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Advances in immune checkpoint inhibitors for hepatocellular carcinoma

Ji Won Han[1,2], Su-Hyung Park[3]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, [2]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul; [3]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, Korea

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Hepatocellular carcinoma (HCC) is the fifth most common cancer, and the second leading cause of cancer-related death worldwide. Although recent advances in immune checkpoint inhibitor-based immunotherapy have initiated a new era for advanced HCC treatment, the majority of HCC patients receiving immune checkpoint blockades do not derive clinical benefit. Thus, there remains an urgent need for novel immunotherapeutic strategies with improved therapeutic efficacy. Here we review recent studies of immune checkpoint blockade in HCC, providing the necessary basis for the rational design of immunotherapy. **(J Liver Cancer 2021;21:139-145)**

Keywords: Hepatocellular carcinoma; Immune checkpoint inhibitors; PD-1-PD-L1 blockade; Immunotherapy

INTRODUCTION

Liver cancer is among the most common cancers worldwide, and hepatocellular carcinoma (HCC) is the most common primary liver cancer.[1] HCC frequently develops in a background of chronic liver disease caused by infection with hepatitis B virus or hepatitis C virus (HCV), or by cirrhosis induced by alcohol abuse, autoimmune hepatitis, or non-alcoholic fatty liver disease.[2] HCC incidence is expected to continue increasing and HCC patients have a poor prognosis, such that the socioeconomic burden of HCC is among the most important global health issues.[3] Patients with advanced HCC have limited therapeutic options. Sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib are the approved systemic treatments that prolong survival,[4-6] but these agents show an unsatisfactory survival benefit and are frequently not tolerated. Therefore, novel HCC therapeutic strategies are urgently needed.

The HCC tumor microenvironment (TME) is a spatially structured mixture of various cells, including tumor cells, immune cells, tumor-associated fibroblasts, and hepatic non-parenchymal resident cells. These cellular components dynamically interact through cell-to-cell contacts, and this cellular interplay influences tumor immune evasion—for

Corresponding author: Ji Won Han

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel. +82-2-2258-2073, Fax. +82-2-3481-4025
E-mail: tmznjf@catholic.ac.kr

Co-corresponding author: Su-Hyung Park

Laboratory of Translational Immunology and Vaccinology, Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, 291 Daehak-ro, Yuseong-gu, Daejeon 34141, Korea
Tel. +82-42-350-4248, Fax. +82-42-350-4240
E-mail: park3@kaist.ac.kr

example, related to T-cell exhaustion. Although T-cell exhaustion was originally identified in chronic viral infections,[7] similar dysfunctional features have been observed in cancers. T-cell exhaustion is defined as an impaired ability to secrete cytokines and proliferate, along with prolonged antigenic stimulation-induced overexpression of immune checkpoint receptors, such as programmed cell death-1 (PD-1), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), cytotoxic T lymphocyte antigen-4 (CTLA-4), and lymphocyte-activation gene-3 (LAG-3).[8-10] Immune checkpoint inhibitors (ICIs) targeting the PD-1/programmed cell death-ligand1(PD-L1) and CTLA-4 pathways are currently available for clinical use, and have revolutionized the treatment of various cancer types.[11] Clinical trials of anti-PD-1 therapy in patients with advanced HCC show objective response rates (ORRs) of 16-20%,[12,13] resulting in approval of the anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab for use in HCC by in U.S. Food and Drug Administration (FDA). However, the majority of HCC patients receiving anti-PD-1 therapy do not have clinical benefit, highlighting that novel immunotherapeutic strategies with improved therapeutic efficacy such as ICI-based therapeutic strategies in combination with targeted agents, locoregional therapy, and other forms of immunotherapy are urgently needed.[14]

Here we review the advancements and clinical implications of immune checkpoint inhibitor use in HCC, focusing on results from clinical trials. In the first part of this paper, we review the usage of immune checkpoint inhibitors as monotherapies for HCC, and the clinical responses. In the second part, we summarize the current status of combined immunotherapy targeting immune checkpoint receptors and other molecules in HCC.

MONOTHERAPIES USING IMMUNE CHECKPOINT INHIBITORS FOR HCC

ICIs, such as anti-CTLA-4 and anti-PD-1 agents, have been tested as monotherapy in patients with unresectable HCC. A small pilot study evaluated the anti-CTLA-4 inhibitor tremelimumab in HCV-related HCC.[15] This agent yielded an ORR of 17.6%, and exhibited good safety, with no patients requiring steroid treatment due to the immune-related adverse events.

However, the current mainstream of ICI treatment for HCC is based on targeting the PD-1/PD-L1 axis. The phase 1/2 trial CheckMate040 tested nivolumab in patients with advanced unresectable HCC including patients previously treated with sorafenib, and nivolumab yielded a promising ORR of 20%.[12] Pembrolizumab has also shown an ORR of 17% in previously sorafenib-treated patients in a phase 2 trial.[13] Consequently, nivolumab and pembrolizumab were approved by the FDA in 2017 as post-sorafenib second-line systemic treatments for HCC.

In the randomized multi-center phase 3 trial CheckMate-459 (NCT02576509), nivolumab was compared to sorafenib as first-line systemic treatment, among patients with advanced HCC who were ineligible for locoregional or surgical treatments.[16] Unfortunately, the overall survival (OS) benefit of nivolumab compared to sorafenib did not reach statistical significance according to the pre-defined threshold in the trial design (HR, 0.84; P=0.042). The median OS was 16.4 months in the nivolumab group versus 14.7 months in the sorafenib group (P=0.075). However, several important findings of this study support the clinical benefit of nivolumab treatment. Firstly, ORR tended to be higher in the nivolumab group (15% versus 7%), including complete response (CR) in 14 patients (14/371, 4%) with nivolumab treatment, compared to only five patients (5/372, 1%) with sorafenib treatment. Secondly, grade 3 or 4 adverse events occurred in 81 patients (81/371, 22%) following nivolumab treatment, compared to in 179 patients (179/372, 49%) after sorafenib treatment, showing the safety and tolerability of nivolumab. A recent subgroup analysis further supports this safety of nivolumab, which also exhibited favorable safety and tolerability in patients with Child-Pugh B liver function.[17]

The randomized double-blind phase 3 trial KEYNOTE-224 evaluated pembrolizumab as a second-line systemic treatment compared with placebo for patients previously treated with sorafenib.[18] The median OS was 13.9 months in the pembrolizumab group versus 10.6 months in the placebo

group (P=0.024), but the statistical significance of this difference was insufficient according to the pre-defined criteria. Treatment-associated adverse events of grade 3 or higher occurred in 52 patients (52/278, 19%). These findings could justify the accelerated FDA approval of these two anti-PD-1 inhibitors as a second-line systemic treatment for HCC. However, the insufficient clinical benefit demonstrated in these phase 3 trials indicates the necessity of complementary combined strategies to improve ICI efficacy in HCC.

On the other hand, phase 3 randomized trials are examining anti-PD-1 agents as adjuvant treatments to reduce tumor recurrence following curative therapy, such as ablation or surgical resection. KEYNOTE-937 compares pembrolizumab versus placebo as adjuvant therapy, in terms of recurrence-free survival (RFS) and OS, in patients who achieved complete radiological response after curative treatments (NCT03867084). Furthermore, CheckMate-9DX compares nivolumab versus placebo as adjuvant therapy, in terms of OS, especially in high-risk patients. HCC has high recurrence rates following curative treatment, about 70% at 5 years after surgical resection,[19] and about 50-70% after radiofrequency ablation.[20] Thus, there is a need to further investigate the potential role of ICIs in improving clinical outcomes following curative treatments. In the phase 3 randomized STORM trial, adjuvant sorafenib following curative treatment failed to show clinical benefit in terms of RFS.[21] Table 1 shows currently on-going phase 3 clinical trials of ICIs.

Table 1. Phase 3 clinical trials of immune checkpoint inhibitors for HCC

Clinical setting	Regimen	Trial name/number	Estimated primary completion date
First-line systemic	Pembrolizumab-envatinib	LEAP-002/NCT03713593	May 2022
First-line systemic	Nivolumab-ipilimumab	CheckMate-9DW/ NCT04039607	Mar 2023
First-line systemic	Durvalumab-tremelimumab	HIMALAYA/NCT03298451	Dec 2021
First-line systemic	Atezolizumab-cabozantinib	COSMIC-312/ NCT03755791	Jun 2021
First-line systemic	SHR-1210-apatinib	NA/NCT03764293	Dec 2021
First-line systemic	Sintilimab-IBI305 (anti-VEGF)	ORIENT-32/ NCT03794440	Dec 2022
First-line systemic	Tislelizumab	RATIONLALE-301/ NCT03412773	May 2022
Adjuvant resection/ablation	Pembrolizumab	KEYNOTE-937/ NCT03867084	Jun 2025
Adjuvant resection/ablation	Nivolumab	CheckMate-9DX/ NCT03383458	Jan 2023
Adjuvant resection/ablation	Atezolizumab-bevacizumab	IMbrave-050/ NCT04102098	Mar 2023
Adjuvant resection/ablation	Durvalumab-bevacizumab	EMERALD-2/ NCT03847428	May 2023
Adjuvant TACE	Durvalumab or Durvalumab-bevacizumab	EMERALD-1/ NCT03778957	Sep 2022
Adjuvant TACE	Nivolumab or Nivolumab-ipilimumab	CheckMate-74W/ NCT04340193	Feb 2026
Adjuvant TACE	Pembrolizumab-lenvatinib	LEAP-012/ NCT04246177	Apr 2025
Adjuvant TACE beads	Nivolumab	TACE-3/NCT04268888	Jun 2025

VEGF, vascular endothelial growth factor; TACE, transcatheter arterial chemoembolization.

CURRENT STATUS OF IMMUNE CHECK-POINT INHIBITORS FOR HEPATOCELLULAR CARCINOMA: ADVANCEMENT OF COMBINED REGIMENS

Table 1 presents the on-going trials investigating combined regimens based on ICIs. As introduced above, tumor-infiltrating lymphocytes (TILs) from HCC patients highly express multiple immune checkpoint molecules, including PD-1, TIM-3, LAG-3, and CTLA-4.[22,23] Treatment with anti-PD-1 or anti-PD-L1 combined with anti-CTLA-4, anti-TIM-3, or anti-LAG-3 synergistically increases TIL proliferation and function.[22,23] Beyond these experimental studies, the phase 1/2 clinical trial CheckMate-040 tested nivolumab plus ipilimumab as a second-line systemic treatment following sorafenib treatment.[24] Administration of ipilimumab plus nivolumab, repeated four times, followed by nivolumab administration every 2 weeks, yielded a promising ORR rate of 32%. Most patients (94%) experienced treatment-related adverse events of any grade, but most adverse events were manageable. Based on these results, the FDA granted accelerated approval to this regimen on March 2020. Moreover, an on-going phase 3 trial is comparing first-line treatment with the nivolumab-ipilimumab regimen versus sorafenib (CheckMate-9DW, NCT04039607).

Targeting the vascular endothelial growth factor (VEGF)/VEGFR pathway is proposed to be a promising strategy for HCC chemotherapy, since this pathway is associated with high vascularization in the HCC microenvironment.[25] Importantly, VEGF is immunosuppressive and affects various types of immune cells within the TME—impacting the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and the inhibition of dendritic cell maturation and T-cell function.[26] A recent preclinical study in mice used orthotopic and induced HCC models to demonstrate that dual PD-1 and VEGFR blockade normalizes vascularity and restores anti-tumor immune responses.[27] They reported $CD8^+$ T-cell activation and Treg reduction, as well as reductions of M1 tumor-associated macrophages (TAMs) and chemokine receptor 2 monocytes. Therefore, the combination of ICI treatment and VEGFR blockade is expected to be a promising strategy to overcome resistance to ICI monotherapy.

Results from the phase 3 trial IMbrave-150 have opened a new horizon for systemic treatment of HCC. Compared to sorafenib, the anti-PD-L1 inhibitor atezolizumab in combination with the anti-VEGF inhibitor bevacizumab yielded a better OS and progression-free survival (PFS).[28] At 12 months of treatment, the OS rate was 67% in the atezolizumab-bevacizumab group versus 55% in the sorafenib group (P<0.001; HR, 0.58). Moreover, the median PFS was 6.8 months in the atezolizumab-bevacizumab group versus 4.3 months in the sorafenib group (P<0.001). The atezolizumab-bevacizumab group was also superior to the sorafenib group in terms of the time to deterioration of quality of life. This finding has also been confirmed by a recent study that investigated patient-reported outcomes, including quality of life, functioning, and symptoms due to the disease, which were all superior in the atezolizumab-bevacizumab group compared to the sorafenib group.[29] Adverse events of grade 3 or higher were comparable between the two groups, occurring in 201/329 (61.1%) of the atezolizumab-bevacizumab group and 95/156 (60.9%) of the sorafenib group. The risk of bleeding (any grade), including variceal bleeding, tended to be higher in the atezolizumab-bevacizumab group (25.2% versus 17.3%), indicating that endoscopic evaluation is required before treatment using this regimen. Overall, the atezolizumab-bevacizumab combination regimen could be a successful substitute for sorafenib, which has been the only option for systemic treatment of HCC for decades. In May 2020, the FDA approved this regimen as a first-line treatment for patients with unresectable or metastatic HCC.

Currently available multi-kinase inhibitors (MKIs) can target the VEGF/VEGFR pathway and angiogenesis, and also have immunomodulatory effects. For example, MKIs can regulate immunosuppressive populations (e.g., TAMs, MDSCs, and Tregs), as well as enhance T-cell responses.[30] In particular, lenvatinib, an MKI that has been approved as a first-line systemic treatment, was recently investigated as part of a combinational regimen with anti-PD-1 in a murine model of HCC.[31] The results demonstrated that lenvatinib downregulated PD-L1 expression on tumor cells, via FGF re-

ceptor 4 (FGFR4). Lenvatinib also acted through FGFR4 to hinder Treg differentiation by IL-2, and thereby synergistically improved anti-tumor immune responses in combination with anti-PD-1. These findings suggest that lenvatinib is a promising MKI in terms of combination immunotherapy with ICIs. A recent report from a phase 1b trial describes the safety and efficacy of lenvatinib plus pembrolizumab in patients with unresectable HCC.[32] Although the study was small and did not have a comparative design, it demonstrated that pembrolizumab-lenvatinib treatment yielded an ORR of 36%, with a median OS of 22 months. Among the patients, 67% experienced adverse events of grade 3 or higher, but they were manageable. This regimen is presently being tested in a phase 3 randomized trial (LEAP-002, NCT03713593).

In addition to the role of combined regimens as systemic chemotherapy, they are also being investigated in phase 3 clinical trials for use as adjuvant treatments following curative treatments or transcatheter arterial chemoembolization (TACE). Specifically, phase 3 trials are examining the use of atezolizumab-bevacizumab (IMbrave-050, NCT04102098) and durvalumab-bevacizumab (EMERALD-2, NCT03847428) following resection or ablation, compared to radiofrequency ablation with placebo. Trials are also investigating durvalumab-bevacizumab (EMERALD-1, NCT03778957), nivolumab-ipilimumab (CheckMate-74W), and pembrolizumab-lenvatinib (LEAP-012, NCT04246177) following TACE. Combined immunotherapy may become a standard means of HCC treatment, not only as a first- or second-line systemic chemotherapy, but also as an adjuvant treatment following locoregional treatment for HCC.

CONCLUDING REMARK

In this review, we have discussed the recent advances in immunotherapy targeting immune checkpoint receptors for HCC treatment. While anti-PD-1 therapy shows great therapeutic success in some HCC patients, it exhibits limited efficacy in the majority of HCC patients. Various studies have investigated the factors that determine clinical responses to ICIs, and the mechanisms by which they modulate tumor-specific immunity in cancer patients. However, most have focused on tumor-intrinsic factors, rather than on the characteristics of exhausted tumor-infiltrating T cells. Overcoming the limitations of anti-PD-1 therapy for HCC will require a better understanding of T-cell exhaustion in TMEs. Recent studies have highlighted the heterogeneity of tumor-infiltrating $CD8^+$ T cells ($CD8^+$ TILs) in the context of T-cell exhaustion and T-cell activation in HCC patients,[23,33] which was associated biomarkers indicating anti-PD-1 response.[23,33] These findings support the importance of detailed characterizations of the heterogeneity within the exhausted $CD8^+$ TIL population for cancer immunotherapy in HCC patients.

Our current knowledge of the mechanisms underlying ICI response lags behind the application of ICIs. Thus, there remains a need for more cross-disciplinary studies to better understand the biological and clinical implications of ICIs, by elucidating the cellular and molecular heterogeneity of tumor-infiltrating immune cells among HCC patients. The results of such investigations could enable the application of immunotherapies targeting various immune checkpoint receptors in combination with currently available ICIs. Considering that HCC patients exhibit variations in the expressions of checkpoint receptors other than PD-1,[23] it will be important to find biomarkers to identify patients specifically eligible for each combinational checkpoint blockade regimen. Therefore, along with evaluations of the therapeutic efficacy of novel combined checkpoint blockade therapies, efforts to develop biomarkers clinically suitable for use as companion diagnostics may help advance personalized immunotherapy.

In conclusion, advances in immune checkpoint inhibitor-based immunotherapy have opened a new era for HCC treatment. Future clinical studies that evaluate the efficacy of combined immune checkpoint blockades in HCC patients, and further investigation of the immune biology of the TME in HCC, may provide the rationale for establishing optimal immunotherapy strategies in patients with HCC.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethics Statement

This article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, institutional review board approval or patient consent was not necessary.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

ORCID

Ji Won Han https://orcid.org/0000-0003-1456-1450
Su-Hyung Park https://orcid.org/0000-0001-6363-7736

Author Contribution

Conception and study design: JWH and SHP
Supervision: SHP
Writing-original draft: JWH and SHP
Writing-review and editing: JWH and SHP
Funding: SHP
All authors reviewed and approved the final draft.

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