80000_Auto_Edited.docx

WORD COUNT 4899
TIME SUBMITTED 30-JAN-2023 01:44PM
PAPER ID 96037373

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 80000

Manuscript Type: MINIREVIEWS

Immunotherapy for Recurrent Hepatocellular Carcinoma

Immunotherapy for Recurrent Hepatocellular Carcinoma

Ahan Bhatt, Jennifer Wu

Abstract

Hepatocellular Carcinoma (HCC) is presented frequently in late stages that are not amendable for curative treatment. Even for patients who can undergo resection for curative resection 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. This includes PD-1 and CTLA4 treatment, combination of PD-1 and VEGF inhibitor, single agent PD1 therapy when all other options are deemed inappropriate. There are also investigational therapies in this area that explore either PD-1 and TKI, or a novel agent in addition to PD-1 with VEGF inhibitor. This mini-review will explore immunotherapy options for patients with recurrent HCC who were not exposed to systemic therapy at the initial diagnosis. We will also discuss potential immunotherapy options for patients with recurrent HCC who were exposed to first line therapy with curative intent at diagnosis.

Key Words: Immunotherapy; Hepatocellular Carcinoma; Liver Cancer

Bhatt A, Wu J. Immunotherapy for Recurrent Hepatocellular Carcinoma. *World J Gastroenterol* 2023; In press

Core Tip: Immunotherapy has made a strong headway in the management of hepatocellular carcinoma (HCC). For patients who recur on local therapy, immunotherapy has become the standard of care treatment option for unresectable HCC. Role of immunotherapy agents is still not explored in patients who progress on prior immunotherapy. This mini-review highlights 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 900,000 new cases in 2020. HCC accounts for the third most cancer deaths, next only to lung cancer and colorectal cancer. It occurs twice as commonly in males compared to females and is more common in Eastern Asian countries compared to Europe [1]. In the United States, 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 (HBV) control measures such as vaccination and effective anti-viral therapy, where HBV is the main cause of HCC in Eastern Asian population[3],[4]. On the other hand, Non Alcoholic 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%) and hepatitis C (22%)[7].Chronic alcohol consumption continues to be a leading cause of HCC as well in US and other western countries[8].

While managing patients with early stage HCC who underwent local therapy using transplantation, hepatic resection, ablation or transarterial chemoembolization (TACE) of the lesion, there is always a chance of recurrence. 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 Hepatocellular cancer [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 had distant recurrence at 5 year Follow up[11] .Surgical resection when compared to ablation for HCC did not show significant improvement in the overall survival (OS); however, the disease free survival (DFS) 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 2 types of systemic therapies: 1) immunotherapy based and 2) non-immunotherapy based.

In this review, we are going to focus on the immunotherapy 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 1b study to evaluate their role for the management of untreated, advanced HCC patients [14-16]. Atezolizumab acts by preventing T cell suppression by selectively inhibiting PD-L1 from attaching to PD-1 receptors[14]. Bevacizumab 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 atezolizumab in combination with bevacizumab as the standard of care for advanced HCC patients[21]. The IMBrave 150(NCT03434379) was a large multicenter, open label phase 3 randomized study which evaluated the safety

and efficacy of atezolizumab in combination with bevacizumab to sorafenib, in the first line setting for systemic therapy naive patients with unresectable HCC [22]. At the time of first analysis at data cutoff, overall survival rate at 12 mo was 67.2% (95% confidence interval [CI], 61.3 to 73.1) with atezolizumab–bevacizumab (atezo+bev) and 54.6% (95%CI, 45.2 to 64.0) with sorafenib. Median overall survival (mOS) was not reached for atezo+bev arm and was 13.2 mo (95%CI, 10.4-not reached) for sorafenib arm. The study had shown median progression-free survival (mPFS) was 6.8 mo (95%CI, 5.7 to 8.3) for atezo + bev arm and 4.3 mo (95%CI, 4.0 to 5.6) for sorafenib arm. Thus, we saw significantly improved overall survival (OS) and progression free survival (PFS) compared to TKI sorafenib. Atezo + Bev arm in the study demonstrated superior overall response rate (ORR), 27.3% (95%CI, 22.5 to 32.5) when compared to sorafenib arm 11.9% (95%CI, 7.4 to 18.0), per RECIST 1.1 (p<0.001).

This is the only first line combination regimen involving immunotherapy 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, the trial required a pre-treatment evaluation of esophageal varices, because of its increased complications with cirrhosis, HCC and due to the side effect profile of the drug bevacizumab. 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 ASCO GI 2021, additional 12 mo data was presented and after a median 15.6 (range, 0-28.6) months of follow-up, the mOS was 19.2 mo (95%CI 17.0 -23.7) with atezo+ bev arm and 13.4 mo (95%CI 11.4-16.9) with sorafenib, whereas the mPFS and ORR was similar to the original presented data[23] . The updated data showed 8% of the patients achieving complete response (CR) with atezo+bev compared to <1% with sorafenib. Moreover, data for PD L1 negative patient subgroup did not reveal meaningful difference in OS, thus suggesting treatment efficacy regardless of PD L1 expression.

Durvalumab and Tremelimumab:

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

At the ASCO 2022 GI Cancers Symposium, HIMALAYA was presented. HIMALAYA is an open-label, multicenter, phase 3 study evaluating immunotherapy combination of tremelimumab and durvalumab (Treme+ durva) *vs* sorafenib. Patients with newly diagnosed unresected HCC, not amenable to local therapy, were initially randomized to Tremelimumab with 1 dose only, plus Durvalumab every 4 wk (STRIDE regimen) or Durvalumab or Sorafenib in 1:1:1 ratio [27].The study met the primary endpoint of improved overall survival in Treme+Durva arm (STRIDE regimen) when compared to sorafenib. This was also the first study to evaluate long term overall survival, with median followup 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 to 19.5) *vs* 13.7 mo (95%CI, 12.2 to 16.1) for sorafenib. The mPFS was 3.8 mo (95%CI, 3.7 to 5.3) in the STRIDE arm, and 4.1 mo (95%CI, 3.8 to 5.5) in the sorafenib arm. Despite a similar PFS for STRIDE and sorafenib, more patients remained progression free at the time of data cut-off for 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. STRIDE regimen showed superiority in ORR (20.1%) compared to sorafenib (5.1%).

In addition, Durvalumab met the objective of OS Non-Inferiority to Sorafenib (HR, 0.86; 96% CI, 0.73–1.03). Overall Response Rates is higher in Durvalumab (17.0%) than for Sorafenib (5.1%).

In contrast to IMBRAVE150 study, HIMALAYA study, did not include Vp4 thrombus patients which is considered a high risk patient group nor any sub group analysis is

available yet[22,27]. The STRIDE regimen is not associated with increased risk of bleeding with esophageal varices, thus eliminating the need for esophago-gastro-duodenoscopy (EGD) for evaluation, as is required for the Atezo Bev combination. Therefore, STRIDE can be a very good option for patients who are contraindicated to Bevacizumab (commonly fistula, recent bleeding, high grade varices, severe hypertension, and proteinuria).

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

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

TABLE 1. A table comparing the immunotherapy regimens for first line use in patients with advanced HCC with no prior systemic therapy.

Tislelizumab:

RATIONALE 301 study is a phase III randomized,open label study which evaluated tislelizumab, a PD-1 inhibitor, *vs* sorafenib as first-line treatment for unresectable hepatocellular carcinoma[29]. The primary objective of the study is to compare overall survival. The patients have unresectable HCC with no prior systemic therapy, Child Pugh A class and ECOG 0 or 1. The patients are randomized 1:1 and will either receive tislelizumab or sorafenib. The study reported non-inferiority of tislelizumab(T) to sorafenib(S) in terms of overall survival, with a favorable safety profile (mOS: 15.9 mo

[T] *vs* 14.1 mo [S]; stratified HR: 0.85 [95.003% CI: 0.712, 1.019])[30]. Based on the results of this study, ingle agent tislelizumab can be considered as a potential first line option for 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 uHCC who have not received systemic therapy[31]. The primary objective is to measure OS and secondary objective is to measure ORR and DOR.

SRF388:

SRF388 is another agent that is being used in combination with Atezolizumab and Bevacizumab in the frontline setting for patients with advanced hepatocellular carcinoma. SRF388 is an inhibitor of Interleukin-27 (IL-27) and as a single agent, has shown that it reduces HCC growth in mouse models [32]. HCC development is suppressed if IL27 is inhibited in NASH induced HCC models. Higher levels of IL27 have also been shown to reduce survival in HCC. IL-27 upregulates PD L1 expression, LAG3, TIM 3 and TIGIT and thus combining PD1 therapy with SRF388 increases cytokines such as TNF-alpha and Interferon-gamma, which can potentially help in reducing tumor growth.

The preliminary results from the phase 1 study showed that there were no significant drug related toxicities (Grade>3 or higher or DLT) and achieved 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 atezolizumab and bevacizumab.

CHILD PUGH SCORE B Group

All currently approved therapies are based on studies which exclude Child Pugh score B patients. There is no prospective data evaluating this group of patients in 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 is seen with ORR of 14.8% in Child score B group, compared to 32.3% for Child score A group. mPFS and OS were 3 (95%CI, 1.6-4.3) and 6 (95%CI, 4.9-7.0) months for Child B compared to mPFS of 6 mo and mOS not reached for Child A group. More grade ¾ adverse events were observed with thrombocytopenia and AST elevation being the most common. A higher discontinuation rate was seen in the Child B group.

Similar retrospective studies have also shown that Nivolumab and Pembrolizumab have limited role in the management of aHCC for Child Pugh class B/ C patients previously treated with other therapies. Poor outcomes were associated with high CP score, portal vein thrombosis and diuretic refractory ascites [35, 36]. Wong *et al* in their study, however demonstrated superior response in Child Pugh B7 patients compared to CP>=8.

A trial is currently open, prospectively evaluating Atezo+Bev combination in HCC patients with Child Pugh B7 score with no prior systemic therapy[37].

IMMUNOTHERAPY BASED APPROACHES IN SECOND LINE SETTING:

For patients exposed to non-immunotherapeutic agents in 1st 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:

Checkmate 040 study was an open label phase ½ dose escalation and expansion trial evaluating single agent nivolumab, a PD-1 inhibitor, in advanced HCC [38]. The drug received accelerated approval for use in HCC in patients who progressed on sorafenib. 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 withdrawal of the drug. [39, 40].

Nivolumab in combination with ipilimumab, CTLA-4 inhibitor, was also studied in patients with hepatocellular carcinoma after progression or intolerance to prior therapy in the randomized phase 2 portion checkmate 040 study [41]. Majority of the patients received prior sorafenib, but included patients who received up to 3 Lines of prior systemic therapy.

There were 3 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 (Ipi 3+Nivo1), administered every 3 wk for 4 doses, followed by nivolumab 240 mg every 2 wk; Arm B had nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (Ipi1+Nivo 3), administered every 3 wk for 4 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 148 patients were enrolled. The ORR was 32%, 27% and 29% respectively for the 3 arms. Time to response occurred early and were similar across all treatment arms, regardless of PD L1 status or baseline AFP levels. Duration of response were also similar. However, mOS was 22.8 (95%CI, 95%CI 9.4-not reached), 12.5(95%CI, 7.6-16.4) and 12.7(95%CI, 7.4 to 33.0) months.

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, with rash, hepatitis and hypothyroidism being the most common immune related adverse events (AEs).

Amongst the 3 arms, arm A achieved the highest CR rate (8%) with best overall survival rates at 30 mo (44%), and based on the longest mOS of 22 mo, this treatment of Ipi3+Nivo1, followed by nivolumab single agent received accelerated approval by FDA for 2nd line use in advanced hepatocellular carcinoma. At ASCO 2021 Gastrointestinal Cancers Symposium, the 44 mo survival data was presented and continues to show promising results in regards to long term survival and safety profile [42].

A few caveats of the study were that it was an open label phase ½ study without a standard of care control arm and 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 Alpha-fetoprotein (AFP) level 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 agent such as sorafenib based on their superior OS and ORR.

Pembrolizumab:

Keynote 224 is a a single arm phase 2 study of pembrolizumab, a PD-1 inhibitor, in patients with advanced hepatocellular carcinoma, who had progressed on or are intolerant to sorafenib [43]. 104 participants received 200mg of pembrolizumab intravenously every 3 wk for 2 years or until disease progression, toxicity or withdrawal from trial. The primary objective of the study was ORR (17%). The mPFS was 4.9 mo (CI 95%, 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 ¾ TRAEs occurred in about 25% of the patients, with increased alanine transferase, increased aspartate transferase and fatigue being the most common.Immune mediated grade ¾ 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 (CPS) 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 (TPS) alone. The limitation of the study was that it was a single arm study, and did not compare pembrolizumab with a control arm.

Keynote 240 is a phase 3 global study tested the efficacy of pembrolizumab with best supportive care (BSC) *vs* placebo with best supportive care in the 2nd 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 to 16.0 mo) for pembrolizumab *vs* 10.6 mo (95%CI, 8.3 to 13.5 mo) for placebo (hazard ratio [HR], 0.78; 95%CI, 0.61 to 0.99; *P* = .024). mPFS for pembrolizumab was 3.0 mo (95%CI, 2.8 to 4.1 mo) *vs* 2.8 mo (95%CI, 1.6 to 3.0 mo) at final analysis (HR, 0.72; 95%CI, 0.57 to 0.90; *P* = .002). The ORR was 18.4% which was similar to the ORR seen in Keynote 224.

Keynote 394 is another phase 3 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 it showed that Pembrolizumab with BSC improves OS, PFS and ORR in Asian patients [45]. At the final analysis, pembrolizumab significantly improved OS *vs* placebo (HR 0.79, 95%CI 0.6-1., *P* = 0.018); median (95%CI) OS was 14.6 mo (12.6-18.0) for pembrolizumab *vs* 13.0 mo (10.5-15.1) for placebo. According to the protocol, if OS was superior, PFS and ORR at 2nd 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-immunotherapy based agent, particularly in Asian patients.

TABLE 2 A table comparing the currently FDA approved Immunotherapy agents in second line use post progression on sorafenib in advanced HCC.

For patients exposed to immunotherapeutic agents in 1st line:

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

Wong *et al* performed a retrospective analysis of 25 patients who had previously progressed on prior ICI monotherapy or combined therapy [46]. 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%. 40% of the patients achieved clinical benefit with this regimen, with 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 2nd line immunotherapy(IO) post progression on 1st line immunotherapy, we can potentially use agents which have not been tried in 1st line setting. Tremelimumab and Durvalumab, which is an IO+IO combination can be tried after progression on atezolizumab and bevacizumab, 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, evaluating 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 1st line or in 2nd line setting post progression. Trials are on-going in this space to evaluate their potential role in combination with an immunotherapeutic agent.

Camrelizumab, an anti PD-1 inhibitor, in combination with Rivoceranib, a anti-VEGFR2 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 were randomized 1:1 to receive Camrelizumab (C) + Rivoceranib (R) /Apatinib or Sorafenib (S). 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. S (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. S (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, DCR and DoR were also better with C+R *vs* S. Grade ≥3 TRAEs occurred in 80.9% with C+R and 52.4% with S. TRAE led to discontinuation of any treatment in 24.3% (of both agents in 3.7%) with C+R and 4.5% with S.

Keynote 524 was a phase 1b 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 complete response. 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 mo, with mPFS 8.6 mo and mOS was 22 mo[48] .

Based on this promising activity, a phase III study LEAP-002 tested Pembrolizumab +Lenvatinib as a combination therapy compared to lenvatinib+placebo[49]. 794 Patients were randomized in 1:1 for lenvatinib + pembro *vs* lenvatinib +placebo. Dual primary endpoints of the study were OS and PFS. After a median follow up of 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 median OS with lenvatinib + pembro 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). Median PFS at final analysis was 8.2 for lenvatinib +pembro *vs* 8 mo for lenvatinib alone arm. HR for PFS at interim analysis 1(IA1) was 0.867 (95%CI: 0.734-1.024, *P*=0.0466. ORR at FA was 26.1% for lenvatinib + pembro *vs* 17.5% for lenvatinib. Grade 3-5 treatment-related adverse events (TRAEs) were 62.5% in the lenvatinib + pembro arm and 57.5% in the lenvatinib arm (grade 5). Notably, in the LEAP-002 trial, OS with lenvatinib monotherapy is the longest we have seen with a TKI – 19.0 mo – which is much longer than the median OS of lenvatinib – 13.6 mo – shown in the REFLECT trial[50]. Based on the data, meaningful difference in activity is not seen with lenvatinib+ pembro *vs* lenvatinib monotherapy alone.

Cosmic 312 is a phase 3 trial comparing cabozantinib plus atezolizumab *vs* sorafenib as first-line systemic treatment for advanced hepatocellular carcinoma [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 OD plus atezolizumab 1200 mg q3 wk, sorafenib 400 mg orally BID, or single-agent cabozantinib 60 mg orally OD. 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 (99% CI 5·6–8·3) in the combination treatment group *vs* 4·2 mo (2·8–7·0) in the sorafenib group (hazard ratio [HR] 0·63, 99% CI 0·44–0·91, *P* = 0·0012). mOS (interim analysis) was 15·4 mo (96% 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, 96% CI 0·69–1·18; *P* = 0·44).

TABLE 3. Possible treatment regimens for patients with advanced HCC, who have recurred on local therapy.

NOVEL AGENTS:

Several novel immunotherapy-based agents are currently in development which could have potential role in the management of HCC.

Lymphocyte activation gene 3(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 T-cells. Relatlimab, a LAG-3 inhibitor, is currently being tested with nivolumab for potential use in patients who have progressed on first line TKI like sorafenib and are immunotherapy naive[52]. The agent is also being investigated with combination of nivolumab and bevacizumab in treatment naïve uHCC patients[53].

Novel therapy targeting the glypican-3(GPC-3) using chimeric antigen receptor-T (CAR-T) cells are underway in advanced hepatocellular cancer. Early results from 2 phase 1 studies have demonstrated their safety, with 2 patients out of 13 showing partial response [54]. GPC-3 expression has been associated with worse prognosis in HCC [55]. There are several trials underway in this space. NK cell activity has also been potentially linked to increased risk of recurrence following curative treatment of HCC [56]. FT500 and FATE NK-100 are some of the NK cell immunotherapy trials currently in development for their potential role in hepatocellular carcinoma[57, 58].

CONCLUSION

The scope of Immunotherapy in the management of hepatocellular carcinoma 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]. Atezolizumab, in combination with bevacizumab, 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. 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* have shown that continuing to use immunotherapy agents in 2nd line setting post progression on prior ICI is certainly protective[46]. Clinical trials to evaluate the role of ICIs in this space are undoubtedly necessary. Partner switching such as using PD-1/PD-L1 inhibitor, VEGF-inhibitor or CTLA-4 inhibitors based on the

currently approved therapies should also be evaluated in the 2nd 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' role 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 on 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 hepatocellular carcinoma. Further immunotherapeutic agents are also being developed to improve the existing agents in the first-line setting.

80000_Auto_Edited.docx

ORIGINALITY REPORT

19%
SIMILARITY INDEX

PRIMARY SOURCES

1	cslide.ctimeetingtech.com Internet	242 words — 5%
2	www.researchgate.net Internet	168 words — 3%
3	www.frontiersin.org Internet	78 words — 1%
4	dailyreporter.esmo.org Internet	71 words — 1%
5	Yifei Xu, Jinhui Jiang, Hui Wang, Wenjing Yu, Guoping Sun. " Synthesis and Preclinical Evaluation of [Ga]SP94 for Micro-PET Imaging of GRP78 Expression in Hepatocellular Carcinoma ", ACS Medicinal Chemistry Letters, 2021 Crossref	61 words — 1%
6	mdpi-res.com Internet	61 words — 1%
7	Friedrich Foerster, Simon Johannes Gairing, Sumera Irie Ilyas, Peter Robert Galle. "Emerging Immunotherapy for Hepatocellular Carcinoma: A Guide for Hepatologists", Hepatology, 2022 Crossref	50 words — 1%

8	www.onclive.com Internet	49 words — 1%
9	www.mdpi.com Internet	43 words — 1%
10	pharmac.govt.nz Internet	28 words — 1%
11	www.antibodysociety.org Internet	25 words — < 1%
12	specialty.mims.com Internet	19 words — < 1%
13	www.ncbi.nlm.nih.gov Internet	18 words — < 1%
14	Priya Hays. "Chapter 5 Great Strides in Precision Medicine: Personalized Oncology, Immunotherapies, and Molecular Diagnostics", Springer Science and Business Media LLC, 2021 Crossref	16 words — < 1%
15	cdn.doctorsonly.co.il Internet	15 words — < 1%
16	Michela Guardascione, Giuseppe Toffoli. "Immune Checkpoint Inhibitors as Monotherapy or Within a Combinatorial Strategy in Advanced Hepatocellular Carcinoma", International Journal of Molecular Sciences, 2020 Crossref	14 words — < 1%
17	"A GLOBAL CONGRESS DIGEST ON SOLID TUMORS. Report from the ESMO Hybrid Congress , 9th – 13th September 2022", memo - Magazine of European Medical Oncology, 2022	13 words — < 1%

Crossref

18	pubmed.ncbi.nlm.nih.gov Internet	13 words — < 1%
19	pure.coventry.ac.uk Internet	13 words — < 1%
20	"Abstracts Poster", American Journal of Transplantation, 5/2008 Crossref	12 words — < 1%
21	www.multi-med.com Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS