CME LIVE OPEN ACCESS

Journal of
Gastroenterology Hepatology and Digestive Disorders

Review Article

Biliary Tract Cancers Review

alfredo colombo[1*], concetta maria porretto[1].

[1]Oncology Unit C.D.C Macchiarella Viale Regina Margherita, 25 Palermo-Italy.

Corresponding Author: Alfredo colombo, Oncology Unit C.D.C Macchiarella Viale Regina Margherita, 25 Palermo-Italy.

Received: 2024 Feb 05 **Accepted:** 2024 Feb 15 **Published:** 2024 Apr 06

Abstract

This article summarizes the progress of treatment in advanced hepatocellular carcinoma, biliary tract cancer, and pancreatic cancer in 2023, 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: Biliary tract cancer, targeted therapy, immunotherapy, pancreatic cancer, and hepatocellular carcinoma.

1. Introduction

Hepatocellular carcinoma (HCC) is a tumour with high incidence, whereas biliary tract cancer (BTC) and pancreatic cancer are tumours with relatively low incidence, although HCC, BTC, and pancreatic cancer have significant mortality. In the past, the treatments were relatively restricted. In recent years, the discovery of immunotherapy and targeted therapy has provided additional therapeutic options for HCC, increasing the survival. BTC is clinically and genetically diverse. Genomic and molecular profile study indicates possible targetable molecular alterations. Research on targeted treatment for some 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. To date, precisely focused therapy directed by distinct driver genes has become a major technique 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. However, chemotherapy is still the major treatment for pancreatic cancer, and optimization of the chemotherapy regimens is still one of the exploration areas for pancreatic cancer, while targeted therapy and immunotherapy have also seen some light in exploratory research. This paper evaluates and summarizes the key advances of advanced hepatobiliary and pancreatic malignancies in 2023, intending to give references for current clinical therapy and future clinical research [1-6].

We searched PubMed (www.ncbi.nlm.nih.gov/pubmed) for full-text articles from 2017 to May 31, 2023, using the keywords: biliary tract cancer, targeted therapy, immunotherapy, pancreatic cancer, hepatocellular carcinoma. The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and October 2023 were examined.

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. Until 2018, no other therapies replaced sorafenib. The REFLECT trial, demonstrated that first-line lenvatinib was not inferior to sorafenib in overall survival (OS), bur was superior to sorafenib in progression-free survival (PFS) and objective response rate (ORR). In 2020, the results of the ZGDH3 trial indicated that sorafenib was better to sorafenib in the first-line therapy of advanced HCC in OS, but only reached noninferiority in ORR and PFS. However, in many clinical trials, sorafenib is still the control arm for the first-line therapy of HCC. There was no conventional second-line therapy for HCC until the RESORCE results of regorafenib in 2017, and the CELESTIAL results of bosutinib in 2018. 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. In addition, lapatinib, a new oral tyrosine kinase inhibitor (TKI) targeting vascular endothelial-derived growth factor (VEGF)-2, has exhibited a substantial improvement in OS compared with placebo in the second-line therapy of HCC patients in the Chinese population. However, there is still little advancement in targeted treatment for HCC in 2022 [7-14].

HCC: First Line Immunotherapy with Single Drug

Single-drug immunotherapy has been examined in several phase III trials in HCC . 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 . However, the indication for nivolumab in HCC was revoked because to unfavourable findings from CheckMate459. Tislelizumab is a monoclonal antibody with a high binding affinity to programmed death protein-1 (PD-1). RATIONALE-301 is a worldwide multicenter phase III trial. The study was released at the European Society for Medical Oncology (ESMO) 2022. Tislelizumab met the primary end point 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 talizumab group was considerably greater 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-related adverse events (AEs) and grade 3 or higher treatment-related AEs with talizumab. Additionally, duralumin 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). The outcomes of the following 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 individuals who are contraindicated or at increased risk of TKIs and antiangiogenic drugs [15-17].

HCC: Second Line Immunotherapy

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. 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. The National Medical Products Administration (NMPA) of China has also authorised two PD-1 antibodies for the second-line therapy of HCC based on the findings of two-phase II trials. In a trial (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. Another research of 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 findings indicated that tislelizumab monotherapy demonstrated excellent 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, aimed 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 co-primary end points 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. A prolonged follow-up in 2021 similarly did not met the prespecified end points. However, a similar research in the Asian population, the KeyNote394 study published at the ASCO-GI conference in 2022, produced good findings on the primary endpoint, when pembrolizumab was compared with placebo plus best supportive care. 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 of previously treated patients with advanced HCC. Long-term survival was also considerably improved in the pembrolizumab group compared with the placebo group, with 2-year survival rates of 34.3% and 24.9%, respectively [18-24].

HCC: Combined Immunotherapy

Combined immunotherapy has become the first-line standard treatment for HCC. The IMbrave150 trial revealed that atezolizumab (PD-L1 antibody) with bevacizumab was better to sorafenib in terms of OS, PFS, and ORR in the first-line therapy of advanced HCC [25, 26]. Similarly, the ORIENT-32 research revealed that first-line similia (PD-1 antibody) with bevacizumab was superior to sorafenib [27]. And these two regimens have been authorised by the FDA and EMA for the first-line treatment of advanced HCC. Several additional immunotherapy trials have also been effective (Table 1). The HIMALAYA project is a multicohort phase III, examining the first-line effectiveness of the combination immunotherapy (STRIDE protocol): durvalumab (PD-L1 antibody) with term Lumumba (cytotoxic T-lymphocyte antigen 4 [CTLA-4] antibody) in advanced HCC. The final data released at the ASCO-GI conference in 2022 indicated 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 the main endpoint of the higher effectiveness 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 durvalumab was manageable, resulting in a lower incidence of treatment-related adverse events than sorafenib. 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. However, in the COSMIC-312 study published in 2021, atezolizumab (anti-PD-L1 antibody) plus bosutinib (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. A phase III investigation

of LEAP-002 was widely expected given the good ORR and PFS findings of lenvatinib + pembrolizumab in a phase Ib study (NCT03006926). 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). The three similar studies above yielded different results, adding to the complexity of the HCC immunotherapy puzzle [17-30].

Biliary Tract Cancer and Targeted Therapy Anti Her-2

HER2 alterations, including amplification, overexpression, or both, were found in about 19% of gallbladder tumors, 17% of extrahepatic cholangiocarcinoma's, 13% of ampullary carcinomas, and 5% of intrahepatic cholangiocarcinoma'. In the previous MyPathway trial, trastuzumab with epratuzumab had an ORR of 23% in HER2-mutated advanced BTC, with mPFS and OS of 4.0 and 10.9 months, respectively. In a phase I research of zanidatamab (ZW25), a HER2 bispecific antibody, was utilised in 21 patients with HER2-mutated advanced BTC, and the ORR was 38%. Neratinib is an 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. The 2022 ASCO conference reported trastuzumab deruxtecan (DS-8201) in the treatment of individuals 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 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 frequency 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 extra care should be made to the adverse drug reactions of DS-8201. In addition, a multicenter phase II study (KCSG-HB19-14) performed by the Korea Cancer Research Group reported at ASCO 2022 that the ORR of trastuzumab + FOLFOX in gemcitabine/cisplatin resistant 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 improved PFS (5.5 vs. 4.9 months, HR = 0.52, 95% CI: 0.23–1.16) [4-36].

Biliary Tract Cancer and Targeted Therapy Anti Fgfr

gene changes are one of the frequent oncogenic drivers of BTC, notably intrahepatic cholangiocarcinomas, where mutations are identified in ~14% of patients, the great majority of which are fusion mutations. Pemigatinib, a pan-inhibitor, was authorised by the FDA on April 17, 2020, for the treatment of adult patients with FGFR2 fusion cholangiocarcinoma based on the findings of the FIGHT-202 research. The findings of the FIGHT-202 research 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. 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 trial, a total of 30 patients with advanced cholangiocarcinoma with FGFR2 fusion/rearrangement mutations who failed conventional treatment received Pemigatinib, resulting in an ORR of 60%, DCR of 100%, and mPFS of 9.1 months, as updated at ASCO 2022. In addition, multiple pan-FGFR inhibitors including immigration, graffitiing, diamantine, and futibatinib were tested in phase II studies in advanced BTC patients with 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. Preliminary effectiveness findings from the ReFocus study with RLY-4008, which were announced at the 2022 ESMO conference, in patients with FGFR2 fusion/rearranged BTC not previously treated with FGFR inhibitors revealed an ORR of 63.2% and a DCR of 94.7% in a total of 38 patients across all dosage groups. The 70 mg dosage group was the recommended dose in the phase II, 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 [38-45].

Biliary Tract Cancer and Immunotherapy

For patients with cholangiocarcinoma with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) mutations, pembrolizumab alone obtained ORR of 53% and 37% in KEYNOTE-016 and KEYNOTE-158 studies, however the percentage of MSI-H/dMMR in cholangiocarcinoma was relatively low. However, for patients with cholangiocarcinoma with non-MSI-H/dMMR, the effectiveness of single-agent immunotherapy is still uncertain, and only small sample trials have been described. Kim et al. found 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. 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. 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. Doka 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 patients with advanced cholangiocarcinoma [47-52].

However, better ORR has been found in numerous phase II trials of immunotherapy paired with chemotherapy. In two phase II studies (NCT03092895 and NCT03486678), 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 nivolum-

ab was 37%, which was significantly improved compared with nivolumab monotherapy (ORR was 3%). In two phase II trials (NCT03796429 and TCOG T1219), the ORR of trimaximal or nivolumab 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. Nevertheless, TOPAZ-1 is the only phase III randomized controlled research with unequivocally revealing a substantial survival advantage of durvalumab + chemotherapy compared with normal treatment. The data published by ASCO-GI in 2022 indicated that compared with GemCis, durvalumab with GemCis substantially increased 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 good, and durvalumab paired with GemCis gives a novel alternative for the first-line treatment of advanced BTC [50-57].

Pancreatic Cancer Chemotherapy

At the 2021 ESMO meeting, Tayebi et al. reported an European real-world trial about of effect of treatment sequence on prognosis in metastatic pancreatic adenocarcinoma, were resulted that the longest OS was found in the sequential treatment-naïve, were first line FOLFIRINOX followed at progression with gemcitabine-based second-line combination, reaching mOS of 20.0 months. In 2022, a lot of trials on optimizing chemotherapy regimens for pancreatic cancer have been published. The SEQUENCE phase III study reported by Carrato et al. at ASCO 2022 showed that first-line gemcitabine combined with nab-paclitaxel (AG) regimen followed by 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). The PRODIGE 65-UCGI 36-GEMPAX UNICANCER study, reported by de la Fouchardier 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 with paclitaxel is not a frequent clinical combination. The HR-IRI-APC study published by Wang et al. is a multicenter, randomized, double-blind, parallel-controlled phase III study. 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 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 [58-61].

Pancreatic Cancer and Targeted Treatment

Pancreatic cancer moving slowly forward precision medicine. It was formerly thought that targeted therapy could not be employed, but in recent years, with the progress of pharmaceutical technologies and targeted treatment, achievements have been realised. The research targeting the KRAS G12C mutation was published at the 2022 ASCO GI conference. The KRYSTAL-1 (NCT03785249) trial is a multicohort phase I/II study examining the effectiveness of adRise alone or in combination in patients with advanced solid tumors with KRAS G12C mutations. Adgrasib is a highly selective KRAS G12C inhibitor that preferentially binds to and inactivates KRAS G12C irreversibly. In this trial, 12 pancreatic cancer patients were included following the failure of various courses of treatment. Clinical activity was examined in 10 patients, of whom 5 obtained a partial response and 5 were stable, with a DCR of 100% and a mPFS of 6.6 months (95% CI: 1.0–9.7). The most prevalent AEs were nausea (48%), diarrhea (43%), vomiting (43%), and exhaustion (29%). Grade 3/4 AEs occurred in 21% of patients, and none grade 5 AEs, showing an overall favourable safety profile. KRAS G12C will be the most promising treatment in the history of targeted therapy for pancreatic cancer, but regrettably, this mutation only accounts for roughly 2% of KRAS [62].

Notable trial for KRAS wild-type pancreatic cancer was announced at the 2022 ASCO conference. The effectiveness of nimotuzumab (EGFR monoclonal antibody) with gemcitabine versus gemcitabine alone in the treatment of KRAS wild-type locally advanced or metastatic pancreatic cancer was examined. In this prospective, randomized, double-blind, multicenter, phase III trial, a good outcome was attained. In the full analysis set (FAS) and the protocol analysis set (PPS), the mOS of the experimental group was substantially longe respect to 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 group, the mPFS was considerably longer in the experimental arm (4.2 months vs. 3.6 months, HR = 0.56, p = 0.013). Therefore, the combination of nimotuzumab with gemcitabine may be an alternative for patients with KRAS wild-type pancreatic cancer who are not candidates for other combination treatment [63].

Pancreatic Cancer and Immunotherapy

Pancreatic cancer has an immune escape, and at the same time, immunosuppressive proteins such as CD47 and VEGF that are significantly expressed. Pancreatic cancer patients are typically in a highly immunosuppressive condition, and many immunotherapy techniques such as immune checkpoint inhibitors, chimeric antigen receptor T, and tumor vaccines have been tested, but no beneficial outcomes have been discovered KN046 is a PD-L1/CTLA-4 bispecific antibody. The findings of the phase II research (NCT04324307) are positive. The ORR of 31 evaluable patients was 45.2%, while the DCR was 93.5%. The phase III research of KN046 with conventional chemotherapy has been undertaken in first-line patients with advanced pancreatic cancer. The CIS-PD3 study is a single-centre, randomized, open-label phase Discussing the effectiveness and safety of sintilimab paired with a modified FOLFRINOX regimen vs FOLFIRINOX alone as first-line or second-line therapy for patients with metastatic or recurrent pancreatic cancer. A total of 110 patients were included, and sintilimab with chemotherapy failed to be superior to chemotherapy alone, and the mOS and PFS were identical in the combination group and chemothera-

py alone group (10.9 vs. 10.8 months, 5.9 vs. 5.73 months). However, the ORR of similia with chemotherapy was much greater (50% vs. 23.9%). The inclusion of immunological drugs enhanced ORR, but this did not convert into a survival advantage, while there was no significant increase in adverse responses 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, suggesting that the combined use of niraparib and ipilimumab is worth further exploration [64-70].

Conclusion

Hepatobiliary and pancreatic cancers 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.

Funding

No funds were received for this paper.

Data Sharing Statement

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.

Acknowledgments

We thank all the authors for their contribution.

References

1. Qiu, H., Cao, S., Xu, R. (2021). Cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with the United States and United Kingdom based on the global epidemiological data released in 2020. Cancer communications, 41(10), 1037-1048.
2. Siegel, R. L., Miller, K. D., Fuchs, H. E., Jemal, A. (2022). Cancer statistics, 2022. CA: a cancer journal for clinicians, 72(1), 7-33.
3. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400(10360):1345–62. https://doi.org/10.1016/S0140-6736(22)01200-4
4. Valle, J. W., Lamarca, A., Goyal, L., Barriuso, J., Zhu, A. X. (2017). New horizons for precision medicine in biliary tract cancers. Cancer discovery, 7(9), 943-962.
5. 5Kam, A. E., Masood, A., Shroff, R. T. (2021). Current and emerging therapies for advanced biliary tract cancers. The lancet Gastroenterology hepatology, 6(11), 956-969.
6. Wood, L. D., Canto, M. I., Jaffee, E. M., Simeone, D. M. (2022). Pancreatic cancer: pathogenesis, screening, diagnosis, and treatment. Gastroenterology, 163(2), 386-402.
7. Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J. F.et al (2008). Sorafenib in advanced hepatocellular carcinoma. New England journal of medicine, 359(4), 378-390.
8. Cheng, A. L., Kang, Y. K., Chen, Z., Tsao, C. J., Qin, S., Kim, J. S. Guan, Z. (2009). Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. The lancet oncology, 10(1), 25-34.
9. Kudo, M., Finn, R. S., Qin, S., Han, K. H., Ikeda, K., Piscaglia, F. Cheng, A. L. (2018). Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet, 391(10126), 1163-1173.
10. Qin, S., Bi, F., Gu, S., Bai, Y., Chen, Z., et al. (2021). Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled phase II-III trial. Journal of Clinical Oncology, 39(27), 3002-3011.
11. Bruix, J., Qin, S., Merle, P., Granito, A., Huang, Y. H., Bodoky, G., et al. (2017). Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 389(10064), 56-66.
12. Abou-Alfa, G. K., Meyer, T., Cheng, A. L., El-Khoueiry, A. B., Rimassa, L., et al. (2018). Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. New England Journal of Medicine, 379(1), 54-63.
13. Zhu, A. X., Kang, Y. K., Yen, C. J., Finn, R. S., Galle, P. R., et al. (2019). Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology, 20(2), 282-296.
14. Qin, S., Li, Q., Gu, S., Chen, X., Lin, L., et al. (2021). Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Gastroenterology Hepatology, 6(7), 559-568.
15. Yau, T., Park, J. W., Finn, R. S., Cheng, A. L., Mathurin, P., et al. (2022). Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. The Lancet Oncology, 23(1), 77-90.
16. Qin, S., Chan, L. S., Gu, S., Bai, Y., Ren, Z., et al. (2022). LBA35 Camrelizumab (C) plus rivoceranib (R) vs. sorafenib (S) as first-line therapy for unresectable hepatocellular carcinoma (uHCC): A randomized, phase III trial. Annals of Oncology, 33, S1401-S1402.
17. Abou-Alfa, G. K., Chan, S. L., Kudo, M., Lau, G., Kelley, R. K., et al. (2022). Phase 3 randomized, open-label, multi-

center study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA.

18. Yau, T., Kang, Y. K., Kim, T. Y., El-Khoueiry, A. B., Santoro, et al. (2020). Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: The CheckMate 040 randomized clinical trial. JAMA oncology, 6(11), e204564-e204564.
19. Zhu, A. X., Finn, R. S., Edeline, J., Cattan, S., Ogasawara, S., et al. (2018). Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. The Lancet Oncology, 19(7), 940-952.
20. Baker, H. (2020). Camrelizumab for hepatocellular carcinoma.
21. Edeline, J., Merle, P., Fang, W., Assenat, E., Pan, H., et al. (2022). Clinical outcomes associated with tislelizumab in patients (pts) with advanced hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (SOR) or lenvatinib (LEN) in RATIONALE-208.
22. Zhang, L., Liu, R., Deng, T., Ba, Y. (2023). Advances in medical treatment of advanced hepatobiliary and pancreatic cancer in 2022. Cancer Innovation, 2(1), 36-51.
23. Finn, R. S., Edeline, J., Bouattour, M., Cheng, A. L., Chan, S. L., et al. (2021). Pembrolizumab (pembro) versus placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (aHCC) previously treated with sorafenib: Updated data from the randomized, phase 3 KEYNOTE-240 study.
24. Qin, S., Chen, Z., Fang, W., Ren, Z., Xu, R., et al. (2022). Pembrolizumab plus best supportive care versus placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): Phase 3 KEYNOTE-394 study.
25. Finn, R. S., Qin, S., Ikeda, M., Galle, P. R., et al. (2020). Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. New England Journal of Medicine, 382(20), 1894-1905.
26. Cheng, A. L., Qin, S., Ikeda, M., Galle, P. R., Ducreux, M., et al. (2022). Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. Journal of hepatology, 76(4), 862-873.
27. Ren, Z., Xu, J., Bai, Y., Xu, A., Cang, S., et al. (2021). Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2–3 study. The Lancet Oncology, 22(7), 977-990.
28. Kelley, R. K., Rimassa, L., Cheng, A. L., Kaseb, A., Qin, S., et al. (2022). Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology, 23(8), 995-1008.
29. Finn, R. S., Ikeda, M., Zhu, A. X., Sung, M. W., Baron, A. D., et al. (2020). Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. Journal of Clinical Oncology, 38(26), 2960.
30. Finn, R. S., Kudo, M., Merle, P., Meyer, T., Qin, S., et al. (2022). LBA34 Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). Annals of Oncology, 33, S1401.
31. Hechtman, J. F., Liu, W., Sadowska, J., Zhen, L., Borsu, L., Arcila, M. E., et al. (2015). Sequencing of 279 cancer genes in ampullary carcinoma reveals trends relating to histologic subtypes and frequent amplification and overexpression of ERBB2 (HER2). Modern Pathology, 28(8), 1123-1129.
32. Javle, M., Borad, M. J., Azad, N. S., Kurzrock, R., Abou-Alfa, G. K., et al. (2021). Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): A multicentre, open-label, phase 2a, multiple basket study. The Lancet Oncology, 22(9), 1290-1300.
33. Meric-Bernstam, F., Hanna, D. L., El-Khoueiry, A. B., Kang, Y. K., Oh, D. Y., et al. (2021). Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study.
34. Meric-Bernstam, F., Beeram, M., Hamilton, E., Oh, D. Y., Hanna, D. L., Kang, Y. K., et al. (2022). Zanidatamab, a novel bispecific antibody, for the treatment of locally advanced or metastatic HER2-expressing or HER2-amplified cancers: a phase 1, dose-escalation and expansion study. The Lancet Oncology, 23(12), 1558-1570.
35. Harding, J. J., Cleary, J. M., Quinn, D., Braña, I., Moreno, V., Borad, M., et al. (2021). Targeting HER2 (ERBB2) mutation-positive advanced biliary tract cancers with neratinib: results from the phase 2 SUMMIT 'basket'trial. Reason, 4, 16.
36. Ohba, A., Morizane, C., Kawamoto, Y., Komatsu, Y., Ueno, M., et al. (2022). Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing unresectable or recurrent biliary tract cancer (BTC): An investigator-initiated multicenter phase 2 study (HERB trial).
37. Lee, C. K., Chon, H. J., Cheon, J., Lee, M. A., Im, H. S., et al. (2023). Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19–14). The Lancet Gastroenterology Hepatology, 8(1), 56-65.
38. Ross, J. S., Wang, K., Gay, L., Al-Rohil, R., Rand, J. V., et al. (2014). New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. The oncologist, 19(3), 235-242.
39. Abou-Alfa, G. K., Sahai, V., Hollebecque, A., Vaccaro, G., Melisi, D., et al. (2020). Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. The Lancet Oncology, 21(5), 671-684.
40. Shi, G., Huang, X., Wen, T., Song, T., Kuang, M., Mou, H., et al. (2022). Pemigatinib in Chinese patients with advanced/metastatic or surgically unresectable cholangiocarcinoma including FGFR2 fusion or rearrangement: Updated data from an open-label, single-arm, multicenter phase II study (CIBI375A201 study).
41. Javle, M., Lowery, M., Shroff, R. T., Weiss, K. H., Springfeld, C., Borad, M. J., et al. (2018). Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. Journal of Clinical Oncology, 36(3), 276.
42. Meric-Bernstam, F., Bahleda, R., Hierro, C., Sanson, M.,

Bridgewater, J., et al. (2022). Futibatinib, an irreversible FGFR1–4 inhibitor, in patients with advanced solid tumors harboring FGF/FGFR aberrations: a phase I dose-expansion study. Cancer discovery, 12(2), 402-415.
43. Bahleda, R., Italiano, A., Hierro, C., Mita, A., Cervantes, A., et al. (2019). Multicenter phase I study of erdafitinib (JNJ-42756493), oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced or refractory solid tumors. Clinical cancer research, 25(16), 4888-4897.
44. Mazzaferro, V., El-Rayes, B. F., Droz dit Busset, M., Cotsoglou, C., Harris, W. P., Damjanov, N., et al. (2019). Derazantinib (ARQ 087) in advanced or inoperable FGFR2 gene fusion-positive intrahepatic cholangiocarcinoma. British journal of cancer, 120(2), 165-171.
45. Hollebecque, A., Borad, M., Goyal, L., Schram, A., Park, J. O., et al. (2022). LBA12 Efficacy of RLY-4008, a highly selective FGFR2 inhibitor in patients (pts) with an FGFR2-fusion or rearrangement (f/r), FGFR inhibitor (FGFRi)-naïve cholangiocarcinoma (CCA): ReFocus trial. Annals of Oncology, 33, S1381.
46. Le, D. T., Durham, J. N., Smith, K. N., Wang, H., Bartlett, B. R., et al. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science, 357(6349), 409-413.
47. Marabelle, A., Le, D. T., Ascierto, P. A., Di Giacomo, A. M., De Jesus-Acosta, A., et al. (2020). Efficacy of pembrolizumab in patients with no colorectal high microsatellite instability/mismatch repair–deficient cancer: results from the phase II KEYNOTE-158 study. Journal of Clinical Oncology, 38(1), 1.
48. Javle, M. M., Murugesan, K., Shroff, R. T., Borad, M. J., Abdel-Wahab, R., et al. (2019). Profiling of 3,634 cholangiocarcinomas (CCA) to identify genomic alterations (GA), tumor mutational burden (TMB), and genomic loss of heterozygosity (gloom).
49. Kim, R. D., Chung, V., Alese, O. B., El-Rayes, B. F., Li, D., et al. (2020). A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer. JAMA oncology, 6(6), 888-894.
50. Ueno, M., Ikeda, M., Morizane, C., Kobayashi, S., Ohno, I., et al. (2019). Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. The lancet Gastroenterology hepatology, 4(8), 611-621.
51. Piha-Paul, S. A., Oh, D. Y., Ueno, M., Malka, D., Chung, H. C., et al. (2020). Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. International journal of cancer, 147(8), 2190-2198.
52. Doki, Y., Ueno, M., Hsu, C. H., Oh, D. Y., et al. (2022). Tolerability and efficacy of durvalumab, either as monotherapy or in combination with tremelimumab, in patients from Asia with advanced biliary tract, esophageal, or head-and-neck cancer. Cancer medicine, 11(13), 2550-2560.
53. Chen, X., Qin, S., Gu, S., Ren, Z., Chen, Z., et al. (2021). Camrelizumab plus oxaliplatin-based chemotherapy as first-line therapy for advanced biliary tract cancer: A multicenter, phase 2 trial. International Journal of Cancer, 149(11), 1944-1954.
54. Chen, X., Wu, X., Wu, H., Gu, Y., Shao, Y., et al. (2020). Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. Journal for immunotherapy of cancer, 8(2).
55. Li, W., Wang, Y., Yu, Y., Li, Q., Wang, Y., et al. (2022). Toripalimab in advanced biliary tract cancer. The Innovation, 3(4).
56. Chiang, N. J., Tan, K. T., Bai, L. Y., Hsiao, C. F., Huang, C. Y., et al. (2022). Impaired chromatin remodeling predicts better survival to modified gemcitabine and S-1 plus nivolumab in advanced biliary tract cancer: a phase II T1219 study. Clinical Cancer Research, 28(19), 4248-4257.
57. Oh, D. Y., He, A. R., Qin, S., Chen, L. T., Okusaka, T., et al. (2022). A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1.
58. Taieb, J., Carrato, A., Westphalen, B., Melisi, D., Prager, G., et al. (2018). First-line (1L) full dose (f) and modified (m) FOLFIRINOX and gemcitabine+ nab-paclitaxel (GN) treatment (tx) for metastatic pancreatic adenocarcinoma (mPAC) patients (pts) in routine clinical practice across Europe. Annals of Oncology, 29, viii244-viii245.
59. Carrato, A., Pazo-Cid, R., Macarulla, T., Gallego, J., Jiménez-Fonseca, P., Rivera, F., et al. (2022). Sequential nab-paclitaxel/gemcitabine followed by modified FOLFOX for first-line metastatic pancreatic cancer: The SEQUENCE trial.
60. de la Fouchardiere, C., Hammel, P., Launay, S., Vienot, A., Raimbourg, J., Perrier, H., et al. (2020). 1566TiP PRODIGE 65-UCGI 36-GEMPAX: A unicancer phase III randomized study evaluating gemcitabine and paclitaxel versus gemcitabine alone after FOLFIRINOX failure or intolerance in metastatic pancreatic ductal adenocarcinoma. Annals of Oncology, 31, S954-S955.
61. Wang, L., Qin, S., Zhou, Y., Zhang, S., Sun, X., et al. (2022). LBA61 HR070803 plus 5-FU/LV versus placebo plus 5-FU/LV in second-line therapy for gemcitabine-refractory locally advanced or metastatic pancreatic cancer: A multicentered, randomized, double-blind, parallel-controlled phase III trial (HR-IRI-APC). Annals of Oncology, 33, S1426.
62. Bekaii-Saab, T. S., Spira, A. I., Yaeger, R., Buchschacher, G. L., et al. (2022). KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRASG12C mutation. J Clin Oncol, 40(4_suppl), 519.
63. Qin, S., Bai, Y., Wang, Z., Chen, Z., et al. (2022). Nimotuzumab combined with gemcitabine versus gemcitabine in K-RAS wild-type locally advanced or metastatic pancreatic cancer: A prospective, randomized-controlled, double-blinded, multicenter, and phase III clinical trial.
64. Bear, A. S., Vonderheide, R. H., O'Hara, M. H. (2020). Challenges and opportunities for pancreatic cancer immunotherapy. Cancer cell, 38(6), 788-802.
65. Gössling, G. C., Zhen, D. B., Pillarisetty, V. G., Chiorean, E.

G. (2022). Combination immunotherapy for pancreatic cancer: challenges and future considerations. Expert Review of Clinical Immunology, 18(11), 1173-1186.

66. Bockorny, B., Grossman, J. E., Hidalgo, M. (2022). Facts and hopes in immunotherapy of pancreatic cancer. Clinical Cancer Research, 28(21), 4606-4617.
67. Zhu, Y. H., Zheng, J. H., Jia, Q. Y., Duan, Z. H., et al. (2023). Immunosuppression, immune escape, and immunotherapy in pancreatic cancer: focused on the tumor microenvironment. Cellular Oncology, 46(1), 17-48.
68. Jin, G., Guo, S., Xu, J., Liu, R., Liang, Q., Yang, Y., et al. A multicenter, randomized, double-blind phase III clinical study to evaluate the efficacy and safety of KN046 combined with nab-paclitaxel and gemcitabine versus placebo combined with nab-paclitaxel and gemcitabine in patients with advanced pancreatic cancer (ENREACH-PDAC-01).
69. Fu, Q., Chen, Y., Huang, D., Guo, C., Zhang, Q.,et al. (2022). Randomized phase III study of sintilimab in combination with modified folfrinox versus folfrinox alone in patients with metastatic and recurrent pancreatic cancer in China: The CISPD3 trial.
70. Reiss, K. A., Mick, R., Teitelbaum, U. R., O'Hara, M. H., Schneider, C. J., et al. (2022). A randomized phase Ib/II study of niraparib (nira) plus nivolumab (nivo) or ipilimumab (ipi) in patients (pts) with platinum-sensitive advanced pancreatic cancer (aPDAC).