Editorial Commentary

Immunotherapy in advanced hepatocellular carcinoma: an evolving space in the systemic treatment paradigm

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Over the past decade, immune checkpoint inhibitors are being increasingly studied and utilized for cancer therapy. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and is currently a rising cause of cancer-related death in the United States (1). Historically, hepatitis B virus infection and hepatitis C virus infection were the most common risk factors for developing HCC (1,2). Currently in the United States, however, metabolic factors, notably diabetes and obesity, have the highest population attributable fraction (3), with HBV and HCV continuing to have the greatest strength of association in the development of HCC (4). The diagnosis of HCC often occurs at late stages in the disease process given its often non-specific presentation, and effective therapies are currently limited. Sorafenib was the first approved multikinase inhibitor for patients with advanced HCC (2). More recently, lenvatinib (oral multikinase inhibitor) has been approved as another first-line option in advanced HCC based on the phase III REFLECT trial (5). For patients with advanced HCC who have been previously treated with sorafenib, cabozantinib (6), regorafenib (7), and ramucirumab (8) have all been FDA approved as standard therapies. Recently the FDA has also given nivolumab and pembrolizumab accelerated approval for use as second-line agents in patients with advanced HCC who had previously received sorafenib based on the results of the checkmate 040 trial. This was a phase 1/2 dose escalation and expansion trial of nivolumab monotherapy in patients with advanced HCC and in both patients who had and had not previously received sorafenib. Nivolumab 3 mg/kg was used in the dose expansion phase. This study showed an objective response rate of 15% in the dose escalation phase and 20% in the dose expansion phase compared to response of 2–3% with sorafenib (2).

Feun and colleagues conducted a phase II study in the United States of the efficacy of pembrolizumab as a second-line agent for treatment of advanced HCC in patients who have had disease progression while receiving sorafenib or have been intolerant to or refused sorafenib (9). This study examined patients with advanced HCC having measurable disease defined by the Reponses Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Pembrolizumab was administered at a dose of 200 mg intravenously every 3 weeks with CT or MRI imaging performed after every 3 doses (every 9th week). RECIST v1.1 criteria were used to assess disease response. The primary endpoint of this trial was disease control rate (DCR) defined as the percentage of patients who achieved complete response, partial response, or stable disease (no change in tumor size or regression less than 30%) for a period of at least 8 weeks. Secondary endpoints included the duration of progression-free survival (PFS), overall survival (OS), duration of response, and

adverse events. Given the conflicting data surrounding current use of PD-L1 expression as a biomarker for response to PD-1/PD-L1 blockade, the current study examined various plasma cytokines both proinflammatory, anti-inflammatory and those that have been reported to upregulate PD-L1 expression to identify predictive biomarkers for treatment response.

Twenty-nine patients were treated with pembrolizumab in this study. Of the 29, 28 patients were evaluated for response. One patient achieved complete response and eight achieved partial response for an overall response rate (ORR) of 32%. Additionally, four patients had stable disease. The DCR achieved was 46%. One patient developed pseudo-progression in which the patient's chest wall mass initially increased in size (based on imaging done at 2 months), then decreased after 9 months of therapy. The median OS of patients in this study was 13 months and the median PFS was 4.5 months. Of note, a response was seen in all patients; those who had and who had not previously been treated with sorafenib.

As suggested in previous studies, no correlation was found between PD-L1 positivity on immunohistochemistry (IHC) staining and response to treatment, though sample size was limited as only 10 patients provided biopsy tissue samples. Investigation of plasma cytokine biomarkers to predict response to PD-1/PD-L1 blockade revealed that the mean TGF-β levels in responders was lower than the level in non-responders. TGF-β ≥200 (pg/mL) was an index of poor response to pembrolizumab (P=0.003). TGF-β level also correlated with OS and PFS with plasma TGF-β ≥200 having a lower OS and PFS compared to patients with a TGF-β <200. Interestingly, plasma PD-L1 concentration did not correlate to PD-L1 tumor expression, however, PD-L1 positive tumors were noted to have higher levels of plasma INF-γ or IL-10, suggesting a role of these cytokines as predictive biomarkers.

It is worthwhile to mention that this phase II trial by Feun *et al.* postdates the phase II KEYNOTE-224 trial that led to the FDA approval of second-line pembrolizumab in advanced HCC (10). This study enrolled 104 patients with HCC who had previously been treated with sorafenib and who either had disease progression or were intolerant to sorafenib. These patients were treated with 200 mg of pembrolizumab every 3 weeks until disease progression, unacceptable toxicity, patient withdrawal or investigator decision. Of the 104 patients enrolled in this study, response was seen in 18 patients (17%). Among these 18 responders, one participant had complete response and 17 (16%) patients had partial response. Stable disease was seen in 46 (44%) participants and progressive disease was seen in 34 (33%) participants. The remaining six participants could not be assessed because they did not have assessment data after baseline due to death or withdrawal from the trial. It is worthwhile to note that the phase II trial by Feun *et al.* enrolled patients who were intolerant to sorafenib or refused sorafenib treatment (9). Specifically, in 10 patients who had received prior sorafenib, 4 responses were observed, while in the 18 patients who had received no prior sorafenib, 5 responses were seen. In contrast, the KEYNOTE-224 trial enrolled 104 patients with HCC, 21 (20%) who were intolerant to sorafenib and 83 (80%) who had progressive disease with sorafenib (10). It is likely that the lower ORR of 17% in KEYNOTE-224 compared to the ORR of 32% by Feun *et al.* to pembrolizumab is due to the larger population of subjects included in KEYNOTE-224 who had progressed on sorafenib, i.e., had more aggressive disease that was already refractory to a standard first-line systemic therapy.

In the confirmatory phase III KEYNOTE-240 trial, however, pembrolizumab failed to achieve statistical significance in the primary endpoint of PFS and OS compared to placebo (11). More recently, nivolumab was investigated against sorafenib in the first-line treatment of advanced HCC via the phase III CheckMate 459 study (12) and similarly failed to reach statistical significance in OS compared to sorafenib. This randomized controlled study enrolled 743 patients with advanced HCC who had received no prior systemic treatment. The patients randomized to the nivolumab group were treated with intravenous nivolumab 240 mg every 2 weeks whereas patients in the sorafenib group received 400 mg oral sorafenib two times daily. At the minimum follow up period of 22.8 months, nivolumab showed the OS of 16.4 months compared to the OS of sorafenib at 14.7 months, however, this difference was not statistically significant (P=0.0419) (12). Together these studies suggest that a single agent whether, PD-1 or PD-L1, is not sufficient to produce a significant survival benefit when compared to sorafenib.

Despite these recent negative trials of pembrolizumab and nivolumab as first- and second-line treatments of advanced HCC, there have been exciting developments to suggest that, on the contrary, immunotherapy does have a place in the treatment paradigm of advanced HCC when used as multi-drug regimens. In a recent groundbreaking presentation, the phase III IMbrave150 study showed that atezolizumab and bevacizumab, a VEGF inhibitor, used in

combination has improved overall survival and progression free survival compared to sorafenib (13). This was a phase III study that randomized 501 patients with unresectable HCC to a combination of atezolizumab (1,200 mg intravenous every 3 weeks) + bevacizumab (15 mg/kg intravenous every 3 weeks) or sorafenib (400 mg two times daily). The mean OS for atezolizumab + bevacizumab has not yet been reached whereas the mean OS for sorafenib alone was 13.2 months (13). The atezolizumab + bevacizumab group also had a significantly higher PFS (6.8 *vs*. 4.3 months respectively, P<0.0001). Additionally, the ORR was 27% in the atezolizumab + bevacizumab group compared to 12% in the sorafenib group (P<0.0001) (13). Though many previous studies have attempted to find a treatment regimen with improved efficacy over the standard of care, sorafenib, results have always been non-significant. The IMbrave150 trial is the first study to provide a treatment regimen with improved OS and PFS over first-line sorafenib.

Altogether, this recent evidence supports that where single-agent immune checkpoint blockade has failed to demonstrate superiority over sorafenib in the first-line treatment of advanced HCC, combination checkpoint inhibitor-based regimens such as atezolizumab and bevacizumab appear promising as possible new standards in the first-line treatment of advanced HCC. A third combination regimen including the checkpoint inhibitors durvalumab and tremelimumab is also undergoing investigation in the ongoing phase III HIMALAYA trial (NCT03298451).

Beyond the first-line setting, immunotherapy has still shown glimpses of activity. With the already approved nivolumab option in those previously treated with or intolerant to sorafenib, single-agent immunotherapy may still have a space, albeit smaller, as the second-line treatment of advanced HCC for patients who received an oral multikinase inhibitor as initial therapy. With the promising data thus far presented for atezolizumab and bevacizumab, however, it is likely that this regimen will be widely established as the new first-line standard in advanced HCC. With novel and promising treatment regimens emerging, currently, the more pressing need is identifying biomarkers to predict response to immune check point therapy.

In conclusion, Feun *et al.* demonstrated clinically-relevant activity to support the use of pembrolizumab as a second-line agent in patients with advanced HCC. Additionally, a major benefit of checkpoint inhibitor therapy compared to other systemic therapies is its relatively tolerable side effect profile, with data from this study suggesting that the major treatment related adverse events and laboratory adverse events are grade 1–2. As discussed by the authors of this study, there may be utility to combining checkpoint inhibitor therapy with current non-systemic therapies for HCC including radiofrequency ablation and more studies are needed to further investigate potential combination therapies. In addition to pembrolizumab efficacy data, this study provided novel data surrounding the association of various plasma cytokines with tumor PD-L1 expression, and larger studies are needed to support this preliminary data.

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