Review Article

Hepatobiliary cancers and immunotherapy: where are we now and where are we heading?

Adam Zayac, Khaldoun Almhanna

Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University/Lifespan Cancer Institute, Rhode Island Hospital, Providence, RI, USA

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Correspondence to: Adam Zayac, MD. Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University/Lifespan Cancer Institute, Rhode Island Hospital, 593 Eddy St, George 312, Providence, RI 02903, USA. Email: azayac@lifespan.org.

Abstract: Primary liver cancers are a heterogenous collection of diseases with variable natural histories and treatments. This review article will focus on hepatocellular carcinoma (HCC), intrahepatic and extrahepatic cholangiocarcinoma, and gallbladder cancer, and the use of immune checkpoint inhibitors (ICIs) in their treatment. This will include the currently studied, approved uses as well as the potential future roles of ICIs in the treatment of cancers of the hepatobiliary system through recent updates on ongoing studies and discussion of phase III studies underway. Currently, only two ICIs are approved for use in hepatobiliary cancers: nivolumab and pembrolizumab. First, pembrolizumab was approved for either microsatellite instability-high (MSI-H) or DNA mismatch repair deficient (dMMR) unresectable, or metastatic solid tumors, including HCC and biliary tract cancer (BTC) in May 2017. After CheckMate-040, nivolumab gained approval in late 2017 in the second-line setting for patients with advanced HCC and Child-Pugh A or B7 liver disease. Pembrolizumab was granted FDA approval in 2018 in the second-line setting after publication of KEYNOTE-224 for patients with advanced HCC and Child-Pugh A liver disease. All three approvals were independent of PD-L1 tumor or immune cell expression. Several other ICIs have been studied in various aspects of these diverse diseases including resectable disease and the advanced, unresectable, or metastatic setting from first-line to later line after failed systemic therapies. Some of these agents are also being assessed in combination with currently utilized tyrosine kinase inhibitors (TKIs) and/or chemotherapy. Lastly, we draw attention to phase III clinical trials in ICIs that are currently recruiting and will be approaching completion in the next 5 years, potentially altering the landscape of treatment in hepatobiliary malignancies for generations to come.

Keywords: Immunotherapy; hepatocellular carcinoma (HCC); cholangiocarcinoma (CCA); gallbladder neoplasms

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Introduction

Liver cancer is a broad term encompassing primary malignancy of the liver. Metastatic tumors to the liver are managed based on the primary tumor location and stage. For the purposes of this article, we will discuss primary malignancies of the liver and adjacent biliary tract. This includes hepatocellular carcinoma (HCC), intrahepatic and extrahepatic cholangiocarcinoma (CCA), and gallbladder cancer (GBC). Due to their rarity, we will not include discussion of angiosarcoma and hemangiosarcoma. Liver and intrahepatic bile duct cancers represent the 13th most common cancer type in the US, with an estimated 42,030 new cases in 2019 (2.4% of new cancers in US in 2019), accounting for 31,780 estimated deaths in 2019 (5.2% of all

cancer deaths) (1). There were an estimated 83,081 people living with liver and intrahepatic bile duct cancer in 2016 with 5-year survival of 18.4% (1). It is more common in men compared with women, across all races, with an average age of 64 years old at diagnosis (1). The incidence and rate of death have been rising since 1975, with an average increase of 2.1% annually in the rates of new diagnoses and an average of 2.4% annually in death rates over each of the last 10 years (1).

Since the first approval for ipilimumab in 2011 for the treatment of BRAF-negative metastatic melanoma there has been a steady stream of approvals for antibodies targeting of either programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) across numerous malignancies, reshaping the field of oncology (2-5). Now, more than 1,000 immunotherapy clinical trials later, we are exploring their uses in countless malignancies in first, second and later-line metastatic disease, as well as in the adjuvant setting. This review article will focus on the use of the currently studied, approved uses and the future roles of these agents in the treatment of cancers of the hepatobiliary system.

Current roles for systemic therapies in the treatment paradigm of HCC

Beyond that of resectable HCC, and locoregional therapy (chemoembolization, radioembolization…, etc.) the role for systemic therapies has been investigated both in the adjuvant and advanced, unresectable setting.

The treatment of advanced, unresectable HCC has been challenging; cytotoxic chemotherapy regimens for advanced HCC used to consist of single agent anthracyclines (namely doxorubicin) and fluoropyrimidines (such as 5-fluorouricil); however, their clinical benefit has been inconsistent. Multi-agent chemotherapy with traditional gastrointestinal malignancy regimens have been studied, namely FOLFOX. The EACH Trial, comparing FOLFOX and doxorubicin, found a benefit in progression-free survival (PFS) with a trend in improved overall survival (OS), but did not reach significance, resulting in a modest 1.5 months (mos) survival benefit (6). Since 2008, the mainstay of systemic treatment of both unresectable, locally advanced and metastatic HCC has largely been tyrosine kinase inhibitors (TKIs) and cytotoxic chemotherapy. Sorafenib became the standard of care for advanced, unresectable HCC after publication of the SHARP Trial results, showing a significant OS benefit (~2.5 mos) and time to radiologic progression (~2.7 mos) compared with placebo in patients with Child-Pugh A liver disease (7). The success of sorafenib in this setting prompted the evaluation of its use in the adjuvant setting, with disappointing results (8). Nearly a decade later, sorafenib remained the unchallenged front-line therapy. Until, in 2018, lenvatinib was approved for front-line treatment after a non-inferiority study comparing it to sorafenib (9).

Even more disappointing was the time before a viable second-line agent treatment was approved. There were limited advances or alternatives in the treatment of HCC after 2008 in targeted, or non-cytotoxic agents, until 2017, when regorafenib, an oral multi-kinase inhibitor, was approved for the second-line, after failure of sorafenib (10).

In 2019, ramucirumab, a direct VEGFR2 antagonist, gained approval in treatment of advanced, unresectable HCC who have an alpha fetoprotein of at least 400 ng/mL after failure on sorafenib (11).

Meanwhile, as immunotherapy was gaining steam in other disease states after 2011, it was not until 2017, after the publication of the initial results of the dose-escalation and dose-expansion study, CheckMate-040 (NCT01658878), that nivolumab was approved for use in HCC (12,13). El-Khoueiry *et al.* enrolled 262 total patients with advanced HCC and Child-Pugh A or B7 cirrhosis, regardless of Hepatitis B or C infection status, between the two phases of the trial (see *Table 1*) (12,13). These patients were previously treated with sorafenib, and became intolerant of treatment, or had progression of their disease (12,13). The results showed promise in these previously pre-treated patients, with an objective response rate (ORR) of 20%, complete response (CR) of 1% and disease control rate (DCR) of 64% (12,13). Median PFS (mPFS) 4.0 mos with a median duration of response (mDOR) of 9.9 mos (12,13). The study also showed treatment related toxicities similar to prior studies of nivolumab in other diseases, with grade 3 or greater treatment-related adverse effects (TRAEs) were seen in 19% of recipients (12,13). Six- and 9-mo OS rates were 83% and 74%, respectively (12,13). Median OS (mOS) was not reached at time of publication (12,13). Of the 262 patients enrolled between the two phases of this study, 75.9% of patients had received prior systemic therapy, with a large proportion receiving sorafenib previously (12,13). Three percent (3%) of patients combined between the two phases discontinued treatment due to drug toxicity (12,13).

The approval of nivolumab was later followed by the approval of pembrolizumab in 2018, based on the results

Table 1 Published studies on FDA-approved immune checkpoint inhibitors in HCC and BTC

Study name	Year	Medication	Disease	Setting	Study design/ study size	Outcomes
KEYNOTE-016 (14)	2017	Pembrolizumab	dMMR deficient solid tumors	Unresectable or metastatic, later-line	Phase II, 86	ORR 53%, CR 21%; DCR 77%; mPFS and mOS NR
CheckMate-040 (12)	2017	Nivolumab	HCC	Advanced, second-line‡	Phase I/II, 262	ORR 20%, CR 1%; DCR 64%; mDOR 9.9 mos; mPFS 4.0 mos; grade 3–5 TRAEs 19%
KEYNOTE-224 (15)	2018	Pembrolizumab	HCC	Advanced, second-line†	Phase II, 104	ORR 17%, CR 1%; DCR 69%; mDOR 9 mos; mPFS 7.0 mos; grade 3–5 TRAEs 26%

†, Child Pugh A only; ‡, Child Pugh A or B7. HCC, hepatocellular carcinoma; BTC, biliary tract cancer; dMMR, mismatch repair deficient; ORR, objective response rate; CR, complete response; mPFS, median progression-free survival; mOS, median overall survival; DCR, disease control rate; mDOR, median duration of response; mos, months; TRAEs, treatment-related adverse effects; NR, not reported.

of KEYNOTE-224 (NCT02702414) (15,16). Zhu *et al.* enrolled 104 patients with advanced HCC with Child-Pugh class A cirrhosis, regardless of hepatitis B or C viral status, who were previously treated with sorafenib and were intolerant to treatment, or showed progression of their disease (see *Table 1*) (15,16). Similar response rates to nivolumab were seen, with ORR of 17%, CR of 1%, and DCR of 62% (15,16). However, mDOR was not reached, mPFS was 4.9 mos and mOS was 12.9 mos (15,16). Pembrolizumab exhibited similar toxicity rates to other studies evaluating its use with 26% of patients experiencing grade 3 or greater TRAEs, but only 5% of patients requiring discontinuation of treatment due to TRAE (15,16).

CheckMate-040 and KEYNOTE-224, along with KEYNOTE-016, have served integral parts in establishing the role of immunotherapy in the treatment paradigm for HCC and biliary tract cancer (BTC).

Current treatment paradigm of BTCs (intrahepatic & extrahepatic CCA, GBCs)

The treatment paradigm for BTCs is quite limited despite the heterogeneous collection of malignancies in this category. First-line treatment for unresectable and metastatic disease utilizes cytotoxic chemotherapy with combined regimens, namely gemcitabine and cisplatin, although other fluoropyrimidine-based or gemcitabine-based regimens can be considered. A recent phase 2 study by Shroff *et al.* evaluated the addition of Nab-paclitaxel to combination cisplatin and gemcitabine in 62 patients with advanced BTCs and showed promising early results: DCR of 84%, mPFS 11.8 mos, and mOS of 19.2 mos (17). However, these patients experienced significant toxicities, including 58% with grade 3 or higher TRAEs, with 16% of patients discontinuing therapy as a result of their toxicities (17). Additionally, Lamarca *et al.* presented results of the Phase III ABC-06 study (NCT01926236) comparing active symptom management alone and active symptom management with mFOLFOX for locally advanced, or metastatic, BTCs in 162 patients previously treated with cisplatin and gemcitabine (18,19). Lamarca *et al.* report clinically significant improvements were reported in mOS (6.2 *vs.* 5.3 mos), 6-mo (50.6% *vs.* 35.5%) and 12-mo OS (25.9% *vs.* 11.4%) with mFOLFOX and active symptom management compared with active symptom management alone, although confidence intervals or P values were not reported (18,19). Additionally, grade 3–4 TRAEs were experienced by 59% of patients receiving mFOLFOX and 39% in those who did not, with no treatment-related deaths in either arm (18,19). Given the results of this study, and no current evidence-based second-line treatments in BTCs, the authors assert that mFOLFOX should become considered standard of care for second-line therapy in BTCs (18,19). Due to the limited effective treatment options, enrollment in clinical trials for eligible patients, or best supportive care for those who are not candidates for systemic treatment is also recommended.

In patients with resectable disease, adjuvant treatment with combinations of fluoropyrimidine-based or gemcitabine-based regimens with or without concurrent radiation therapy depending on nodal and resection status after primary resection represent the current standards of care. Clinical trial enrollment is also recommended in both settings. However, observation could also be considered

with R0 resection and negative regional lymph nodes.

Rationale for use of immunotherapy in treatment in hepatobiliary cancers

Prior to 2017, the use of immunotherapy was considered experimental and was often only available as either compassionate use or if enrolled on clinical trial. However, since then, hepatobiliary cancers have seen three FDA approvals following the publication of key early phase trials in the last two years. First, pembrolizumab gained approval for either microsatellite instability-high (MSI-H) or DNA mismatch repair deficient (dMMR) unresectable, or metastatic solid tumors in May 2017 (14,20). This approval came in the wake of a study by Le *et al.* (see *Table 1*). evaluating patients with mismatch repair-deficient malignancies, after this signal was seen in colorectal cancers (14,20). ORR was seen in 53% of patients with dMMR malignancies across 12 different tumor types, including HCC and BTCs (14). Mismatch repair deficiencies are seen in between 2–3% of HCCs and BTCs (14).

Later, nivolumab and pembrolizumab were both studied in the second-line setting in advanced HCC, independent of tumor PD-L1 expression (12,13,15,16). Following CheckMate-040, nivolumab gained approval in late 2017 in the second-line setting for patients with advanced HCC and Child-Pugh A or B7 liver disease (12,13). CheckMate-040 has also gone on to study combination immunotherapy with nivolumab and Ipilimumab, which is discussed later in this review. Pembrolizumab was granted FDA approval in 2018 after publication of KEYNOTE-224 for patients with advanced HCC and Child-Pugh A liver disease (15,16). The phase 3 KEYNOTE-240 study (NCT02702401) followed these early auspicious studies to further assess the utility and safety of pembrolizumab compared with placebo in patients with advanced HCC after failing first-line treatment in 413 enrolled patients (21,22). However, pembrolizumab did not meet pre-specified endpoints for OS and PFS (see *Table 2*) despite a 22% reduction in the risk of death compared with placebo (21,22). This lack of significant improvement was felt to be due to the high rates of subsequent anticancer treatment in the placebo arm compared with treatment arm (47% *vs.* 42%) (21,22). Despite the lack of significant survival benefit, pembrolizumab did show an improved ORR compared with placebo (16.9% *vs.* 2.2%) with a mDOR of 13.8 mos at 13.8 mos follow-up (21,22). The safety profile was reported to be similar to prior pembrolizumab studies, namely KEYNOTE-224 (21,22).

With these approvals, immunotherapy entered the treatment algorithm for HCC and BTC, including inclusion as subsequent treatment options after failure of first-line therapy. However, little was known about immunotherapy's role in resectable disease, following locoregional therapy or first-line in advanced disease. Since the approvals above, further studies have been undertaken to answer these questions.

Future directions of immunotherapy in hepatobiliary cancers

Several established and novel immune checkpoint inhibitors (ICIs) are being evaluated for use is HCC and BTC in both the resectable and advanced setting, first-line and after failed systemic therapies. Some agents are also being assessed in combination with TKIs and/or chemotherapy. Currently, there are nine [9] different ICIs are being evaluated for efficacy and safety in HCC and BTCs. Below, we will discuss each of these agents, their recent clinical trial updates and future phase III studies on the horizon for select agents with the information summarized in *Tables 2* and *3* respectively.

Atezolizumab

Atezolizumab has been assessed in a phase Ib study in combination with bevacizumab in the first-line setting for advanced HCC with up to Child-Pugh B7 liver disease (24). This study showed promising early findings with ORR of 34% with one CR (23,24). mPFS was 14.9 mos, while mOS and mDOR had not been reached after at least 18 weeks of follow-up (24). Furthermore, the treatment combination appeared to be well tolerated in this population, with grade 3 or higher TRAEs occurring in 25% of patients; only 6% of patients required corticosteroids for immune-related adverse events (irAEs) (24). This study was limited to patients in Asia, limiting its generalizability. However, given these findings suggesting tolerability and promising responses, the phase III IMBrave150 Trial is underway to further evaluated the use of this combination compared with sorafenib (56,57).

Avelumab

Avelumab is an anti-PD-L1 monoclonal antibody currently FDA approved for use in Merkel cell carcinoma. Its role in other advanced solid tumors is yet to be established, with

Table 2 Recent updates on ongoing immunotherapy clinical trials

Study name/ identifier	Conference/ year	Medication	Disease	Setting	Phase/population size reported	Outcomes
NCT02715531 (23,24)	ESMO/2018	Atezolizumab 1,200 mg + bevacizumab 15 mg/kg q3w	HCC	Unresectable or metastatic, first-line‡	Phase Ib/68	ORR 34%; CR 1%; DCR 78%; mPFS 14.9 mos; mOS NR; grade 3–5 TRAEs 25%
NCT03289533 (25,26)	ASCO/2019	Avelumab 10 mg/kg q2w + axitinib 5 mg PO BID	HCC	Locally advanced or metastatic, first-line†	Phase Ib/22	RECIST: ORR 13.6%; mPFS 5.5 mos mRECIST: ORR 31.8%; mPFS 3.8 mos Grade 3 TRAEs: HTN 50%; HFS 22.7%; no grade 4–5 TRAEs Grade 3 irAEs: hypothyroidism 31.8%; hyperthyroidism 13.6% No discontinuation due to TRAEs/ irAEs
NCT02989922 (27,28)	ESMO/2018	Camrelizumab 3 mg/kg q2w or q3w	HCC	Advanced, second-line or later‡	Phase II/220 Chinese patients only	ORR 13.8%; DCR 44.7%; mDOR NR; mPFS 2.1 mos; mOS NR; 6-mo OS: 74.7%; grade 3–5 TRAEs 19.4%
NCT03092895 (29,30)	ASCO/2019	Camrelizumab 3 mg/kg q2w + FOLFOX4 or GEMOX	HCC	Advanced, first-line‡	Phase II/34 Chinese patients only	ORR 26.5%; DCR 79.4%; mPFS 5.5 mos; mOS NR; grade 3–5 irAEs 5.9%
			BTC		Phase II/47 Chinese patients only	ORR 7.0%; DCR 67.4%; mPFS & mOS NR; grade 3–5 irAEs 3.8%
NCT03486678 (31,32)	ASCO/2019	Camrelizumab 3 mg/kg q2w + GEMOX	BTC	Advanced, first-line	Phase II/26	ORRs: GBC 63.64%; CCA 33.33%
NCT02383212 (33,34)	ESMO/2018 ESMO Immuno-Oncology/2018	Cemiplimab 3 mg/kg q2w	HCC	Advanced, second-line	Phase I/26	ORR 19.2%; DCR 73%; mPFS 3.7 mos; TEAE related-deaths 7.7%
NCT01693562 (35,36)	ASCO/2017	Durvalumab 10 mg/kg q2w for 12 mos	HCC	Locally advanced, unresectable, or metastatic, second-line or later†	Phase I/II, 40	Overall: ORR 10.3%; DCR 33.3%; mOS 13.2 mos; grade 3–4 TRAEs 20.0% HCV+ (8 pts): ORR 25.0%; DCR 62.5%; mOS 19.3 mos HBV+ (9 pts): ORR 0%; DCR 11.1%; mOS 6.3 mos
NCT02519348 (37-39)	ASCO/2017	Durvalumab 20 mg/kg + tremelimumab 1 mg/kg q4w for 4 doses followed by durvalumab 20 mg//kg q4w	HCC	Advanced, second-line or later	Phase I/40	Overall: ORR 15%; DCR 57.5% (16 weeks); grade 3–5 TRAEs 20% (no TR deaths) Uninfected (20 pts): ORR 30%; DCR 70% HBV+ (11 pts): ORR 0%; DCR 45.5% HCV+ (9 pts): ORR 0%; DCR 44.4%

Table 2 (*continued*)

Table 2 (*continued*)

Study name/ identifier	Conference/ year	Medication	Disease	Setting	Phase/population size reported	Outcomes
NCT02821754 (40,41)	ASCO/2019	Durvalumab 1,500 mg + tremelimumab 75 mg monthly for 4 doses followed by durvalumab 1,500 mg monthly	HCC	Advanced, second line or later‡	Phase II/10	ORR 20%; DCR 60%; mPFS 7.8 mos; mOS 15.9 mos
			BTC		Phase II/12	ORR 0%; DCR 41.7%; mPFS 3.1 mos; mOS 5.45 mos
NCT02572687 (42,43)	ASCO/2019	Durvalumab 750 mg + ramucirumab 8 mg/kg q2w	HCC	Locally advanced, unresectable, or metastatic, second-line or later†	Phase Ib/28	Overall: ORR 11%; DCR 61%; mDOR NR; mPFS 4.4 mos; mOS 10.7 mos PD-L1 ≥25%: ORR 18%; DCR 73%; mPFS 5.6 mos; mOS 16.5 mos
NCT02829918 (44,45)	ASCO/2019	Nivolumab 240 mg IV q2w for 16 weeks, then 480 mg IV q4w	BTC	Advanced, second-line or later†	Phase II/54	PR 22%; DCR 60%; mPFS 3.98 mos; mOS 14.22 mos; grade 3–5 irAEs 20%
NCT03222076 (46,47)	ASCO/2019	Nivolumab 240 mg q2w for 6 weeks or nivolumab 240 mg q2w + ipilimumab 1 mg/kg q6w for 6 weeks	HCC	Pre-operative, resectable†	Phase II/14	pCR rate 29%; grade 3–5 TRAEs 34%
NCT01658878 CheckMate-040 (13,48)	ASCO/2019	Nivolumab + ipilimumab (variable dosage regimens)	HCC	Advanced, second-line‡	Phase Ib/148	ORR 31%; CR 5%; DCR 54%; mDOR 17 mos; mOS 22.8 mos; grade 3–5 TRAEs 34% (5% leading to discontinuation)
NCT02576509 CheckMate-459 (49,50)	N/A, BMS press release/2019	Nivolumab *vs.* sorafenib	HCC	Advanced, unresectable, first-Line†	Phase III/1,009 (planned enrollment, total studied not reported)	OS HR =0.85 (95% CI: 0.72–1.02) P=0.0752 (NS) No new safety signals
NCT02702401 KEYNOTE-240 (21,22)	ASCO/2019	Pembrolizumab 200 mg q3w *vs.* placebo	HCC	Advanced, second-line†	Phase III/413	ORR 16.9%; mDOR 13.8 mos; OS (HR =0.78); PFS (HR =0.78)
NCT02054806 (KEYNOTE-028) (51,52)	ASCO/2019	Pembrolizumab 10 mg/kg q2w	BTC	Advanced, later line	Phase I/24 pts with PD-L1+ (≥1%) tumors	ORR 13.0%; mPFS 2.0 mos; mOS 7.4 mos; irAEs 20.8%
NCT02628067 (KEYNOTE-158) (51,53)	ASCO/2019	Pembrolizumab 200 mg q3w	BTC	Advanced, later line	Phase II/104 (61 pts with PD-L1+ tumors)	ORR 5.8%; mPFS 1.8 mos; mOS 6.2 mos; irAEs 18.3%
NCT03006926 KEYNOTE-524 (54,55)	ASCO/2018	Pembrolizumab 200 mg q3w + lenvatinib (8 or 12 mg/day weight-based)	HCC	Unresectable, first-line†	Phase Ib/18	ORR 46%; DCR 92%; No DLTs, 94% TEAEs

†, Child Pugh A Only; ‡, Child Pugh A or B7. TEAEs, treatment-emergent adverse events; GBC, gallbladder cancer; CCA, cholangiocarcinoma; DLT, dose-limiting toxicities; NS, not significant; HCC, hepatocellular carcinoma; BTC, biliary tract cancer; ORR, objective response rate; CR, complete response; DCR, disease control rate; mPFS, median progression-free survival; mOS, median overall survival; pts, patients; TRAEs, treatment-related adverse effects; irAEs, immune-related adverse events; mDOR, median duration of response; HCV, hepatitis C virus; HBV, hepatitis B virus; pCR, pathologic CR; HR, hazard ratio; CI, confidence interval; TR, treatment-related; HTN, hypertension; HFS, hand-foot syndrome.

ongoing clinical trials investigating its efficacy and safety in various disease states, including HCC. Kudo *et al.* recently presented early results from their phase Ib study evaluating the combination of first-line avelumab and axitinib at the ASCO 2019 Annual Meeting (25,26). The combination of these treatments yielded early promising responses of tumor activity (ORR 31.8% by mRECIST and 13.6% by RECIST) and toxicity profiles similar to individual medications without any discontinuations due to medication toxicities (25,26). OS data was immature with estimated study completion in June 2020 (25,26).

Camrelizumab

Other novel immunotherapies have recently been studied in both the first- and later-line settings. Two phase II studies with the novel PD-1 antibody, camrelizumab (SHR-1210), both alone and in combination with combination chemotherapy in advanced HCC signaled tolerability and potential efficacy (27-30). The first is a study of single agent camrelizumab (SHR-1210) in advanced, previously treated HCC in Chinese patients (27,28). The primary endpoints were 6-mo OS and confirmed ORR (27,28). Study participants were randomized to 3 mg/kg IV every 2 weeks or every 3 weeks (27,28). The study showed similar ORR response rates to nivolumab in the later-line setting, with acceptable toxicities. Interestingly, camrelizumab 3 mg/kg every 3 weeks showed a trend towards higher ORR (16.7% *vs.* 11.0%) and less grade 3 or higher TRAEs (6.5% *vs.* 12.8%), but lower 6-mo OS (73.1% *vs.* 76.1%), although significance was not reported (27,28).

Another phase II multicenter study of camrelizumab in combination with chemotherapy (GEMOX or FOLFOX4) in treatment naïve patients with either advanced HCC or BTC (29,30). The primary endpoints of this study were confirmed ORR and safety. This study has another ongoing study arm evaluating the combination of camrelizumab with apatinib (VEGF-2 TKI) in chemotherapy pretreated patients (30). The ORRs were 26.5% in HCC and 7% in BTC in the first-line setting and grade 3 or higher irAEs were rare, 5.9% in HCC and 3.8% in BTC (29). This study suggests tolerability and efficacy (29). Another study evaluating the combination of GEMOX and camrelizumab in first-line treatment of BTCs reported more promising results (31,32). With twelve patients (46.15%) achieving a partial response (31,32). ORRs were higher in patients with GBC than CCA, 64% vs 33% respectively, although this did not reach statistical significance (31,32). Furthermore, 19 of 26 patients had next-generation sequencing performed on tissue samples, with GBCs showing a higher median tumor mutational burden (TMB) than CCA, although this did not reach statistical significance (31,32). When assessing ORR based on TMB, those with high TMB (>8.6 mut/Mb), had significantly higher ORR (100% *vs.* 26%) (31,32).

Cemiplimab

Cemiplimab (REGN2810), an anti-PD-1 agent currently FDA-approved in locally advanced or metastatic cutaneous squamous cell carcinoma, was evaluated in a small, phase I dose escalation study in advanced malignancies who had failed prior systemic therapy (33,34). Results from the HCC expansion cohort were presented at two 2018 ESMO meetings (33,34). The study cohort consisted of 26 patients with median follow-up of 7.2 mos (33,34). Partial responses were seen in 19.2% of patients with stable disease in 53.8% of patients with mPFS of 3.7 mos (33,34). Two patients (7.7%) had a treatment-emergent adverse event (TEAE) resulting in death (33,34).

Durvalumab

Durvalumab (MEDI4736) is another anti-PD-L1 monoclonal antibody under investigation in HCC, BTCs, and other solid malignancies. Its only current FDA approvals are in unresectable stage III non-small cell lung cancer that has not progressed (i.e., maintenance) after concurrent platinum-based chemotherapy and radiation therapy and in locally advanced or metastatic urothelial cancer following progression on platinum-containing chemotherapy or within 12 mos of receiving platinum-containing chemotherapy perioperatively (neoadjuvant or adjuvant). Durvalumab is being evaluated as monotherapy and in combination with ramucirumab, a VEGFR2 inhibitor, in advanced HCC, and as part of combination immune checkpoint inhibition with tremelimumab, a CTLA-4 inhibitor, in both BTC and HCC (35-43).

In a phase I/II study of durvalumab monotherapy in advanced HCC patients with Child-Pugh A liver disease, ORR (10.3%) was slightly lower compared with other approved ICIs; however, in patients with hepatitis C virus (HCV) infections, ORR (25.0%) was comparable, or slightly better, with similar rates of TRAEs (see *Table 2*) (35,36).

Two early phase studies are investigating combination immune checkpoint inhibition with durvalumab and tremelimumab in patients with advanced HCC or BTC

Table 3 Key ongoing phase III clinical trials for immunotherapy in hepatobiliary cancers

Disease	Setting	Phase/study size	Interventions	Status, estimated completion date	Study name & identifier
Hepatocellular carcinoma (HCC)	Untreated, locally advanced or metastatic[†]	Phase III, 480	Atezolizumab + bevacizumab *vs.* sorafenib	Recruiting, June 2022	NCT03434379 (IMBrave150) (56,57)
HCC	Systemically untreated, advanced[†]	Phase III, 1310	Durvalumab + tremelimumab *vs.* durvalumab *vs.* sorafenib	Recruiting, June 2021	NCT03298451 (HIMALAYA) (58,59)
HCC	Non-metastatic and non-curative, amenable to TACE[‡]	Phase III, 600	TACE + durvalumab *vs.* TACE + durvalumab + bevacizumab *vs.* TACE + placebo	Recruiting, November 2023	NCT03778957 (EMERALD-1) (60)
HCC	Adjuvant after successfully completed curative therapy (resection or ablation)[†]	Phase III, 888	Durvalumab + tremelimumab *vs.* durvalumab *vs.* placebo	Recruiting, June 2023	NCT03847428 (EMERALD-2) (61)
HCC	Previously systemically treated advanced[†]	Phase III, 450 (Asian patients only)	Pembrolizumab (MK-3475) or placebo + best supportive care	Recruiting, January 2022	NCT03062358 (KEYNOTE-394) (62)
HCC	First-line, advanced[†]	Phase III, 750	Lenvatinib + pembrolizumab (MK-3475) *vs.* lenvatinib	Recruiting, July 2022	NCT03713593 (LEAP-002) (63)
HCC	Adjuvant after successfully completed curative therapy (resection or ablation)[†]	Phase III, 530	Nivolumab *vs.* placebo	Recruiting, June 2025	NCT03383458 (CheckMate-9DX) (64)
Biliary tract cancers (BTCs)	Untreated, locally advanced or metastatic[§]	Phase III, 390	KN035 + gemcitabine + oxaliplatin *vs.* gemcitabine + oxaliplatin	Recruiting, June 2022	NCT03478488 (65)

[†], Child Pugh A only; [‡], Child Pugh A or B7; [§], Child Pugh A or B. TACE, transarterial chemoembolization.

who received, or refused, at least one prior therapy (40,41). Amongst the 10 patients with advanced HCC, ORR was 20% with mPFS of 7.8 mos and mOS of 15.9 mos (40,41). None of the 12 patients with advanced BTC had objective responses; which was coupled with poor mPFS (3.1 mos) and mOS (5.45 mos), reflective of the grim prognosis with advanced BTC after failing first-line treatment (40,41). These results were similar to outcomes with pembrolizumab in advanced, later-line treatment of BTC, but worse when compared with nivolumab. Kelley *et al.* published the Phase I safety and efficacy analysis for this combination ICI in unresectable advanced HCC, including 93% with Child-Pugh A liver disease (37-39). ORR (15%) was similar to other single agent approved ICIs (37-39). However, in contrast to durvalumab monotherapy, ORR was higher amongst the 20 uninfected patients, 30%; while none of the hepatitis B virus (HBV) or HCV infected patients had confirmed ORR (see *Table 2*) (37-39).

The last doublet to discuss is combination of durvalumab and the VEGF2 inhibitor, ramucirumab as part of a basket study included a cohort of advanced HCC (42,43). ORR was modest (11%) amongst all 28 enrolled patients, although slightly better (18%) in the 11 patients with "high" PD-L1 expression (greater than or equal to 25% of tumor cells and/or immune cells) (42,43). mPFS had similar results amongst all patients and those with high PD-L1 expression (4.4 and 5.6 mos, respectively), as did mOS (10.7 and 16.5 mos, respectively) (42,43).

Due to the promise of these early phase studies, there are multiple phase 3 studies evaluating the use of durvalumab in various settings (see *Table 3*). The first is the phase 3 HIMALAYA study (NCT03298451) evaluating durvalumab and tremelimumab compared with sorafenib as well as durvalumab monotherapy in the first-line setting

in unresectable HCC is underway (see *Table 3*) (58,59). Two ongoing phase III studies are investigating the use of durvalumab alone, and in combination with other targeted agents in combination with other interventional procedures [transarterial chemoembolization (TACE) and surgery], EMERALD-1 (NCT03778957) and EMERALD-2 (NCT03847428) (60,61). EMERALD-1 is assessing the efficacy and safety of the combination of TACE with durvalumab alone, or in combination with bevacizumab, compared with placebo in patients with Child Pugh A or B7 liver disease and non-metastatic, non-resectable HCC (60). Meanwhile, EMERALD-2 will look at the use of immunotherapy in the adjuvant setting after successful curative therapy (surgery or ablation) for patients with HCC and Child Pugh A liver disease with durvalumab alone or in combination with tremelimumab compared with placebo (61).

KN035

The novel, subcutaneous anti-PD-L1 monoclonal antibody is currently under investigation with no current FDA approvals in HCC or BTC. It is currently being studied in patients with Child Pugh A or B liver disease and untreated, locally advanced or metastatic BTCs in combination with gemcitabine and oxaliplatin compared with chemotherapy alone in an ongoing phase 3 study (NCT03478488) with an estimated completion date of June 2022 (65).

Nivolumab

At the 2019 ASCO Annual Meeting, early data from CheckMate-040 (NCT01658878) showed significant promise with the use of combination immunotherapy in the treatment of advanced, unresectable HCC after treatment with sorafenib (see *Table 2*) (13,48). The combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 240 mg every 2 weeks showed the most promise (13,48). This treatment arm saw mOS of 22.8 mos, ORR 31% (compared with 14% for single agent nivolumab), 5% with CR and 26% with PR, DCR of 54%, mDOR of 17 mos with 34% grade 3 or greater TRAEs, with low rates of discontinuation for toxicity (5%) at median follow-up of 24 mos (13,48).

Nivolumab was further evaluated after failure of first-line systemic therapy for BTCs [63% intrahepatic cholangiocarcinoma (IHC), 11% extrahepatic cholangiocarcinoma (EHC), 26% GBC] in a phase II study by Kim *et al.* (NCT02829918) (44,45). The study enrolled 54 patients, with 45 patients evaluated for response (44,45). Patients had a median age of 65 years (44,45). The study found a DCR of 60% with 20% grade 3 or 4 TRAEs (44,45). All of the patients who responded were microsatellite stable. Furthermore, none of the patients who experienced TRAEs required discontinuation of nivolumab at median follow-up of 13.34 mos (44,45).

Some early promising data for the use of nivolumab +/– ipilimumab in the pre-operative (neoadjuvant) setting (NCT03222076) in 14 evaluable patients showing 29% pathologic CR (pCR) with nivolumab or nivolumab and Ipilimumab with 34% TRAEs (46,47). Due in part to this promise, nivolumab is currently under investigation in the phase III CheckMate-9DX study (NCT033833458) as adjuvant treatment after curative therapy (surgery or ablation) in patients with Child Pugh A liver disease and HCC compared with placebo (64).

More recently in June 2019, Bristol-Myers Squibb (BMS), the manufacturer of both nivolumab and ipilimumab, announced results from CheckMate-459 (NCT02576509) (49,50). This randomized, phase III study comparing nivolumab and sorafenib in the first-line treatment of advanced, unresectable HCC had a primary endpoint of OS with a goal enrollment of 1,009 (see *Table 2*) (49,50). The press release notes that the trial did not achieve statistical significance for OS based on a pre-specified analysis (49,50). The hazard ratio (HR) for OS was 0.85 (95% CI: 0.72–1.02) with P=00752 (49,50). The release does not note the total number of patients evaluated in the analysis, or details about median follow-up (49,50). It is also noted that no new safety signals were seen with nivolumab and that full study results will be presented at an future medical conference (49,50).

Pembrolizumab

Pembrolizumab has a number of ongoing studies assessing its efficacy and safety in advanced HCC and BTC. Most notably is the phase 3 KEYNOTE-240 study (NCT02702401) investigating the use of pembrolizumab's utility and safety in patients with advanced HCC after failing first-line treatment compared to placebo, discussed in detail above (21,22). Additionally, both the KEYNOTE-028 (NCT02054806) and -158 (NCT02628067) basket studies included a cohort of patients with advanced BTCs who have failed at least one prior treatment (51-53). PD-L1 positivity (≥1%) was required in KEYNOTE-028, but not

for KEYNOTE-158 (51-53). This resulted in modest ORR (13.0% *vs.* 5.8%), mOS (7.4 vs 6.2 mos), and PFS (2.0 *vs.* 1.8 mos) differences, respectively (51-53). However, the rates of irAE were fairly similar (20.8% *vs.* 18.3%) (51-53). These findings are in keeping with a prospective cohort study out of South Korea (66). The phase III KEYNOTE-394 study (NCT03062358) investigating the role of pembrolizumab compared with placebo and best supportive care in Asian patients with Child Pugh A liver disease and advanced, previously systemically treated HCC amongst is currently ongoing (62).

Given the non-inferiority of lenvatinib compared with sorafenib, additional first-line studies to assess the combination of lenvatinib and pembrolizumab have been undertaken. Initially, a phase Ib study, part of KEYNOTE-524, evaluated the tolerability of this combination in patients with Child-Pugh A liver disease with no dose-limiting toxicities or discontinuation of therapy amongst the 18 patients receiving this combination at time of interim analysis in 2018 (54,55). Furthermore, it showed promising early ORR (46%), prompting the development of the phase III LEAP-002 study to assess efficacy and safety compared with first-line lenvatinib monotherapy (54,55,63).

Tremelimumab

Tremelimumab (formerly ticilimumab, CP-675,206) is an anti-CTLA-4 monoclonal antibody without any FDA approvals, but has recently received orphan drug status for mesothelioma. Its role in HCC and BTC is under investigation as both monotherapy and in combination therapy. A pilot study by Sangro *et al.* evaluated its safety and role in patients with advanced HCC and HCV infection (67,68). Tremelimumab resulted in partial response of 17.6%, DCR of 76.4% and time to progression (TTP) of 6.48 mos with no patients requiring steroids for irAEs (67,68). Tremelimumab has since been studied in combination with the PD-L1 inhibitor, durvalumab in advanced HCC in the second-line (or later) setting (37-39). Another phase 1/2 study evaluating combination ICI with durvalumab and tremelimumab in patients with advanced HCC or BTC who received, or refused, at least one prior therapy has recently released some early results (40,41). Kelley *et al.* published the phase I safety and efficacy analysis for this combination. The results of this phase 1/2 study are discussed above (see section on durvalumab) (37-39).

Due to the promise of these early phase studies, the phase 3 HIMALAYA study (NCT03298451) evaluating durvalumab and tremelimumab compared with sorafenib as well as durvalumab monotherapy in the first-line setting in unresectable HCC is underway (see *Table 3*) (58,59). Additionally, this combination of ICIs is being studied in the phase III EMERALD-2 study (NCT03847428) for efficacy and safety of immunotherapy in the adjuvant setting after successful curative therapy (surgery or ablation) for HCC compared with placebo (61).

Conclusions

Primary liver cancer and other BTCs are a heterogenous collection of diseases with limited effective treatment options. The treatment of advanced disease has had limited advances until recent years with the discovery of immunotherapy being. The approval of pembrolizumab in both MSI-H or dMMR-deficient advanced BTC and HCC, has provided an alternative treatment option in a select number of patients. However, the addition of pembrolizumab and nivolumab in advanced HCC with limited liver disease, agnostic of PD-L1 expression, has bolstered the sparse armamentarium of treatment options in patients who have failed prior systemic therapy. However, the full extent of the benefit of immunotherapies has not yet been fully established. The early signals of efficacy with manageable toxicity profiles seen in several other agents, as well as nivolumab and pembrolizumab in various settings (perioperative, advanced disease: first-line or beyond, etc.) within HCC and BTC provide home for the future. In addition, the number of ongoing phase III studies that are nearing completion in the next 5 years provide a glimpse of what may be ahead in these devastating and difficult to treat collection of diseases. Their results will hopefully provide a vast array of options within the treatment paradigm of advanced hepatobiliary cancers.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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