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Biliary Tract Cancer: A Review

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Abstract
The goal of this article is to better improve the prognosis and quality of life for patients with hepatobiliary by providing a summary of the drug therapy progress for advanced hepatocellular carcinoma, biliary tract cancer in 2023. This includes chemotherapy, molecular targeted therapy, and immunotherapy.

Keywords: Hepatocellular Carcinoma, Biliary Tract Cancer, Cholangiocarcinoma, Immunotherapy

Introduction

In contrast to biliary tract cancer (BTC) and pancreatic cancer, which have relatively low incidence but high fatality rates, hepatocellular carcinoma (HCC) is a tumour with a high incidence, particularly in China [1, 2]. In the past, the therapeutic treatments were relatively restricted, resulting in a major restricted access in the treatment of advanced HCC. In recent years, the development of immunotherapy and targeted therapy has provided additional therapeutic choices for HCC, boosting the survival rate of advanced HCC [3]. BTC is clinically and genetically different. Genomic and molecular profiling study indicates possible targetable molecular abnormalities. Research on targeted treatment for particular gene mutations (e.g., isocitrate dehydrogenase 1, human epidermal growth factor receptor 2 [HER2], fibroblast growth factor receptor [FGFR], and other altered molecules, has made considerable progress in the area of biliary tract malignancies [4]. To date, precisely focused therapy directed by distinct driver genes has become a major strategy for the clinical treatment of BTC, increasing the therapeutic choices for biliary tract cancers. Immunotherapy has also produced good outcomes in BTC, giving additional therapeutic options [5, 6]. This paper examines and summarizes the key advances of advanced hepatobili- ary and pancreatic malignancies in 2023, expecting to give references for current clinical therapy and future clinical research.

HCC

Targeted therapies

Both the SHARP trial in 2008 and the ORIENTAL study in 2009 demonstrated that, compared with placebo, first-line sorafenib increased the survival of patients with advanced HCC, thereby confirming sorafenib as the first-line standard therapy for inoperable HCC [7, 8]. Until 2018, no other therapies replaced sorafenib. First-line lenvatinib was shown to be superior to sorafenib in progression-free survival (PFS) and objective response rate (ORR), but inferior in overall survival (OS) according to the REFLECT study [9]. In 2020, the findings of the ZGDH3 study confirmed that donafenib was better to sorafenib in the first-line therapy of advanced HCC in OS, but only achieved noninferiority in ORR and PFS [10]. However, in many clinical trials, sorafenib is currently the control arm for the first-line therapy of HCC. There was no standard second-line therapy for HCC until the RESORCE study in 2017 thath employed Regorafenib [11], and the CELESTIAL trials of cabozantinib in 2018 [12]. The REACH trial was negative; however, a subgroup analysis indicated a benefit for ramucirumab in individuals with blood alpha-fetoprotein (AFP) amounts of 400 ng/mL or higher, and the following REACH-2 trials were undertaken in patients with AFP levels more than 400 and obtained favourable outcomes for ramucirumab [13]. In addition, Apatinib, a new oral tyrosine kinase inhibitor (TKI) targeting vascular endothelial-derived growth factor (VEGF)-2, demonstrated a substantial improvement in OS compared with placebo in the second-line therapy of HCC patients in the Chinese population [14]. However, there is still little advancement in targeted treatment for HCC in 2022 (Tables 1-2).

Table 1: Results of phase III clinical trials of first-line treatment for advanced HCC

Trial	Treatment	Control	*n*	ORR (%)	Median PFS/ TTP (mo), HR (95% CI)	Median OS (mo), HR (95% CI)	Result
Chemotherapy							
EACH	FOLFOX	Doxorubicin	371	8.15 vs. 2.67	2.93 vs. 1.77 0.62 (0.49–0.79)	6.4 vs 4.97 0.80 (0.63–1.02)	Negative
Targeted therapy							
SHARP	Sorafenib	Placebo	602	2.0 vs. 1.0	5.5 vs. 2.8 0.58 (0.45–0.74)	10.7 vs. 7.9 0.69 (0.55–0.87)	Positive
ORIENTAL	Sorafenib	Placebo	226	3.3 vs. 1.3	2.8 vs. 1.4 0.57 (0.42–0.79)	6.5 vs. 4.2 0.68 (0.50–0.93)	Positive
REFLECT	Lenvatinib	Sorafenib	954	24.1 vs. 9.2	7.4 vs. 3.7 0.66 (0.57–0.77)	13.6 vs. 12.3 0.92 (0.79–1.06)	Positive
ZGDH3	Donafenib	Sorafenib	668	4.6 vs. 2.7	3.7 vs. 3.6 0.91 (0.76–1.08)	12.1 vs. 10.3 0.83 (0.699–0.988)	Positive
Immunotherapy							
CheckMate459	Nivolumab	Sorafenib	743	15.0 vs. 7.0	3.7 vs. 3.8 0.93 (0.79–1.10)	16.4 vs. 14.7 0·85 (0.72–1.02)	Negative
RATIONALE-301	Tislelizumab	Sorafenib	674	14.3 vs. 5.4	2.1 vs. 3.4 1.11 (0.92–1.33)	15.9 vs. 14.1 0.85 (0.71–1.02)	Positive
HIMALAYA	Durvalumab	Sorafenib	778	17.0 vs. 5.1	3.65 vs. 4.07 1.02 (0.88–1.19)	16.6 vs. 13.8 0.86 (0.73–1.03)	Positive
IMbrave150	Atezolizumab + bevacizumab	Sorafenib	501	30.0 vs. 11.0	6.9 vs. 4.3 0.65 (0.53–0.81)	19.2 vs. 13.4 0.66 (0.52–0.85)	Positive
ORIENT-32	Sintilimab + bevacizumab	Sorafenib	571	21.0 vs. 4.0	4.6 vs. 2.8 0.56 (0.46–0.70)	NR vs. 10.4 0.57 (0.43–0.75)	Positive
HIMALAYA	Trimetrelizumab + durvalumab	Sorafenib	782	20.1 vs. 5.1	3.78 vs. 4.07 0.90 (0.77–1.05)	16.4 vs. 13.8 0.78 (0.65–0.92)	Positive
NCT03764293	Camrelizumab + apatinib	Sorafenib	543	25.4 vs. 5.9	5.6 vs. 3.7 0.52 (0.41–0.65)	22.1 vs. 15.2 0.62 (0.49–0.80)	Positive
COSMIC-312	Atezolizumab + cabozantinib	Sorafenib	649	11.0 vs. 4.0	6.8 vs. 4.2 0.63 (0.44–0.91)	15.4 vs. 15.5 0.90 (0.69–1.18)	Negative
LEAP-002	Pembrolizumab + lenvatinib	Lenvatinib	794	26.1 vs. 17.5	8.2 vs. 8.0 0.867 (0.734–1.024)	21.1 vs. 19.0 0.84 (0.708–0.997)	Negative

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Table 2: Results of clinical trials of second-line treatment for advanced HCC

Trial	Treatment	Control	*n*	ORR (%)	Median PFS/TTP (mo), HR (95% CI)	Median OS (mo), HR (95% CI)	Result
Targeted therapy							
RESORCE (III)	Regorafenib	Placebo	573	7.0 vs. 3.0	3.1 vs. 1.5	10.6 vs. 7.8	Positive
					0.46 (0.37–0.56)	0.63 (0.50–0.79)	
REACH-2 (III)	Ramucirumab	Placebo	292	4.6 vs. 1.1	2.8 vs. 1.6	8.5 vs. 7.3	Positive
					0.45 (0.34–0.60)	0.71 (0.53–0.95)	
CELESTIAL (III)	Cabozantinib	Placebo	760	4.0 vs. <1.0	5.2 vs. 1.9	10.2 vs. 8.0	Positive
					0.44 (0.36–0.52)	0.76 (0.63–0.92)	
AHELP (III)	Apatinib	Placebo	393	10.7 vs. 1.5	4.5 vs. 1.9	8.7 vs. 6.8	Positive
					0.47 (0.37–0.60)	0.79 (0.617–0.998)	
Immunotherapy							
CheckMate040 (I/II)	Nivolumab	–	145	14.0	4.0	15.6	Approved by FDA
KeyNote224 (II)	Pembrolizumab	–	104	17.0	4.9	12.9	Approved by FDA
NCT02989922 (II)	Camrelizumab	Placebo	217	14.7	2.1	13.8	Approved by NMPA
RATIONALE-208 (II)	Tislelizumab	Placebo	249	12.4	2.7	12.4	Approved by NMPA
KeyNote240 (III)	Pembrolizumab	Placebo	413	18.3 vs. 4.4	3.0 vs. 2.8	13.8 vs. 10.6	Negative
					0.72 (0.57–0.90)	0.78 (0.611–0.998)	
KeyNote 394 (III)	Pembrolizumab	Placebo	453	12.7 vs. 1.3	2.6 vs. 2.3	14.6 vs. 13.0	Positive
					0.74 (0.60–0.92)	0.79 (0.63–0.99)	

Note: –, not available or applicable.

Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; NMPA, National Medical Products Administration; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Single agent immunotherapy in first line

Single-drug immunotherapy has been studied in many phase III trials in HCC (Table 1). CheckMate459 study head-to-head comparing nivolumab with sorafenib as first-line treatment failed to show superiority for nivolumab over sorafenib in terms of OS, whereby median OS (mOS) was 16.4 months (95% [confidence interval] CI: 13.9–18.4) in the nivolumab group and 14.7 months (95% CI: 11.9–17.2) in the sorafenib group, with a hazard ratio of 0.85 (95% CI: 0.72–1.02, p = 0.075), but a good safety profile was reported in the nivolumab arm [15]. However, the indication for nivolumab in HCC was removed owing to disappointing findings from Check- Mate459. Tislelizumab is a monoclonal antibody with a strong binding affinity to programmed death protein-1 (PD-1). RATIONALE-301 is a worldwide multicenter phase III trial. The final analysis was released at the European Society for Medical Oncology (ESMO) 2022. Tislelizumab met the main endpoint of OS in a noninferiority efficacy test compared to sorafenib as a first-line therapy for unresectable HCC (15.9 vs. 14.1 months, hazard ratio [HR] = 0.85, p = 0.040). However, the ORR in the tislelizumab group was considerably superior than that in the sorafenib group (14.3% vs. 5.4%), notably in the median duration of response (DOR) (36.1 vs. 11.0 months). There were also fewer treatment- associated adverse events (AEs) and grade 3 or higher treatment-related AEs with tislelizumab [16]. Additionally, durvalumab is a programmed death ligand-1 (PD- L1) monoclonal antibody. In the HIMALAYA trial, durvalumab monotherapy was compared with sorafenib, and obtained OS with noninferiority and non-superiority (16.56 vs. 13.77 months, HR = 0.86, p = 0.0398) [17]. The outcomes of the above three trials are nearly consistent: First-line single-drug immunotherapy is noninferior to but not superior to sorafenib, however the ORR and tolerability are better than sorafenib. Therefore, the aforementioned three drugs may be employed as therapy choices for people who are contraindicated or at increased risk of TKIs and antiangiogenic agenrs.

Second-line

CheckMate040 (phase I/II) (ORR: 14%, median PFS [mPFS]: 4.0 months, mOS: 15.6 months) and KeyNote224 (phase II) (ORR: 17%, mPFS: 4.9 months, mOS: 12.9 months) have launched HCC immunotherapy [18, 19] (Table 2). Based on these two trials, nivolumab and pembrolizumab acquired Food and Drug Administration (FDA) approval in July 2017 and November 2018, respectively, for the treatment of HCC patients who had failed sorafenib. In a study (NCT02989922) released in 2018, the ORR of camrelizumab in the second-line therapy of HCC was 14.7%, the mPFS was 2.1 months, and the mOS was 13.8 months [20]. Another trial, RATIONALE 208 is an open-label, worldwide multicenter, phase II clinical investigation (NCT03419897), which was presented at the American Society of Clinical Oncology gastrointestinal (ASCO-GI) in 2022. The results have showed that Tislelizumab monotherapy had acceptable clinical activity and was well tolerated in previously treated patients with advanced HCC, with an ORR of 13.3% (95% CI: 9.3–18.1),

the mPFS was 2.7 months (95% CI: 1.4–2.8), and the mOS was 13.2 months (95% CI: 10.8–15.0) [21]. KeyNote-240 is a phase III, randomized controlled, worldwide multicenter study based on KeyNote224, aiming to investigate the effectiveness and safety of pembrolizumab against placebo in patients with advanced HCC treated with sorafenib. However, the data reported by ASCO in 2019 did not fulfil the established end points of OS and PFS. At the end analysis, the mOS was 13.9 and 10.6 months, mPFS was 3.0 and 2.8 months, and ORR was 18.3% and 4.4% in the pembrolizumab group and placebo group, respectively [22]. A prolonged follow-up in 2021 also did not satisfy the statistical analysis [23]. However, comparable research in the Asian population was KeyNote394, presented at the ASCO-GI 2022. The mOS was 14.6 months (95% CI: 12.6–18.0), and there was a 21% decrease in the risk of mortality (HR = 0.79, 95% CI: 0.63–0.99, p = 0.018) in the pembrolizumab group compared to placebo in previously treated patients with advanced HCC. Long-term survival was also considerably enhanced in the pembrolizumab group compared with the placebo group, with 2-year survival rates of 34.3% and 24.9%, respectively [24].

Combined immunotherapy

Combined immunotherapy is to date, the first-line standard treatment for HCC. The IMbrave150 revealed that atezolizumab (PD-L1 antibody) with bevacizumab was superior to sorafenib in terms of OS, PFS, and ORR in first-line therapy of advanced HCC [25, 26]. Similarly, the ORIENT-32 indicated that first-line sintilimab (PD-1 antibody) with bevacizumab was superior to sorafenib [27] (Table 1). The HIMALAYA project is a multicohort phase III research examining the first-line effectiveness of the combination immunotherapy (STRIDE protocol): Durvalumab (PD- L1 antibody) with tremelimumab (cytotoxic T- lymphocyte antigen 4 [CTLA-4] antibody) in advanced HCC. The final findings given at the ASCO-GI conference in 2022 reported that the mOS of the STRIDE regimen was 16.4 months, whereas the mOS of sorafenib was 13.8 months (HR = 0.78, p = 0.004), satisfying primary endpoint of the higher effectiveness in terms of OS. The ORR of the STRIDE regimen was greater (20.1% vs. 5.1%), but the mPFS was not better to that of sorafenib (3.78 vs. 4.07, HR = 0.90, 95% CI: 0.77–1.05), Regarding the safety of single beginning dose of tremelimumab + regularly durvalumab was tolerable, resulting in a lower frequency of treatment related side events than sorafenib [17]. The ultimate results of a phase III study (NCT03764239) announced at ESMO in 2022 demonstrated that camrelizumab (anti-PD-1 IgG4 anti- body) with apatinib (small-molecule TKI targeting VEGF receptor type 2) was better to sorafenib: OS (22.1 vs. 15.2 months, HR = 0.62, 95% CI: 0.49–0.80, p < 0.0001), PFS (5.6 vs. 3.7 months, HR = 0.52, 95% CI: 0.41–0.65, p < 0.0001), and ORR (25.4% vs. 5.9%, p < 0.0001) were considerably improved, and the combination of camrelizumab with apatinib was likewise well tolerated [16]. However, in the COSMIC-312 study published in 2021, atezolizumab (anti-PD-L1 antibody) + cabozantinib (a multitargeted small-molecule TKI) against sorafenib in the first-line therapy of advanced HCC revealed enhanced mPFS (6.8 vs. 4.2 months, HR = 0.63, 95% CI: 0.44–0.91, p = 0.001) in the combination group, whereas mOS (15.4 vs. 15.5, HR = 0.90, 95% CI: 0.69–1.18, p = 0.440) and ORR (11% vs. 4%) did not improve dramatically [28]. A phase III trial of LEAP-002 was largely predicted given the strong ORR and PFS outcomes of lenvatinib + pembrolizumab in a phase Ib trial (NCT03006926) [29]. Regrettably, the major findings of the LEAP-002 research published at the ESMO conference in 2022 indicated that the combination following first-line therapy did not substantially enhance OS (21.1 months vs. 19.0 months, HR = 0.84, p = 0.023) and PFS (8.2 months vs. 8.0 months, HR = 0.87, p = 0.047) compared to lenvatinib alone (failed to satisfy prespecified statistical difference), and only improvements were detected in ORR (26.1% vs. 17.5%) and DOR (11.2 vs. 8.5 months) [30].

Biliary tract cancer

HER 2 positive

HER2 alterations, including amplification, overexpression, or both, were found in about 19% of gallbladder tumors, 17% of extrahepatic cholangiocarcinomas, 13% of ampullary carcinomas, and 5% of intrahepatic cholangio-carcinomas [4, 31]. In the previous MyPathway trial, trastuzumab with pertuzumab had an ORR of 23% in HER2-mutated advanced BTC, with mPFS and OS of 4.0 and 10.9 months, respectively [32] (Table 3). In a phase I of zanidatamab (ZW25), a HER2 bispecific antibody, was utilised in 21 patients with HER2-mutated advanced BTC, and the ORR was 38% [33, 34]. Neratinib is irreversible pan-HER TKI. In the SUMMIT trial, 25 patients with HER2-mutated advanced biliary tumors treated with neratinib had an ORR of 16%, a mPFS of 2.8 months, and a mOS of 5.4 months [35]. The 2022 ASCO conference reported trastuzumab deruxtecan in the treatment of patients with HER2-expressing unresectable or recurrent BTC. The investigator-initiated multicenter phase II research (HERB trial) in a total of 22 HER2-positive patients showed an ORR of 36.4%, a mPFS of 4.4 months, and a mOS of 7.1 months. For the eight patients with low HER2 expression (immunohistochemistry [IHC]/in situ hybridiza- tion status 0/+, 1+/−, 1+/+, 2+/−), the ORR was 12.5%, and the mPFS and OS were 4.2 and 8.9 months, respectively. However, the prevalence of grade 3/4 AEs in this trial was as high as 81.3%, and eight patients complicated with interstitial lung disease or pneumonia, indicating that additional care should be given to the adverse drug reactions of trastuzumab deruxtecan [36]. In addition, a multicenter phase II study (KCSG-HB19-14) undertaken by the Korea Cancer Research Group published at ASCO 2022 demonstrated the ORR of trastuzumab with FOLFOX in gemcitabine/ cisplatin refractory HER2-positive BTC reached 29.4% of 34 patients. The mPFS and OS were 5.1 and 10.7 months, respectively, with HER2 expressing IHC3+ (n = 23, 67.6%) indicating a tendency toward higher PFS (5.5 vs. 4.9 months, HR = 0.52, 95% CI: 0.23–1.16) [37].

Table 3: Results of clinical trials of treatment for advanced BTC

Trial	Treatment	Phase	Line	*n*	ORR (%)	Median PFS (mo), HR (*p*-value)	Median OS (mo), HR (*p*-value)	Result
Chemotherapy								
ABC-02	GemCis vs. Gemcitabine	III	1st	410	26.1 vs. 15.5	8.0 vs. 5.0 ($p < 0.001$)	11.7 vs. 8.1 ($p < 0.001$)	Positive
JCOG1113	Gemcitabine + S-1 vs. GemCis	III	1st	354	29.8 vs. 32.4	6.8 vs. 5.8	15.1 vs. 13-4 ($p = 0.046$)	Noninferiority
KHBO1401	GemCis + S-1 vs. GemCis	III	1st	246	41.5 vs. 15.0	7.4 vs. 5.5 ($p = 0.0015$)	13.5 vs. 12.6 ($p = 0.046$)	Positive
ABC-06	FOLFOX + ASC vs. ASC	III	2nd	292	5.0	4.0	6.2 vs. 5.3	Positive
HER2 targeted								
MyPathway	Trastuzumab + pertuzumab	II	2nd	39	23.0	4.0	10.9	–
NCT02892123	Zanidatamab	I	2nd	21	38.0	3.5	–	–
SUMMIT (II)	Neratinib	II	2nd	25	16.0	2.8	5.4	–
KCSG-HB19-14	Trustuzumab + FOLFOX	II	2nd	34	29.4	5.1	10.7	–
HERB	T-DXd (DS-8201)	II	2nd	30	36.4	5.1	7.1	–
IDH1 targeted								
ClarIDHy	Ivosidenib vs. placebo	III	2nd	187	2.4	2.7 vs. 1.4 ($p < 0.001$)	10.3 vs. 7.5 ($p = 0.093$)	Positive
FGFR trageted								
FIGHT202	Pemigatinib	II	2nd	107	37.0	7.0	17.5	Approved by FDA
CIBI375A201	Pemigatinib	II	2nd	30	60.0	9.1	–	Approved by NMPA
NCT02150967	Infigratinib	II	2nd	108	23.1	7.3	12.2	–
NCT02699606	Erdafitinib	II	2nd	22	40.9	5.6	40.2	–
FIDES-01	Derazantinib	II	2nd	103	21.4	8.0	17.2	–
FOENIX-CCA2	Futibatinib	II	2nd	28	41.7	8.9	20.0	–
ReFocus	RLY-4008	II	2nd	38	63.2	–	–	–
BRAF-V600E targeted								
NCT02034110	Dabrafenib + trametinib	II	2nd	43	47.0	9.0	14.0	–
Immunotherapy (MSI-H/dMMR)								
KEYNOTE-016	Pembrolizumab	II	2nd	4	53.0	–	–	–
KEYNOTE-158	Pembrolizumab	II	2nd	9	37.0	–	–	–
Immunotherapy (MSS/pMMR)								
Kim et al.	Nivolumab	II	2nd	54	22.0	3.68	14.24	–
Ueno et al.	Nivolumab	I	1st	30	3.3	1.4	5.2	–
KEYNOTE-158	Pembrolizumab	II	2nd	104	5.8	2.0	7.4	–

FGFR targeted treatment

FGFR 1–4 gene mutations are one of the major oncogenic drivers of BTC, particularly intrahepatic cholangiocarcinomas, where FGFR2 mutations are detect possible in ~14% of individuals, the great majority of which are fusion mutations [5, 38]. Pemigatinib, a pan-FGFR (FGFR 1–3) inhibitor, was authorised by the FDA on April 2020, for the treatment of adult patients with FGFR2 fusion cholangiocarcinoma based on the findings of the FIGHT-202 [39] (Table 3). The findings of the FIGHT-202 were updated at ESMO 2022. In 107 patients with FGFR2 fusion/rearrangement mutations, ORR was 37%, disease control rate (DCR) was 82%, and mPFS and mOS were 7.0 and 17.5 months [16].

The Phase II CIBI375A201 trial, enrolled a total of 30 patients with advanced cholangiocarcinoma with FGFR2 fusion/rearrangement mutations who failed conventional treatment first line, received pemigatinib in second line and resulting in an ORR of 60%, DCR of 100%, and mPFS of 9.1 months, as revised at ASCO 2022 [40]. In addition, numerous pan-FGFR inhibitors like infigratinib, erdafitinib, dera- zantinib, and futibatinib were evaluated in phase II trials in advanced BTC patients with FGFR2 fusion/ rearrangement mutations, leading in ORRs of 21.4%–41.7%, DCR of 75.7%–84.3%, mPFS of 5.6–8.9 months and mOS of 12.2–40.2 months [41-44]. RLY-4008, a high selective FGFR2 inhibitor, is a powerful and selective FGFR2 inhibitor compared with pan-FGFR inhibitors, which displayed good action in FGFRi- sensitive or drug-resistant exosomal model of cholangio- carcinoma [45]. Preliminary effectiveness findings from the ReFocus study with RLY-4008, which were announced at the 2022 ESMO meeting, in patients with FGFR2 fusion/Altered BTC not previously treated with FGFR inhibitors demonstrated an ORR of 63.2% and a DCR of 94.7% in a total of 38 patients across all dosage groups [45]. The 70 mg dosage group was the recommended dose in the phase II research, in which the 17 patients who received the 70 mg dose had an ORR of

88.2% and a DCR of 100%, encouraging future extension of the study.

Immunotherapy

For patients with cholangiocarcinoma with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) mutations, pembrolizumab alone achieved ORR of 53% and 37% in KEYNOTE-016 [46] and KEYNOTE-158 studies [47], while the percentage of MSI-H/dMMR in cholangiocarcinoma was quite low [48]. However, for patients with cholangiocarcinoma with non-MSI-H/dMMR, the effectiveness of single-agent immunotherapy is still unknown, and only small sample studies have been reported (Table 3). Kim *et al*. observed that the ORR of nivolumab in the second- line or beyond the treatment of advanced cholangiocarcinoma was 22%, and mPFS and mOS were 3.68 and 14.24 months, respectively [49]. In contrast, Ueno *et al*. found an ORR of 3.3% with first line nivolumab, and mPFS and mOS were 1.4 and 5.2 months, respectively [50]. In the KEYNOTE-158 trial, 104 patients with advanced cholangiocarcinoma who received single agent pembrolizumab had an ORR of 5.8%, mPFS and mOS of 2.0 and 7.4 months, respectively [51]. Doki *et al*. found an ORR of 4.8%, mPFS, and mOS of 1.5 and 8.1 months, respectively, in second-line or beyond durvalumab treatment in 42 individuals with advanced cholangiocarcinoma [52].

However, better ORR has been found in numerous phase II trials of immunotherapy with chemotherapy. In two phase II investigations (NCT03092895 and NCT03486678) [53, 54], camrelizumab in combination with GEMOX or FOLFOX showed an ORR of 10.3%–54%, but in the JapicCTI-153098, the ORR of gemcitabine plus cisplatin (Gem-Cis) + nivolumab was 37%, which was considerably improved compared with nivolumab monotherapy (ORR was 3%) [50]. In two further phase II trials (NCT03796429 and TCOG T1219), the ORR of toripalimab or nivolumab combination with gemcitabine and TS-1 (tegafur, gimeracil, and oteracil potassium capsules) were 30.6% and 43.8%, respectively, and mPFS were 7.0 and 9.1 months, respectively [55, 56]. Nevertheless, TOPAZ-1 is the only phase III randomized controlled trial with good outcomes revealing a substantial survival advantage of durvalumab with chemotherapy compared with chemotherapy. The findings reported at ASCO-GI in 2022 demonstrated that compared with GemCis, durvalumab with GemCis substantially enhanced ORR (26.7% vs. 18.7%), PFS (7.2 vs. 5.7 months, HR = 0.75, 95% CI: 0.64–0.89, p = 0.001), and OS (12.8 vs. 11.5 months, HR = 0.80, 95% CI: 0.66–0.97, p = 0.021). The safety of combo therapy is manageable, and durvalumab paired with GemCis gives a novel alternative for the first-line treatment of advanced BTC [57].

Conclusion

Hepatobiliary are malignancies with unfavourable prognoses. However, for advanced conditions, systematic treatment may obviously deliver survival advantages to patients. Looking back to 2023, these accomplishments in the area of medical treatment of hepatobiliary and pancreatic cancers will have a substantial influence on future clinical practice and guide future clinical research.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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