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Editorial Board Member of *World Journal of Gastroenterology*, Hirayuki Enomoto, MD, PhD, Associate Professor, Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo Medical University, Nishinomiya 663-8501, Hyogo, Japan. enomoto@hyo-med.ac.jp

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Immunotherapy for recurrent hepatocellular carcinoma

Ahan Bhatt, Jennifer Wu

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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

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

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 inhibitor or 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 factor inhibitors. This mini-review explored IO options for patients with recurrent HCC who were not exposed to systemic therapy at the initial diagnosis. We also discussed potential IO options for patients with recurrent HCC who 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.

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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.

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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 survival period 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-Immunotherapy based. In this review, we focused on the IO-based systemic approaches.

IMMUNOTHERAPY BASED 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 and 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 Bev in comparison to sorafenib in the first-line setting for systemic therapy naïve patients with unresectable HCC[22]. At the time of the first analysis at data cutoff, the OS rate at 12 months (mo) was 67.2% [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) of 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), per response evaluation

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 |

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.

criteria in solid tumors 1.1 (RECIST 1.1) ($P < 0.001$).

The Atezo+Bev is the only first-line combination regimen involving IO that evaluated high risk patients having 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 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 the sorafenib 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; 95%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 ORR was 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 unresectable HCC[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 received either tislelizumab or sorafenib. The study reported non-inferiority of tislelizumab to sorafenib in terms of OS, with a favorable safety profile (mOS: 15.9 mo for 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 9DW is 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 (TIGIT). 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 a 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 the 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-Pugh score 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].

IMMUNOTHERAPY BASED 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/II dose 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]. Majority of the patients received prior sorafenib and included patients who received up to three lines of prior systemic therapy. The study involved 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 weeks for four doses, followed by nivolumab 240 mg every 2 weeks. Arm B had nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (Ipi1 + Nivo3), administered every 3 weeks for four doses, followed by nivolumab 240 mg every 2 weeks. Arm C had nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks.

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 was 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 were 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) for Arms A, B and C respectively. 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 2021 Gastrointestinal 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 stratified per risk 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 treatment option for patients who progressed or are intolerant to first-line non-immunotherapeutic agents such as sorafenib or lenvatinib.

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 weeks 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 mOS or mPFS[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.

Table 2 Current 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 |
| FDA approval | 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.

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 that pembrolizumab with BSC improves OS, PFS and ORR in Asian patients[44]. At the final analysis, pembrolizumab significantly improved mOS *vs* placebo. mOS was noted to be 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 second interim 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-IO based 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 were 10.9 mo. The drugs had an acceptable safety profile.

In clinical practice, when patients desire second-line IO after 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-progression.

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 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 unresectable HCC[47]. In this randomized, open-label, phase III trial, 543

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.

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% per RECIST 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 2.0 mo, with mPFS of 8.6 mo and mOS of 22.0 mo[48].

Based on this promising activity, a phase III study, LEAP-002, tested pembrolizumab + lenvatinib as a combination therapy[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 mo for lenvatinib + pembrolizumab *vs* 8 mo for the lenvatinib alone 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 weeks, 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 the 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 IO-based 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 the activation of exhausted T cells. 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 IO naïve[52]. The agent is also being investigated in combination with nivolumab and Bev in treatment naïve unresectable HCC patients[53].

A novel therapy targeting glypican-3 (GPC-3) using chimeric antigen receptor T 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 a 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 IMBRAVE150 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 already being developed to improve the existing agents in the first-line setting.

FOOTNOTES

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Country/Territory of origin: United States

ORCID number: Ahan Bhatt 0000-0003-1396-1735; Jennifer Wu 0000-0002-1714-0021.

S-Editor: Liu GL

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P-Editor: Liu GL

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