**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 80000

**Manuscript Type:** MINIREVIEWS

**Immunotherapy for recurrent hepatocellular carcinoma**

BhattA*et al.* Immunotherapy for recurrent HCC

Ahan Bhatt, Jennifer Wu

**Ahan Bhatt, Jennifer Wu,** Division of Hematology and Oncology, Perlmutter Cancer Center of NYU Langone Health, NYU School of Medicine, New York, NY 10016, United States

**Author contributions:** Bhatt A drafted the manuscript, coordinated all the authors’ efforts and provided the final revisions; Wu J provided the concept of the manuscript, established the structure of the manuscript and revised the drafts.

**Corresponding author: Jennifer Wu, MD, Associate Professor, Attending Doctor,** Division of Hematology and Oncology, Perlmutter Cancer Center of NYU Langone Health, NYU School of Medicine, 462 First Ave, BCD556, New York, NY 10016, United States. jennifer.wu@nyulangone.org

**Received:** September 15, 2022

**Revised:** January 25, 2023

**Accepted:** March 14, 2023

**Published online:**

**Abstract**

Hepatocellular carcinoma (HCC) is presented frequently in late stages that are not amenable for curative treatment.Even for patients who can undergo resection for curative treatment of HCC, up to 50% recur.For patients who were not exposed to systemic therapy prior to recurrence,recurrence frequently cannot be subjected to curative therapy or local treatments. Such patients have several options of immunotherapy (IO).This includes programmed cell death protein 1 (PD-1) and cytotoxic T- lymphocyte associated protein 4 treatment, combination of PD-1 and vascular endothelial growth factor inhibitoror single agent PD-1 therapy when all other options are deemed inappropriate. There are also investigational therapies in this area that explore either PD-1 and tyrosine kinase inhibitors or a novel agent in addition to PD-1 with vascular endothelial growth factorinhibitors. This mini-review exploredIO options for patients with recurrent HCCwho were not exposed to systemic therapy at the initial diagnosis. We also discussed potential IO options for patients withrecurrent HCCwho were exposed to first-line therapy with curative intent at diagnosis.

**Key Words:**Liver neoplasms;Immune checkpoint blockade; Combination drug therapy; PD-1- PD-L1 blockade; CTLA-4 inhibitor.

Bhatt A, Wu J. Immunotherapy for recurrent hepatocellular carcinoma. *World J Gastroenterol* 2023; In press

**Core Tip:** Immunotherapy (IO) has made strong headway in the management of hepatocellular carcinoma (HCC). For patients who recur on local therapy, IO has become the standard of care treatment option for unresectable HCC. The role of IO agents is still not explored in patients who progress on prior IO. This mini-review highlighted the various treatment options available in clinical practice as well as upcoming novel management strategies in recurrent HCC.

**INTRODUCTION**

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, with more than 900000 new cases in 2020. HCC accounts for the third most cancer deaths, next only to lung cancer and colorectal cancer. It occurs twice as frequently in males compared to females and is more common in Eastern Asian countries compared to Europe[1]. In the United States (US), there is a shift in the incidence and mortality of HCC from predominantly Asians/Pacific Islanders to African American and Hispanic communities[2].

Such change is most likely due to the successful implementation of hepatitis B virus control measures such as vaccination and effective anti-viral therapy (hepatitis B virus is the main cause of HCC in Eastern Asian populations)[3,4]. On the other hand, nonalcoholic steatohepatitis (NASH) is another common cause of HCC in the Western world and is quickly becoming a key contributor to increasing HCC cases[5]. Between the period of 2010 to 2019, NASH has seen the fastest growth in HCC-associated deaths globally[6]. In the US, NASH is viewed as the most common risk factor (59%), followed by hepatitis C (22%)[7]. Chronic alcohol consumption continues to be a leading cause of HCC as well in the US and other Western countries[8].

Managing patients with early-stage HCC includes local therapy using transplantation, hepatic resection, ablation or transarterial chemoembolization (TACE), but there is always a chance of recurrence. The rate of recurrence was found to be 16% with liver transplantations for HCC, which is the lowest among all local therapy approaches.Thus, for patients eligible for liver transplantation, it is the best treatment option for patients with early HCC[9].

In patients treated with surgical resection, recurrence is seen in >50% of the patients[10]. Radiofrequency ablation showed recurrence in more than 80% of the patients, either locally or distant at the 5-year follow-up[11]. Surgical resection when compared to ablation for HCC did not show significant improvement in overall survival (OS); however, the disease-free survivalperiod was significantly better for surgical resection[12]. Therefore, resection is often preferred over ablation in HCC.TACE is traditionally used as a bridge to transplantation. For patients who cannot proceed with transplantation, TACE can still provide effective local control. In a large study of 681 patients, of which 287 were treated in the first-line therapy with TACE, recurrence was seen in 43.2% of the patients that achieved complete response (CR)[13].

If HCC recurs, patients can be candidates again for local therapy as described above. However, if they are not amenable to local therapy, systemic therapy is used.There are two types of systemic therapies: (1) Immunotherapy (IO) based; and (2) Non-IO based.In this review, we focused on the IO based systemic approaches.

**IOBased approaches in the first-line setting**

***Atezolizumab with bevacizumab***

Atezolizumab (Atezo), a programmed death ligand 1 (PD-L1) inhibitor and bevacizumab (Bev), a vascular endothelial growth factor receptor (VEGF) inhibitor were initially tested in a phase Ib study to evaluate their role for the management of untreated, advanced HCC patients[14-16]. Atezo acts by preventing T cell suppression by selectively inhibiting PD-L1 from attaching to programmed cell death protein 1 (PD-1)receptors[14]. Bev inhibits VEGF, which is commonly associated with progression and development of liver cancer[17]. It acts by inhibiting angiogenesis and tumor growth[18]. The combination of Atezo and Bev can act by reversing VEGF mediated immunosuppression and increased T cell infiltration in the tumor microenvironment, which can be efficacious in treating cancer[19,20].

The IMBRAVE150 study established Atezo in combination with Bev as the standard of care for advanced HCC patients[21] (Table 1). The IMBRAVE 150(NCT03434379) was a large multicenter, open label phase III randomized study that evaluated the safety and efficacy of Atezo in combination with Bevcomparedsorafenib in the first-line setting for systemic therapy naïve patients with unresectableHCC[22]. At the time of the first analysis at data cutoff, the OS rate at 12 mo was67.2% [95% confidence interval (CI): 61.3-73.1] with Atezo + Bev and 54.6% (95%CI: 45.2-64.0) with sorafenib. Median OS (mOS) was not reached for the Atezo + Bev arm and was 13.2 mo (95%CI: 10.4-not reached) for the sorafenib arm. The study had shown median progression-free survival (mPFS) was 6.8 mo (95%CI: 5.7-8.3) for the Atezo + Bev arm and 4.3 mo (95%CI: 4.0 to 5.6) for the sorafenib arm. Thus, the OS and PFS were significantly improved compared to the tyrosine kinase inhibitor (TKI) sorafenib. The Atezo + Bev arm in the study demonstrated a superior overall response rate (ORR)of 27.3% (95%CI: 22.5-32.5)when compared to the sorafenib arm of 11.9% (95%CI: 7.4-18.0), perresponse evaluation criteria in solid tumors 1.1 (RECIST 1.1) (*P* <0.001).

This is the only first-line combination regimen involving IO that evaluated high risk patientshaving Vp4 thrombus, bile duct invasion or liver infiltration>50%. The improved OS, mPFS and ORR compared to sorafenib regardless of patient etiology and disease risk stamped its role in first-line management of treatment naïve unresectable HCC. The only caveat is that the trial required a pretreatment evaluation of esophageal varices because of its increased complications with cirrhosis and HCC and due to the side effect profile of Bev. Varices, if present, also needed to be treated otherwise the patients were excluded from the trial. Hence, the trial selectively looked at patients who had preserved liver function (Child-Pugh class A) and a decreased risk of variceal bleeding.

At the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers symposium 2021, additional 12 mo data was presented.After a median 15.6mo(range: 0-28.6) follow-up, the mOS was 19.2 mo (95%CI: 17.0-23.7) in the Atezo + Bev arm and 13.4 mo (95%CI: 11.4-16.9) in thesorafenib arm, whereas the mPFS and ORR were similar to the original presented data[23]. The updated data showed 8% of the patients achieving CR with Atezo + Bev compared to < 1% with sorafenib. Moreover, data for a PD-L1 negative patient subgroup did not reveal a meaningful difference in OS, thus suggesting treatment efficacy regardless of PD-L1 expression.

***Durvalumab and tremelimumab***

Durvalumab (Durva), a PD-L1 inhibitor, and tremelimumab (Treme), a cytotoxic T lymphocyte associated protein 4 (CTLA-4) inhibitor, based on their additive and complementary immunostimulatory activity, were combined in the treatment of HCC[24-26].

At the ASCO 2022 Gastrointestinal Cancers Symposium, the HIMALAYA study was presented. HIMALAYA is an open-label, multicenter, phase III study evaluating the IO combination of Treme+ Durva*vs*sorafenib. Patients with newly diagnosed unresected HCC not amenable to local therapy were initially randomized to the Single Treme Regular Interval Durva (STRIDE regimen) or Durva or sorafenib in a 1:1:1 ratio[27]. The study met the primary endpoint of improved OS in the Treme + Durva arm (STRIDE regimen) when compared to sorafenib. This was also the first study to evaluate long-term OS, with a median follow-up duration of more than 30 mo.

OS was significantly improved for STRIDE *vs*sorafenib[hazard ratio (HR): 0.78; 96%CI: 0.65-0.92; *P*= 0.0035). The mOS for STRIDE was 16.4 mo (95%CI: 14.1-19.5) *vs*13.7 mo (95%CI: 12.2-16.1) for sorafenib. The mPFS was 3.8 mo (95%CI: 3.7-5.3) in the STRIDE arm and 4.1 mo (95%CI: 3.8-5.5) in the sorafenib arm. Despite a similar PFS for STRIDE and sorafenib, more patients remained progression free at the time of data cutoff for the STRIDE arm. Patients also continued on treatment with STRIDE (46.9%) for at least one cycle compared to sorafenib (36%) past disease progression, which would suggest that more patients derived clinical benefit from this combination. The STRIDE regimen showed superiority in ORR (20.1%) compared to sorafenib (5.1%).In addition, Durva met the objective of OS non-inferiority to sorafenib (HR: 0.86; 95%CI: 0.73-1.03). The ORRwas higher for Durva (17.0%) than for sorafenib (5.1%).

In contrast to the IMBRAVE150 study, the HIMALAYA study did not include Vp4 thrombus patients, which is considered a high risk patient group.The subgroup analyses are not available yet[22,27]. The STRIDE regimen was not associated with an increased risk of bleeding with esophageal varices, thus eliminating the need for esophagogastroduodenoscopy for evaluation, as is required for the Atezo+ Bev combination. Therefore, STRIDE can be a very good option for patients who are contraindicated to Bev (commonly fistula, recent bleeding, high grade varices, severe hypertension and proteinuria).

Even though benefits were seen with the STRIDE regimen, it only involved a single dose of Treme, a CTLA-4 inhibitor, which drives the majority of the toxicities in the IO combination and was seen in this study as well. STRIDE is a proposed treatment regimen for patients who are treatment naïve and have unresectable disease. The treatment was approved for first-line use in October 2022 by the Food and Drug Administration (FDA)[28].

The OS non-inferiority of Durva to sorafenib, along with higher ORR and lower toxicity profile, makes Durva a very attractive option compared to sorafenib. Durva is not FDA approved yet for HCC.

***Tislelizumab***

The RATIONALE 301 study is a phase III randomized, open label study that evaluated tislelizumab, a PD-1 inhibitor, *vs*sorafenib as first-line treatment for unresectableHCC[29]. The primary objective of the study is to compare OS. The patients have unresectable HCC with no prior systemic therapy, Child-Pugh A class and Eastern Cooperative Oncology Group(ECOG) score 0 or 1. The patients are randomized 1:1 and will either receive tislelizumab or sorafenib. The study reported non-inferiority of tislelizumab to sorafenib in terms of OS, with a favorable safety profile (mOS: 15.9 mofor tislelizumab*vs*14.1 mo for sorafenib; stratified HR: 0.85; 95%CI: 0.712-1.019][30]. Based on the results of this study, single agent tislelizumab can be a potential first-line option for the management of HCC.

***Ipilimumab+nivolumab***

Checkmate 9DWis another phase III trial evaluating ipilimumab and nivolumab*vs*standard of care TKIs sorafenib or lenvatinib in patients with unresectable HCC who have not received systemic therapy[31]. The primary objective is to measure OS, and the secondary objective is to measure ORR and duration of response.

***SRF388***

SRF388 is another agent that is being used in combination with Atezo and Bev in the frontline setting for patients with advanced HCC. SRF388 is an inhibitor of interleukin-27 (IL-27), and as a single agent has reduced HCC growth in mouse models[32]. HCC development is suppressed if IL-27 is inhibited in NASH-induced HCC models. Higher levels of IL-27 have also been shown to reduce survival in HCC. IL-27 upregulates PD-L1 expression, lymphocyte activation gene 3(LAG-3), T cell immunoglobulin and mucin-domain containing protein 3 and T cell immunoglobulin and ITIM domain.Thus, combining PD1 therapy with SRF388 increases cytokines such as tumor necrosis factor- alpha and interferon-gamma, which can potentially help in reducing tumor growth.

The preliminary results from the phase I study showed that there were no significant drug-related toxicities (grade>3 or higher or dose limiting toxicity) and achieved a response similar to preclinical mouse models in humans[33]. Phase II of the study,SRF388-201 study,is currently open and actively recruiting patients who are newly diagnosed with no prior systemic therapy, Child class A, not eligible for TACE and have ECOG 0 or 1. The patients will be randomized 1:1 and will either receive SRF388 or placebo in combination with Atezo and Bev.

**CHILD-PUGH SCORE B GROUP**

All currently approved therapies are based on studies that exclude Child-Pugh score B patients. There is no prospective data evaluating this group of patients in a first-line setting. A retrospective study evaluated 27 advanced HCC patients with Child-Pugh score B after treatment with Atezo + Bev[34]. The study compared these patients with 130 patients with Child-Pugh score A. Modest activity of Atezo + Bev combination was seen with an ORR of 14.8% in the Child-Pugh score B group compared to 32.3% for Child-Pugh score A group. mPFS and OS were 3 mo(95%CI: 1.6-4.3) and 6 mo(95%CI: 4.9-7.0), respectively,for Child-Pugh score B compared to mPFS of 6 mo and mOS not reached for Child-Pugh score A group. More grade 3/4 adverse events were observed, with thrombocytopenia and aspartate transaminase elevation being the most common. A higher discontinuation rate was seen in the Child-Pugh score B group.

Similar retrospective studies have also shown that nivolumab and pembrolizumab have a limited role in the management of advanced HCC for Child-Pugh score B/C patients previously treated with other therapies. Poor outcomes were associated with high Child-Pugh score, portal vein thrombosis and diuretic refractory ascites[35,36]. Wong *et al*[36]demonstrated a superior response in Child-Pugh score B7 patients compared to Child-Pughscore B ≥8.A trial is currently open that is prospectively evaluating Atezo + Bev combination in HCC patients with Child-Pugh score B7 with no prior systemic therapy[37].

**IObased approaches in second-line setting**

***For patients exposed to non-immunotherapeutic agents in first-line***

Current strategies involve using immunotherapeutic or non-immunotherapeutic agents in the first-line setting for advanced HCC. For patients who recur following non-immunotherapeutic agents like sorafenib or lenvatinib, several agents are currently approved by the FDA.

***Nivolumab +ipilimumab***

The Checkmate 040 study was an open label phase I/IIdose escalation and expansion trial evaluating single agent nivolumab, a PD-1 inhibitor, in advanced HCC[38] (Table 2). The drug received accelerated approval for use in HCC in patients who progressed on sorafenib. The Checkmate 459 study evaluated nivolumab*vs*sorafenib for HCC. The study did not show significant improvement in OS with single agent nivolumab, which later resulted in the withdrawal of the drug[39,40].

Nivolumab in combination with ipilimumab, a CTLA-4 inhibitor, was also studied in patients with HCC after progression or intolerance to prior therapy in the randomized phase II portion Checkmate 040 study[41]. The majority of the patients received prior sorafenib and included patients who received up to three lines of prior systemic therapy.

There were three arms with 1:1:1 randomization using different dose combinations of ipilimumab and nivolumab. Arm A had nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (Ipi3 + Nivo1), administered every 3 wk for four doses, followed by nivolumab 240 mg every 2 wk. Arm B had nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (Ipi1 + Nivo3), administered every 3 wk for four doses, followed by nivolumab 240 mg every 2 wk. Arm C had nivolumab 3 mg/kg every 2 wk plus ipilimumab 1 mg/kg every 6 wk.

A total of 148 patients were enrolled. The ORR was 32%, 27% and 29%, respectively, for the three arms. Time to response occurred early and were similar across all treatment arms, regardless of PD-L1 status or baseline alpha-fetoprotein (AFP) levels. The duration of response was also similar. However, mOS was 22.8mo (95%CI: 9.4-not reached), 12.5mo(95%CI: 7.6-16.4) and 12.7mo(95%CI: 7.4-33.0).

Arm A reported higher grade 3/4 treatment-related adverse events (53%) (TRAEs) and higher immune-mediated events compared to Arms B (29%) and C (31%), most likely correlative of the higher dose of ipilimumab.Rash, hepatitis and hypothyroidism were the most common immune-related AEs.

Amongst the three arms, arm A achieved the highest CR rate (8%) with the best OS at 30 mo (44%) and the longest mOS of 22 mo.This treatment of Ipi3 + Nivo1, followed by nivolumab single agent received accelerated approval by the FDA for second-line use in advanced HCC. At the ASCO 2021Gastrointestinal Cancers Symposium, the 44 mo survival data was presented and continues to show promising results regarding long-term survival and safety profile[42].

A few caveats of the study were that it was an open label phase I/II study without a standard of care control arm and a small number of patients in each arm. The patients were also not stratifiedperrisk factors. However, the study included high risk patients with extrahepatic spread and elevated AFP levels and multiple lines of prior systemic therapy.

Ipilimumab + nivolumab is the standard of care for patients who progressed or are intolerant to first-line non-immunotherapeutic agents such as sorafenib based on their superior OS and ORR.

***Pembrolizumab***

Keynote 224 is a single arm phase II study of pembrolizumab, a PD-1 inhibitor, in patients with advanced HCC who had progressed on or were intolerant to sorafenib[43]. In total, 104 participants received 200mg of pembrolizumab intravenously every 3 wk for 2 years or until disease progression, toxicity or withdrawal from the trial. The primary objective of the study was ORR (17%). The mPFS was 4.9 mo (95%CI: 3.4-7.2), and mOS was 12.9 mo (95%CI: 9.7-15.5). TRAEs were observed in 73% of the patients, and 15% of the patients had serious TRAEs. Grade 3/4 TRAEs occurred in about 25% of the patients, with increased alanine transferase, increased aspartate transferase and fatigue being the most common. Immune-mediated grade 3/4 AEs were seen in only 4% of the patients, with adrenal insufficiency being the most common. Based on the data, pembrolizumab is an effective and tolerable option for patients previously treated with sorafenib.

The study also suggested that PD-L1 expression based on combined positive score using tumor and immune cells was correlative of anti PD-1 activity with pembrolizumab. This association was not significant when correlated to tumor positivity score alone. The limitations of the study were that it was a single arm study and did not compare pembrolizumab with a control arm.

Keynote 240 was a phase III global study that tested the efficacy of pembrolizumab with best supportive care (BSC) *vs*placebo with BSC in the second-line setting following progression or intolerance to sorafenib. However, there was no statistical difference seen in OS or PFS[44]. The mOS was 13.9 mo (95%CI: 11.6-16.0 mo) for pembrolizumab*vs*10.6 mo (95%CI: 8.3-13.5 mo) for placebo (HR: 0.78; 95%CI: 0.61-0.99;*P*= 0.024). mPFS for pembrolizumab was 3.0 mo (95%CI: 2.8-4.1 mo) *vs*2.8 mo (95%CI: 1.6-3.0 mo) for placebo at the final analysis (HR: 0.72; 95%CI: 0.57-0.90;*P*= 0.002). The ORR was 18.4%, which was similar to the ORR seen in Keynote 224.

Keynote 394 is another phase III randomized study evaluating pembrolizumab + BSC *vs*placebo + BSC, specifically in Asian patients with advanced HCC with progression on or intolerance to sorafenib or oxaliplatin chemotherapy. Early results were presented at ASCO 2022, and they showed thatpembrolizumab with BSC improves OS, PFS and ORR in Asian patients[44]. At the final analysis, pembrolizumab significantly improved OS *vs*placebo (HR: 0.79; 95%CI: 0.6-1.0;*P*= 0.018),mOS was 14.6 mo (95%CI:12.6-18.0) for pembrolizumab*vs*13.0 mo (95%CI: 10.5-15.1) for placebo. According to the protocol, if OS was superior, PFS and ORR at the secondinterim analysis were studied. Pembrolizumab significantly improved PFS (HR: 0.74; 95%CI: 0.6-0.9;*P*= 0.003) and ORR (estimated difference: 11.4%; 95%CI: 6.7-16.0;*P*= 0.00004).

Based on these studies, PD-1 single agent may have a differential benefit according to various pharmacodynamic changes amongst ethnic groups. Pembrolizumab therefore could be a better tolerated option for patients with progression or intolerance to first-line non-IObased agents, particularly in Asian patients.

***For patients exposed to immunotherapeutic agents in first-line***

There is no prospective data for any therapy in patients who recur following first-line IO. Clinical trials are currently underway exploring this space.

Wong *et al*[46]performed a retrospective analysis of 25 patients who had previously progressed on prior immune checkpoint inhibitor(ICI) monotherapy or combined therapy. Patients received ipilimumab in combination with either nivolumab or pembrolizumab. The 3-year follow-up data revealed that ORR was 16%, and CR rate was 12%. Overall, 40% of the patients achieved clinical benefit with this regimen, with a median duration of response of 11.5 mo (2.7-30.3 mo), and mOS was 10.9 mo. The drugs had an acceptable safety profile.

In clinical practice, when patients desire second-line IOafter progression on first-line IO, we can potentially use agents that have not been tried in the first-line setting. Treme and Durva, which is an IO+IO combination can be tried after progression on Atezo and Bev, which is an IO + VEGF combination. The reverse order can also be offered for patients who are offered IO+ IO combination first. Further clinical trials in this space are also required to evaluate the role of these agents post-recurrence.

**Combination therapy trials with systemic therapy**

Several non-immunotherapeutic agents have been approved by the FDA for use in the management of advanced HCC, either in first-line or in second-line settings post-progression. Trials are ongoing in this space to evaluate their potential role in combination with an immunotherapeutic agent (Table 3).

Camrelizumab, an anti PD-1 inhibitor, in combination with rivoceranib, an anti-VEGF receptor type 2 TKI(apatinib), is the first phase III study to show positive survival benefits with a PD-1/PD-L1 inhibitor and anti-angiogenic TKI for unresectableHCC[47]. In this randomized, open-label, phase III trial, 543 patients were randomized 1:1 to receive camrelizumab (C) + rivoceranib (R) /apatinib or sorafenib. Patients were stratified by macrovascular invasion and/or extrahepatic metastases, geographical region (Asia *vs* non-Asia) and baseline serum AFP (< 400 *vs* ≥ 400 ng/mL). The primary endpoints were PFS as well as OS. With a median follow-up time of 7.8 mo, PFS was significantly improved with C + R *vs*sorafenib [median 5.6 mo(95%CI: 5.5-6.3)*vs* 3.7 mo(2.8-3.7); HR: 0.52;95%CI: 0.41-0.65; *P*<0.0001]. With a median follow-up of 14.5 mo, OS was significantly prolonged with C + R *vs*sorafenib [median 22.1 mo(95%CI: 19.1-27.2) *vs* 15.2 mo(13.0-18.5); HR: 0.62;95%CI: 0.49-0.80; 1-sided *P*<0.0001]. ORR, disease control rate and duration of response were also better with C+R *vs*sorafenib. Grade ≥3 TRAEs occurred in 80.9% with C + R and 52.4% with sorafenib. TRAE led to discontinuation of any treatment in 24.3% (of both agents in 3.7%) with C + R and 4.5% with sorafenib.

Keynote 524 was a phase Ib study to assess the antitumor activity of lenvatinib in combination with pembrolizumab. The initial data showed that the combination was safe for use with no drug limiting toxicities, and Grade ≥ 3 toxicities were seen in 67% of the patients. The ORR was 36%perRECIST 1.1, with 1 patient having CR. Median duration of response was 12.6 mo, and the ORR findings were consistent for subgroups with poor prognostic features. The time to treatment response was less than 2.0mo, with mPFSof8.6 mo and mOSof 22.0 mo[48].

Based on this promising activity, a phase III study, LEAP-002, tested pembrolizumab + lenvatinib as a combination therapy compared to envatinib + placebo[49]. Patients (*n* = 794) were randomized 1:1 for lenvatinib + pembrolizumab*vs*lenvatinib + placebo. The dual primary endpoints of the study were OS and PFS. After the follow-up,the authors observed 17.6 mo for the final PFS and 32.1 mo for the final OS.The primary endpoints of OS and PFS did not meet pre-specified statistical significance. The mOS with lenvatinib + pembrolizumab was 21.2 mo*vs*19.0 mo with lenvatinib, and the HR was 0.840 (95%CI: 0.708-0.997;*P*=0.0227). mPFS at final analysis was 8.2 mofor lenvatinib + pembrolizumab*vs*8 mo for the lenvatinibalone arm. HR for PFS at interim analysis 1 was 0.867 (95%CI: 0.734-1.024;*P*=0.04660. ORR at final analysis was 26.1% for lenvatinib + pembrolizumab*vs*17.5% for lenvatinib. Grade 3-5 TRAEs were 62.5% in the lenvatinib + pembrolizumab arm and 57.5% in the lenvatinib arm (grade 5). Notably, in the LEAP-002 trial, OS with lenvatinib monotherapy was the longest observed with a TKI (19.0 mo), which was much longer than the mOS of lenvatinib(13.6 mo) shown in the REFLECT trial[50]. Based on the data, a meaningful difference in activity was not seen with lenvatinib + pembrolizumab*vs*lenvatinib monotherapy alone.

Cosmic 312 is a phase III trial comparing cabozantinib plus Atezo*vs*sorafenib as first-line systemic treatment for advanced HCC[51]. Patients with tumors invading the main portal vein were not excluded from the trial. Patients were randomly assigned (2:1:1) to cabozantinib 40 mg orally once daily plus Atezo 1200 mg q3 wk, sorafenib 400 mg orally BID or single agent cabozantinib 60 mg orally once daily. Primary endpoints for the study were PFS in the first 372 patients in intention to treat patient population and OS for all patients. mPFS was 6.8 mo (95%CI: 5.6-8.3) in the combination treatment group *vs*4.2 mo (95%CI: 2.8-7.0) in the sorafenib group (HR: 0.63; 95%CI: 0.44-0.91;*P*= 0.0012). mOS (interim analysis) was 15.4 mo (95%CI: 13.7-17.7) in the combination treatment group *vs*15.5 mo (12.1-not estimable) in the sorafenib group (HR: 0.90; 95%CI: 0.69-1.18; *P*= 0.44).

**Novel Agents**

Several novel IObased agents are currently in development that could have a potential role in the management of HCC.

LAG-3 inhibitors are potential agents in development and are currently being tested in their role in HCC.LAG-3 inhibition leads to activation of exhausted Tcells. Relatlimab, a LAG-3 inhibitor, is currently being tested with nivolumab for potential use in patients who have progressed on first-line TKIs, like sorafenib, and are IOnaïve[52]. The agent is also being investigated incombination withnivolumab and Bev in treatment naïve unresectable HCC patients[53].

A novel therapy targeting glypican-3(GPC-3) using chimeric antigen receptorT cells is underway in advanced HCC. Early results from two phase I studies have demonstrated their safety, with 2 patients out of 13 showing partial response[54]. Glypican-3 expression has been associated with worse prognosis in HCC[55]. There are several trials underway in this space. Natural killer cell activity has also been potentially linked to an increased risk of recurrence following curative treatment of HCC[56]. FT500 and FATE NK-100 are some of the natural killer cell IO trials currently in development for their potential role in HCC[57,58].

**CONCLUSION**

The scope of IO in the management of HCC is indeed promising. We have moved beyond sorafenib, the standard of care in the first-line management of advanced HCC for the past decade[59]. Atezo, in combination with Bev, based on the IMBRAVE study can now be considered the new standard of care for patients who have a recurrence of disease and are not amenable to local therapy. The STRIDE regimen, based on the HIMALAYA study, can also be considered a potential option if a patient is not a good candidate for the IMBRAVE regimen. For patients previously treated with sorafenib and recur or progress, ipilimumab + nivolumab or pembrolizumab are currently identified agents in the second-line setting. In their study, Wong *et al*[46]have shown that continuing to use IO agents in the second-line setting post-progression on prior ICI is certainly protective. Clinical trials to evaluate the role of ICIs in this space are undoubtedly necessary. Partner switching such as using PD-1/PD-L1 inhibitors, VEGF-inhibitors or CTLA-4 inhibitors based on the currently approved therapies should also be evaluated in the second-line setting. The role of these agents in patients with Child-Pugh score B also needs further evaluation.We are also looking at emerging combinations of non-immunotherapeutic agents like lenvatinib and cabozantinib with immunotherapeutic agents, based on the LEAP-002 and COSMIC-312 trials. Further clinical trials are warranted to assess these agents’ roles in managing HCC.

With the increasing use of immunotherapeutic agents in the neoadjuvant and adjuvant setting for early-stage HCC, we will see patients exposed to IO agents before recurrence and require systemic therapy. These patients may recur while still being on treatment with an IO agent or can recur after completion of treatment. The scope of immunotherapeutic agents in this setting will further need exploration.There is an unmet need for clinical trials to evaluate treatments involving HCC. Further immunotherapeutic agents are also being developed to improve the existing agents in the first-line setting.

**REFERENCES**

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Altekruse SF**, Henley SJ, Cucinelli JE, McGlynn KA. Changing hepatocellular carcinoma incidence and liver cancer mortality rates in the United States. *Am J Gastroenterol* 2014; **109**: 542-553 [PMID: 24513805 DOI: 10.1038/ajg.2014.11]

3 **Ashtari S**, Pourhoseingholi MA, Sharifian A, Zali MR. Hepatocellular carcinoma in Asia: Prevention strategy and planning. *World J Hepatol* 2015; **7**: 1708-1717 [PMID: 26140091 DOI: 10.4254/wjh.v7.i12.1708]

4 **Arbuthnot P**, Kew M. Hepatitis B virus and hepatocellular carcinoma. *Int J ExpPathol* 2001; **82**: 77-100 [PMID: 11454100 DOI:[10.1111/j.1365-2613.2001.iep0082-0077-x](https://doi.org/10.1111/j.1365-2613.2001.iep0082-0077-x)]

5 **Anstee QM**, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. *Nat Rev GastroenterolHepatol* 2019; **16**: 411-428 [PMID: 31028350 DOI: 10.1038/s41575-019-0145-7]

6 **Huang DQ**, Singal AG, Kono Y, Tan DJH, El-Serag HB, Loomba R. Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. *Cell Metab* 2022; **34**: 969-977.e2 [PMID: 35793659 DOI: 10.1016/j.cmet.2022.05.003]

7 **Sanyal A**, Poklepovic A, Moyneur E, Barghout V. Population-based risk factors and resource utilization for HCC: US perspective. *Curr Med Res Opin* 2010; **26**: 2183-2191 [PMID: 20666689 DOI: 10.1185/03007995.2010.506375]

8 **Morgan TR**, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S87-S96 [PMID: 15508108 DOI: 10.1053/j.gastro.2004.09.020]

9 **de'Angelis N**, Landi F, Carra MC, Azoulay D. Managements of recurrent hepatocellular carcinoma after liver transplantation: A systematic review. *World J Gastroenterol* 2015; **21**: 11185-11198 [PMID: 26494973 DOI: 10.3748/wjg.v21.i39.11185]

10 **Shah SA**, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, Langer B, Grant DR, Greig PD, Gallinger S. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. *Surgery* 2007; **141**: 330-339 [PMID: 17349844 DOI: 10.1016/j.surg.2006.06.028]

11 **N'Kontchou G**, Mahamoudi A, Aout M, Ganne-Carrié N, Grando V, Coderc E, Vicaut E, Trinchet JC, Sellier N, Beaugrand M, Seror O. Radiofrequency ablation of hepatocellular carcinoma: long-term results and prognostic factors in 235 Western patients with cirrhosis. *Hepatology* 2009; **50**: 1475-1483 [PMID: 19731239 DOI: 10.1002/hep.23181]

12 **Wang JH**, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *J Hepatol* 2012; **56**: 412-418 [PMID: 21756858 DOI: 10.1016/j.jhep.2011.05.020]

13 **Jeong SO**, Kim EB, Jeong SW, Jang JY, Lee SH, Kim SG, Cha SW, Kim YS, Cho YD, Kim HS, Kim BS, Kim YJ, Goo DE, Park SY. Predictive Factors for Complete Response and Recurrence after Transarterial Chemoembolization in Hepatocellular Carcinoma. *Gut Liver* 2017; **11**: 409-416 [PMID: 28208001 DOI: 10.5009/gnl16001]

14 **Herbst RS**, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**: 563-567 [PMID: 25428504 DOI: 10.1038/nature14011]

15 **Ferrara N**, Hillan KJ, Novotny W. Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. *BiochemBiophys Res Commun* 2005; **333**: 328-335 [PMID: 15961063 DOI: 10.1016/j.bbrc.2005.05.132]

16 **Lee M,**Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, Hack S, Spahn J, Liu B, Abdullah H, He R, Lee KH. LBA39 - Randomised efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC). *Annals of Oncology* 2019;**30**:v875 [DOI:10.1093/annonc/mdz394.030]

17 **Morse MA**, Sun W, Kim R, He AR, Abada PB, Mynderse M, Finn RS. The Role of Angiogenesis in Hepatocellular Carcinoma. *Clin Cancer Res* 2019; **25**: 912-920 [PMID: 30274981 DOI: 10.1158/1078-0432.CCR-18-1254]

18 **Finn RS**, Bentley G, Britten CD, Amado R, Busuttil RW. Targeting vascular endothelial growth factor with the monoclonal antibody bevacizumab inhibits human hepatocellular carcinoma cells growing in an orthotopic mouse model. *Liver Int* 2009; **29**: 284-290 [PMID: 18482274 DOI: 10.1111/j.1478-3231.2008.01762.x]

19 **Fukumura D**, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev ClinOncol* 2018; **15**: 325-340 [PMID: 29508855 DOI: 10.1038/nrclinonc.2018.29]

20 **Wallin JJ**, Bendell JC, Funke R, Sznol M, Korski K, Jones S, Hernandez G, Mier J, He X, Hodi FS, Denker M, Leveque V, Cañamero M, Babitski G, Koeppen H, Ziai J, Sharma N, Gaire F, Chen DS, Waterkamp D, Hegde PS, McDermott DF. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. *Nat Commun* 2016; **7**: 12624 [PMID: 27571927 DOI: 10.1038/ncomms12624]

21 **Food and Drug Administration.** FDA approves atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma. Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-plus-bevacizumab-unresectable-hepatocellular-carcinoma>

22 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]

23 **Cheng AL**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Lim HY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Ma N, Nicholas A, Wang Y, Li L, Zhu AX, Finn RS. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022; **76**: 862-873 [PMID: 34902530 DOI: 10.1016/j.jhep.2021.11.030]

24 **Stewart R**, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, Watkins A, Mullins S, Chodorge M, Andrews J, Bannister D, Dick E, Crawford N, Parmentier J, Alimzhanov M, Babcook JS, Foltz IN, Buchanan A, Bedian V, Wilkinson RW, McCourt M. Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody. *Cancer Immunol Res* 2015; **3**: 1052-1062 [PMID: 25943534 DOI: 10.1158/2326-6066.CIR-14-0191]

25 **Tarhini AA**, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. *Expert OpinBiolTher* 2008; **8**: 1583-1593 [PMID: 18774925 DOI: 10.1517/14712598.8.10.1583]

26 **Kudo M**. Scientific Rationale for Combination Immunotherapy of Hepatocellular Carcinoma with Anti-PD-1/PD-L1 and Anti-CTLA-4 Antibodies. *Liver Cancer* 2019; **8**: 413-426 [PMID: 32479569 DOI: 10.1159/000503254]

27 **Abou-Alfa GK,** Chan SL, Kudo M, Lau G, Kelley RK, Furuse J, Sukeepaisarnjaroen W, Kang YK, Dao TV, De Toni EN, Rimassa L, Breder VV, Vasilyev A, Heurgue A, Tam V, Mody K, Thungappa SC, He P, Negro A, Sangro B. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *Journal of Clinical Oncology* 2022;**40**:379-379 [DOI:10.1200/jco.2022.40.4\_suppl.379]

28 **Kudo M**. Durvalumab Plus Tremelimumab: A Novel Combination Immunotherapy for Unresectable Hepatocellular Carcinoma.*Liver Cancer*2022;**11**: 87-93 [PMID: 35634425 DOI: 10.1159/000523702]

29 **Qin S**, Finn RS, Kudo M, Meyer T, Vogel A, Ducreux M, Macarulla TM, Tomasello G, Boisserie F, Hou J, Li X, Song J, Zhu AX. RATIONALE 301 study: tislelizumab*vs*sorafenib as first-line treatment for unresectable hepatocellular carcinoma. *Future Oncol* 2019; **15**: 1811-1822 [PMID: 30969136 DOI: 10.2217/fon-2019-0097]

30 **Qin S,** Kudo M, Meyer T, Finn RS, Vogel A, Bai Y, Guo Y, Meng Z, Zhang T, Satoh T, Hiraoka A, Marino D, Assenat E, Wyrwicz L, Campos MC, Hsing-Tao K, Boisserie F, Li S, Chen Y, Zhu AX. LBA36 Final analysis of RATIONALE-301: Randomized, phase III study of tislelizumab*vs*sorafenib as first-line treatment for unresectable hepatocellular carcinoma. *Annals of Oncology* 2022;**33**:S1402-S3 [DOI:10.1016/j.annonc.2022.08.033]

31 A Study of Nivolumab in Combination With Ipilimumab in Participants With Advanced Hepatocellular Carcinoma (CheckMate 9DW). [Internet] [cited31 July 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT04039607

32 **Rausch M,** Hua J, Moodley D, White KF, Walsh KH, Miller CE, Tan G, Lee BH, Cousineau I, Lattouf J-B, Stagg J, Palombella VJ, Holland PM, Hill JA. Abstract 4550: Increased IL-27 is associated with poor prognosis in renal cell carcinoma and supports use of SRF388, a first-in-class IL-27p28 blocking antibody, to counteract IL-27-mediated immunosuppression in this setting. *Cancer Research* 2020;**80(16\_Supplement)**:4550 [DOI:10.1158/1538-7445.AM2020-4550]

33 **Naing A,**Mantia C, Morgensztern D, Kim T-Y, Li D, Kang Y-K, Marron TU, Tripathi A, George S, Rini BI, El-Khoueiry AB, Vaishampayan UN, Kelley RK, Ornstein MC, Appleman LJ, Harshman LC, Lee B, Tannir NM, Hammers HJ, Patnaik A. First-in-human study of SRF388, a first-in-class IL-27 targeting antibody, as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors. *Journal of Clinical Oncology* 2022;**40(16\_suppl)**:2501 [DOI:10.1200/jco.2022.40.16\_suppl.2501]

34 **Kim H,**Cheon J, Ha Y, Kim HS, Kim CG, Kim I, Kim C, Jung S-h, Chon HJ. Atezolizumab plus bevacizumab in Child-Pugh B advanced hepatocellular carcinoma patients. *Journal of Clinical Oncology*2022;**40(4\_suppl)**:397 [DOI:10.1200/jco.2022.40.4\_suppl.397]

35 **Choi WM**, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Yoo C, Park SR, Ryu MH, Ryoo BY, Choi J. Effectiveness and Safety of Nivolumab in Child-Pugh B Patients with Hepatocellular Carcinoma: A Real-World Cohort Study. *Cancers (Basel)* 2020; **12** [PMID: 32698355 DOI: 10.3390/cancers12071968]

36 **Wong JSL,** Kwok GW, Tang V, Li B, Leung RC-Y, Chiu JWY, Ma KW, She W-H, Tsang WYJ, Cheung TT, Yau T. Nivolumab/pembrolizumab in Child-Pugh grade B/C patients with advanced HCC. *Journal of Clinical Oncology* 2021;**39(15\_suppl)**:e16184 [DOI:10.1200/jco.2021.39.15\_suppl.e16184]

37 . A Study of Atezolizumab and Bevacizumab in Hepatocellular Carcinoma (AB7). Available from: https://clinicaltrials.gov/ct2/show/NCT04829383. [DOI:10.1200/jco.2022.40.4\_suppl.tps493]

38 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]

39 **Yau T**, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, Kudo M, Harding JJ, Merle P, Rosmorduc O, Wyrwicz L, Schott E, Choo SP, Kelley RK, Sieghart W, Assenat E, Zaucha R, Furuse J, Abou-Alfa GK, El-Khoueiry AB, Melero I, Begic D, Chen G, Neely J, Wisniewski T, Tschaika M, Sangro B. Nivolumab*vs*sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2022; **23**: 77-90 [PMID: 34914889 DOI: 10.1016/S1470-2045(21)00604-5]

40 **Bristol Myers Squibb**. Bristol Myers Squibb Statement on Opdivo® (nivolumab) Monotherapy Post-Sorafenib Hepatocellular Carcinoma U.S. Indication.Available from: https://news.bms.com/news/details/2021/Bristol-Myers-Squibb-Statement-on-Opdivo-nivolumab-Monotherapy-Post-Sorafenib-Hepatocellular-Carcinoma-U.S.-Indication/default.aspx#:~:text=In%20consultation%20with%20the%20U.S., sorafenib%20from%20the%20U.S.%20market

41 **Yau T**, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, Tovoli F, Knox JJ, Ruth He A, El-Rayes BF, Acosta-Rivera M, Lim HY, Neely J, Shen Y, Wisniewski T, Anderson J, Hsu C. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: e204564 [PMID: 33001135 DOI: 10.1001/jamaoncol.2020.4564]

42 **El-Khoueiry AB,**Yau T, Kang YK, Kim TY, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, Tovoli F, Knox JJ, He AR, El-Rayes BF, Acosta-Rivera M, Lim HY, Memaj A, Sama AR, Hsu C. Nivolumab (NIVO) plus ipilimumab (IPI) combination therapy in patients (Pts) with advanced hepatocellular carcinoma (aHCC): Long-term results from CheckMate 040. *Journal of Clinical Oncology* 2021;**39**:269 [DOI:10.1200/jco.2021.39.3\_suppl.269]

43 **Zhu AX**, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]

44 **Finn RS**, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, Breder V, Edeline J, Chao Y, Ogasawara S, Yau T, Garrido M, Chan SL, Knox J, Daniele B, Ebbinghaus SW, Chen E, Siegel AB, Zhu AX, Cheng AL; KEYNOTE-240 investigators. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J ClinOncol* 2020; **38**: 193-202 [PMID: 31790344 DOI: 10.1200/JCO.19.01307]

45 **Qin SK,** Chen ZD, Fang WJ, Ren ZG, Xu RC, Ryoo BY, Meng ZQ, Bai YX, Chen XM, Liu XF, Xiao JX, Ho GF, Mao YM, Ye X, Ying JE, Li JF, Zhong WY, Zhou Y, Siegel AB, Hao CY. Pembrolizumab plus best supportive care *vs* placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): Phase 3 KEYNOTE-394 study. *Journal of Clinical Oncology* 2022;**40**:383 [DOI:10.1200/jco.2022.40.4\_suppl.383]

46 **Wong JSL**, Kwok GGW, Tang V, Li BCW, Leung R, Chiu J, Ma KW, She WH, Tsang J, Lo CM, Cheung TT, Yau T. Ipilimumab and nivolumab/pembrolizumab in advanced hepatocellular carcinoma refractory to prior immune checkpoint inhibitors. *J Immunother Cancer* 2021; **9** [PMID: 33563773 DOI: 10.1136/jitc-2020-001945]

47 **Qin S,** Chan LS, Gu S, Bai Y, Ren Z, Lin X, Chen Z, Jia W, Jin Y, Guo Y, Sultanbaev AV, Pazgan-Simon M, Pisetska M, Liang X, Chen C, Nie Z, Wang L, Cheng AL, Kaseb A, Vogel A. 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* 2022;**33**:S1401-S2 [DOI:10.1016/j.annonc.2022.08.032]

48 **Finn RS**, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, Okusaka T, Kobayashi M, Kumada H, Kaneko S, Pracht M, Mamontov K, Meyer T, Kubota T, Dutcus CE, Saito K, Siegel AB, Dubrovsky L, Mody K, Llovet JM. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. *J ClinOncol* 2020; **38**: 2960-2970 [PMID: 32716739 DOI: 10.1200/JCO.20.00808]

49 **Finn RS,** Kudo M, Merle P, Meyer T, Qin S, Ikeda M, Xu R, Edeline J, Ryoo BY, Ren Z, Cheng AL, Galle PR, Kaneko S, Kumada H, Wang A, Mody K, Dubrovsky L, Siegel AB, Llovet J. LBA34 Primary results from the phase III LEAP-002 study: Lenvatinib plus pembrolizumab*vs*lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). *Annals of Oncology* 2022;**33**:S1401 [DOI:10.1016/j.annonc.2022.08.031]

50 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib*vs*sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

51 **Kelley RK**, Rimassa L, Cheng AL, Kaseb A, Qin S, Zhu AX, Chan SL, Melkadze T, Sukeepaisarnjaroen W, Breder V, Verset G, Gane E, Borbath I, Rangel JDG, Ryoo BY, Makharadze T, Merle P, Benzaghou F, Banerjee K, Hazra S, Fawcett J, Yau T. Cabozantinib plus atezolizumab*vs*sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2022; **23**: 995-1008 [PMID: 35798016 DOI: 10.1016/S1470-2045(22)00326-6]

52 A Phase 2, Randomized, Open-label Study of Relatlimab in Combination With Nivolumab in Participants With Advanced Hepatocellular Carcinoma Who Are Naive to IO Therapy But Progressed on Tyrosine Kinase Inhibitors (RELATIVITY-073). [Internet] [cited 28 September 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT04567615

53 A Study of Nivolumab and Relatlimab in Combination With Bevacizumab in Advanced Liver Cancer (RELATIVITY-106).[Internet] [cited 20 April 2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT05337137

54 **Shi D**, Shi Y, Kaseb AO, Qi X, Zhang Y, Chi J, Lu Q, Gao H, Jiang H, Wang H, Yuan D, Ma H, Wang H, Li Z, Zhai B. Chimeric Antigen Receptor-Glypican-3 T-Cell Therapy for Advanced Hepatocellular Carcinoma: Results of Phase I Trials. *Clin Cancer Res* 2020; **26**: 3979-3989 [PMID: 32371538 DOI: 10.1158/1078-0432.CCR-19-3259]

55 **Shirakawa H**, Suzuki H, Shimomura M, Kojima M, Gotohda N, Takahashi S, Nakagohri T, Konishi M, Kobayashi N, Kinoshita T, Nakatsura T. Glypican-3 expression is correlated with poor prognosis in hepatocellular carcinoma. *Cancer Sci* 2009; **100**: 1403-1407 [PMID: 19496787 DOI: 10.1111/j.1349-7006.2009.01206.x]

56 **Lee HA**, Goh HG, Lee YS, Jung YK, Kim JH, Yim HJ, Lee MG, An H, Jeen YT, Yeon JE, Byun KS, Seo YS. Natural killer cell activity is a risk factor for the recurrence risk after curative treatment of hepatocellular carcinoma. *BMC Gastroenterol* 2021; **21**: 258 [PMID: 34118869 DOI: 10.1186/s12876-021-01833-2]

57 FT500 as Monotherapy and in Combination With Immune Checkpoint Inhibitors in Subjects With Advanced Solid Tumors. [Internet] [cited15 February 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT03841110

58 FATE-NK100 as Monotherapy and in Combination With Monoclonal Antibody in Subjects With Advanced Solid Tumors. [Internet] [cited24 October 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT03319459

59 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

**Footnotes**

**Conflict-of-interest statement:** All authors report having no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 15, 2022

**First decision:** January 3, 2023

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Al-Haggar M, Egypt; Chen T, China; Rajer M, Slovenia**S-Editor:** Liu GL **L-Editor:** Filipodia**P-Editor:** Liu GL

**Table 1 Immunotherapy regimens for first-line use in patients with advanced hepatocellular carcinoma with no prior systemic therapy**

|  |  |  |
| --- | --- | --- |
| Immunotherapy regimen | IMBRAVE150 (NCT03434379) | HIMALAYA (NCT03298451) |
| Drugs | Atezolizumab, Bevacizumab | Durvalumab, Tremelimumab |
| Drug class combination | PD-L1 inhibitor, VEGF inhibitor | PD-1 inhibitor, CTLA-4 inhibitor |
| Study population | Child-Pugh A, ECOG score 0/1, no prior systemic therapy | Child-Pugh A, ECOG score 0/1, BCLC B or C, no prior systemic therapy |
| Key difference | Portal vein thrombosis patients included | Portal vein thrombosis patients excluded |
| EGD required? | Yes | No |
| Overall survival | 19.2 mo (95%CI: 17.0-23.7) | 16.4 mo (95%CI: 14.2-19.6) |
| Median progression free survival | 6.8 mo (95%CI: 5.7-8.3) *vs* 4.3 (95%CI: 4.0-5.6) | 3.8 mo (95%CI: 3.7-5.3) |
| Overall response rate | 27.3% (95%CI: 22.5-32.5) | STRIDE arm: 20.1% |
| Long-term survival data | Not available | Available |
| Most common treatment related AE | Hypertension, fatigue, proteinuria | diarrhea, pruritus, rash |
| Ae leading to discontinuation | 15.5% | 13.7% |
| Child-Pugh B patients | Retrospective data available | No data |
| FDAapproval | Yes | Yes |

AE: Adverse event; BCLC: Barcelona Clinic Liver Cancer; CI: Confidence interval; CTLA-4: Cytotoxic T lymphocyte associated protein-4; ECOG: Eastern Cooperative Oncology Group; EGD: Esophagogastroduodenoscopy; FDA: Food and Drug Administration; PD-1: Programmed cell death protein-1; PD-L1: Programmed death- ligand 1; STRIDE: Single Tremelimumab Regular Interval Durvalumab;VEGF: Vascular endothelial growth factor;

**Table 2Current Food and Drug Administration-approved immunotherapy agents in second-line use post-progression on sorafenib in advanced hepatocellular carcinoma**

|  |  |  |
| --- | --- | --- |
| Immunotherapy agent | Checkmate 040 (NCT01658878) | Keynote 224 (NCT02702414) |
| Drugs | Ipilimumab, nivolumab | Pembrolizumab |
| Drug class combination | CTLA-4 inhibitor, PD-1 inhibitor | PD-1 inhibitor |
| Study population | Child-Pugh A, ECOG score 0/1, prior systemic therapy with sorafenib or intolerance to sorafenib | Child-Pugh A, ECOG score 0/1, prior systemic therapy with sorafenib or intolerance to sorafenib |
| Overall survival | 22.8mo(95%CI: 9.4-not reached) | 12.9 mo (95%CI: 9.7-15.5) |
| Median progression free survival | 3.9 mo (95%CI: 2.6-8.3) | 4.9 mo (95%CI: 3.4-7.2) |
| Overall response rate | 32% | 18% |
| Most common treatment related AE | Rash, hepatitis, hypothyroidism | Hypothyroidism, hepatitis, adrenal insufficiency |
| Child-Pugh score B group studied | No data available | Retrospective data available |
| FDAapproval | Yes | Yes |

CI: Confidence interval;CTLA-4: Cytotoxic T lymphocyte associated protein-4; ECOG: Eastern cooperative oncology group; FDA: Food and Drug Administration;PD-1: Programmed cell death protein- 1.

**Table 3 Possible treatment regimens for patients with advanced hepatocellular carcinoma who have recurred on local therapy**

|  |  |  |
| --- | --- | --- |
| Patient group | Treatment | Status |
| Advanced HCC patients with no prior systemic therapy | Atezolizumab + bevacizumab | FDA approved for first-line use (no contraindications to atezolizumab/bevacizumab or both) |
| Durvalumab + tremelimumab | Contraindications to atezolizumab or bevacizumab or both; FDA approved for first-line use |
| Single agent immunotherapy | Poor ECOG 3-4 |
| Advanced HCC with prior systemic therapy with TKIs like sorafenib or lenvatinib | Ipilimumab + nivolumab | FDA approved for second-line use |
| Pembrolizumab | FDA approved for second-line use; High risk subgroups: Asian patients, poor ECOG |
| Atezolizumab + bevacizumab | Warrants further evaluation |
| Durvalumab + tremelimumab |
| Clinical trials |  |
| HCC patients with prior IO based systemic therapy | Partner switching from currently available first-line options | Using drugs with different mechanism of action in comparison to first line IO therapy |
| Pembrolizumab | Warrants further evaluation |
| Ipilimumab + nivolumab |
| Clinical trials |  |

ECOG: Eastern cooperative oncology group; FDA: Food and Drug Administration; HCC: Hepatocellular carcinoma; IO: Immunotherapy;TKI: Tyrosine kinase inhibitor.