improving accessibility to targeted therapies and immunotherapy, exploring new combination strategies to further improve

outcomes with manageable toxicity, and resistance solutions in patients with advanced BTC.

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Compliance with ethics guidelines

Conflicts of interest Xijie Zhang and Lu Liang are employed by MSD China. Zhen Huang, Wen Zhang, Yongkun Sun, Dong Yan, and Hong Zhao report no conflicts of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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References

1. NCCN Clinical Practice Guidelines in Oncology. Biliary Tract Cancers. Version 6. 2024. Available at the website of NCCN
2. Baria K, De Toni EN, Yu B, Jiang Z, Kabadi SM, Malvezzi M. Worldwide incidence and mortality of biliary tract cancer. Gastro Hep Advances. 2022; 1(4): 618–626
3. Chen S, Han K, Song Y, Liu S, Li X, Wang S, Li H, Li R, Wang J, He Y, Liu M. Current status, trends, and predictions in the burden of gallbladder and biliary tract cancer in China from 1990 to 2019. Chin Med J (Engl) 2022; 135(14): 1697–1706
4. Ellington TD, Momin B, Wilson RJ, Henley SJ, Wu M, Ryerson AB. Incidence and mortality of cancers of the biliary tract, gallbladder, and liver by sex, age, race/ethnicity, and stage at diagnosis: United States, 2013 to 2017. Cancer Epidemiol Biomarkers Prev 2021; 30(9): 1607–1614
5. Xie W, Yang T, Zuo J, Ma Z, Yu W, Hu Z, Song Z. Chinese and global burdens of gastrointestinal cancers from 1990 to 2019. Front Public Health 2022; 10: 941284
6. An L, Zheng R, Zhang S, Chen R, Wang S, Sun K, Lu L, Zhang X, Zhao H, Zeng H, Wei W, He J. Hepatocellular carcinoma and intrahepatic cholangiocarcinoma incidence between 2006 and 2015 in China: estimates based on data from 188 population-based cancer registries. Hepatobiliary Surg Nutr 2023; 12(1): 45–55
7. Kang MJ, Lim J, Han SS, Park HM, Kim SW, Lee WJ, Woo SM, Kim TH, Won YJ, Park SJ. Distinct prognosis of biliary tract cancer according to tumor location, stage, and treatment: a population-based study. Sci Rep 2022; 12(1): 10206
8. Hsu HP, Yang TM, Hsieh YH, Shan YS, Lin PW. Predictors for patterns of failure after pancreaticoduodenectomy in ampullary cancer. Ann Surg Oncol 2007; 14(1): 50–60
9. Jarnagin WR, Ruo L, Little SA, Klimstra D, D'Angelica M, DeMatteo RP, Wagman R, Blumgart LH, Fong Y. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003; 98(8): 1689–1700
10. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, Wan X, Liu G, Wu D, Shi L, Lau W, Wu M, Shen F. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013; 31(9): 1188–1195
11. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362(14): 1273–1281
12. Ciombor KK, Goff LW. Advances in the management of biliary tract cancers. Clin Adv Hematol Oncol 2013; 11(1): 28–34
13. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012; 30(16): 1934–1940
14. Zhou J, Tan G, Zhang L, Xie G, Chen W, Zhang X, Liang H. Epidemiology of biliary tract cancer in China: a narrative review. Chin J Cancer Res 2024; 36(5): 474–488
15. Huang D, Joo H, Song N, Cho S, Kim W, Shin A. Association between gallstones and the risk of biliary tract cancer: a systematic review and meta-analysis. Epidemiol Health 2021; 43: e2021011
16. Andreotti G, Liu E, Gao YT, Safaeian M, Rashid A, Shen MC, Wang BS, Deng J, Han TQ, Zhang BH, Hsing AW. Medical history and the risk of biliary tract cancers in Shanghai, China: implications for a role of inflammation. Cancer Causes Control 2011; 22(9): 1289–1296
17. Tavolari S, Brandi G. Mutational landscape of cholangiocarcinoma according to different etiologies: a review. Cells 2023; 12(9): 1216
18. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: epidemiology and risk factors. Liver Int 2019; 39(Suppl 1): 19–31
19. Lundberg Båve A, Bergquist A, Bottai M, Warnqvist A, von Seth E, Nordenvall C. Increased risk of cancer in patients with primary sclerosing cholangitis. Hepatol Int 2021; 15(5): 1174–1182
20. Aune D, Sen A, Norat T, Riboli E, Folseraas T. Primary

sclerosing cholangitis and the risk of cancer, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of cohort studies. Sci Rep 2021; 11(1): 10646
21. Zhou HB, Wang H, Zhou DX, Wang H, Wang Q, Zou SS, Hu HP. Etiological and clinicopathologic characteristics of intrahepatic cholangiocarcinoma in young patients. World J Gastroenterol 2010; 16(7): 881–885
22. Shebl FM, Andreotti G, Meyer TE, Gao YT, Rashid A, Yu K, Shen MC, Wang BS, Han TQ, Zhang BH, Stanczyk FZ, Hsing AW. Metabolic syndrome and insulin resistance in relation to biliary tract cancer and stone risks: a population-based study in Shanghai, China. Br J Cancer 2011; 105(9): 1424–1429
23. Shebl FM, Andreotti G, Rashid A, Gao YT, Yu K, Shen MC, Wang BS, Li Q, Han TQ, Zhang BH, Fraumeni JF Jr, Hsing AW. Diabetes in relation to biliary tract cancer and stones: a population-based study in Shanghai, China. Br J Cancer 2010; 103(1): 115–119
24. Lee SH, Song SY. Recent advancement in diagnosis of biliary tract cancer through pathological and molecular classifications. Cancers (Basel) 2024; 16(9): 1761
25. Zhang X, Cai Y, Xiong X, Liu A, Zhou R, You Z, Li F, Cheng N. Comparison of current guidelines and consensus on the management of patients with cholangiocarcinoma: 2022 update. Intractable Rare Dis Res 2022; 11(4): 161–172
26. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klumpen HJ, Malka D, Primrose JN, Rimassa L, Stenzinger A, Valle JW, Ducreux M. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023; 34(2): 127–140
27. Liu T, Li Q, Lin Z, Liu C, Pu W, Zeng S, Lai J, Cai X, Zhang L, Wang S, Chen M, Cao W, Gou H, Zhu Q. A single-arm phase II study of nab-paclitaxel plus gemcitabine and cisplatin for locally advanced or metastatic biliary tract cancer. Cancer Res Treat 2024; 56(2): 602–615
28. Yang X, Zhuang L, Dai Y, Qiu H, Yuan X. A prospective, multicenter, phase II trial of albumin-paclitaxel plus cisplatin versus gemcitabine plus cisplatin in first-line treatment of advanced biliary tract tumors (2022 ASCO abstract 4099). J Clin Oncol 2022; 40(16 suppl): 4099
29. Zhang W, Sun Y, Jiang Z, Qu W, Gong C, Zhou A. Nab-paclitaxel plus tegafur gimeracil oteracil potassium capsule (S-1) as first-line treatment for advanced biliary tract adenocarcinoma: a phase 2 clinical trial. Hepatobiliary Surg Nutr 2023; 12(1): 37–44
30. Li H, Zhang ZY, Zhou ZQ, Guan J, Tong DN, Zhou GW. Combined gemcitabine and S-1 chemotherapy for treating unresectable hilar cholangiocarcinoma: a randomized open-label clinical trial. Oncotarget 2016; 7(18): 26888–26897
31. Zou L, Li X, Wu X, Cui J, Cui X, Song X, Ren T, Han X, Zhu Y, Li H, Wu W, Wang X, Gong W, Wang L, Li M, Lau WY, Liu Y. Modified FOLFIRINOX versus gemcitabine plus oxaliplatin as first-line chemotherapy for patients with locally advanced or metastatic cholangiocarcinoma: a retrospective comparative study. BMC Cancer 2021; 21(1): 818
32. Yang P, Javle M, Pang F, Zhao W, Abdel-Wahab R, Chen X, Meric-Bernstam F, Chen H, Borad MJ, Liu Y, Zou C, Mu S, Xing Y, Wang K, Peng C, Che X. Somatic genetic aberrations in gallbladder cancer: comparison between Chinese and US patients. Hepatobiliary Surg Nutr 2019; 8(6): 604–614
33. Yu H, Xu Y, Gao W, Li M, He J, Deng X, Xing W. Comprehensive germline and somatic genomic profiles of Chinese patients with biliary tract cancer. Front Oncol 2022; 12: 930611
34. Lin J, Cao Y, Yang X, Li G, Shi Y, Wang D, Long J, Song Y, Mao J, Xie F, Bai Y, Zhang L, Yang X, Wan X, Wang A, Guan M, Zhao L, Hu K, Pan J, Huo L, Lu X, Mao Y, Sang X, Zhang H, Wang K, Wang X, Zhao H. Mutational spectrum and precision oncology for biliary tract carcinoma. Theranostics 2021; 11(10): 4585–4598
35. Guo L, Zhou F, Liu H, Kou X, Zhang H, Chen X, Qiu J. Genomic mutation characteristics and prognosis of biliary tract cancer. Am J Transl Res 2022; 14(7): 4990–5002
36. Shen J, Kong R, Guo D, Chen S, Han T, Wang M, Lu G, Deng W, Ding R, Bu F. Spectrum of germline pathogenic mutations in 1087 Chinese patients with biliary tract cancer (2022 ESMO abstract 58P). Ann Oncol 2022; 33: S567
37. Chen C, Wang T, Yang M, Song J, Huang M, Bai Y, Su H. Genomic profiling of blood-derived circulating tumor DNA from patients with advanced biliary tract cancer. Pathol Oncol Res 2021; 27: 1609879
38. Li G, Pu P, Pan M, Weng X, Qiu S, Li Y, Abbas SJ, Zou L, Liu K, Wang Z, Shao Z, Jiang L, Wu W, Liu Y, Shao R, Liu F, Liu Y. Topological reorganization and functional alteration of distinct genomic components in gallbladder cancer. Front Med 2024; 18(1): 109–127
39. Xue L, Guo C, Zhang K, Jiang H, Pang F, Dou Y, Liu X, Lin H, Dong X, Zhao S, Yao M, Wang K, Feng Y, Gu W. Comprehensive molecular profiling of extrahepatic cholangiocarcinoma in Chinese population and potential targets for clinical practice. Hepatobiliary Surg Nutr 2019; 8(6): 615–622
40. Tian W, Hu W, Shi X, Liu P, Ma X, Zhao W, Qu L, Zhang S, Shi W, Liu A, Cao J. Comprehensive genomic profile of cholangiocarcinomas in China. Oncol Lett 2020; 19(4): 3101–3110
41. Jiang G, Zhang W, Wang T, Ding S, Shi X, Zhang S, Shi W, Liu A, Zheng S. Characteristics of genomic alterations in Chinese cholangiocarcinoma patients. Jpn J Clin Oncol 2020; 50(10): 1117–1125
42. Xu S, Guo Y, Zeng Y, Song Z, Zhu X, Fan N, Zhang Z, Ren G, Zang Y, Rao W. Clinically significant genomic alterations in the Chinese and Western patients with intrahepatic cholangiocarcinoma. BMC Cancer 2021; 21(1): 152
43. Zou S, Li J, Zhou H, Frech C, Jiang X, Chu JS, Zhao X, Li Y, Li Q, Wang H, Hu J, Kong G, Wu M, Ding C, Chen N, Hu H. Mutational landscape of intrahepatic cholangiocarcinoma. Nat Commun 2014; 5(1): 5696
44. Zhou W, Jiang C, Zhan N, Lv X, Fan L, Ninu M. Human epidermal growth factor receptor 2, epidermal growth factor receptor, and c-MET overexpression and survival in biliary tract cancer: a meta-analysis. J Cancer Res Ther 2018; 14(Suppl 1): S28–S35
45. Pu X, Zhu L, Li F, Zheng J, Wu H, Fu Y, Chen J, Qi L. Target molecular treatment markers in intrahepatic cholangiocarcinoma based on Chinese population. Pathol Res Pract 2020; 216(9): 153116
46. Xin HY, Sun RQ, Zou JX, Wang PC, Wang JY, Ye YH, Liu KX,

Hu ZQ, Zhou ZJ, Fan J, Zhou J, Zhou SL. Association of BRAF variants with disease characteristics, prognosis, and targeted therapy response in intrahepatic cholangiocarcinoma. JAMA Netw Open 2023; 6(3): e231476

47. Zhou SL, Xin HY, Sun RQ, Zhou ZJ, Hu ZQ, Luo CB, Wang PC, Li J, Fan J, Zhou J. Association of KRAS variant subtypes with survival and recurrence in patients with surgically treated intrahepatic cholangiocarcinoma. JAMA Surg 2022; 157(1): 59–65
48. Ruan J, Li Q, Jin Y, Yin J, Ye C, Cheng F, Xu S, Chen R, Liu C, Rong X, Jiang M, Fu W, Zheng D, Chen J, Bao X, Wang H, Sheng J, Zhao P. Multiple-omics analysis reveals a dedifferentiation-immune loop in intrahepatic cholangiocarcinoma. Mol Ther 2025; 33(4): 1803–1824
49. Shi GM, Huang XY, Wen TF, Song TQ, Kuang M, Mou HB, Bao LQ, Zhao HT, Zhao H, Feng XL, Zhang BX, Peng T, Zhang YB, Li XC, Yu HS, Cao Y, Liu LX, Zhang T, Wang WL, Ran JH, Liu YB, Gong W, Chen MX, Cao L, Luo Y, Wang Y, Zhou H, Yang GH, Fan J, Zhou J. Pemigatinib in previously treated Chinese patients with locally advanced or metastatic cholangiocarcinoma carrying FGFR2 fusions or rearrangements: a phase II study. Cancer Med 2023; 12(4): 4137–4146
50. Ye J, Qi L, Liang J, Zong K, Liu W, Li R, Feng R, Zhai W. Lenvatinib induces anticancer activity in gallbladder cancer by targeting AKT. J Cancer 2021; 12(12): 3548–3557
51. Xu J, Bai Y, Sun H, Bai C, Jia R, Li Y, Zhang W, Liu L, Huang C, Guan M, Zhou J, Su W. A single-arm, multicenter, open-label phase 2 trial of surufatinib in patients with unresectable or metastatic biliary tract cancer. Cancer 2021; 127(21): 3975–3984
52. Zhuang X, Xiao YP, Tan LH, Wang LT, Cao Q, Qu GF, Xiao S, Duan H. Efficacy and safety of chemotherapy with or without targeted therapy in biliary tract cancer: a meta-analysis of 7 randomized controlled trials. J Huazhong Univ Sci Technolog Med Sci 2017; 37(2): 172–178
53. Wang Y, Wen N, Wang S, Nie G, Tian Y, Lu J, Li B. Chemotherapy and targeted therapy for advanced biliary tract cancers: an umbrella review. BMC Cancer 2023; 23(1): 378
54. Scott AJ, Sharman R, Shroff RT. Precision medicine in biliary tract cancer. J Clin Oncol 2022; 40(24): 2716–2734
55. Zhang B, Yao W. Prognostic role of the systemic immune-inflammation index in biliary tract cancers: a meta-analysis of 3, 515 patients. World J Surg Oncol 2022; 20(1): 320
56. Peng X, Wang X, Hua L, Yang R. Prognostic and clinical value of the systemic immune-inflammation index in biliary tract cancer: a meta-analysis. J Immunol Res 2022; 2022: 6988489
57. Mao J, Wang D, Long J, Yang X, Lin J, Song Y, Xie F, Xun Z, Wang Y, Wang Y, Li Y, Sun H, Xue J, Song Y, Zuo B, Zhang J, Bian J, Zhang T, Yang X, Zhang L, Sang X, Zhao H. Gut microbiome is associated with the clinical response to anti-PD-1 based immunotherapy in hepatobiliary cancers. J Immunother Cancer 2021; 9(12): e003334
58. Yu F, Gong L, Mo Z, Wang W, Wu M, Yang J, Zhang Q, Li L, Yao J, Dong J. Programmed death ligand-1, tumor infiltrating lymphocytes and HLA expression in Chinese extrahepatic cholangiocarcinoma patients: Possible immunotherapy implications. Biosci Trends 2019; 13(1): 58–69
59. Yu J, Zhang X, Huang Q, Tan S, Xiong X, Gou H. Rare DNA mismatch repair-related protein loss in patients with intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma and their response to immunotherapy. Cancer Manag Res 2021; 13: 4283–4290
60. Song G, Shi Y, Meng L, Ma J, Huang S, Zhang J, Wu Y, Li J, Lin Y, Yang S, Rao D, Cheng Y, Lin J, Ji S, Liu Y, Jiang S, Wang X, Zhang S, Ke A, Wang X, Cao Y, Ji Y, Zhou J, Fan J, Zhang X, Xi R, Gao Q. Single-cell transcriptomic analysis suggests two molecularly distinct subtypes of intrahepatic cholangiocarcinoma. Nat Commun 2022; 13(1): 1642
61. Lin J, Dai Y, Sang C, Song G, Xiang B, Zhang M, Dong L, Xia X, Ma J, Shen X, Ji S, Zhang S, Wang M, Fang H, Zhang X, Wang X, Zhang B, Zhou J, Fan J, Zhou H, Gao D, Gao Q. Multimodule characterization of immune subgroups in intrahepatic cholangiocarcinoma reveals distinct therapeutic vulnerabilities. J Immunother Cancer 2022; 10(7): e004892
62. Piha-Paul SA, Oh DY, Ueno M, Malka D, Chung HC, Nagrial A, Kelley RK, Ros W, Italiano A, Nakagawa K, Rugo HS, de Braud F, Varga AI, Hansen A, Wang H, Krishnan S, Norwood KG, Doi T. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer 2020; 147(8): 2190–2198
63. Mao Y, Wu X, Xu N, Bai Y, Wang D, Chen X, Yin X, Deng Y, Yang J, Zhang J, Tang J, Huang Y, Li J, Xu M, Li N, Mao Y, Gozman A, Xu J. Pembrolizumab in patients of Chinese descent with microsatellite instability-high/mismatch repair deficient advanced solid tumors: KEYNOTE-158 (2023 ESMO abstract 136P). Ann Oncol 2023; 34: S235
64. Yang X, Lian B, Li Y, Xue J, Wang Y, Wang Y, Xun Z, Zhang N, Sun H, Long J, Song Z, Lu L, Pan J, Zhao L, Guan M, Yang X, Mao Y, Sang X, Wang K, Zhao HT. Genomic characterization and translational immunotherapy of microsatellite instability-high (MSI-H) in cholangiocarcinoma (2022 ASCO abstract 4101). J Clin Oncol 2022; 40(16 suppl): 4101
65. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, Yau T, Klümpen HJ, Chan SL, Ozaka M, Verslype C, Bouattour M, Park JO, Barajas O, Pelzer U, Valle JW, Yu L, Malhotra U, Siegel AB, Edeline J, Vogel A; KEYNOTE-966 Investigators. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023; 401(10391): 1853–1865
66. Yoo C, Finn RS, Klümpen HJ, Kelley RK, Vogel A, Furuse J, Ren Z, Yau T, Chan SL, Ozaka M, Oh SC, Gu S, Park JO, Valle JW, Edeline J, Kamble S, Norquist JM, Yu L, Malhotra U, Ueno M. Health-related quality of life (HRQoL) in the phase 3 KEYNOTE-966 study of pembrolizumab (pembro) plus gemcitabine and cisplatin (gem/cis) versus placebo plus gem/cis for advanced biliary tract cancer (BTC). J Clin Oncol 2023; 41(16 suppl): 4003
67. Qin S, Liang T, Gu S, Gou H, Peng C, Pan Y, Song T, Su H, Cao K, Liang H, Ying J, Geng Z, Yu W, Zhao H, Bai Y, Hao CY, Wang W, Li N, Malhotra U, Ren Z. 47P First-line pembrolizumab (pembro) + gemcitabine and cisplatin (gem/cis) for advanced biliary tract cancer (BTC) in the China subpopulation from the phase III KEYNOTE-966 study. Ann Oncol 2024; 35: S230
68. Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A, Kim

JW, Suksomboon charoen T, Ah Lee M, Kitano M, Burris H, Bouattour M, Tanasanvimon S, McNamara MG, Zaucha R, Avallone A, Tan B, Cundom J, Lee CK, Takahashi H, Ikeda M, Chen JS, Wang J, Makowsky M, Rokutanda N, He P, Kurland JF, Cohen G, Valle JW. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid 2022; 1(8): EVIDoa2200015

69. Oh DY, He AR, Qin S, Chen LT, Okusaka T, Vogel A, Kim JW, Lee T, Lee MA, Kitano M, Burris HA, Bouattour M, Tanasanvimon S, Zaucha RE, Avallone A, Cundom JE, Rokutanda N, Żotkiewicz M, Cohen G, Valle JW. 78P Updated overall survival (OS) from the phase III TOPAZ-1 study of durvalumab (D) or placebo (PBO) plus gemcitabine and cisplatin (+ GC) in patients (pts) with advanced biliary tract cancer (BTC). Ann Oncol 2022; 33: S1462–S1463
70. Qin S, Cai JQ, Li E, Xing B, Zhao L, Dai C, Li J, Shen Y, Chen Z, Liu L, Lu Z, Zang A, Bai Y, Liang H, Liang J, Liu X, Wang J, Chen MH, Miao R, Qu X. Efficacy and safety of durvalumab plus gemcitabine and cisplatin in Chinese participants with advanced biliary tract cancer: Extension cohort of the phase III, randomised, double-blind, placebo-controlled, global TOPAZ-1 study (2023 ESMO abstract 98P). Ann Oncol 2023; 34: S216–S7
71. Hui Z, Yu W, Fuzhen W, Liping S, Guomin Z, Jianhua L, Feng W, Ning M, Jian L, Guowei D, Tongtong M, Lin T, Shuang Z, Mingshuang L, Yuan L, Xiaoqi W, Qianqian L, Qian Z, Dan W, Tingting Y, Qiudong S, Miao W, Li L, Qian H, Yixing L, Yi L, Shaodong Y, Zhijie A, Rodewald LE, Jidong J, Huaqing W, Wenzhou Y, Zhongfu L, Qun L, Zijian F, Zundong Y, Yu W. New progress in HBV control and the cascade of health care for people living with HBV in China: evidence from the fourth national serological survey, 2020. Lancet Reg Health West Pac. 2024; 51: 101193
72. Chen X, Qin S, Gu S, Ren Z, Chen Z, Xiong J, Liu Y, Meng Z, Zhang X, Wang L, Zhang X, Zou J. Camrelizumab plus oxaliplatin-based chemotherapy as first-line therapy for advanced biliary tract cancer: a multicenter, phase 2 trial. Int J Cancer 2021; 149(11): 1944–1954
73. Qin S, Chen Z, Liu Y, Xiong J, Ren Z, Meng Z, Gu SZ, Wang L, Zou J. A phase II study of anti-PD-1 antibody camrelizumab plus FOLFOX4 or GEMOX systemic chemotherapy as first-line therapy for advanced hepatocellular carcinoma or biliary tract cancer. J Clin Oncol 2019; 37(15 suppl): 4074
74. Chen X, Wu X, Wu H, Gu Y, Shao Y, Shao Q, Zhu F, Li X, Qian X, Hu J, Zhao F, Mao W, Sun J, Wang J, Han G, Li C, Xia Y, Seesaha PK, Zhu D, Li H, Zhang J, Wang G, Wang X, Li X, Shu Y. Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. J Immunother Cancer 2020; 8(2): e001240
75. Yuan Z-g, Zeng T-m, Tao C-j, Yang G, Xu H-m, Wei W, et al. Biomarker analysis of first-line sintilimab plus gemcitabine and cisplatin in patients with advanced biliary tract cancers: results from a phase II study (2022 ASCO abstract e16189). J ClinOncol 2022; 40(16_suppl): e16189
76. Zhao S, Guo XG, Zhang D, Zhou G, Song P, Yang J, Zhang Y, Li P, Hu Y, Wang P. First-line chemotherapy or in combination with programmed cell death protein-1 antibody in patients with metastatic or recurrent biliary tract cancer. J Gastroenterol Hepatol 2021; 36(12): 3541–3547
77. Gou M, Zhang Y, Liu T, Si H, Wang Z, Yan H, Qian N, Dai G. PD-1 inhibitors could improve the efficacy of chemotherapy as first-line treatment in biliary tract cancers: a propensity score matching based analysis. Front Oncol 2021; 11: 648068
78. Tan S, Yu J, Huang Q, Zhou N, Gou H. PD-1 inhibitors plus nab-paclitaxel-containing chemotherapy for advanced gallbladder cancer in a second-line setting: a retrospective analysis of a case series. Front Oncol 2022; 12: 1006075
79. Sun D, Ma J, Wang J, Han C, Qian Y, Chen G, Li X, Zhang J, Cui P, Du W, Wu Z, Chen S, Zheng X, Yue Z, Song J, Gao C, Zhao X, Cai S, Hu Y. Anti-PD-1 therapy combined with chemotherapy in patients with advanced biliary tract cancer. Cancer Immunol Immunother 2019; 68(9): 1527–1535
80. Fan J, Zhou J, Shi G, Huang X, Guo X, Lu J, Liang F, Chen Y, Wu D, Ji Y, Hou Y, Meng X, Tang Z, Huang X, Ye Q, Qiu S, Gao Q, Shi Y, Sun H, Li H. A phase II study of SHR-1316 plus IBI310 in patients with advanced intrahepatic cholangiocarcinoma after failure of first-line therapy (2023 ESMO abstract 105P). Ann Oncol 2023; 34: S221
81. Wang X, Fu S, Zheng K, Cao G, Xu L, Yang R, Zhu X, Liu P, Gao S, Xu H, Guo J, Chen H, Wang K, Li J, Zhou J, Zhang X, Hao C, Xing B, Shen L. A phase II trial of hepatic arterial infusion chemotherapy and bevacizumab in combination with toripalimab for advanced biliary tract cancers: Interim report (2022 ESMO abstract 60P). Ann Oncol 2022; 33: S568
82. Guo Y, Feng K, Liu Y, Wu Z, Dai H, Yang Q, Wang Y, Jia H, Han W. Phase I study of chimeric antigen receptor-modified T cells in patients with EGFR-positive advanced biliary tract cancers. Clin Cancer Res 2018; 24(6): 1277–1286
83. Leem G, Jang SI, Cho JH, Jo JH, Lee HS, Chung MJ, Park JY, Bang S, Yoo DK, Cheon HC, Kim JE, Lim KP, Jung IH, Im JM, Chung YY, Park SW. Safety and efficacy of allogeneic natural killer cells in combination with pembrolizumab in patients with chemotherapy-refractory biliary tract cancer: a multicenter open-label phase 1/2a trial. Cancers (Basel) 2022; 14(17): 4229
84. Lu Z, Chang L, Zhou J, Ji Y, Sun M, Wen Q, Gao SG, Ma XL, Zhong D, Guo Q, Xiao S, Wang H, Zhu H, Zhu Y, Shen L. BL-B01D1, an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic biliary tract carcinoma (BTC). Ann Oncol 2024; 35(Suppl 2): S233
85. Zhang Q, Liu X, Wei S, Zhang L, Tian Y, Gao Z, Jin M, Yan S. Lenvatinib plus PD-1 inhibitors as first-line treatment in patients with unresectable biliary tract cancer: a single-arm, open-label, phase II study. Front Oncol 2021; 11: 751391
86. Wu Z, Zhu X, Zhong X, Wang Y, Zheng Y, Han W, Pan H, Yao J. Efficacy and safety of PD-1 inhibitor plus antiangiogenic treatment in patients with unresectable biliary tract cancer: a multicenter retrospective study. Exp Ther Med 2023; 26(1): 352
87. Shen J, Kong W, Zhu S, Liu B. A phase II study to evaluate the safety and efficacy of anlotinib combined with toripalimab for advanced biliary cancer (2022 ASCO abstract 4077). J Clin Oncol 2022; 40(16 suppl): 4077
88. Villanueva L, Lwin Z, Chung HC, Gomez-Roca C, Longo F, Yanez E, Senellart H, Doherty M, García-Corbacho J, Hendifar AE, Maurice-Dror C, Gill SS, Kim TW, Heudobler D, Penel N, Ghori R, Kubiak P, Jin F, Norwood KG, Graham D. Lenvatinib plus pembrolizumab for patients with previously treated biliary tract cancers in the multicohort phase II LEAP-005 study. J Clin

Oncol 2021; 39(3 suppl): 321 (ASCO abstract 321)
89. O'Bryan J, Yin C, Weinberg BA, Noel MS, Mukherji R, Kulasekaran M, Agarwal S, Kupfer G, Wang H, Hartley ML, Marshall J, He AR. Phase II clinical trial of olaparib plus pembrolizumab in the treatment of patients with advanced biliary tract cancer. J Clin Oncol 2023; 41(16 suppl): 4087
90. Wang D, Yang X, Long J, Lin J, Mao J, Xie F, Wang Y, Wang Y, Xun Z, Bai Y, Yang X, Guan M, Pan J, Seery S, Sang X, Zhao H. The efficacy and safety of apatinib plus camrelizumab in patients with previously treated advanced biliary tract cancer: a prospective clinical study. Front Oncol 2021; 11: 646979
91. Shi C, Li Y, Yang C, Qiao L, Tang L, Zheng Y, Chen X, Qian Y, Yang J, Wu D, Xie F. Lenvatinib plus programmed cell death protein-1 inhibitor beyond first-line systemic therapy in refractory advanced biliary tract cancer: a real-world retrospective study in China. Front Immunol 2022; 13: 946861
92. Lin J, Yang X, Long J, Zhao S, Mao J, Wang D, Bai Y, Bian J, Zhang L, Yang X, Wang A, Xie F, Shi W, Yang H, Pan J, Hu K, Guan M, Zhao L, Huo L, Mao Y, Sang X, Wang K, Zhao H. Pembrolizumab combined with lenvatinib as non-first-line therapy in patients with refractory biliary tract carcinoma. Hepatobiliary Surg Nutr 2020; 9(4): 414–424
93. Zhu S, Liu C, Dong Y, Shao J, Liu B, Shen J. A retrospective study of lenvatinib monotherapy or combined with programmed cell death protein 1 antibody in the treatment of patients with hepatocellular carcinoma or intrahepatic cholangiocarcinoma in China. Front Oncol 2021; 11: 788635
94. Chao J, Wang S, Wang H, Zhang N, Wang Y, Yang X, Zhu C, Ning C, Zhang X, Xue J, Zhang L, Piao M, Wang M, Yang X, Lu L, Zhao H. Real-world cohort study of PD-1 blockade plus lenvatinib for advanced intrahepatic cholangiocarcinoma: effectiveness, safety, and biomarker analysis. Cancer Immunol Immunother 2023; 72(11): 3717–3726
95. Jingjing L, Xu Q, Xu X, Cong L, Ying J. A phase 2 randomized, open-label, multicentre study of sintilimab and anlotinib in combination with gemcitabine plus cisplatin (GemCis) as first-line therapy in patients (pts) with advanced biliary tract cancer (BTC): SAGC. J Clin Oncol 2023; 41(16 suppl): 4015 (ASCO abstract 4015)
96. Jingjing L, Qi X, Wei Q, Han Z, Cong L, Zhang F, Ying J. A phase 2, randomized, open-label, multicenter study of sintilimab and anlotinib in combination with gemcitabine plus cisplatin (GemCis) as first-line therapy in patients (pts) with advanced biliary tract cancer (BTC): SAGC (2022 ASCO abstract 4100). J Clin Oncol 2022; 40(16 suppl): 4100
97. Shi GM, Huang XY, Wu D, Sun HC, Liang F, Ji Y, Chen Y, Yang GH, Lu JC, Meng XL, Wang XY, Sun L, Ge NL, Huang XW, Qiu SJ, Yang XR, Gao Q, He YF, Xu Y, Sun J, Ren ZG, Fan J, Zhou J. Toripalimab combined with lenvatinib and GEMOX is a promising regimen as first-line treatment for advanced intrahepatic cholangiocarcinoma: a single-center, single-arm, phase 2 study. Signal Transduct Target Ther 2023; 8(1): 106
98. Li H. A single-arm, open-label, phase II study of tislelizumab combined with lenvatinib and Gemox regimen for conversion therapy of potentially resectable locally advanced biliary tract cancers (2022 ESMO abstract 65P). Ann Oncol 2022; 33: S570
99. Guo J, Zhou Q, Zhou M, Dai H, Li L, Qiu Y, Mao L, Liu B, Shen J. Survival benefit and biomarker of PD-1 inhibitor combination therapy in first-line of advanced biliary tract cancer: a retrospective study. Cancer Med 2023; 12(22): 20699–20711
100. Zeng J, Ma J, Zeng Z, Yang L, Jiang Y, Mo N, Ma F, Liu C, Li R, Tang J, Qin S, Jiang H. A retrospective cohort study on the efficacy and safety for combination therapy of immunotherapy, targeted agent, and chemotherapy versus immunochemotherapy or chemotherapy alone in the first-line treatment of advanced biliary tract carcinoma. J Gastrointest Oncol 2023; 14(2): 758–767
101. Zhu C, Li H, Yang X, Wang S, Wang Y, Zhang N, Wang Y, Xue J, Zhang L, Ning C, Yang X, Xun Z, Chao J, Long J, Sang X, Zhu Z, Zhao H. Efficacy, safety, and prognostic factors of PD-1 inhibitors combined with lenvatinib and Gemox chemotherapy as first-line treatment in advanced intrahepatic cholangiocarcinoma: a multicenter real-world study. Cancer Immunol Immunother 2023; 72(9): 2949–2960
102. Zhu C, Xue J, Wang Y, Wang S, Zhang N, Wang Y, Zhang L, Yang X, Long J, Yang X, Sang X, Zhao H. Efficacy and safety of lenvatinib combined with PD-1/PD-L1 inhibitors plus Gemox chemotherapy in advanced biliary tract cancer. Front Immunol 2023; 14: 1109292
103. Ye Z, Zhang Y, Chen J, Wang X, Hong Y, Zhao Q. First-line PD-1 inhibitors combination therapy for patients with advanced cholangiocarcinoma: a retrospective real-world study. Int Immunopharmacol 2023; 120: 110344
104. Wang K, Liu ZH, Yu HM, Cheng YQ, Xiang YJ, Zhong JY, Ni QZ, Zhou LP, Liang C, Zhou HK, Pan WW, Guo WX, Shi J, Cheng SQ. Efficacy and safety of a triple combination of atezolizumab, bevacizumab plus GEMOX for advanced biliary tract cancer: a multicenter, single-arm, retrospective study. Therap Adv Gastroenterol 2023; 16: 17562848231160630
105. Zhang N, Yu BR, Wang YX, Zhao YM, Zhou JM, Wang M, Wang LR, Lin ZH, Zhang T, Wang L. Clinical outcomes of hepatic arterial infusion chemotherapy combined with tyrosine kinase inhibitors and anti-PD-1 immunotherapy for unresectable intrahepatic cholangiocarcinoma. J Dig Dis 2022; 23(8–9): 535–545
106. Wang Y, Xun Z, Yang X, Wang Y, Wang S, Xue J, Zhang N, Yang X, Lu Z, Zhou J, Zhou K, Sang X, Zhao H. Local-regional therapy combined with toripalimab and lenvatinib in patients with advanced biliary tract cancer. Am J Cancer Res 2023; 13(3): 1026–1037
107. Wei Z, Wang Y, Wu B, Liu Y, Wang Y, Ren Z, Yang X, Chen Q, Zhang Y. Hepatic arterial infusion chemotherapy plus lenvatinib with or without programmed cell death protein-1 inhibitors for advanced cholangiocarcinoma. Front Immunol 2023; 14: 1235724
108. Zhang T, Yang X, Yang X, Zheng K, Wang Y, Wang Y, Sang X, Lu X, Xu Y, Wang X, Zhao H. Different interventional time of hepatic arterial infusion with PD-1 inhibitor for advanced biliary tract cancer: a multicenter retrospective study. Am J Cancer Res 2022; 12(7): 3455–3463
109. Zheng Z, Wang J, Wu T, He M, Pan Y, Wang J, Chen J, Hu D, Xu L, Zhang Y, Chen M, Zhou Z. Hepatic arterial infusion chemotherapy plus targeted therapy and immunotherapy versus systemic chemotherapy for advanced intrahepatic cholangiocarcinoma: a retrospective cohort study. Int J Surg 2025; 111(1): 1552–1557

110. Cercek A, Boerner T, Tan BR, Chou JF, Gonen M, Boucher TM, Hauser HF, Do RKG, Lowery MA, Harding JJ, Varghese AM, Reidy-Lagunes D, Saltz L, Schultz N, Kingham TP, D'Angelica MI, DeMatteo RP, Drebin JA, Allen PJ, Balachandran VP, Lim KH, Sanchez-Vega F, Vachharajani N, Majella Doyle MB, Fields RC, Hawkins WG, Strasberg SM, Chapman WC, Diaz LA Jr, Kemeny NE, Jarnagin WR. Assessment of hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin in patients with unresectable intrahepatic cholangiocarcinoma: a phase 2 clinical trial. JAMA Oncol 2020; 6(1): 60–67
111. Wang Y, Zhang N, Xue J, Zhu C, Wang Y, Zhang L, Yang X, Wang H, Wang S, Chao J, Yang X, Zhao H. Safety and feasibility of toripalimab plus lenvatinib with or without radiotherapy in advanced BTC. Front Immunol 2023; 14: 1084843
112. Chen W, Xu D, Liu Q, Wu Y, Wang Y, Yang J. Unraveling the heterogeneity of cholangiocarcinoma and identifying biomarkers and therapeutic strategies with single-cell sequencing technology. Biomed Pharmacother 2023; 162: 114697
113. Xu X, Cheng S, Ding C, Lv Z, Chen D, Wu J, Zheng S. Identification of bile biomarkers of biliary tract cancer through a liquid chromatography/mass spectrometry-based metabolomic method. Mol Med Rep 2015; 11(3): 2191–2198
114. Helmink BA, Roland CL, Kiernan CM, Wargo JA. Toxicity of immune checkpoint inhibitors: considerations for the surgeon. Ann Surg Oncol 2020; 27(5): 1533–1545
115. Du R, Wang X, Ma L, Larcher LM, Tang H, Zhou H, Chen C, Wang T. Adverse reactions of targeted therapy in cancer patients: a retrospective study of hospital medical data in China. BMC Cancer 2021; 21(1): 206
116. Hsing AW, Gao YT, McGlynn KA, Niwa S, Zhang M, Han TQ, Wang BS, Chen J, Sakoda LC, Shen MC, Zhang BH, Deng J, Rashid A. Biliary tract cancer and stones in relation to chronic liver conditions: a population-based study in Shanghai, China. Int J Cancer 2007; 120(9): 1981–1985
117. Wu Q, He XD, Yu L, Liu W, Tao LY. The metabolic syndrome and risk factors for biliary tract cancer: a case-control study in China. Asian Pac J Cancer Prev 2012; 13(5): 1963–1969
118. Conde J, Oliva N, Zhang Y, Artzi N. Local triple-combination therapy results in tumour regression and prevents recurrence in a colon cancer model. Nat Mater 2016; 15(10): 1128–1138
119. Qu WF, Ding ZB, Qu XD, Tang Z, Zhu GQ, Fu XT, Zhang ZH, Zhang X, Huang A, Tang M, Tian MX, Jiang XF, Huang R, Tao CY, Fang Y, Gao J, Wu XL, Zhou J, Fan J, Liu WR, Shi YH. Conversion therapy for initially unresectable hepatocellular carcinoma using a combination of toripalimab, lenvatinib plus TACE: real-world study. BJS Open 2022; 6(5): zrac114
120. Camidge DR, Barlesi F, Goldman JW, Morgensztern D, Heist RS, Vokes EE, Spira AI, Angevin E, Su WC, Hong DS, Strickler JH, Motwani M, Sun Z, Parikh A, Noon E, Wu J, Kelly K. Results of the phase 1b study of ABBV-399 (telisotuzumab vedotin; teliso-v) in combination with erlotinib in patients with c-Met+ non-small cell lung cancer by EGFR mutation status. J Clin Oncol 2019; 37(15 suppl): 3011 (ASCO abstract 3011)
121. Han HS, Alemany CA, Brown-Glaberman UA, Pluard TJ, Sinha R, Sterrenberg D, Albain KS, Basho RK, Biggs D, Boni V, Diab S, Tsai ML, Tkaczuk KH, Wang Y, Wang Z, Meisel JL. SGNLVA-002: Single-arm, open label phase Ib/II study of ladiratuzumab vedotin (LV) in combination with pembrolizumab for first-line treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (ASCO abstract TPS1110). J Clin Oncol 2019; 37(15 suppl): TPS1110
122. Demir T, Moloney C, Mahalingam D. Emerging targeted therapies and strategies to overcome resistance in biliary tract cancers. Crit Rev Oncol Hematol 2024; 199: 104388
123. Mayr C, Kiesslich T, Modest DP, Stintzing S, Ocker M, Neureiter D. Chemoresistance and resistance to targeted therapies in biliary tract cancer: what have we learned? Expert Opin Investig Drugs 2022; 31(2): 221–233
124. Toledo B, Deiana C, Scianò F, Brandi G, Marchal JA, Perán M, Giovannetti E. Treatment resistance in pancreatic and biliary tract cancer: molecular and clinical pharmacology perspectives. Expert Rev Clin Pharmacol 2024; 17(4): 323–347
125. Bai X, Chen J, Zhang W, Zhou S, Dong L, Huang J, He X. YTHDF2 promotes gallbladder cancer progression and gemcitabine resistance via m^6A-dependent DAPK3 degradation. Cancer Sci 2023; 114(11): 4299–4313
126. Xu S, Jiang C, Lin R, Wang X, Hu X, Chen W, Chen X, Chen T. Epigenetic activation of the elongator complex sensitizes gallbladder cancer to gemcitabine therapy. J Exp Clin Cancer Res 2021; 40(1): 373
127. Yang L, Wang H, Guo M, He M, Zhang W, Zhan M, Liu Y. ELF3 promotes gemcitabine resistance through PKMYT1/CDK1 signaling pathway in gallbladder cancer. Cell Oncol (Dordr) 2023; 46(4): 1085–1095
128. Shi X, Hu Z, Bai S, Zong C, Xue H, Li Y, Li F, Chen L, Xuan J, Xia Y, Wei L, Shen F, Wang K. YBX1 promotes stemness and cisplatin insensitivity in intrahepatic cholangiocarcinoma via the AKT/β-catenin axis. J Gene Med 2024; 26(5): e3689
129. Song F, Wang CG, Wang TL, Tao YC, Mao JZ, Hu CW, Zhang Y, Tang PJ, Lu CL, Qing HL, Han L, Chen Z. Enhancement of gemcitabine sensitivity in intrahepatic cholangiocarcinoma through Saikosaponin-a mediated modulation of the p-AKT/BCL-6/ABCA1 axis. Phytomedicine 2024; 133: 155944
130. Yuan F, Zhou H, Liu C, Wang Y, Quan J, Liu J, Li H, von Itzstein M, Yu X. Heparanase interacting BCLAF1 to promote the development and drug resistance of ICC through the PERK/eIF2α pathway. Cancer Gene Ther 2024; 31(6): 904–916
131. Huang T, Cao H, Liu C, Sun X, Dai S, Liu L, Wang Y, Guo C, Wang X, Gao Y, Tang W, Xia Y. MAL2 reprograms lipid metabolism in intrahepatic cholangiocarcinoma via EGFR/SREBP-1 pathway based on single-cell RNA sequencing. Cell Death Dis 2024; 15(6): 411
132. He S, Shen J, Sun X, Liu L, Dong J. A phase II FOLFOX-4 regimen as second-line treatment in advanced biliary tract cancer refractory to gemcitabine/cisplatin. J Chemother 2014; 26(4): 243–247
133. Chen JS, Hsu C, Chiang NJ, Tsai CS, Tsou HH, Huang SF, Bai LY, Chang IC, Shiah HS, Ho CL, Yen CJ, Lee KD, Chiu CF, Rau KM, Yu MS, Yang Y, Hsieh RK, Chang JY, Shan YS, Chao Y, Chen LT, Shen WC, Hsu HC, Hsu CH, Shen YC, Wang TE, Li CP, Chen MH, Kao WY, Chang PY, Wu CC, Teng CL, Lu CH, Lin SJ, Wang BW, Chen YY, Chin YH, Chung TR, Yu WL, Lee MH, Lin LF, Lin PC, Wu YL, Wang HL, Lu LJ, Chen SY, Wu CC, Wei TC. A KRAS mutation status-stratified randomized phase II trial of gemcitabine and oxaliplatin alone or in

combination with cetuximab in advanced biliary tract cancer. Ann Oncol 2015; 26(5): 943–949

134. Chen X, Wang D, Liu J, Qiu J, Zhou J, Ying J, Shi Y, Wang Z, Lou H, Cui J, Zhang J, Liu Y, Zhao F, Pan L, Zhao J, Zhu D, Chen S, Li X, Li X, Zhu L, Shao Y, Shu Y. Genomic alterations in biliary tract cancer predict prognosis and immunotherapy outcomes. J Immunother Cancer 2021; 9(11): e003214
135. Li W, Wang Y, Yu Y, Li Q, Wang Y, Zhang C, Xu X, Guo X, Cui Y, Hao Q, Huang L, Liu H, Liu T. Toripalimab combined with gemcitabine and S-1 in the first-line treatment of advanced biliary tract cancer (2022 ASCO abstract 4081). J Clin Oncol 2022; 40(16 suppl): 4081
136. Tsurutani J, Iwata H, Krop I, Janne PA, Doi T, Takahashi S, Park H, Redfern C, Tamura K, Wise-Draper TM, Saito K, Sugihara M, Singh J, Jikoh T, Gallant G, Li BT. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. Cancer Discov 2020; 10(5): 688–701
137. Kim SB, Meric-Bernstam F, Kalyan A, Babich A, Liu R, Tanigawa T, Sommer A, Osada M, Reetz F, Laurent D, Wittemer-Rump S, Berlin J. First-in-human phase I study of aprutumab ixadotin, a fibroblast growth factor receptor 2 antibody-drug conjugate (BAY 1187982) in patients with advanced cancer. Target Oncol 2019; 14(5): 591–601