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REVIEW

CANCER INNOVATION

Advances in medical treatment of advanced hepatobiliary and pancreatic cancer in 2022

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Abstract

This article summarizes the drug therapy progress of advanced hepatocellular carcinoma, biliary tract cancer, and pancreatic cancer in 2022, including chemotherapy, molecular targeted therapy, and immunotherapy, to provide reference information for current clinical treatment and future clinical research, and to better improve prognosis and quality of life in patients with hepatobiliary and pancreatic cancer.

KEYWORDS

hepatocellular carcinoma, biliary tract cancer, cholangiocarcinoma, pancreatic cancer, chemotherapy, targeted therapy, immunotherapy

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is a tumor with high incidence, especially in China, while biliary tract cancer (BTC) and pancreatic cancer are tumors with relatively low incidence, while HCC, BTC, and pancreatic cancer are tumors with high mortality [1, 2]. In the past, the treatment drugs were very limited, resulting in a great bottleneck in the treatment of advanced HCC. In recent years, the development of immunotherapy and targeted therapy has brought more treatment options for HCC, raising the survival rate of advanced HCC to a new high [3]. BTC is clinically and genetically heterogeneous. Genomic and molecular profiling analysis reveals potential targetable molecular aberrations. Research on targeted therapy for specific gene mutations (e.g., isocitrate dehydrogenase 1, human epidermal growth factor receptor 2 [HER2], fibroblast growth factor receptor [FGFR], and other mutated molecules) has made great progress in the field of biliary tract malignancies [4]. At present, precisely targeted therapy guided by different driver genes has become an important strategy for the clinical treatment of BTC, enriching the treatment options for biliary tract tumors. Immunotherapy has also achieved positive results in BTC, adding new treatment options [5]. However, chemotherapy is still the main treatment for pancreatic cancer, and optimization of the chemotherapy regimens is

Abbreviations: AEs, adverse events; AFP, alpha-fetoprotein; ASCO, American Society of Clinical Oncology; BTC, biliary tract cancer; CTLA-4, cytotoxic T-lymphocyte antigen 4; DCR, disease control rate; dMMR, deficient of mismatch repair; DOR, duration of response; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GI, gastrointestinal; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; MSI-H, microsatellite instability-high; NMPA, National Medical Products Administration; ORR, objective response rate; OS, overall survival; PD-1, programmed death protein-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial-derived growth factor.

still one of the exploration directions for pancreatic cancer, while targeted therapy and immunotherapy have also seen some dawn in exploratory research [6]. This article reviews and summarizes the main progress of advanced hepatobiliary and pancreatic tumors in 2022, hoping to provide references for current clinical treatment and future clinical research.

2 | HCC

2.1 | Targeted therapy

Both the SHARP study in 2008 and the ORIENTAL study in 2009 confirmed that compared with placebo, first-line sorafenib improved the survival of patients with advanced HCC, thus establishing sorafenib as the first-line standard treatment for inoperable HCC [7, 8]. Until 2018, no other drug could replace sorafenib. The REFLECT study confirmed that first-line lenvatinib was not inferior to sorafenib in overall survival (OS), and is superior to sorafenib in progression-free survival (PFS) and objective response rate (ORR) [9]. In 2020, the results of the ZGDH3 study confirmed that donafenib was superior to sorafenib in the first-line treatment of advanced HCC in OS, but only achieved noninferiority in ORR and PFS [10]. However, in many clinical studies, sorafenib is still the standard control for the first-line treatment of HCC. There was no standard second-line treatment for HCC until the RESORCE results of regorafenib in 2017 [11], and the CELESTIAL results of cabozantinib in 2018 [12]. The REACH study was negative, but a subgroup analysis found a benefit for ramucirumab in those with serum alpha-fetoprotein (AFP) concentrations of 400 ng/mL or higher, and the subsequent REACH-2 studies were conducted in those with AFP levels greater than 400 and achieved positive results for ramucirumab [13]. In addition, apatinib, a novel oral tyrosine kinase inhibitor (TKI) targeting vascular endothelial-derived growth factor (VEGF)-2, also achieved a significant improvement in OS compared with placebo in the second-line treatment of HCC patients in the Chinese population [14]. However, there is still no progress in targeted therapy for HCC in 2022 (Tables 1–2).

2.2 | Immunotherapy

2.2.1 | Single-drug immunotherapy

2.2.1.1 | *First-line treatment*

Single-drug immunotherapy has been explored in many phase III studies in HCC (Table 1). CheckMate459 study head-to-head comparing nivolumab and sorafenib as first-line therapy failed to demonstrate superiority for nivolumab over sorafenib in terms of OS, which 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 favorable safety profile was observed in the nivolumab arm [15]. However, the indication for nivolumab in HCC was withdrawn due to negative results from CheckMate459. Tislelizumab is a monoclonal antibody with a high binding affinity to programmed death protein-1 (PD-1). RATIONALE-301 is a global multicenter phase III study. The final analysis was published at the European Society for Medical Oncology (ESMO) 2022. Tislelizumab met the primary endpoint of OS in a noninferiority efficacy test compared to sorafenib as a first-line treatment 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 significantly better than that in the sorafenib group (14.3% vs. 5.4%), especially in the median duration of response (DOR) (36.1 vs. 11.0 months). There were also fewer treatment-related 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 study, durvalumab monotherapy was compared with sorafenib, and achieved OS with noninferiority and non-superiority (16.56 vs. 13.77 months, HR = 0.86, $p = 0.0398$) [17]. The results of the above three studies are almost consistent: first-line single-drug immunotherapy is noninferior to but not superior to sorafenib, but the ORR and tolerability are better than sorafenib. Therefore, the above three drugs can be used as treatment options for patients who are contraindicated or at greater risk of TKIs and antiangiogenic drugs.

2.2.1.2 | *Second-line treatment*

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 initiated HCC immunotherapy [18, 19] (Table 2). Based on these two studies, nivolumab and pembrolizumab received Food and Drug Administration (FDA) approval in July 2017 and November 2018, respectively, for the treatment of HCC patients who had failed sorafenib. The National Medical Products Administration (NMPA) of China has also approved two PD-1 antibodies for the second-line treatment of HCC based on the results of two phase II studies. In a study (NCT02989922) published in 2018, the ORR of camrelizumab in the second-line treatment of HCC was 14.7%, the mPFS was 2.1 months, and the mOS was 13.8 months [20].

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.

Another study of RATINALE-208 is an open-label, global multicenter, phase II clinical study (NCT03419897), which was presented at the American Society of Clinical Oncology gastrointestinal (ASCO-GI) in 2022. The results showed that tislelizumab monotherapy showed favorable 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, global multicenter study based on KeyNote224, designed to evaluate the efficacy

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.

and safety of pembrolizumab versus placebo in patients with advanced HCC treated with sorafenib. However, the results published by ASCO in 2019 did not meet the preset common endpoints of OS and PFS. At the final 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 longer follow-up in 2021 also did not reach the statistical endpoint [23]. However, a similar study in the Asian population, the KeyNote394 study presented at the ASCO-GI meeting in 2022, achieved positive results on the expected endpoint compared with placebo plus best supportive care. The mOS was 14.6 months (95% CI: 12.6–18.0), and there was a 21% reduction in the risk of death (HR = 0.79, 95% CI: 0.63–0.99, $p = 0.018$) in the pembrolizumab group of previously treated patients with advanced HCC. Long-term survival was also significantly improved in the pembrolizumab group compared with the placebo group, with 2-year survival rates of 34.3% and 24.9%, respectively [24].

2.2.2 | Combined immunotherapy

Combined immunotherapy has become the first-line standard treatment for HCC. The IMbrave150 study confirmed that atezolizumab (PD-L1 antibody) combined with bevacizumab was significantly superior to sorafenib in terms of OS, PFS, and ORR in the first-line treatment of advanced HCC [25, 26]. Similarly, the ORIENT-32 study demonstrated that first-line sintilimab (PD-1 antibody) plus bevacizumab was superior to sorafenib [27]. And these two regimens have been approved by the NMPA of China for the first-line treatment of advanced HCC. Several other immunotherapy studies have also been successful (Table 1). The

HIMALAYA study is a multicohort phase III study exploring the first-line efficacy of the combined immunotherapy (STRIDE protocol): durvalumab (PD-L1 antibody) plus trimetrelizumab (cytotoxic T-lymphocyte antigen 4 [CTLA-4] antibody) in advanced HCC. The final results reported at the ASCO-GI meeting in 2022 showed that the mOS of the STRIDE regimen was 16.4 months, while the mOS of sorafenib was 13.8 months (HR = 0.78, $p = 0.004$), reaching the primary endpoint of the superior efficacy in terms of OS. The ORR of the STRIDE regimen was higher (20.1% vs. 5.1%), but the mPFS was not superior to that of sorafenib (3.78 vs. 4.07, HR = 0.90, 95% CI: 0.77–1.05), and the safety of single starting dose of tremelimumab plus regularly spaced durvalumab was manageable, resulting in a lower incidence of treatment-related adverse events than sorafenib [17]. The final results of a phase III study (NCT03764239) reported at ESMO in 2022 showed that camrelizumab (anti-PD-1 IgG4 antibody) plus apatinib (small-molecule TKI targeting VEGF receptor type 2) was superior 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 significantly improved, and the combination of camrelizumab and apatinib was also well tolerated [16]. However, in the COSMIC-312 study published in 2021, atezolizumab (anti-PD-L1 antibody) plus cabozantinib (a multitargeted small-molecule TKI) versus sorafenib in the first-line treatment of advanced HCC showed improved mPFS (6.8 vs. 4.2 months, HR = 0.63, 95% CI: 0.44–0.91, $p = 0.001$) in the combination group, but 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 significantly [28]. A phase III study of LEAP-002 was widely anticipated given the excellent ORR and PFS results of lenvatinib plus pembrolizumab in a phase Ib study (NCT03006926) [29]. Regrettably, the primary results of the LEAP-002 study presented at the ESMO meeting in 2022 showed that the combination regimen first-line treatment did not significantly improve 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 reach prespecified statistical difference), and only improvements were observed in ORR (26.1% vs. 17.5%) and DOR (11.2 vs. 8.5 months) [30]. The three similar studies above yielded different results, adding to the complexity of the HCC immunotherapy puzzle. Whether the results are different due to different populations, different immunotherapy drugs, different TKI drugs, or different control groups is still unclear and needs to be further explored.

3 | BTC

3.1 | Targeted therapy

3.1.1 | HER2 targeted therapy

HER2 mutations, including amplification, overexpression, or both, were observed in approximately 19% of gallbladder tumors, 17% of extrahepatic cholangiocarcinomas, 13% of ampullary carcinomas, and 5% of intrahepatic cholangiocarcinomas [4, 31]. In the earlier MyPathway study, trastuzumab plus 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 study of zanidatamab (ZW25), a HER2 bispecific antibody, was used in 21 patients with HER2-mutated advanced BTC, and the ORR was 38% [33, 34]. Neratinib is an irreversible pan-HER TKI. In the SUMMIT study, 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 meeting reported trastuzumab deruxtecan (DS-8201) in the treatment of patients with HER2-expressing unresectable or recurrent BTC. The investigator-initiated multicenter phase II study (HERB trial) in a total of 22 HER2-positive patients had 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 hybridization 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 incidence of grade 3/4 AEs in this study was as high as 81.3%, and eight patients complicated with interstitial lung disease or pneumonia, suggesting that special attention should be paid to the adverse drug reactions of DS-8201 [36]. In addition, a multicenter phase II trial (KCSG-HB19-14) conducted by the Korea Cancer Research Group reported at ASCO 2022 that the ORR of trastuzumab plus 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%) showing a trend toward better PFS (5.5 vs. 4.9 months, HR = 0.52, 95% CI: 0.23–1.16) [37].

3.1.2 | FGFR targeted therapy

FGFR 1–4 gene alterations are one of the common oncogenic drivers of BTC, especially intrahepatic cholangiocarcinomas, where FGFR2 mutations are detectable in ~14% of patients, the vast majority of which are fusion mutations [5, 38]. Pemigatinib, a pan-FGFR (FGFR 1–3) inhibitor, was approved by the FDA on

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								
ClarlDHy	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	–

(Continues)

TABLE 3 (Continued)

Trial	Treatment	Phase	Line	*n*	ORR (%)	Median PFS (mo), HR (*p*-value)	Median OS (mo), HR (*p*-value)	Result
Doki et al.	Durvalumab	II	2nd	42	4.8	1.5	8.1	–
NCT03092895	Camrelizumab + Gemox	II	1st	63	19.0	3.8	13.6	–
	Camrelizumab + FOLFOX	II	1st	29	10.3	5.5	12.0	–
NCT03486678	Camrelizumab + Gemox	II	1st	38	54.0	6.1	11.8	–
JapicCTI-153098	Nivolumab + GemCis vs. nivolumab	I	1st	60	37.0 vs. 3.0	4.2 vs. 1.4	15.4 vs. 5.2	–
NCT03796429	Toripalimab + Gemcitabine + S-1	II	1st	50	30.6	7.0	15.0	–
TCOG T1219	Nivolumab + Gemcitabine + S-1	II	1st	48	43.8	9.1	–	–
TOPAZ-1	Durvalumab + GemCis vs. GemCis	III	1st	685	26.7 vs. 18.7	7.2 vs. 5.7 ($p = 0.001$)	12.8 vs. 11.5 ($p = 0.021$)	Positive

Note: –, not available or applicable.

Abbreviations: ASC, active symptom control; BTC, biliary tract cancer; CI, confidence interval; dMMR, deficient of mismatch repair; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GemCis, gemcitabine plus cisplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDH1, isocitrate dehydrogenase 1; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NMPA, National Medical Products Administration; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, proficient mismatch repair; T-DXd, trastuzumab deruxtecan.

April 17, 2020, for the treatment of adult patients with FGFR2 fusion cholangiocarcinoma based on the results of the FIGHT-202 study [39] (Table 3). The results of the FIGHT-202 study 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]. Based on the results of the Phase II CIBI375A201 bridging trial of pemigatinib in China, pemigatinib was officially approved by the NMPA of China in April 2022 for the treatment of adults with advanced, metastatic or inoperable cholangiocarcinoma, who have received at least one prior systemic therapy and have detected FGFR2 fusion or rearrangement. In this study, a total of 30 patients with advanced cholangiocarcinoma and FGFR2 fusion/rearrangement mutations who failed standard therapy received pemigatinib, resulting in an ORR of 60%, DCR of 100%, and mPFS of 9.1 months, as updated at ASCO 2022 [40]. In addition, multiple pan-FGFR inhibitors including infigratinib, erdafitinib, derazantinib, and futibatinib were tested in phase II studies in advanced BTC patients with FGFR2 fusion/rearrangement mutations, resulting 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]. Whereas, RLY-4008, a highly selective FGFR2 inhibitor, is a potent and selective FGFR2 inhibitor compared with pan-FGFR inhibitors, which exhibited strong activity in FGFRi-sensitive or drug-resistant exosomal model of cholangiocarcinoma [45]. Preliminary efficacy data from the ReFocus trial of RLY-4008, which were reported at the 2022 ESMO congress, in patients with FGFR2 fusion/rearranged BTC not previously treated with FGFR inhibitors showed an ORR of 63.2% and a DCR of 94.7% in a total of 38 patients across all dose groups [45]. The 70 mg dose group was the recommended dose in the phase II study, in which the 17 patients who received the 70 mg dose had an ORR of 88.2% and a DCR of 100%, supporting further expansion of the study.

3.2 | Immunotherapy

For patients of 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 study [47], but the proportion of

MSI-H/dMMR in cholangiocarcinoma was very low [48]. However, for patients of cholangiocarcinoma with non-MSI-H/dMMR, the efficacy of single-agent immunotherapy is still unclear, and only small sample studies have been reported (Table 3). Kim et al. reported 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. reported 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 study, 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. reported an ORR of 4.8%, mPFS, and mOS of 1.5 and 8.1 months, respectively, in second-line or beyond durvalumab therapy in 42 patients with advanced cholangiocarcinoma [52].

However, improved ORR has been observed in many phase II studies of immunotherapy combined with chemotherapy. In two phase II studies (NCT03092895 and NCT03486678) [53, 54], camrelizumab in combination with GEMOX or FOLFOX had an ORR of 10.3%–54%, while in the JapicCTI-153098 study, the ORR of gemcitabine plus cisplatin (GemCis) plus nivolumab was 37%, which was significantly improved compared with nivolumab monotherapy (ORR was 3%) [50]. In two other phase II studies (NCT03796429 and TCOG T1219), the ORR of toripalimab or nivolumab combined 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 study with definitively positive results demonstrating a significant survival benefit of durvalumab plus chemotherapy compared with standard chemotherapy. The results published by ASCO-GI in 2022 showed that compared with GemCis, durvalumab plus GemCis significantly improved 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 combination therapy is controllable, and durvalumab combined with GemCis provides a new option for the first-line treatment of advanced BTC [57]. In addition to the above-mentioned schemes, there are many other immunocombined treatment schemes for advanced BTC, such as PD-1 antibody or PD-L1 antibody combined with antiangiogenic TKI drugs or CTLA4 antibody, or on the basis of the above combination chemotherapy. However, most of them are small-sample studies, and there is no definite conclusion yet.

4 | PANCREATIC CANCER

4.1 | Chemotherapy

At the 2021 ESMO meeting, Taieb et al. reported a European real-world study on the effect of treatment sequence on prognosis in metastatic pancreatic adenocarcinoma, finding that the longest OS line was found in the sequential treatment-naive FOLFIRINOX and gemcitabine-based second-line combination, with mOS reaching 20.0 months [58]. In 2022, multiple studies on optimizing chemotherapy regimens for pancreatic cancer have been reported (Table 4). The SEQUENCE phase III study reported by Carrato et al. at ASCO 2022 showed that the first-line gemcitabine combined with nab-paclitaxel (AG) regimen sequentially modified FOLFOX significantly improved ORR (39.7% vs. 20.3%, $p = 0.009$), PFS (7.9 vs. 5.2 months, $p < 0.001$), and OS (13.2 vs. 9.7 months, $p = 0.023$) [59]. The PRODIGE 65-UCGI 36-GEMPAX UNICANCER study, reported by de la Fouchardiere et al. at the 2022 ESMO conference, was a phase III randomized trial comparing gemcitabine plus paclitaxel versus gemcitabine in patients with metastatic pancreatic cancer who failed or intolerant to FOLFIRINOX, and the results showed improvements in ORR (19.2% vs. 4.8%), PFS (3.1 vs. 2.0 months, HR = 0.64, 95% CI: 0.47–0.89) compared with gemcitabine alone, but failed to improve OS (6.4 vs. 5.9 months, HR = 0.87, 95% CI: 0.63–1.20, $p = 0.410$) [60]. However, gemcitabine plus paclitaxel is not a common clinical combination. The HR-IRI-APC study reported by Wang et al. is a multicenter, randomized, double-blind, parallel-controlled phase III trial. The results showed that HR070803 (liposome irinotecan) combined with 5-fluorouracil/leucovorin (FU/LV) compared with placebo combined with 5-FU/LV in the second-line treatment of gemcitabine refractory advanced pancreatic cancer, the combination significantly prolonged the mPFS (4.21 vs. 1.48 months, HR = 0.36, 95% CI: 0.27–0.48, $p < 0.0001$) and OS (7.39 vs. 4.99 months, HR = 0.63, 95% CI: 0.48–0.84, $p = 0.002$), and safety was manageable [61].

4.2 | Targeted therapy

Pancreatic cancer is developing slowly toward precision therapy. It was once believed that targeted drugs could not be used, but in recent years, with the advancement of pharmaceutical methods and targeted therapy,

TABLE 4 Results of clinical trials of treatment for advanced pancreatic cancer.

Trial	Treatment	Control	Phase	Line	*n*	ORR (%)	Median PFS/TTP (mo), HR (95% CI)	Median OS (mo), HR (95% CI)	Result
Chemotherapy									
Burris HA et al.	Gemcitabine	5-FU	II	1st	124	5.4 vs. 0	–	5.65 vs. 4.41	Positive
NCT00112658	FOLFIRINOX	Gemcitabine	III	1st	342	31.6 vs. 9.4	6.4 vs. 3.3	11.1 vs. 6.8	Positive
							0.47 (0.37–0.59)	0.57 (0.45–0.73)	
MPACT	AG	Gemcitabine	III	1st	861	23.0 vs. 7.0	5.5 vs. 3.7	8.5 vs. 6.7	Positive
							0.69 (0.581–0.821)	0.72 (0.617–0.835)	
SEQUENCE	AG-mFOLFOX	AG	III	1st	157	39.7 vs. 20.3	7.9 vs. 5.2	13.2 vs. 9.7	Positive
							0.51 (0.36–0.73)	0.68 (0.48–0.95)	
NCT03943667	Gemcitabine + palitaxol	Gemcitabine	III	2nd	210	19.2 vs. 4.8	3.1 vs. 2.0	6.4 vs. 5.9	Negative
							0.64 (0.47, 0.89)	0.87 (90.63–1.20)	
HR-IRI-APC	HR070803 + 5-FU/LV	Placebo + 5-FU/LV	III	2nd	298	–	4.21 vs. 1.48	7.39 vs. 4.99	Positive
							0.36 (0.27, 0.48)	0.63 (0.48–0.84)	
Targeted therapy									
POLO	Olaparib	Placebo	III	1st	154	–	7.4 vs. 3.8	19.0 vs. 19.2	Positive
							0.53 (0.35–0.82)	0.79 (0.55–1.15)	
KRYSTAL-1	Adagrasib	–	I	≧2nd	12	50.0	6.6		
NOTABLE	Nimotuzumab + gemcitabine	Gemcitabine	III	1st	90	7.3 vs. 9.8	4.2 vs. 3.6	10.9 vs. 8.5	Positive
							0.56 (0.12–0.99)	0.50 (0.06–0.94)	
Immunotherapy									
Henriksen A et al.	Ipilimumab	–	II	≧2nd	27	0	–	4.5	–
NCT02054806	Pembrolizumab	–	Ib	≧2nd	24	0	1.7	3.9	–
NCT02558894	Durvalumab	–	II	≧2nd	32	0	–	3.6	–
NCT00556023	Tremelimumab + gemcitabine	–	I	1st	34	5.8	–	7.4	–
NCT01473940	Ipilimumab + gemcitabine	–	Ib	1st	21	14.0	2.78	6.90	–
NCT02331251	Pembrolizumab + AG	–	II	1st	17	17.7	9.1	15.0	–
JapicCTI-184230	Nivolumab + mFOLFIRINOX	–	II	1st	31	32.3	>7	>13	–

TABLE 4 (Continued)

Trial	Treatment	Control	Phase	Line	*n*	ORR (%)	Median PFS/TTP (mo), HR (95% CI)	Median OS (mo), HR (95% CI)	Result
NCT04324307	KN046 + AG	–	II	1st	31	45.2	–	–	–
NCT03404960	Niraparib + ipilimumab	Niraparib + nivolumab	Ib/II	1st	84	15.4 vs. 7.1	8.1 vs. 1.9	17.3 vs. 14.0	–
CISPD3	Sintilimab + mFOLFIRINOX	mFOLFIRINOX	III	1st	110	50.0 vs. 23.9	5.9 vs. 5.73	10.9 vs. 10.8	Negative
							0.93 (0.62–1.41)	1.083 (0.68–1.69)	

Note: –, not available or applicable.

Abbreviations: 5-FU, 5-fluorouracil; AG, Nab-paclitaxel/gemcitabine; CI, confidence interval; HR, hazard ratio; LV, leucovorin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

breakthroughs have been made (Table 4). The study targeting the KRAS G12C mutation was reported at the 2022 ASCO GI meeting. The KRYSTAL-1 (NCT03785249) study is a multicohort phase I/II study evaluating the efficacy of adgrasib monotherapy or in combination in patients with advanced solid tumors with KRAS G12C mutations. Adgrasib is a highly selective KRAS G12C inhibitor that selectively binds to and inactivates KRAS G12C irreversibly. In this study, 12 pancreatic cancer patients were enrolled after the failure of multiple lines of therapy. Clinical activity was assessed in 10 patients, of whom 5 achieved a partial response and 5 were stable, with a DCR of 100% and an mPFS of 6.6 months (95% CI: 1.0–9.7).

Across the entire cohort, the most common AEs were nausea (48%), diarrhea (43%), vomiting (43%), and fatigue (29%). Grade 3/4 AEs occurred in 21% of patients, and none grade 5 AEs, indicating an overall good safety profile [62]. KRAS G12C will be the most promising direction in the history of targeted therapy for pancreatic cancer, but unfortunately, this mutation only accounts for about 2% of KRAS. For other mutations of KRAS, drugs are expected to be developed soon. On the other hand, the NOTABLE study for KRAS wild-type pancreatic cancer was reported at the 2022 ASCO meeting. The efficacy of nimotuzumab (EGFR monoclonal antibody) combined with gemcitabine versus gemcitabine in the treatment of KRAS wild-type locally advanced or metastatic pancreatic cancer was evaluated. In this prospective, randomized, double-blind, multicenter, phase III study, a positive result was reached. In the full analysis set (FAS) and the protocol analysis set (PPS), the mOS of the experimental group was significantly longer than that of the control group (FAS group: 10.9 vs. 8.5 months, HR = 0.50, $p = 0.024$; PPS population: 11.5 vs. 8.5 months, HR = 0.60, $p = 0.039$). In the FAS population, the mPFS was significantly longer in the experimental arm (4.2 months vs. 3.6 months, HR = 0.56, $p = 0.013$) [63]. Therefore, the combination of nimotuzumab and gemcitabine may be an option for patients with KRAS wild-type pancreatic cancer who are not candidates for other combination therapy.

4.3 | Immunotherapy

Pancreatic cancer itself has an immune escape, and at the same time, immunosuppressive factors such as CD47 and VEGF are often highly expressed [64]. Pancreatic cancer patients are generally in a highly immunosuppressive state, and various immunotherapy methods such as immune checkpoint inhibitors, chimeric antigen receptor T, and tumor vaccines have been tried, but no positive

results have been found [65–67] (Table 4). KN046 is a PD-L1/CTLA-4 bispecific antibody. The results of the phase II study (NCT04324307) are encouraging. The ORR of 31 evaluable patients was 45.2%, and the DCR was 93.5%. The phase III study of KN046 combined with standard chemotherapy has been conducted in first-line patients with advanced pancreatic cancer, which is worth looking forward to [68]. The CISPD3 study is a single-center, randomized, open-label phase III trial comparing the efficacy and safety of sintilimab combined with a modified FOLFRINOX regimen versus FOLFIRINOX alone as first-line or second-line treatment for patients with metastatic or recurrent pancreatic cancer. A total of 110 patients were enrolled, and sintillimab combined with chemotherapy failed to prove superior to chemotherapy alone, and the mOS and PFS were similar in the combination group and chemotherapy alone group (10.9 vs. 10.8 months, 5.9 vs. 5.73 months). However, the ORR of sintilimab combined with chemotherapy was significantly higher (50% vs. 23.9%) [69]. The addition of immune drugs improved ORR, but this did not translate into a survival benefit, although there was no significant increase in adverse reactions in the combination group. However, a randomized phase Ib/II study of niraparib plus nivolumab or ipilimumab in patients with advanced platinum-sensitive pancreatic cancer reported at ASCO 2022 showed that maintenance therapy with niraparib plus ipilimumab was effective in patients with platinum-sensitive advanced pancreatic cancer. In the patients, the mPFS was 8.1 months, the 6-month PFS rate was 59.6%, and continued to be effective in patients without any known DNA damage repair subtype while niraparib combined with nivolumab was ineffective under the same conditions [70], suggesting that the combined use of niraparib and ipilimumab is worth further exploration. The failure of immunotherapy to achieve breakthroughs may be related to the inherent immunosuppressive properties of pancreatic cancer and the complexity of the tumor microenvironment. It is necessary to further study the immune microenvironment of pancreatic cancer and screen the population sensitive to immunotherapy to improve the poor prognosis of pancreatic cancer.

5 | CONCLUSIONS AND FUTURE OUTLOOK

Hepatobiliary and pancreatic tumors are tumors with poor prognoses. However, for advanced diseases, systematic therapy can clearly bring survival benefits to patients. Looking back to 2022, these achievements in the field of medical treatment of hepatobiliary and pancreatic tumors will have an important impact on future clinical practice and guide future clinical research.

Patients with HCC are often accompanied by underlying liver disease, resulting in poor tolerance to chemotherapy, poor efficacy of chemotherapy, and lack of standardization of chemotherapy drugs. Due to the lack of standard chemotherapy drugs, the first-line and second-line treatment of HCC is mainly targeted drug therapy. At present, first-line single-drug immunotherapy has not been proven to be superior to sorafenib, but not inferior to sorafenib. However, studies have shown higher ORR and better immunotherapy tolerance than sorafenib. Therefore, for the first-line treatment of HCC, immunotherapy can be considered as an alternative treatment option for patients in whom TKIs and antiangiogenic drugs are contraindicated or at significant risk. Atezolizumab or sintilimab plus bevacizumab have both been shown to be superior to sorafenib alone and have become the first-line standard of care. In 2022, the regimens of tremelimumab plus durvalumab or camrelizumab plus apatinib are significantly better than sorafenib alone, which will add more options for the first-line treatment of HCC. However, LEAP-002 study failed. In terms of the PD-1 antibody combined with TKI drugs, camrelizumab plus apatinib and pembrolizumab plus lenvatinib have achieved different test results. The lenvatinib monotherapy OS in the LEAP-002 study control group exceeded expectations, and the different populations of the two studies may be an important factor leading to the different results. The biggest difference between KEYNOTE-240 and KEYNOTE-394 is the population. In KEYNOTE-394, where the population was predominantly Asian, the proportions of hepatitis B virus (HBV)-associated HCC in the experimental and placebo groups were 78.7% and 81%, respectively [24], compared with 25.9% and 21.5% in the KEYNOTE-240 group [22]. The results of the subgroup analysis showed that HBV-associated HCC was more likely to benefit from immunotherapy for survival. Similar subgroup analysis results were seen in the CheckMate459, COSMIC-312, and IMbrave150 studies. In a phase III study of camrelizumab combined with rivoceranib (apatinib), the percentages of HBV-associated HCC were 76.5% and 72.7% in the experimental group and sorafenib group, respectively [16], but only 48.6% and 48.4% in the LEAP-002 study [30]. Pfister et al. found that nonviral HCC, especially NASH-HCC, may respond poorly to immunotherapy, which may be due to tissue damage caused by abnormal T cell activation associated with NASH, resulting in impaired immune surveillance [71]. A first-line retrospective study found that in the general population of nonviral HCC, especially in the NASH/NAFLD population, the OS time of atezolizumab combined with bevacizumab was significantly worse than lenvatinib, but not sorafenib [72]. Such conclusions still

need to be further verified through prospective studies, but future research on HCC may need to consider the impact of different etiologies on treatment outcomes. Based on the current research progress of HCC, more exploratory studies on combination therapy models, the rationality of the treatment sequence, and population screening for benefit should be expected.

For systemic treatment of BTC, GemCis has been established as the first-line standard since the ABC-02 study, and FOLFOX has been established as the second-line treatment since the ABC-06 study, which can improve the survival of patients with advanced BTC. However, the efficacy of chemotherapy alone for advanced BTC is very limited. Single-agent immunotherapy also has very limited efficacy in non-MSI-H/dMMR biliary tract tumors. However, the TOPAZ-1 study in 2022 confirmed that durvalumab combined with chemotherapy is significantly better than chemotherapy alone. Durvalumab plus GemCis will become a new option for first-line treatment of advanced BTC. But, the addition of immunotherapy in the TOPAZ-1 study was unsatisfactory in terms of survival improvement. Further exploration is needed to screen out the population that really benefits from immunotherapy, or to explore other combination schemes to find more effective treatment options. On the other hand, precisely targeted therapy guided by genetic characteristics is an important treatment strategy for advanced BTC. Phase II studies of trastuzumab combined with FOLFOX or DS-8201 in 2022 all suggest that anti-HER2 therapy is effective for advanced biliary tract tumors, and further studies are needed to clarify its efficacy and provide evidence to support its clinical application. In addition, as a highly selective FGFR2 inhibitor, LGY-4008 showed a high ORR of up to 88.2% at the recommended dose against FGFR2 fusion/rearranged cholangiocarcinoma patients not receiving FGFR inhibitor therapy, which may provide a more effective response in patients with FGFR2 fusion/rearrangement mutations and further studies should be highly anticipated. In addition, two Phase III studies (NCT03656536, NCT03773302) evaluating FGFR inhibitors for first-line treatment of advanced biliary tract tumors with FGFR2 gene fusion/rearrangement are noteworthy.

However, chemotherapy is still the main systemic treatment for pancreatic cancer, with FOLFIRINOX, gemcitabine combined with nab-paclitaxel, gemcitabine, or FU monotherapy being the most commonly used regimens. In 2022, the SEQUENCE study showed that first-line gemcitabine plus nab-paclitaxel (AG) sequentially modified FOLFOX was significantly better than AG alone, suggesting that this sequential regimen can be used as a first-line treatment option, but whether it is better than FOLFIRINOX remains to be explored. In terms of second-line treatment, liposome irinovican (HR070803) combined with 5-FU/LV is superior to 5-FU/LV, and can be used as a new second-line option to further enrich the evidence-based data of chemotherapy for pancreatic cancer. As for targeted therapy, the results of the KRYSTAL-1 study in 2022 are encouraging, and the follow-up extended research is worth looking forward to. However, while KRAS mutations occur more frequently in pancreatic cancer, KRAS G12C mutation is very rare, and it is unclear whether the other mutations in KRAS can achieve the same result. For KRAS wild-type pancreatic cancer, the results of the NOTABLE study support nimotuzumab plus gemcitabine as a first-line option. For immunotherapy, there is currently no evidence to support its use in non-MSI-H/dMMR pancreatic cancer, but a randomized phase Ib/II study of niraparib combined with ipilimumab is considered a potential breakthrough. Further research results should be expected. Furthermore, given the excellent performance of the Phase II study, we are looking forward to the results of the phase III study of KN046 in combination with chemotherapy (NCT05149326).

To sum up, in the field of hepatobiliary and pancreatic tumors, more and more clinical studies have formed more and more evidence-based medical evidence in the continuous exploration of new drugs and new treatment schemes, which will change clinical practice, promote the progress of clinical treatment and ultimately benefit patients.

AUTHOR CONTRIBUTIONS

Le Zhang: Conceptualization (lead); data curation (lead); investigation (lead); writing—original draft (lead); writing—review and editing (lead). **Rui Liu:** Data curation (supporting); investigation (supporting); writing—original draft (supporting); writing—review and editing (supporting). **Ting Deng:** Conceptualization (supporting); supervision (supporting); validation (supporting). **Yi Ba:** Conceptualization (lead); funding acquisition (lead); supervision (lead); validation (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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