Annals of Hepatology 28 (2023) 100886

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Editorial

# Immunotherapy for HCC: limitations in patients with NASH

Hepatocellular carcinoma (HCC) is a global health problem, with chronic hepatitis B and C viral infection accounting for well over half the cases worldwide [1]. NASH is emerging as the most rapidly rising cause for developing HCC in the West. The vast majority of patients with NASH-related HCC present at an advanced stage, when curative options, such as ablation, resection, or liver transplantation, are unavailable. Therefore, optimizing the strategic use of loco-regional and systemic therapy serve a vital role in improving long-term outcomes for patients with HCC. Although recent data on the use of combinations of checkpoint inhibitors and anti-angiogenic antibodies are encouraging, there remains concern that not all tumors are equally responsive to checkpoint inhibition.

## 1. Introduction

The prognosis of patients with early-stage HCC has improved over the past two decades following advances in diagnosis and treatment, including curative options including surgical resection, ablation and liver transplantation and the adoption of multidisciplinary management strategies by tumor boards [2,3]. Despite these advances, the vast majority of patients with HCC are unfortunately diagnosed with the advanced-stage disease when curative options are not feasible. Those patients for whom cure is not possible are often managed with palliative non-surgical liver-directed therapies and/or systemic therapies. It is estimated that over half of all patients with HCC will receive systemic therapy at some point during the course of their illness [4]. It is, therefore, imperative to determine the most effective systemic treatment strategies early in the disease course to improve clinical outcomes for patients with HCC.

## 2. Systemic Therapy

Historically, HCC has been a relatively chemotherapy-refractory tumor [5]. Until 2008, no systemic treatment options were found to provide a survival benefit in advanced disease or following liver-directed therapy as investigated in randomized controlled trials. The SHARP trial, a phase III randomized controlled trial, compared sorafenib, an oral multi-kinase inhibitor, to a placebo in patients with HCC and well-compensated cirrhosis but who were unsuitable for surgical resection [6]. This trial demonstrated the superiority of sorafenib over placebo, with an improvement in median overall survival of 10.7 months in the treatment arm, up from 7.9 months in the placebo group. This represented a significant improvement leading to FDA approval as a first-line agent for the treatment of advanced-stage HCC. Following the approval of sorafenib for unresectable HCC, other multi-kinase inhibitors have been approved. Unfortunately, the overall survival benefit of sorafenib and the other multi-kinase inhibitors when introduced into clinical practices has been less satisfactory, with significant rates of adverse effects being common and necessitating withdrawal of therapy in approximately 15% of patients [7–12].

## 3. Immune Checkpoint Inhibitors

The microenvironment of many cancers has repressed T-cell responses. Immune checkpoint inhibitors (ICIs) target specific inhibitory sites within the inflammatory cascade, including representative examples of the programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4). The inhibition of these targets using monoclonal antibody therapy has been shown across cancer types to restore anti-tumor T-cell response, including melanoma, lung, renal, and bladder cancer [13]. The efficacy of ICI in combination with anti-angiogenic agent for advanced HCC not amenable to potentially curative regimens was tested in phase III IMbrave150 trial. The trial was designed as an open-label study, randomized patients to sorafenib ('the standard of care') or a combination of a ICI (atezolizumab) and an anti-angiogenic antibody directed at the vascular endothelial growth factor (bevacizumab) as first-line therapy for advanced HCC [14]. Updated survival analysis revealed an improvement in median patient survival from 13.4 months in those receiving sorafenib to 19.2 months in the patients in the combination arm [15]. Combination therapy also prolonged progression-free survival (PFS) (6.9 months versus 4.3 months for the sorafenib arm). IMbrave150 was a landmark study that established atezolizumab/bevacizumab as the new standard-of-care first-line therapy for patients with advanced HCC not amenable to curative therapy without prior exposure to systemic therapy.

## 4. Limitations of Immune Checkpoint Inhibitors

There is mounting clinical evidence, however, that ICIs may be less effective in patients with non-virally-associated HCC. In the IMbrave150 trial, nearly 70% of the study population had viral HCC as an international trial design. Subgroup analysis of this trial showed a limited benefit of a combination atezolizumab/bevacizumab in overall survival in patients with non-viral HCC compared to sorafenib with median overall survival of 17 months vs. 18.1 months, within the limitations of this particular subgroup with 30 events [16]. A recent meta-analysis of three phases III trials studying the efficacy of ICIs in HCC, including IMbrave150, KEYNOTE-240 and CheckMate-459, totaling 1656 patients, showed that ICIs improved overall survival in patients with viral HCC but not those with non-viral HCC [17]. Another large meta-analysis of eight randomized controlled trials with a total of 3739 patients showed that ICIs are less beneficial in

https://doi.org/10.1016/j.aohep.2022.100886

patients with non-viral HCC, whereas the efficacy of tyrosine-kinase inhibitors or anti-VEGF-agents was unaffected by the underlying driver of HCC [18]. It is important to note that patients with non-viral HCC in these meta-analyses were not differentiated further and included patients with HCC related to NASH, alcoholic liver disease, and other non-viral etiologies.

These differences in the efficacy of ICIs based on the etiological driver of HCC may at least partly be explained by inherent alterations in the tumor micro-environment, as suggested by *in vivo* studies. Recently, Pfister *et al.* reported that despite increased CD8+ PD-1+ cells in the NASH-related HCC mice model, anti-PD1/PD-L1 immunotherapy did not reduce tumor incidence, size, or number but rather progressed liver fibrosis in these livers [17]. In contrast, tumors in the non-NASH HCC models regressed using the same treatment [17]. Further, treatment with anti-CD8 antibody and anti-PD-1 monoclonal antibody appeared to ameliorate the incidence of HCC development as well as liver fibrosis. To assess if these results can be extrapolated to human NASH, they found similar profiles of CD8+ PD-1+ T cells in the liver biopsies of patients with NAFLD and NASH. Separate in vitro studies imply that ICIs impair HCC development in a non-NASH mouse model [19] but not intrahepatic melanoma metastases in the NASH model [20]. Taken together, clinical and pre-clinical data would appear to suggest that ICIs may not have the same success in patients with NASH-related HCC as observed with virally mediated disease and that these findings may be unique in the context of HCC.

Despite this evidence, it is premature to discount immunotherapy's role in managing patients with NASH-related or non-viral HCC. The heterogeneous nature of HCC does not afford itself to readily actionable targets outside of a clinical trial. It is important to acknowledge the heterogeneity inherent in 'non-viral HCC' subgroups included in the meta-analyses were not further stratified by the cause of liver disease. The subgroup analysis reported in IMbrave150 was not designed to address the clinical benefit of this question. There remain many unanswered questions about the influence of the immune microenvironment on the development of HCC. The immune microenvironment may be further influenced by the gut microbiome, which is thought to play a key role in the pathogenesis of NAFLD and NASH [21,22]. Clinical data with nivolumab, an anti-PD1 antibody, as well as pembrolizumab, antibody directed against PD-1, have shown both agents have similar efficacy in inducing durable HCC response in a subset of patients with viral-HCC and non-viral HCC [17]. Further, in the IMbrave150 trial, progression-free survival in the combination of atezolizumab/bevacizumab arm in non-viral HCC patients was comparable to that in patients with viral HCC (6.3 months in non-viral HCC, 4.5 months in HBV-HCC, and 6.6 months in HCV-HCC) [21]. The PFS in patients with non-viral HCC treated with combination atezolizumab/bevacizumab was significantly longer than in patients treated with sorafenib, suggesting that the addition of VEGF inhibitor may ameliorate reduced efficacy of ICIs in patients with non-viral HCC [23].

## 5. Conclusions

HCC has been defined as a chemotherapy-resistant tumor requiring the use of multi-kinase inhibition. However, immunotherapy has emerged as a mainstay of systemic therapy for patients with advanced disease. There is mounting evidence that cirrhosis's underlying etiology may influence immune-based therapies' efficacy. These differences are most likely accounted for by variations in the tumor micro-environment conferring differences in the host immune response and local contributions from local niches, including the native liver and associated microbiome. Given the molecular heterogeneity of HCC among differing disease etiologies, future clinical trials would benefit from patient stratification based on disease etiology and/or the use of biomarker-based treatment algorithms to optimize and personalize therapeutic strategies for patients with advanced-stage HCC.

## Declaration of interest

None

## References


[1] McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology 2021;73:4–13. https://doi.org/10.1002/hep.31288.

[2] Agarwal PD, Phillips P, Hillman L, Lucey MR, Lee F, Mezrich JD, et al. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. Journal of Clinical Gastroenterology 2017;51:845–9. https://doi.org/10.1097/MCG.0000000000000825.

[3] Rabiee A, Taddei T, Aytaman A, Rogal SS, Kaplan DE, Morgan TR. Development and Implementation of Multidisciplinary Liver Tumor Boards in the Veterans Affairs Health Care System: A 10-Year Experience. Cancers 2021;13:4849. https://doi.org/10.3390/cancers13194849.

[4] Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nature reviews Clinical oncology 2018;15:599–616. https://doi.org/10.1038/s41571-018-0073-4.

[5] Kim DW, Talati C, Kim R. Hepatocellular carcinoma (HCC): beyond sorafenib—chemotherapy. Journal of gastrointestinal oncology 2017;8:256. https://doi.org/10.21037/jgo.2016.09.07.

[6] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. NEJM 2008;359:378–90. https://doi.org/10.1056/NEJMoa0708857.

[7] Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. Journal of hepatology 2017;67:999–1008. https://doi.org/10.1016/j.jhep.2017.06.026.

[8] Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet 2018;391:1163–73. https://doi.org/10.1016/S0140-6736(18)30207-1.

[9] Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2017;389:56–66. https://doi.org/10.1016/S0140-6736(16)32453-9.

[10] Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. New England Journal of Medicine 2018;379:54–63. https://doi.org/10.1056/NEJMoa1717002.

[11] Blanchet B, Billemont B, Barete S, Garrigue H, Cabanes L, Coriat R, et al. Toxicity of sorafenib: clinical and molecular aspects. Expert opinion on drug safety 2010;9:275–87. https://doi.org/10.1517/14740330903510608.

[12] Kolamunnage-Dona R, Berhane S, Potts H, Williams EH, Tanner J, Janowitz T, et al. Sorafenib is associated with a reduced rate of tumour growth and liver function deterioration in HCV-induced hepatocellular carcinoma. Journal of hepatology 2021;75:879–87. https://doi.org/10.1016/j.jhep.2021.05.015.

[13] Smyth MJ, Ngiow SF, Ribas A, Teng MW. Combination cancer immunotherapies tailored to the tumour microenvironment. Nature reviews Clinical oncology 2016;13:143–58. https://doi.org/10.1038/nrclinonc.2015.209.

[14] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. New England Journal of Medicine 2020;382:1894–905. https://doi.org/10.1056/NEJMoa1915745.

[15] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo)+ bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). American Society of Clinical Oncology; 2021.

[16] Cheng A-L, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. Journal of hepatology 2021. https://doi.org/10.1016/j.jhep.2021.11.030.

[17] Pfister D, Núñez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450–6. https://doi.org/10.1038/s41586-021-03362-0.

[18] Haber PK, Puigvehí M, Castet F, Lourdusamy V, Montal R, Tabrizian P, et al. Evidence-based management of hepatocellular carcinoma: systematic review and meta-analysis of randomized controlled trials (2002–2020). Gastroenterology 2021;161:879–98. https://doi.org/10.1053/j.gastro.2021.06.008.

[19] Chung AS, Mettlen M, Ganguly D, Lu T, Wang T, Brekken RA, et al. Immune checkpoint inhibition is safe and effective for liver cancer prevention in a mouse model of hepatocellular carcinoma. Cancer Prevention Research 2020;13:911–22. https://doi.org/10.1158/1940-6207.CAPR-20-0200.

[20] Heinrich B, Brown ZJ, Mathias V, Ma C; Yu SJ; Sahin U, et al. Nonalcoholic steatohepatitis (NASH) impairs treatment of intrahepatic metastases with CD4+ T cell dependent RNA vaccine, AACR, 2018. DOI: 10.1158/1538-7445.AM2018-1728

[21] Jayakumar S, Loomba R. Emerging role of the gut microbiome in the progression of nonalcoholic fatty liver disease and potential therapeutic implications. Alimentary Pharmacology & Therapeutics 2019;50:144–58. https://doi.org/10.1111/apt.15314.
[22] Behary J, Amorim N, Jiang XT, Raposo A, Gong L, McGovern E, et al. Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma. Nature communications 2021;12:1–14. https://doi.org/10.1038/s41467-020-20422-7.
[23] Eso Y, Taura K, Seno H. Does immune checkpoint inhibitor exhibit limited efficacy against non-viral hepatocellular carcinoma?: A review of clinical trials. Hepatology Research 2022;52:67–74. https://doi.org/10.1111/hepr.13712.

Parul D. Agarwal*
Michael R. Lucey
Adnan Said
Jeremy Kratz
*The University of Wisconsin, School of Medicine and Public Health, 4224 MFCB, 1685 Highland Avenue, Madison, WI 53705, The United States*

*Corresponding author.
*E-mail address:* pagarwal@medicine.wisc.edu (P.D. Agarwal).