Review Article
J Liver Cancer 2023;23(2):316-329
pISSN 2288-8128 • eISSN 2383-5001
https://doi.org/10.17998/jlc.2023.09.04

# A multidisciplinary approach with immunotherapies for advanced hepatocellular carcinoma

Yu Rim Lee

Department of Internal Medicine, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Hepatocellular carcinoma (HCC) is a highly aggressive disease that is usually diagnosed at an advanced stage. Advanced HCC has limited treatment options and often has a poor prognosis. For the past decade, tyrosine kinase inhibitors have been the only treatments approved for advanced HCC that have shown overall survival (OS) benefits; however, but their clinical efficacy has been limited. Recent trials have demonstrated promising advancements in survival outcomes through immunotherapy-based treatments, such as combinations of immune checkpoint inhibitors (ICIs) with other ICIs, antiangiogenic drugs, and locoregional therapies. The atezolizumab-bevacizumab and durvalumab-tremelimumab (STRIDE) regimen has significantly improved survival rates as a first-line treatment and has become the new standard of care. Therefore, combined treatments for advanced HCC can result in better treatment outcomes owing to their synergistic effects, which requires a multidisciplinary approach. Ongoing studies are examining other therapeutic innovations that can improve disease control and OS rates. Despite improvements in the treatment of advanced HCC, further studies on the optimal treatment selection and sequences, biomarker identification, combination approaches with other therapies, and development of novel immunotherapy agents are required. This review presents the current treatment options and clinical data of the ICI-based combination immunotherapies for advanced HCC from a multidisciplinary perspective. **(J Liver Cancer 2023;23:316-329)**

**Keywords:** Carcinoma, hepatocellular; Systemic treatment; Immune checkpoint inhibitors; Combined modality therapy; Locoregional therapy

**Received** Aug. 4, 2023
**Revised** Aug. 30, 2023
**Accepted** Sep. 4, 2023

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide.[1] Despite active surveillance, HCC is frequently diagnosed at an advanced stage.[2] Over the past few decades, the development of molecularly targeted therapies has significantly improved the treatment of advanced HCC. Sorafenib, a multitargeted tyrosine kinase inhibitor (TKI) targeting the vascular endothelial growth factor receptor (VEGFR), Raf-1, and the platelet-derived growth factor receptor (PDGFR), has been the first-line systemic treatment for advanced HCC.[3,4] Median overall survival (OS) was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.55-0.87; $P<0.001$) in a SHARP study. In the Asia-Pacific region, patients treated with sorafenib showed a median OS of 6.5 months, while those who received placebo

**Corresponding author:** Yu Rim Lee

Department of Internal Medicine, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, 807 Hoguk-ro, Buk-gu, Daegu 41404, Korea
Tel. +82-53-200-3869, Fax. +82-53-200-3870
E-mail: deblue00@naver.com

had a median OS of 4.2 months (HR, 0.68; 95% CI, 0.50-0.93; *P*=0.014). Lenvatinib has also been approved as a first-line treatment for unresectable HCC. Lenvatinib is a TKI that targets VEGFR, fibroblast growth factor receptors, PDGFRα, KIT, and RET.[5] The lenvatinib group achieved a median OS of 13.6 months, which was non-inferior to the sorafenib group (12.3 months) (HR, 0.92, 95% CI, 0.79-1.06). Several targeted agents, such as regorafenib, cabozantinib, and ramucirumab, have also been approved as second-line treatments for patients with HCC who show disease progression after receiving first-line sorafenib treatment.[6] However, the effectiveness of these treatments is limited, with low response rates and minimal improvements in OS.[4,5]

In recent years, remarkable changes have occurred in systemic treatment settings, with the introduction of immunotherapies. Immune checkpoint inhibitors (ICIs) have emerged as promising treatments for HCC.[7] Notably, nivolumab and pembrolizumab, anti-programmed cell death protein 1 (PD-1) antibodies, have shown an improvement in OS in patients with advanced HCC who have previously received sorafenib, leading to their approval by the US Food and Drug Administration (FDA) as second-line treatments for advanced HCC.[8,9] However, immunotherapy alone exhibits limited antitumor efficacy and, fails to significantly enhance OS compared to sorafenib in treatment-naïve patients. Therefore, it is necessary to develop treatment strategies to improve therapeutic effects in patients with advanced HCC.

Several studies have demonstrated the effectiveness of combining ICIs with other treatment modalities for patients with HCC, such as multi-ICI combinations, TKIs, and locoregional therapies.[10] Based on remarkable results from the IMbrave150 trial, the FDA has approved the combination of atezolizumab and bevacizumab as a first-line treatment for patients with unresectable HCC.[11,12] Combination strategies have been evaluated and are still being used to overcome resistance and improve the effectiveness of treatment. These findings emphasize the importance of multidisciplinary approaches in HCC treatment. This review provides the current data and ongoing trials investigating ICI-based combination therapies for HCC, aiming to optimize treatment strategies and achieve satisfactory clinical outcomes in HCC treatment.

## CURRENT AND EMERGING IMMUNOTHERAPIES IN ADVANCED HCC

### 1. Immunology of HCC

The liver possesses distinctive immunological tolerance to antigens derived from bacteria and dietary products via the portal vein.[13,14] Furthermore, the majority of cases of HCC originate from pre-existing liver diseases, such as chronic hepatitis B and C virus infections, alcoholic hepatitis, nonalcoholic steatohepatitis, and autoimmune hepatitis.[15] These contribute to chronic inflammation that impairs immune surveillance and disrupts the immune environment.[16,17] This exceptional tolerogenic feature of the liver with the immunosuppressive tumor microenvironment (TME) in HCC may impede antitumor immune responses against HCC. Dysfunctional interactions between tumors and the immune system can lead to immune evasion, either through the impaired recognition of tumor-associated antigens (TAAs) or the establishment of an immunosuppressive TME.[18] The presence of an immunosuppressive TME can be attributed to a number of factors, including the recruitment of suppressive immune cells such as regulatory T cells (Tregs), myeloid-derived suppressor cells, and tumor-associated macrophages, as well as the reduction of antitumor effector cells such as dendritic cells (DCs) and natural killer (NK) cells. The immune suppression observed in the TME is also influenced by changes in cytokine levels and an increase in the levels of immune checkpoint proteins (PD-1/programmed cell death-ligand 1 [PD-L1] and cytotoxic T lymphocyte associated antigen-4 [CTLA-4]).[19] Overcoming these challenges to improve the ability of the immune system to effectively eliminate tumor cells is a crucial form of immunotherapy.

Co-inhibitory molecules expressed by lymphocytes act as immune checkpoints to prevent excessive immune activation. HCC uses this mechanism to avoid immune responses against tumors by expressing the corresponding ligands in both tumor cells and stromal cells, thus evading antitumor immune surveillance.[20] Immune checkpoints, PD-1/PD-L1 and CTLA-4, play a crucial role in initiating and maintaining tumor immune evasion. PD-1 is expressed on activated T cells, B cells, NK cells, and DCs. When PD-1 binds to PD-L1,

inhibitory signals are generated, deactivating immune cells, leadings to the apoptosis of $CD8^+$ T cells and a reduction in their activity against cancer cells.[21,22] Persistent PD-1 signaling causes T cell exhaustion.[23] Increased expression of PD-L1 is associated with HCC etiologies, such as chronic viral infections and other inflammatory liver diseases. This increased expression of PD-L1 is linked to greater tolerance toward TAAs and provides a favorable environment for HCC development.[24,25] Another significant immune checkpoint, CTLA-4, which is expressed on activated T cells and Tregs, weakens the immune response against tumors and accelerates immune evasion by tumor cells.[26]

## 2. Rationale of immunotherapy

Monoclonal antibodies (ICIs) prevent T cell inactivation by blocking the interaction between checkpoint proteins and their ligands. They can enhance the immune response, leading to the elimination of tumor cells and significantly improving the effectiveness of cancer treatment.[27] Hence, ICIs such as anti-PD-1 (nivolumab and pembrolizumab), anti-PD-L1 (atezolizumab and durvalumab), and anti-CTLA-4 (ipilimumab and tremelimumab) are promising treatments for HCC that promote immune cell proliferation reinforcing antitumor immune responses.

A range of immune-stimulating responses are experienced when the dual blockade of CTLA-4 and PD-1/PD-L1 is used. This includes the distinctive modulation of terminally differentiated effector $CD8^+$ T cells, which could may be significant in the treatment of immunologically "cold" tumors that exhibit poor immunotherapy responses.[28] In a murine HCC model, the combination therapy of anti-CTLA-4 and anti-PD-1 monoclonal antibodies increased the infiltration of $CD8^+$ and $CD4^+$ T cells into tumors as compared to monotherapy, while reducing the infiltration of Tregs. These outcomes were related to the improved effectiveness.[29]

Proangiogenic factors, such as vascular endothelial growth factors (VEGFs), prevent the cytokine-induced adhesion of endothelial cells. This results in endothelial cell anergy, which tumors use to evade immune infiltration.[30] The upregulation of immune checkpoint molecules and direct inhibition of T cell proliferation and cytotoxic activity by these factors also contribute to T cell exhaustion.[31] VEGF blocking enhances antigen presentation by stimulating the differentiation and maturation of DCs and activates cytotoxic $CD8^+$ T cells.[31,32] Additionally, anti-VEGF therapy facilitates lymphocyte infiltration into tumors by restoring the microvessels, thereby increasing the effectiveness of immunotherapy.[33] As a result, the combination of ICIs and VEGF inhibitors is a highly promising treatment approach for patients with HCC.[34,35] The combination of ICIs and TKIs represents another VEGF-based strategy to improve therapeutic effectiveness. Unlike monoclonal antibodies (mAbs), TKIs also affect various other kinases that could affect the activity of ICIs. The efficacy of TKIs in overcoming tumor-intrinsic resistance to immune checkpoint blockade has been demonstrated, supporting the use of combination therapies.[36] By inhibiting MAPK, WNT-β-catenin, CDK4-CDK6, or PTEN-dependent signaling, TKIs have the potential to convert immunologically "cold" tumors into "hot" tumors. This transformation is characterized by T cell infiltration, DC activation, enhanced tumor antigen presentation, and improved responsiveness to checkpoint inhibition.[37]

## 3. Management of HCC: immunotherapy in a clinic

### 1) Single-agent immunotherapy

ICIs have triggered a paradigm shift in HCC treatment. Nivolumab, an anti-PD-1 antibody, inhibits the interaction between PD-1 receptor on T cells and PD-L1 on tumor cells, thereby restoring the antitumor activity of T cells. One notable study, CheckMate 040, provided insights into the use of a single-agent PD-1 antibody, nivolumab.[9] In a subsequent phase III trial, CheckMate 459, the efficacy of nivolumab as a first-line treatment for advanced HCC was compared with that of sorafenib (Table 1).[38] In this trial, the objective response rate (ORR) was 15%, including a complete response of 4%, in the nivolumab group versus 7% in the control group. However, the difference in OS was not statistically significant, with a median OS of 16.4 months in the nivolumab group and 14.7 months in the sorafenib group (HR, 0.85; 95% CI, 0.72-1.02; $P$=0.0752). Grade 3/4 treatment-related adverse events (TRAEs) were less frequent in the nivolumab

**Table 1.** Results of clinical trials for immunotherapy in patients with advanced HCC

| Study | Drug | Phase | Setting | Median OS | HR for OS | Median PFS | ORR |
|---|---|---|---|---|---|---|---|
| IMbrave150[42] | Atezolizumab and bevacizumab vs. sorafenib | III | First-line | 19.2 mo for atezolizumab and bevacizumab vs. 13.4 mo for sorafenib | 0.66 | 6.9 mo for atezolizumab and bevacizumab vs. 4.3 mo for sorafenib | 30% for atezolizumab and bevacizumab vs. 11% for sorafenib |
| HIMALAYA[46] | Durvalumab and tremelimumab or durvalumab vs. sorafenib | III | First-line | 16.43 mo for STRIDE vs. 13.77 mo for sorafenib | 0.78 | 3.78 mo for STRIDE and 3.65 mo for durvalumab vs. 4.07 for sorafenib | 20.1% for STRIDE, 17% for durvalumab vs. 5.1 for sorafenib |
| ORIENT-32[92] | Sintilimab and bevacizumab biosimilar IBI305 vs. sorafenib | III | First-line | NR for Sintilimab and IBI305 vs. 10.4 mo for sorafenib | 0.57 | 4.6 mo for Sintilimab and IBI305 vs. 2.8 mo for sorafenib | 21% for Sintilimab and IBI305 vs. 4.7% for sorafenib |
| COSMIC-321[93] | Cabozantinib and atezolizumab vs. sorafenib | III | First-line | 15.4 mo for cabozantinib and atezolizumab vs. 15.5 mo for sorafenib | 0.90 | 6.8 mo for cabozantinib and atezolizumab vs. 4.2 mo for sorafenib | 13% for cabozantinib and atezolizumab vs. 6% for sorafenib |
| CheckMate 459[38] | Nivolumab vs. sorafenib | III | First-line | 16.4 mo for nivolumab vs. 14.7 mo for sorafenib | 0.85 | 3.7 mo for nivolumab vs. 3.8 mo for sorafenib | 15% for nivolumab and 7% for sorafenib |
| LEAP-002[49] | Lenvatinib and pembrolizumab vs. lenvatinib | III | First-line | 21.2 mo for lenvatinib and pembrolizumab vs. 19 mo for lenvatinib | 0.83 | 8.2 mo for lenvatinib and pembrolizumab vs. 8.1 mo for lenvatinib | 26.1% for lenvatinib and pembrolizumab vs. 17.5% for lenvatinib |
| Qin, et al.[94] | Camrelizumab and rivoceranib vs. sorafenib | III | First-line | 22.1 mo for camrelizumab and rivoceranib vs. 15.2 mo for sorafenib | 0.62 | 5.6 mo for camrelizumab and rivoceranib vs. 3.7 mo for sorafenib | 25.4% for camrelizumab and rivoceranib vs. 5.9% for sorafenib |
| KEYNOTE-240[8] | Pembrolizumab vs. BSC | III | Second-line (after sorafenib) | 13.9 mo for pembrolizumab vs. 10.6 mo for BSC | 0.78 | 3.0 mo for pembrolizumab vs. 2.8 mo for BSC | 18.3% for pembrolizumab vs. 4.4% for BSC |
| KEYNOTE-394[39] | Pembrolizumab vs. placebo | III | Second-line | 14.6 mo for pembrolizumab vs. 13.0 mo for placebo | 0.79 | 2.6 mo for pembrolizumab vs. 2.3 mo for placebo | 12.7% for pembrolizumab vs. 1.3% for placebo |

HCC, hepatocellular carcinoma; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; ORR, objective response rate; mo, months; NR, not reached; BSC, best supportive care.

group (22%) than those in the sorafenib group (49%). While the results did not show statistical significance for OS, these outcomes suggest a therapeutic advantage of nivolumab for advanced HCC, particularly in patients with PD-L1 expression ≥1%.

The phase III KEYNOTE-394 trial aimed to assess the efficacy and safety of pembrolizumab when used as second-line treatment for previously treated advanced HCC.[39] Pembrolizumab demonstrated a significantly longer median OS of 14.6 months compared to 13.0 months in the placebo group (HR, 0.79; 95% CI, 0.63-0.99; $P$=0.0180), as well as a longer median progression-free survival (PFS) of 2.6 vs. 2.3 months (HR, 0.74; 95% CI, 0.60-0.92; $P$=0.0032). Furthermore, the ORR was 12.7% for pembrolizumab compared to 1.3% for the placebo ($P$<0.0001). TRAEs were observed in 66.9% of patients receiving pembrolizumab and 49.7% of patients receiving the placebo. Consequently, pembrolizumab was approved by the FDA as a second-line treatment for patients with advanced HCC who had previously received sorafenib.[40] Several prospective trials have demonstrated that PD-1 and

PD-L1 inhibitors, such as nivolumab, pembrolizumab, durvalumab, and atezolizumab, yield objective tumor responses in the range of 15-20% and have well-tolerated side effect profiles.[27,38,39,41] However, PD-1 and PD-L1 inhibitors did not show potent antitumor activity to significantly improve OS compared to sorafenib in treatment-naïve patients.[38]

### 2) Immune checkpoint inhibitors with a combined regimen

The limited success of single-agent ICIs in improving the clinical outcomes has prompted the development of combined therapies. The IMbrave150 study, a global phase III open-label trial, investigated the efficacy of combination therapy of atezolizumab and bevacizumab compared to sorafenib (Table 1).[11,12,42] The trial enrolled 501 patients who were randomized to receive atezolizumab (1,200 mg) plus bevacizumab (15 mg/kg) or sorafenib. The median OS in the atezolizumab-bevacizumab group was 19.2 months, compared to 13.4 months in the sorafenib group (HR, 0.66; 95% CI, 0.52-0.85; $P$<0.001). The median PFS was 6.9 months in the atezolizumab–bevacizumab group and 4.3 months in the sorafenib group (HR, 0.65; 95% CI, 0.53-0.81; $P$<0.001). The ORRs were 30% for atezolizumab-bevacizumab and 11% for sorafenib. The median time to deterioration in patient-reported quality of life was longer with the combination treatment as compared to sorafenib monotherapy (11.2 vs. 3.6 months; HR, 0.63; 95% CI, 0.46-0.85).[12] Notably, all participants in the study were required to undergo an upper endoscopy within 6 months before enrollment to address concerns about the risk of bleeding associated with bevacizumab. This precautionary approach resulted in a low occurrence of high-grade bleeding events; there were six grade 5 bleeding events in the combination therapy group, while one was reported in the sorafenib group. Grade 3 or 4 adverse events (AEs) were observed in 63% and 57% of the patients in the atezolizumab-bevacizumab and sorafenib groups, respectively. Grade 3 or 4 hypertension was reported in 12% of the patients receiving atezolizumab-bevacizumab treatment. However, other high-grade toxic effects have rarely been reported. The most common TRAE in the sorafenib group was palmar-plantar erythrodysesthesia syndrome, which was observed in 48% of the patients, whereas it was documented in 2% of the patients in the atezolizumab-bevacizumab group. Based on these remarkable findings, a combination of atezolizumab and bevacizumab was approved by the FDA as a first-line systemic treatment for advanced HCC.[43-45]

The HIMALAYA trial was a phase III study, which assessed the combination of tremelimumab with durvalumab in comparison to sorafenib.[46] A single dose of 300 mg of tremelimumab with durvalumab every 4 weeks, known as the STRIDE regimen, was determined based on the results of a phase I/II expansion trial.[47] According to pharmacodynamic studies, the addition of tremelimumab at high doses increased the level of $CD8^+$ T cells in the peripheral blood, possibly contributing to the improved efficacy of the combination treatment.[48] The trial successfully achieved its primary endpoint, demonstrating that tremelimumab and durvalumab improved the OS compared to sorafenib (median OS 16.43 months for the combination vs. 13.77 months for sorafenib; HR, 0.78; 96.02% CI, 0.65-0.93; $P$=0.0035). The study also achieved a secondary endpoint of demonstrating non-inferiority of single-agent durvalumab compared to sorafenib (median OS of 16.56 months with durvalumab alone vs. 13.77 months with sorafenib; HR, 0.86; 95.67% CI, 0.73-1.03; non-inferiority margin, 1.08). The ORRs were 20.1%, 17%, and 5.1% for STRIDE, durvalumab, and sorafenib groups, respectively. With regard to the safety profile, grade 3 or 4 AEs occurred in 50.5%, 37.1%, and 52.4% of the patients receiving STRIDE, durvalumab, and sorafenib, respectively. The FDA has approved the STRIDE regimen as a first-line treatment option for unresectable HCC.

The multicenter phase III LEAP-002 study also examined a combination of lenvatinib and pembrolizumab. This trial compared the efficacy of lenvatinib plus pembrolizumab versus lenvatinib alone as a first-line treatment for advanced HCC.[49] In the study, the median OS was reported as 21.2 months in the combination group and 19 months in the lenvatinib group (HR, 0.84; 95% CI, 0.708-0.997; $P$=0.0227; with a one-sided alpha of 0.0185 for superiority threshold). The median PFS was 8.2 months in the lenvatinib and pembrolizumab group and 8.1 months in the lenvatinib group (HR, 0.834; 95% CI, 0.712-0.978). Combination treatment demonstrated an ORR of 26.1%, whereas treatment with lenvatinib

alone had an ORR of 17.5%. The combination therapy did not reach the predefined superiority threshold for OS, resulting in a negative outcome. Interestingly, the efficacy of lenvatinib as a single agent stood out significantly when compared to the results from the REFLECT study, which reported a PFS of 7.3 months and OS of 13.6 months.[5] The improvement in OS for lenvatinib observed between the two studies can be attributed to several factors, which include the improved management of AEs associated with lenvatinib by investigators and the greater proportion of patients who received further therapies following disease progression (44.1% in LEAP-002 vs. 33% in REFLECT). In the LEAP-002 trial, 14.4% of the patients received ICI-based treatments as part of their subsequent therapy.

Furthermore, the combination of nivolumab and ipilimumab as a second-line treatment following prior sorafenib treatment was evaluated.[50] Nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks (four doses) followed by a single-agent nivolumab treatment regimen had demonstrated ORR of 32% and exhibited a median OS of 22.8 months. This dosing strategy obtained an accelerated approval from the FDA on March 2020, as a second-line treatment for advanced HCC. Any-grade TRAEs were reported in 46 patients (94%) of 49 patients, with most being low grade. Elevated aspartate aminotransferase levels were the most common grade 3 or 4 event.

Recently, the phase III CARES-310 trial aimed to compare the efficacy and safety of camrelizumab plus rivoceranib (also known as apatinib) versus sorafenib as a first-line treatment for unresectable HCC. The results showed that camrelizumab-rivoceranib significantly improved the median PFS compared to sorafenib (5.6 vs. 3.7 months; HR, 0.52; 95% CI, 0.41-0.65; one-sided $P<0.0001$). In the interim analysis for OS, the median OS was also significantly extended with camrelizumab-rivoceranib versus sorafenib (22.1 vs. 15.2 months; HR, 0.62; 95% CI, 0.49-0.80; one-sided $P<0.0001$). Hypertension was the most common grade 3 or 4 TRAE, occurring in 38% and 15% of the patients in the camrelizumab-rivoceranib and sorafenib groups, respectively. This treatment has emerged as an effective and promising first-line therapy for patients with unresectable HCC. Several treatment modality combinations are currently being investigated in clinical trials to evaluate their efficacy in patients with advanced HCC (Table 2).

**Table 2.** Ongoing randomized trials of immunotherapy in patients with advanced HCC

| Drug | Phase | Setting | Primary endpoint | ClinicalTrials.gov identifier |
|---|---|---|---|---|
| Nivolumab and ipilimumab vs. sorafenib/Lenvatinib | III | First-line | OS | NCT04039607 |
| Finotonlimab (anti PD-1) and SCT510 (bavacizumab) vs. sorafenib | II/III | First-line | OS, PFS | NCT04560894 |
| Toripalimab and lenvatinib vs. lenvatinib | III | First-line | OS | NCT04523493 |
| Nofazinlimab (CS1003) and lenvatinib vs. Lenvatinib | III | First-line | OS | NCT04194775 |
| Atezolizumab and lenvatinib or sorafenib vs. lenvatinib/sorafenib | III | Second-line | OS | NCT04770896 |
| Pembrolizumab and bavituximab | II | First-line | ORR | NCT03519997 |
| Pembrolizumab and regorafenib | II | Second-line | ORR | NCT04696055 |
| Nofazinlimab and lenvatinib vs. lenvatinib | III | First-line | OS | NCT04194775 |
| Tislelizumab and regorafenib vs. regorafenib | II | First-line | Safety, ORR, PFS | NCT04183088 |
| Nivolumab and ipilimumab vs. sorafenib/lenvatinib | III | First-line | OS | NCT04039607 (CheckMate 9DW)* |
| Atezolizumab and lenvatinib/sorafenib vs. lenvatinib/sorafenib | III | Second-line | OS | NCT04770896 (IMbrave 251)* |
| IBI310 and sintilimab vs. sorafenib | III | First-line | OS, ORR | NCT04720716 |

HCC, hepatocellular carcinoma; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival; ORR, objective response rate.
*Study name.

**Table 3.** Completed clinical trials of combining immune checkpoint inhibitors with locoregional therapies in advanced HCC

| Drug and treatment | Phase | Setting | Result | ClinicalTrials.gov identifier |
|---|---|---|---|---|
| Tremelimumab and RFA/TACE[52] | I/II | Second-line | PR, 26.3%; median TTP, 7.4 months; median OS, 12.3 months | NCT01853618 |
| Pembrolizumab/nivolumab and thermal ablation[62] | II | Second-line | ORR, 24%; median PFS, 5 months; median TTP, 6.1 months; OS, 16.9 months | NCT03939975 |
| Nivolumab and $^{90}$Y radioembolization[70] | II | First-line | ORR, 30.6%; DCR, 58.3%; median PFS, 4.6 months; median OS, 15.1 months; Grade 3/4 TRAEs, 11% | NCT03033446 |
| Nivolumab and SIRT[95] | II | First-line | ORR, 41.5%; median TTP, 8.8 months; median OS, 20.9 months | NCT03380130 |

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; PR, partial response, TTP, time to tumor progression; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; DCR, disease control rate; TRAEs, treatment-related adverse events; SIRT, selective internal radiation therapy.

### 3) Combining with locoregional therapies

According to recent preclinical and clinical studies, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radiation can all be used in conjunction with ICIs to improve its efficacy.[51,52] These locoregional therapies (LRTs) eliminate primary malignancies and also stimulate antitumor immunity by releasing tumor antigens from destroyed cancer cells.[53,54] While LRTs enhance the antitumor immune response, these treatments can also increase hypoxia and generate cytokines, such as VEGFs and transforming growth factor-β, which can hinder the effectiveness of the immune response against tumors.[55] Consequently, the synergistic interaction between locoregional therapies and immunotherapeutic agents can provide benefits for HCC treatment.[56] To optimize the effectiveness of this approach, multidisciplinary collaborations are crucial.

Multiple studies provide evidence that ablative therapy can stimulate antigen-specific $CD4^+$ and $CD8^+$ T cell responses in patients with HCC.[57-59] Active NK cell responses have also been observed after RFA, demonstrating that this immune priming effect is not limited to T cells alone.[60] Another study demonstrated that RFA induced the infiltration of APCs and immune responses against tumors.[61] Patients with advanced HCC who received tremelimumab with partial tumor ablation showed promising results (Table 3).[52] The response rate was 26%, and the disease control rate was 89%. Among these patients, the OS was 12.3 months, and 45% experienced stable disease lasting over 6 months. Notably, tumor biopsies at 6 weeks revealed a substantial increase in the number of $CD8^+$ T cells in patients with clinical benefits. Another phase II trial demonstrated that combining ablation with immunotherapy could enhance the treatment efficacy in HCC.[62] Among the 50 patients who received an anti-PD-1 inhibitor (nivolumab/pembrolizumab) as second-line treatment, 33 patients with stable disease or a poor response to anti-PD-1 agents underwent subtotal thermal ablation. Promisingly, the addition of ablation improved efficacy, increasing the response rate from 10% to 24%, with tolerable toxicity.

TACE remains the standard treatment for intermediate-stage HCC.[63] TACE-induced tumor necrosis triggers immunological stimulation.[64] A recent study revealed that TACE leads to elevated PD-1 expression in peripheral mononuclear cells.[65] These findings suggest that targeting the PD-1/PD-L1 pathway might enhance the clinical outcomes of TACE. Several trials have investigated the use of TACE in combination with immunotherapy. A phase II trial, the IMMUTACE study, provided evidence for the safety and efficacy of combining nivolumab with TACE as a first-line treatment for patients with intermediate-stage HCC.[66,67] Currently, the LEAP-012 study is assessing the efficacy and safety of combining TACE with lenvatinib and pembrolizumab compared to TACE alone in patients with non-metastatic/incurable HCC (NCT04246177) (Table 4).

Radiotherapy, including stereotactic body radiotherapy (SBRT) and selective internal radiation therapy is an additional treatment modality for patients with HCC. In various tumors,

**Table 4.** Ongoing clinical trials on immune checkpoint inhibitors and locoregional therapies for patients with advanced HCC

| Drug and treatment | Phase | Setting | Primary endpoint | ClinicalTrials.gov identifier |
|---|---|---|---|---|
| Lenvatinib and pembrolizumab and TACE vs. TACE | III | First-line | PFS, OS | NCT04246177 (LEAP-012)* |
| Tremelimumab and durvalumab and radiation therapy | II | First-line | ORR | NCT03482102 |
| Pembrolizumab and SBRT | II | Second-line | ORR | NCT03316872 |
| Durvalumab and tremelimumab and ablative therapies | II | Second-line | PFS | NCT02821754 |
| Pembrolizumab and SIRT | I | First-line | PFS | NCT03099564 |
| SBRT followed by sintilimab vs. SBRT | II/III | First-line | PFS | NCT04167293 |
| HAIC and apatinib and camrelizumab | II | First-line | ORR | NCT04191889 |
| Toripalimab and thermal ablation | II | Second-line | PFS | NCT03864211 |
| TACE and sintilimab | II | First-line | ORR | NCT04297280 |

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiation therapy; HAIC, hepatic arterial infusion chemotherapy.
*Study name.

including HCC, radiation has shown the abscopal effect, the regression of non-irradiated lesions following radiotherapy.[55,68] The combination of immunotherapy with radiotherapy can enhance the abscopal effect.[69] With respect to the combination of SBRT with ICIs, ongoing clinical trials are evaluating the effect of pembrolizumab in combination with SBRT for patients with advanced HCC who experienced disease progression after sorafenib treatment (NCT03316872), and the efficacy of SBRT followed by an anti-PD1 antibody in a phase II/III study (NCT04167293) (Table 4). $^{90}$Y-radioembolization in combination with nivolumab was tested in the CA 209-678 study, a nonrandomized phase II trial, for patients with advanced HCC.[70] The study demonstrated promising clinical activity, including an ORR of 30.6% with a favorable safety profile (11% experienced grade 3/4 TRAE). Several ongoing trials have investigated combinations of ICIs and radiotherapy (Table 4).

A significant proportion of patients with advanced HCC are unsuitable for initial surgical resection. ICIs can reduce the tumor size, making patients eligible for surgical treatment. Previous studies showed that ICIs were administered to patients for whom curative resection was initially unsuitable as they had high-risk factors such as portal vein invasion, multifocality, or an advanced tumor size.[71] After treatment with cabozantinib and nivolumab, margin-negative resection was achieved in 12 of the 15 patients. In another study, ICI treatment was administered to patients with HCC with major vascular invasion, and subsequent salvage surgery was possible in eight of the ten patients.[72]

Liver transplantation (LT) is not the primary therapeutic option for patients with advanced HCC. LT can be considered cautiously in patients who are highly responsive to immunotherapy. However, the risk of transplant rejection or liver failure following liver transplantation should be considered.[73] There is limited data on organ transplantation after ICIs, the occurrence of rejection seems to be observed in approximately 30-40%.[74] Therefore, the advantages and potential risk associated with LT after immunotherapy need to be evaluated through multidisciplinary practice.

## FUTURE DIRECTIONS

### 1. Second-line treatments and treatment sequence decisions

Currently, the optimal treatment sequence after first-line ICI combination therapy remains unresolved. For patients who have received sorafenib or lenvatinib as first-line treatment, the FDA has approved five options, three antiangiogenic drugs (regorafenib, ramucirumab, and cabozantinib), pembrolizumab, and a combination of immunotherapies (nivolumab and ipilimumab). With the combination of atezolizumab and bevacizumab emerging as the preferred and standard first-line treatment, it is necessary to establish sub-

sequent treatment options in the second- and later-line settings. Although further data are urgently required to determine the optimal treatment sequences, TKIs can primarily be used after the progression of atezolizumab plus bevacizumab. This revealed comparable effectiveness and manageable side effects of sorafenib and lenvatinib in patients with advanced HCC.[75] According to preliminary real-world evidence, nivolumab plus ipilimumab may be effective after other ICI regimens.[76] The IMbrave251 study is evaluating atezolizumab–lenvatinib/sorafenib compared to sorafenib or lenvatinib following disease progression after atezolizumab and bevacizumab treatment (NCT04770896). However, the potential efficacy of alternative ICI combinations remains uncertain when the initial combination therapy is ineffective. In the absence of such data, treatment sequence decisions are made by considering factors such as patient characteristics, prior therapy tolerability, and side effect profile of each treatment regimen.[45]

## 2. Biomarkers for immunotherapy

To date, no reliable biomarker has been definitively established for immunotherapy of HCC. With the availability of various treatment options, the development of biomarkers for identifying patients who are more likely to benefit from a specific combination of treatments is valuable. By establishing predictive biomarkers, healthcare providers can choose the most effective therapy for patients and avoid the costs associated with ineffective treatments.[77] Biomarkers will contribute to a better understanding of personalized treatment sequences for advanced HCC.

PD-L1 expression has received significant attention as a potential biomarker for immunotherapy. PD-1/PD-L1 checkpoint inhibitors target PD-1 and PD-L1 receptors expressed on cell membranes. In an analysis of biomarkers from the CheckMate 040 trial, it was observed that high PD-L1 expression on tumor cells correlated with improved OS and ORR.[9] In the IMbrave150 trial, PD-L1 expression exhibiting a combined positive score ≥1% showed improved PFS and ORR in the atezolizumab-bevacizumab treatment group compared to the sorafenib group, although another study did not find any difference in ORR.[42,78] In HCC patients treated with nivolumab, higher levels of baseline $CD3^+$ and $CD8^+$ tumor-infiltrating lymphocytes (TILs) measured by immunohistochemistry correlated with improved OS.[79] Moreover, an increased $CD3^+$ and $CD8^+$ TILs 6 weeks after tremelimumab treatment for HCC related to the ORR.[52] In gadoxetic acid-enhanced magnetic resonance imaging (MRI), the hepatobiliary phase has been proposed as a potential imaging biomarker for identifying β-catenin mutations in HCC, which has implications for the ICI response.[80] A recent study reported that the ratio of relative enhancement and visual assessment of the hepatobiliary phase affects the prognosis of HCC. The heterogeneous/hyperintense type on baseline MRI exhibited a considerably shorter PFS than the homogeneous/hypointense types. Imaging features on $^{18}$F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) revealed an association with poorly differentiated HCC. This retrospective study assessed the tumor-to-normal liver ratio (TLR) of fluorodeoxyglucose (FDG) uptake before atezolizumab-bevacizumab treatment. This investigation revealed that a baseline TLR ≥2 was associated with poor PFS, but not with OS.[81] As these pathologic and radiologic features reflect the effectiveness of ICI treatments, multidisciplinary care of HCC is necessary.

In the study of durvalumab and tremelimumab, the data demonstrated a correlation between increased proliferation of peripheral $CD8^+$ T cells during treatment and response to treatment.[47] A recent analysis of biomarkers in patients treated with atezolizumab-bevacizumab has revealed that pre-existing immunity such as high expression of CD274, T-effector signature and intratumoral $CD8^+$ T cell density was linked to better clinical outcomes.[78] In addition, tumor-specific mutations play a significant role in the effectiveness of immunotherapies and serve as biomarkers for assessing the response to anti-PD-1 therapy.[82,83] Microsatellite instability (MSI) is a condition characterized by a high number of somatic mutations caused by deficient mismatch repair activity. MSI is regarded as a histological indicator for identifying individuals who are likely to respond to ICI therapy.[84,85] A previous study showed that PD-$L1^+$ circulating tumor cells (CTCs) served as prognostic biomarkers for OS. Among the 10 patients with HCC who were treated with ICIs (pembroli-

zumab or nivolumab), only those with PD-L1$^{+}$ CTCs showed any positive response.[86] The gut microbiota is currently being investigated as a promising biomarker in immunotherapy, potentially influencing the efficacy of cancer treatments. Tumor and circulating biomarker analyses, as well as noninvasive imaging-based metrics in ongoing immunotherapy studies, will establish the basis for precision medicine in HCC.[87,88] Further investigations are required to fully understand the potential significance of these factors.

## CONCLUSION

Over the past decade, the management of HCC has significantly improved owing to the development of new therapeutic options. Remarkable advancements have been made in immunotherapy for the treatment of HCC. However, immunotherapy alone has shown limited response rates.[89] Combination therapy based on ICIs with other therapeutic approaches, such as antiangiogenic drugs, other ICIs, and locoregional therapies, has emerged as a promising modality for HCC treatment through synergistic mechanisms. These findings emphasize the significance of adopting multidisciplinary care in the treatment of HCC. The tumor management board plays a crucial role in determining the most suitable treatment plan for each patient. The optimal timing for switching treatments can also be determined through multidisciplinary care.

With the growing number of available treatment options for advanced HCC, optimizing the treatment sequence to achieve the most favorable patient outcomes is necessary. To improve the treatment efficacy, there is an immediate need to discover reliable biomarkers that can precisely identify patients who are likely to respond to immunotherapy. Several studies have shown that PD-L1 expression and radiologic features are associated with the ICI response.[82,90,91] Through the discovery of effective biomarkers, personalized treatment for each patient is possible, which will significantly increase the survival rates.

## Conflicts of Interest

The author has no conflicts of interest to disclose.

## Ethics Statement

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

## Funding Statement

None.

## Data Availability

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

## ORCID

Yu Rim Lee https://orcid.org/0000-0003-1916-1448

## Author Contribution

Conceptualization: YRL
Writing-original draft: YRL
Writing-review & editing: YRL
Approval of final manuscript: YRL

## Acknowledgement

I gratefully acknowledge the support of the 24th Scientific Committee of the Korean Liver Cancer Association.

## References

1. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, et al. Breast cancer statistics, 2022. CA Cancer J Clin 2022;72:524-541.
2. Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019; 380:1450-1462.
3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
5. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Len-

vatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
6. Marino D, Zichi C, Audisio M, Sperti E, Di Maio M. Second-line treatment options in hepatocellular carcinoma. Drugs Context 2019;8:212577.
7. Greten TF, Lai CW, Li G, Staveley-O'Carroll KF. Targeted and immune-based therapies for hepatocellular carcinoma. Gastroenterology 2019;156:510-524.
8. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Results of KEYNOTE-240: phase 3 study of pembrolizumab (Pembro) vs best supportive care (BSC) for second line therapy in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2019;37 Suppl 15:4004.
9. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-2502.
10. Cheng AL, Hsu C, Chan SL, Choo SP, Kudo M. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. J Hepatol 2020;72:307-319.
11. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-1905.
12. Galle PR, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:991-1001.
13. Makarova-Rusher OV, Medina-Echeverz J, Duffy AG, Greten TF. The yin and yang of evasion and immune activation in HCC. J Hepatol 2015;62:1420-1429.
14. Zheng M, Tian Z. Liver-mediated adaptive immune tolerance. Front Immunol 2019;10:2525.
15. Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology 2019;156:477-491.e1.
16. Jenne CN, Kubes P. Immune surveillance by the liver. Nat Immunol 2013;14:996-1006.
17. Cariani E, Missale G. immune landscape of hepatocellular carcinoma microenvironment: implications for prognosis and therapeutic applications. Liver Int 2019;39:1608-1621.
18. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. Annu Rev Immunol 2007;25:267-296.
19. Zhou J, Wang W, Li Q. Potential therapeutic targets in the tumor microenvironment of hepatocellular carcinoma: reversing the protumor effect of tumor-associated macrophages. J Exp Clin Cancer Res 2021;40:73.
20. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol 2013;13:227-242.
21. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111-122.
22. Dai X, Xue J, Hu J, Yang SL, Chen GG, Lai PBS, et al. Positive expression of programmed death ligand 1 in peritumoral liver tissue is associated with poor survival after curative resection of hepatocellular carcinoma. Transl Oncol 2017;10:511-517.
23. Sen DR, Kaminski J, Barnitz RA, Kurachi M, Gerdemann U, Yates KB, et al. The epigenetic landscape of T cell exhaustion. Science 2016;354:1165-1169.
24. Shi F, Shi M, Zeng Z, Qi RZ, Liu ZW, Zhang JY, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. Int J Cancer 2011;128:887-896.
25. Jiang X, Wang J, Deng X, Xiong F, Ge J, Xiang B, et al. Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. Mol Cancer 2019;18:10.
26. Nishikawa H, Koyama S. Mechanisms of regulatory T cell infiltration in tumors: implications for innovative immune precision therapies. J Immunother Cancer 2021;9:e002591.
27. Sangro B, Sarobe P, Hervás-Stubbs S, Melero I. Advances in immunotherapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2021;18:525-543.
28. Wei SC, Anang NAS, Sharma R, Andrews MC, Reuben A, Levine JH, et al. Combination anti-CTLA-4 plus anti-PD-1 checkpoint blockade utilizes cellular mechanisms partially distinct from monotherapies. Proc Natl Acad Sci U S A 2019;116:22699-22709.
29. Hage C, Hoves S, Ashoff M, Schandl V, Hört S, Rieder N, et al. Characterizing responsive and refractory orthotopic mouse models of hepatocellular carcinoma in cancer immunotherapy. PLoS One 2019;14:e0219517.
30. Dirkx AE, Egbrink MGAO, Kuijpers MJ, van der Niet ST, Heijnen VV, Steege JCAB, et al. Tumor angiogenesis modulates leukocyte-vessel wall interactions in vivo by reducing endothelial adhesion molecule expression. Cancer Res 2003;63:2322-2329.
31. Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med 2015;212:139-148.
32. Malo CS, Khadka RH, Ayasoufi K, Jin F, AbouChehade JE, Hansen MJ, et al. Immunomodulation mediated by anti-angiogenic therapy improves CD8 T cell immunity against experimental glioma. Front Oncol 2018;8:320.
33. Shrimali RK, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immu-

notherapy of cancer. Cancer Res 2010;70:6171-6180.
34. Georganaki M, van Hooren L, Dimberg A. Vascular targeting to increase the efficiency of immune checkpoint blockade in cancer. Front Immunol 2018;9:3081.
35. Song Y, Fu Y, Xie Q, Zhu B, Wang J, Zhang B. Anti-angiogenic agents in combination with immune checkpoint inhibitors: a promising strategy for cancer treatment. Front Immunol 2020;11:1956.
36. Kalbasi A, Ribas A. Tumour-intrinsic resistance to immune checkpoint blockade. Nat Rev Immunol 2020;20:25-39.
37. Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56-61.
38. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77-90.
39. Qin S, Chen Z, Fang W, Ren Z, Xu R, Ryoo BY, et al. Pembrolizumab versus placebo as second-line therapy in patients from Asia with advanced hepatocellular carcinoma: a randomized, double-blind, phase III trial. J Clin Oncol 2023;41:1434-1443.
40. Kudo M. Pembrolizumab for the treatment of hepatocellular carcinoma. Liver Cancer 2019;8:143-154.
41. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol 2020;38:193-202.
42. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-873.
43. Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. J Clin Oncol 2020;38:4317-4345.
44. Vogel A, Martinelli E; ESMO Guidelines Committee. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO clinical practice guidelines. Ann Oncol 2021;32:801-805.
45. Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. J Hepatol 2021;75:960-974.
46. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, Sukeepaisarnjaroen W, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1:1-12.
47. Kelley RK, Sangro B, Harris W, Ikeda M, Okusaka T, Kang YK, et al. Safety, efficacy, and pharmacodynamics of tremelimumab plus durvalumab for patients with unresectable hepatocellular carcinoma: randomized expansion of a phase I/II study. J Clin Oncol 2021;39:2991-3001.
48. Kelley RK, Sangro B, Harris WP, Ikeda M, Okusaka T, Kang YK, et al. Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC). J Clin Oncol 2020;38 Suppl 15:4508.
49. Finn RS, Kudo M, Merle P, Meyer T, Qin S, Ikeda M, et al. LBA34 primary results from the phase III LEAP-002 study: lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). Ann Oncol 2022;33 Suppl 7:S1401.
50. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncol 2020;6:e204564.
51. Cui J, Wang N, Zhao H, Jin H, Wang G, Niu C, et al. Combination of radiofrequency ablation and sequential cellular immunotherapy improves progression-free survival for patients with hepatocellular carcinoma. Int J Cancer 2014;134:342-351.
52. Duffy AG, Ulahannan SV, Makorova-Rusher O, Rahma O, Wedemeyer H, Pratt D, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol 2017;66:545-551.
53. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol 2017;17:97-111.
54. Han JW, Yoon SK. Immune responses following locoregional treatment for hepatocellular carcinoma: possible roles of adjuvant immunotherapy. Pharmaceutics 2021;13:1387.
55. Rodriguez-Ruiz ME, Rodriguez I, Leaman O, López-Campos F, Montero A, Conde AJ, et al. Immune mechanisms mediating abscopal effects in radioimmunotherapy. Pharmacol Ther 2019;196:195-203.
56. Rodríguez-Ruiz ME, Perez-Gracia JL, Rodríguez I, Alfaro C, Oñate C, Pérez G, et al. Combined immunotherapy encompassing intratumoral poly-ICLC, dendritic-cell vaccination and radiotherapy in advanced cancer patients. Ann Oncol 2018;29:1312-1319.
57. Zerbini A, Pilli M, Penna A, Pelosi G, Schianchi C, Molinari A, et al. Radiofrequency thermal ablation of hepatocellular carcinoma liver nodules can activate and enhance tumor-specific T-cell responses. Cancer Res 2006;66:1139-1146.
58. Nobuoka D, Motomura Y, Shirakawa H, Yoshikawa T, Kuronuma T, Takahashi M, et al. Radiofrequency ablation for hepatocellular carcinoma induces glypican-3 peptide-specific cytotoxic T lymphocytes. Int J Oncol 2012;40:63-70.
59. Mizukoshi E, Yamashita T, Arai K, Sunagozaka H, Ueda T, Arihara F, et al. Enhancement of tumor-associated antigen-specific T cell responses by radiofrequency ablation of hepatocellular carcinoma. Hepatology 2013;57:1448-1457.

60. Zerbini A, Pilli M, Laccabue D, Pelosi G, Molinari A, Negri E, et al. Radiofrequency thermal ablation for hepatocellular carcinoma stimulates autologous NK-cell response. Gastroenterology 2010;138:1931-1942.
61. Dromi SA, Walsh MP, Herby S, Traughber B, Xie J, Sharma KV, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. Radiology 2009;251:58-66.
62. Zhao M, Huang J, Lyu N, Kong Y, Mu L, Lin Y. Local thermal ablation reboots the response in advanced hepatocellular carcinoma with stable or atypical progressive diseases during anti-PD-1 therapy. Ann Oncol 2019;30 Suppl 11:XI45.
63. Llovet JM, De Baere T, Kulik L, Haber PK, Greten TF, Meyer T, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2021;18:293-313.
64. Kim MJ, Jang JW, Oh BS, Kwon JH, Chung KW, Jung HS, et al. Change in inflammatory cytokine profiles after transarterial chemotherapy in patients with hepatocellular carcinoma. Cytokine 2013;64:516-522.
65. Guo J, Wang S, Han Y, Jia Z, Wang R. Effects of transarterial chemoembolization on the immunological function of patients with hepatocellular carcinoma. Oncol Lett 2021;22:554.
66. Vogel A, Saborowski A, Hinrichs J, Ettrich TJ, Ehmer U, Martens UM, et al. LBA37 IMMUTACE: a biomarker-orientated, multi center phase II AIO study of transarterial chemoembolization (TACE) in combination with nivolumab performed for intermediate stage hepatocellular carcinoma (HCC). Ann Oncol 2021;32 Suppl 5:S1312.
67. Marinelli B, Kim E, D'Alessio A, Cedillo M, Sinha I, Debnath N, et al. Integrated use of PD-1 inhibition and transarterial chemoembolization for hepatocellular carcinoma: evaluation of safety and efficacy in a retrospective, propensity score-matched study. J Immunother Cancer 2022;10:e004205.
68. Cytlak UM, Dyer DP, Honeychurch J, Williams KJ, Travis MA, Illidge TM. Immunomodulation by radiotherapy in tumour control and normal tissue toxicity. Nat Rev Immunol 2022;22:124-138.
69. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer 2018;18:313-322.
70. Tai WMD, Loke KSH, Gogna A, Tan SH, Ng DCE, Hennedige TP, et al. A phase II open-label, single-center, nonrandomized trial of Y90-radioembolization in combination with nivolumab in Asian patients with advanced hepatocellular carcinoma: CA 209-678. J Clin Oncol 2020;38 Suppl 15:4590.
71. Ho WJ, Zhu Q, Durham J, Popovic A, Xavier S, Leatherman J, et al. Neoadjuvant cabozantinib and nivolumab converts locally advanced HCC into resectable disease with enhanced antitumor immunity. Nat Cancer 2021;2:891-903.
72. Zhang W, Hu B, Han J, Wang Z, Ma G, Ye H, et al. Surgery after conversion therapy with PD-1 inhibitors plus tyrosine kinase inhibitors are effective and safe for advanced hepatocellular carcinoma: a pilot study of ten patients. Front Oncol 2021;11:747950.
73. Nordness MF, Hamel S, Godfrey CM, Shi C, Johnson DB, Goff LW, et al. Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: are checkpoint inhibitors safe for the pretransplant patient? Am J Transplant 2020;20:879-883.
74. Laschtowitz A, Roderburg C, Tacke F, Mohr R. Preoperative immunotherapy in hepatocellular carcinoma: current state of the art. J Hepatocell Carcinoma 2023;10:181-191.
75. Yoo C, Kim JH, Ryu MH, Park SR, Lee D, Kim KM, et al. Clinical outcomes with multikinase inhibitors after progression on first-line atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma: a multinational multicenter retrospective study. Liver Cancer 2021;10:107-114.
76. Wong JSL, Kwok GGW, Tang V, Li BCW, Leung R, Chiu J, et al. Ipilimumab and nivolumab/pembrolizumab in advanced hepatocellular carcinoma refractory to prior immune checkpoint inhibitors. J Immunother Cancer 2021;9:e001945.
77. Tai D, Choo SP, Chew V. Rationale of immunotherapy in hepatocellular carcinoma and its potential biomarkers. Cancers (Basel) 2019;11:1926.
78. Zhu AX, Abbas AR, de Galarreta MR, Guan Y, Lu S, Koeppen H, et al. Molecular correlates of clinical response and resistance to atezolizumab in combination with bevacizumab in advanced hepatocellular carcinoma. Nat Med 2022;28:1599-1611.
79. Sangro B, Melero I, Wadhawan S, Finn RS, Abou-Alfa GK, Cheng AL, et al. Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma. J Hepatol 2020;73:1460-1469.
80. Sasaki R, Nagata K, Fukushima M, Haraguchi M, Miuma S, Miyaaki H, et al. Evaluating the role of hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging in predicting treatment impact of lenvatinib and atezolizumab plus bevacizumab on unresectable hepatocellular carcinoma. Cancers (Basel) 2022;14:827.
81. Kawamura Y, Kobayashi M, Shindoh J, Matsumura M, Okubo S, Muraishi N, et al. Pretreatment positron emission tomography with 18F-fluorodeoxyglucose may be a useful new predictor of early progressive disease following atezolizumab plus bevacizumab in patients with unresectable hepatocellular carcinoma. Oncology 2022;100:320-330.
82. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med 2017;377:2500-2501.
83. Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet 2019;51:202-

206.
84. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-413.
85. Ang C, Klempner SJ, Ali SM, Madison R, Ross JS, Severson EA, et al. Prevalence of established and emerging biomarkers of immune checkpoint inhibitor response in advanced hepatocellular carcinoma. Oncotarget 2019;10:4018-4025.
86. Winograd P, Hou S, Court CM, Lee YT, Chen PJ, Zhu Y, et al. Hepatocellular carcinoma-circulating tumor cells expressing PD-L1 are prognostic and potentially associated with response to checkpoint inhibitors. Hepatol Commun 2020;4:1527-1540.
87. Liu F, Liu D, Wang K, Xie X, Su L, Kuang M, et al. Deep learning radiomics based on contrast-enhanced ultrasound might optimize curative treatments for very-early or early-stage hepatocellular carcinoma patients. Liver Cancer 2020;9:397-413.
88. Yao S, Ye Z, Wei Y, Jiang HY, Song B. Radiomics in hepatocellular carcinoma: a state-of-the-art review. World J Gastrointest Oncol 2021;13:1599-1615.
89. Jilkova ZM, Aspord C, Decaens T. Predictive factors for response to PD-1/PD-L1 checkpoint inhibition in the field of hepatocellular carcinoma: current status and challenges. Cancers (Basel) 2019;11:1554.
90. Yau T, Hsu C, Kim TY, Choo SP, Kang YK, Hou MM, et al. Nivolumab in advanced hepatocellular carcinoma: sorafenib-experienced Asian cohort analysis. J Hepatol 2019;71:543-552.
91. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. CheckMate 459: a randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Ann Oncol 2019;30 Suppl 5:V874-V875.
92. Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. Lancet Oncol 2021;22:977-990.
93. Kelley RK, Rimassa L, Cheng AL, Kaseb A, Qin S, Zhu AX, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2022;23:995-1008.
94. Qin S, Chan SL, Gu S, Bai Y, Ren Z, Lin X, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet. 2023 Jul 24. doi: 10.1016/S0140-6736(23)00961-3. [Epub ahead of print].
95. de la Torre-Alaez M, Matilla A, Varela M, Inarrairaegui M, Reig M, Lledo JL, et al. Nivolumab after selective internal radiation therapy for the treatment of hepatocellular carcinoma: a phase 2, single-arm study. J Immunother Cancer 2022;10:e005457.