

REVIEW

Emerging immunotherapy for HCC: A guide for hepatologists

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Abstract

HCC is one of the most common cancers worldwide, and the third leading cause of cancer-related death globally. HCC comprises nearly 90% of all cases of primary liver cancer. Approximately half of all patients with HCC receive systemic therapy during their disease course, particularly in the advanced stages of disease. Immuno-oncology has been paradigm shifting for the treatment of human cancers, with strong and durable antitumor activity in a subset of patients across a variety of malignancies including HCC. Immune checkpoint inhibition with atezolizumab and bevacizumab, an anti-vascular endothelial growth factor neutralizing antibody, has become first-line therapy for patients with advanced HCC. Beyond immune checkpoint inhibition, immunotherapeutic strategies such as oncolytic viroimmunotherapy and adoptive T-cell transfer are currently under investigation. The tumor immune microenvironment of HCC has significant immunosuppressive elements that may affect response to immunotherapy. Major unmet challenges include defining the role of immunotherapy in earlier stages of HCC, evaluating combinatorial strategies that use targeting of the immune microenvironment plus immune checkpoint inhibition, and identifying treatment strategies for patients who do not respond to the currently available immunotherapies. Herein, we review the rationale, mechanistic basis and supporting preclinical evidence, and available clinical evidence for immunotherapies in HCC as well as ongoing clinical trials of immunotherapy.

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; Breg, regulatory B cells; CAR-T cell, chimeric antigen receptor T cell; CIK, cytokine-induced killer; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCR3, chemokine (C-X-C motif) receptor 3-positive; DC, dendritic cell; DCR, disease control rate; FDA, Food and Drug Administration; GPC3, glypican 3; ICI, immune checkpoint inhibitors; IFN- γ , interferon-gamma; irAE, immune-related adverse events; LAG-3, lymphocyte-activation gene 3; LAMP3, lysosome-associated membrane glycoprotein 3; LAYN, layilin; MDSC, myeloid-derived suppressor cells; mRECIST, modified RECIST; NK cell, natural killer cell; NKT cell, natural killer T cell; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; T4, thyroxine; TACE, transarterial chemoembolization; TAE, transarterial embolization; TAM, tumor-associated macrophage; TIME, tumor-immune microenvironment; TKI, tyrosine kinase inhibitor; TME, tumor microenvironment; trAE, treatment-related adverse events; Treg, regulatory T cell; TSH, thyroid-stimulating hormone.

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INTRODUCTION

Liver cancer is one of the most common cancers in the world and has a rising incidence worldwide, particularly in the West.^[1] HCC is the most common type of liver cancer, accounting for over 90% of cases. HCC typically arises in a background of chronic liver disease including chronic viral hepatitis, alcohol-associated liver disease, and NASH. Although hepatitis B is the most notable risk factor, as it accounts for a significant proportion of HCC cases, NASH is becoming the fastest growing risk factor for HCC, particularly in the Western world.^[2] Management options for HCC vary based on the tumor burden, liver function, comorbidities, and performance status of a patient. For early-stage disease, surgical resection and liver transplantation are the primary potentially curative treatment options with excellent long-term outcomes.^[3] Radiofrequency ablation is the primary local modality used for early-stage HCC,^[4] and transarterial chemoembolization (TACE) remains the standard of care for patients with intermediate-stage HCC.^[5] The use of systemic anticancer therapy for advanced stage HCC was controversial before 2008 due to lack of efficacy and poor patient tolerance. In 2007, the tyrosine kinase inhibitor (TKI) sorafenib received Food and Drug Administration (FDA) approval for patients with advanced HCC with preserved liver function. This was based on the SHARP trial, a phase 3, randomized controlled trial that demonstrated an overall survival (OS) benefit in the sorafenib group compared with placebo.^[6] Over the last 4 years, three other TKIs were approved for advanced HCC; lenvatinib was found to be noninferior to sorafenib in the first-line setting,^[7] whereas regorafenib (in patients who are tolerant to sorafenib) and cabozantinib had a survival benefit in the second-line setting.^[8,9] In addition, ramucirumab, a monoclonal antibody against VEGFR2, was approved in patients with baseline alpha-fetoprotein (AFP) concentrations ≥ 400 ng/dl after progression on sorafenib.^[10]

Over the past decade, immuno-oncology has been a paradigm shift in the treatment of malignancies including liver cancer. The antitumor immune response harnesses elements of the innate and adaptive immune system.^[11] However, tumors can co-opt this response and enact immune evasion by different mechanisms such as fostering an immunosuppressive microenvironment or mediating cytotoxic cell dysfunction. An immunosuppressive tumor-immune microenvironment (TIME) is characterized by an abundance of regulatory T cells (Treg), immunosuppressive myeloid cells such as tumor-associated macrophages (TAMs) or myeloid-derived suppressor cells (MDSCs), and inhibitory B cells.^[12] Activation of immune checkpoints, including coinhibitory molecules, restrains activation of effector lymphocytes and is integral to tumor immune evasion.^[13] These negative regulators of T-cell

activation include programmed death-1 (PD-1) and its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) among others. Immunotherapeutic approaches to treat cancer include immune checkpoint inhibition (ICI) with monoclonal antibodies that block the checkpoint receptor–ligand interactions, thereby fostering a robust cytotoxic T lymphocyte (CTL) response.^[14] Adoptive cell-based therapies use infusion of cytotoxic immune cells into patients. Transgenic tumor antigen-specific T-cell receptors or chimeric antigen receptors are the two primary approaches of adoptive cell therapy. ICI therapies have demonstrated robust efficacy in a subset of patients across a variety of malignancies including HCC. The combination of the anti-PDL1 antibody atezolizumab and the VEGF neutralizing antibody bevacizumab has become first-line therapy for HCC.^[15] Herein, we review the rationale, mechanistic basis and supporting preclinical evidence, and available clinical evidence for immunotherapies in HCC as well as ongoing clinical trials of immunotherapy.

TIME OF HCC

The liver plays an essential role in immune surveillance and thus has a distinctive microenvironment.^[16] The liver is continually exposed to blood-borne pathogens, particularly gut-derived pathogens, as it has both an arterial and portal venous blood supply. Accordingly, the baseline liver microenvironment has a plethora of innate and adaptive immune cells to facilitate pathogen clearance, while maintaining tolerance to non-pathogenic exogenous molecules in portal blood. This balance is critical and accounts for the liver having a unique immune tolerogenic niche, which in turn can facilitate HCC development.^[17] The immune microenvironment of HCC likely has an impact on efficacy of ICI. Accordingly, a comprehensive understanding of the HCC TIME is essential in the effort to develop effective immunotherapies. Notably, the current insights into the HCC TIME have been based primarily on early-stage tumors. It is plausible that the TIME varies by disease stage, with advanced-stage HCC having a distinct TIME compared with early-stage HCC.

CYTOTOXIC ELEMENTS OF THE HCC TIME AND THERAPEUTIC IMPLICATIONS

The cytotoxic immune response is attenuated in HCC. CD8⁺ T lymphocytes are the primary cytotoxic tumor-infiltrating lymphocyte subset in HCC. Enrichment of CD8⁺ T lymphocytes is associated with a better prognosis.^[18,19] However, these CTLs have impaired interferon-gamma (IFN- γ) production, suggesting that they are dysfunctional.^[19] There are a variety of factors

and cell types that contribute to a dysfunctional state of CD8⁺ T lymphocytes. For instance, accumulation of liver-resident immunoglobulin A-producing cells in murine and human NASH is associated with a robust inhibition of the tumor-directed CTL response in HCC. Immune checkpoints are negative regulators of CTL function across a variety of malignancies including HCC. Immune checkpoints in the HCC TIME include PD-1, CTLA-4, lymphocyte-activation gene 3 (LAG-3), V-domain immunoglobulin suppressor of T-cell activation, and T-cell immunoglobulin and mucin domain containing-3.

Similarly, natural killer cell (NK) dysfunction also occurs in HCC and correlates with patient survival. For instance, patients with better outcomes have NK cells with higher expression of cytotoxic granules or the activating KIR2DS5, and lower levels of the inhibitor NK receptor NKG2A.^[20,21] Moreover, accumulation of CD11b⁺CD27⁺ NK cells, an immature and inactive phenotype with poor cytolytic activity, is associated with HCC progression.^[22] NK cell function can also be dampened by immunosuppressive cells such as MDSCs and Tregs, as well as immunosuppressive cytokines including IL-10 and TGFβ.^[23,24]

Immunosuppressive elements of the HCC TIME and their therapeutic potential

An accumulation of immunosuppressive elements dampens the cytotoxic immune response in the HCC TIME and is associated with poor patient outcomes. Pro-tumor, immunosuppressive cell types in HCC include lymphocytes and myeloid cells.

Immunosuppressive lymphocytes

Tregs have an essential role in maintenance of self-tolerance and regulation of immune responses under physiologic conditions as well as in disease states including cancer. Circulating CD4⁺CD25⁺FoxP3⁺ Tregs are increased in patients with HCC and correlate with tumor progression and decreased patient survival.^[25] Moreover, accumulation of Tregs in the tumor core is associated with reduced infiltration and effector function of CD8⁺ T cells.^[25] Intratumoral balance of Tregs and CD8⁺ T cells is also prognostic, with a balance favoring CD8⁺ T cells being associated with improved OS.^[26] However, it remains to be determined whether the balance of CD8⁺ T cells and Tregs correlates with response to ICI. In a comprehensive biomarker analysis of tumor specimens from patients enrolled in CheckMate 040, increased frequency of CD3⁺ T cells was associated with response to ICI with nivolumab. Moreover, the presence of tumor-infiltrating CD3⁺ and CD8⁺ T cells was associated with a trend toward

improved OS. The presence of inflammatory signatures including an IFN-γ signature correlated with either objective response rate (ORR) or OS. However, FoxP3⁺ Treg abundance did not correlate with response to nivolumab.^[27] Tumor-infiltrating Tregs are recruited to the HCC TIME by chemokines such as chemokine ligand 20 and other immunosuppressive cells such as MDSCs.^[28,29] TGF-β can promote abundance and differentiation of CD4⁺FoxP3⁺ Tregs. Similarly, VEGF augments infiltration of MDSCs and Tregs in tumors with concomitant attenuation of effector T-cell activation.^[30] Accordingly, blockade of either VEGF or TGF-β restrains tumor growth via modulation of the TIME including reduction in Treg and MDSC abundance and increased effector T-cell activation. Blockade of the TGF-β receptor using a specific inhibitor, SM-16, reduced Treg infiltration and HCC progression in a N-nitrosodiethylamine-induced murine model.^[31]

Although B cells are an abundant element in tumors, their role in liver cancer is not well-defined.^[32] Regulatory B cells (Bregs) have a pro-tumorigenic role via production of immunosuppressive cytokines and regulation of the cytotoxic T-cell response.^[33–36] There is some evidence that such an immunosuppressive population is also present in HCC. Chemokine (C-X-C motif) receptor 3-positive (CXCR3⁺) B cells comprise a significant proportion of the B-cell population in HCC, and their accumulation is correlated with early recurrence of HCC. CXCR3⁺ B cells facilitate transition of macrophages to an alternatively activated “M2-like” phenotype in HCC and their depletion using anti-CD20 attenuated M2-like polarization and HCC growth in preclinical models.^[34] PD-1⁺ Bregs have a phenotype distinct from peripheral Bregs and constitute approximately 10% of all B cells in advanced-stage HCC.^[36] After encountering PD-L1⁺ cells, PD-1⁺ Bregs acquire regulatory functions via IL-10 signaling with consequent T-cell dysfunction and disease progression.

Immunosuppressive myeloid cells

Immunosuppressive myeloid cells play an essential role in HCC as they contribute to a pro-tumor microenvironment (TME) and are associated with a poor prognosis. TAMs with high levels of CD163 and scavenger receptor are characterized as M2-like, and abundance of M2-like macrophages in patients with HCC is associated with increased tumor nodules and venous infiltration.^[37] An immunogenomic analysis of 10,000 tumors across 33 cancers assessed lymphocyte and myeloid signatures using The Cancer Genome Atlas (TCGA) data and identified six immune subtypes. HCCs were categorized under the lymphocyte-depleted subtype characterized by a prominent macrophage signature and a high M2 response.^[38] However, single-cell transcriptomics has highlighted that TAM phenotypes are

more complex and dynamic than the conventional M1/M2 model.^[39]

MDSCs are pathologically activated potent immunosuppressive cells, and their accumulation in cancer is associated with poor patient outcomes. The two primary subsets of MDSCs are classified according to their origin as granulocytic or polymorphonuclear and monocytic MDSCs.^[40] Several subsets of MDSCs have been described in liver cancer. CD14⁺HLA-DR^{low} cells are present in the peripheral blood of patients with HCC and have potent immunosuppressive properties including suppression of autologous T-lymphocyte proliferation and induction of Tregs.^[29] MDSCs foster tumor growth and progression, in part, via production of VEGF, a soluble factor that augments tumor vascularization and neoangiogenesis.^[40] MDSCs from patients with HCC also inhibit autologous NK-cell cytotoxicity and cytokine secretion in an NKp30-dependent manner.^[23] Depletion of MDSCs from peripheral blood mononuclear cells of patients with HCC restored CTL effector function, as evidenced by production of granzyme B, and increased the number of IFN- γ -producing CD4⁺ T cells.^[41] MDSCs also play an important role in immune evasion in HCC. Adoptive cell transfer of cytokine-induced killer (CIK) into tumor-bearing mice had impaired antitumor activity, due to an increase in MDSCs in two different HCC models.^[42] The robust pro-tumor, immunosuppressive function of MDSCs has garnered interest as a potential immunotherapeutic approach. Phosphodiesterase-5 (PDE5) inhibition is one approach that has been used to target MDSCs.^[43] PDE5 inhibition in preclinical models of HCC attenuated MDSC function via blockade of arginase 1 and inducible nitric oxide synthase.^[42] This reversal of MDSC-mediated immunosuppression enhanced CIK activity.

Tumor-associated neutrophils (TANs) can support tumor progression and promote an immunosuppressive TIME by fostering tumor angiogenesis, migration, and invasion.^[44] CXCL5 promotes TAN infiltration in HCC, and CXCL5 overexpression and TAN abundance is associated with poor patient prognosis in HCC.^[45] CCL2⁺ or CCL17⁺ TANs correlate with tumor size, microvascular invasion, tumor differentiation, and stage in HCC.^[46] Moreover, TANs modulate the HCC TIME via recruitment of macrophages and Tregs. Accordingly, the combination of TAN depletion, and sorafenib attenuated neovascularization and tumor growth in preclinical models of HCC.

Dendritic cells (DCs) are antigen-presenting cells with an essential role in activation of the antitumor adaptive immune response. DCs acquire tumor antigens and activate CTLs. However, tolerogenic DCs are a regulatory DC subtype that can suppress the antitumor immune response.^[47] CD14⁺CTLA-4⁺ regulatory DCs suppress the CTL response in HCC through IL-10 and indoleamine-2,3-dioxygenase.^[48] LAMP3⁺ (lysosome-associated membrane glycoprotein 3) DCs are a mature form of

conventional DCs, and are another DC subset that may be associated with dysfunctional CTLs, as they can potentially regulate a variety of lymphocytes in human HCC.^[39] The immunostimulatory role of DCs can be leveraged in immunotherapeutics. AFP has been identified as a tumor rejection antigen in murine HCC. In a phase 1/2 clinical trial, patients ($n = 10$) with AFP-positive HCC were immunized with intradermal vaccinations of AFP peptides pulsed onto autologous DC.^[49] Six of the 10 subjects had a significant increase in AFP-specific T cells following vaccine. In a subsequent study, the same investigators demonstrated that vaccination of patients with HCC with peptide-loaded DCs enhanced NK cell activation and reduced Treg frequency in the HCC TIME.^[50]

Single immune cell landscape, crosstalk, and mechanisms of immune evasion in HCC

Single-cell omics has provided essential insight into the dynamics and diversity encountered within complex tumor ecosystems. Such high-resolution analyses have identified distinct immune subsets and their functional states as well as predictions of complex cellular crosstalk.^[39,51–53] In-depth single-cell transcriptomic analysis of 5063 single T cells isolated from 6 patients with HCC revealed enrichment and potential clonal expansion of Tregs and exhausted CD8⁺ T cells with high expression of a regulatory gene, *layilin* (LAYN).^[51] LAYN-overexpressed CD8⁺ T cells were dysfunctional with repressed cytotoxic function, including attenuation of IFN- γ production, whereas LAYN-overexpressed Tregs were potentially more repressive and stable. Transcriptome profiling of 75,000 CD45⁺ single immune cells from 16 patients with HCC demonstrated dynamic properties of diverse CD45⁺ immune cell types. For instance, two distinct states of macrophages in HCC tumors, TAM-like macrophages and MDSC-like macrophages, were described.^[36] TAM-like macrophages had high expression of *C1QA*⁺ and expressed *GPNMB* (*glycoprotein nonmetastatic melanoma protein B*) and *SLC40A1* (*solute carrier family 40 member 1*); both genes were linked to poor patient prognosis based on TCGA analysis. In comparison, MDSC-like macrophages had high expression of *S100A* family genes *FCN1* (*ficolin 1*) and *VCAN* (*versican*). A unique subset of conventional DCs, LAMP3⁺, was also detected. LAMP3⁺ DCs had a lymphocyte regulatory function, correlated with dysfunctional T cells, and had the potential to migrate to lymph nodes. This study also demonstrated that lymphocytes and macrophage subsets identified in ascites of patients with HCC could originate from the primary tumor. The immune ecosystem of early-relapse HCC is unique and may, in part, explain the high relapse rate and poor overall prognosis associated with HCC. Profiling of the transcriptomes of 17,000 cells from 18 patients with primary or early-relapse HCC

revealed clonal expansion of innate-like CD8⁺ T cells that exhibited low cytotoxicity.^[52] In aggregate, these findings provide insight into the dynamic nature of various immune cell subsets, and their contribution to largely immunosuppressive TIME in HCC (Figure 1).

HCC mutational landscape, hepatic environment, and the TIME

Oncogenic pathways driven by genetic alterations may have an impact on the immune microenvironment and immune surveillance. This in turn can impact response to immunotherapies. The Wnt- β -catenin signaling pathway is activated in 30%–50% of HCCs.^[54] β -catenin-activated HCCs are characterized by lower immune signatures and down-regulation of chemokine (c-c motif) ligands 4, which is associated with failure of T-cell priming.^[55] Accordingly, these tumors are also characterized by T-cell exclusion. In a unique genetic mouse model of HCC, β -catenin activation resulted in immune evasion via defective recruitment of DCs and impaired T-cell activity with consequent resistance to anti-PD-1 therapy.^[56]

HCC induction and antitumor immune response can be regulated by the hepatic environment, which in turn may vary according to HCC etiology. Emerging pre-clinical data suggest that tumor immune surveillance is impaired in HCC arising in the context of NASH.^[57] In mouse models of NASH-related HCC, but not HCC due to other etiologies, immunotherapy with anti-PD-1 led

to an enrichment of CD8⁺PD1⁺ T cells without tumor regression. Prophylactic anti-PD-1 therapy in murine models of NASH unexpectedly led to an increase in CXCR6⁺CD8⁺PD1⁺ T cells and increased incidence of HCC in NASH mice. CXCR6⁺CD8⁺PD1⁺ T cells had high expression of *cxcr6*, *Gzmb* (granzyme B), *Ifng*, *Tnf* and *Pdcd1* (programmed cell death 1), suggesting features of tissue residency, effector function, and exhaustion, respectively. A similar CD8⁺PD1⁺ T-cell profile was observed in human NASH. These data suggest that the liver immune microenvironment may be unique in NASH. However, it remains to be seen whether immune surveillance and immunotherapy response may differ according to the underlying etiology of HCC.

Modulation of the HCC TIME by microbiome and stromal factors

The gut microbiota has an integral role in regulation of bile acid production, and disruption of this crosstalk can facilitate inflammation and carcinogenesis, including HCC.^[58] Patients with chronic liver disease have accumulation of gut-derived endotoxin or lipopolysaccharide (LPS). Attenuation of LPS levels using antibiotics or genetic ablation of its receptor toll-like receptor 4 (TLR4) inhibits tumor growth in preclinical models of HCC.^[59] Moreover, in murine models of chronic liver injury, intestinal microbiota and TLR4 activation facilitate hepatocarcinogenesis.^[60] The commensal microbiome

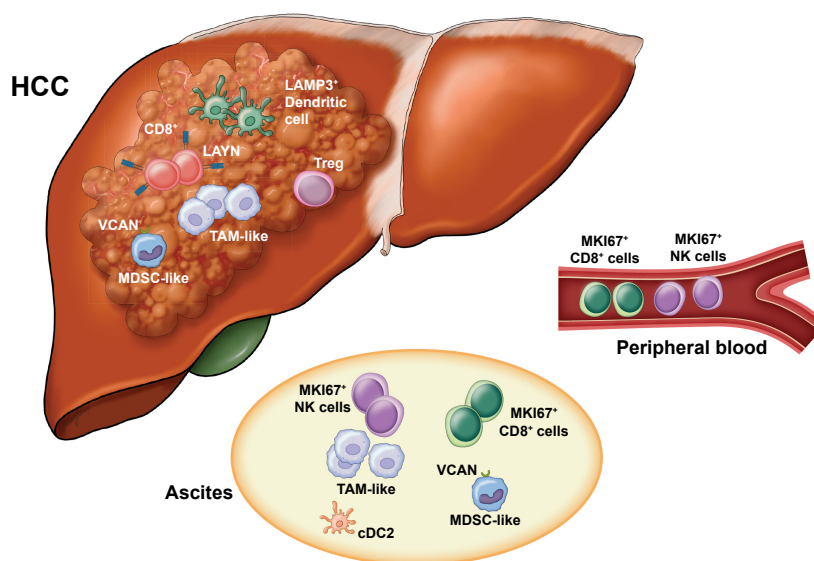


FIGURE 1 Dynamics of the tumor-immune microenvironment (TIME) of HCC. High-resolution analysis using single-cell omics has provided insight into the dynamic nature of various immune subsets and their contribution to a largely immunosuppressive immune microenvironment in HCC. Immunosuppressive cell populations in the HCC TIME including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) contribute to dysfunction of CD8⁺ T cells and dendritic cells (DCs). LAMP3⁺ DCs may be a common DC subset that has maturation features and may play a role in T-cell dysfunction. In patients with HCC with ascites, immune cell subsets may migrate from the primary tumor (TAM-like, MDSC-like) or from the peripheral blood (MKI67⁺ CD8⁺ cells or natural killer [NK] cells). Abbreviations: LAYN, layilin; LAMP3, lysosome-associated membrane glycoprotein 3; VCAN, versican

may affect antitumor immunity in cancer, and is associated with anti-PD-1 efficacy in melanoma.^[61] Alteration of commensal gut bacteria in mice had an antitumor effect in preclinical models of liver cancer via an increase in hepatic CXCR6⁺ natural killer T (NKT) cells.^[62] Conversion of primary-to-secondary bile acids via the gut microbiome led to NKT cell accumulation. In aggregate, these studies suggest there is a link between regulation of commensal gut microbiome and liver antitumor immunity.

TGF- β is implicated in cancer progression and metastasis. High TGF- β levels in patients with HCC are associated with lower OS, and poor response to sorafenib.^[63] Activated TGF- β signaling can promote an immunosuppressive TIME via several mechanisms including induction of tolerogenic DCs and facilitating a switch to pro-tumor, M2-like macrophages.^[47,64] Accordingly, high baseline plasma TGF- β levels are associated with resistance to the anti-PD-L1 antibody, pembrolizumab.^[65]

VEGF, another soluble factor that plays an integral role in the TME, is produced by tumor cells as well as stromal cells. VEGFA amplification in a subset of human HCCs mediates paracrine interactions within the HCC TME with increased production of hepatocyte growth factor (HGF) and consequent tumor growth and progression. Accordingly, VEGFA inhibition down-regulated HGF production and attenuated tumor growth in a preclinical model of HCC. Moreover, murine and human HCCs harboring VEGFA amplification had enhanced sensitivity to the multikinase

inhibitor sorafenib.^[66] The function of VEGF extends beyond promoting tumor angiogenesis. Single-cell RNA sequencing of primary liver cancers has demonstrated that these tumors have high diversity, which has a negative correlation with patient prognosis.^[53] Malignant cells with high diversity produce VEGFA, which reprograms the TME of liver cancer, including promotion of T-cell dysfunction. Furthermore, VEGF has extensive immunomodulatory effects including expansion of immunosuppressive elements such as Tregs and MDSCs in the TIME, attenuation of effect T-cell activation, and inhibition of DC function.^[30] The VEGF inhibitor bevacizumab restores antitumor immunity partly via reduction of circulating S100A9-positive MDSCs.^[67] This essential role of VEGF in the HCC TIME provides rationale for the success of combination anti-VEGF and ICI in the first-line setting for HCC.

IMMUNOTHERAPY FOR ADVANCED-STAGE HCC

The benefit of immunotherapy for advanced HCC has been clearly established. The predominant drug class are the ICIs, in particular those that block PD-1 or PD-L1. They have been tested both alone and in combination in large clinical trials and have become an integral part of systemic treatment of HCC. Moreover, emerging immunotherapeutics such as adoptive cell therapy have the potential to enhance the efficacy of ICI in HCC (Figure 2).

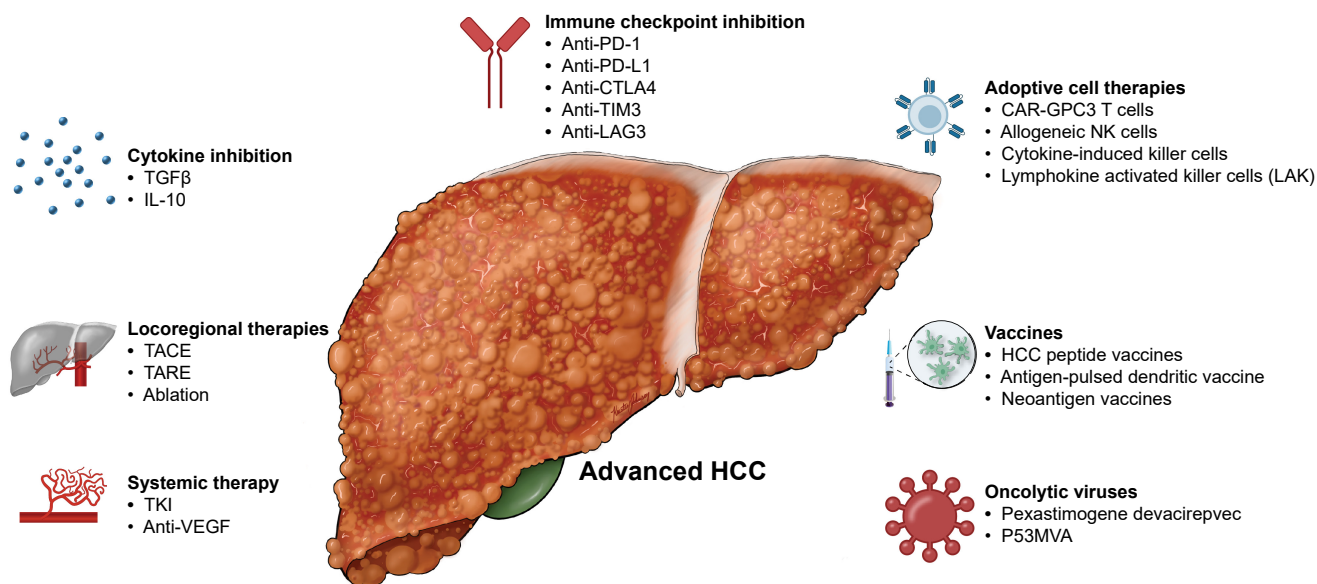


FIGURE 2 Potential combination strategies using immune checkpoint inhibition (ICI) in HCC. Multiple therapies under investigation have the potential to enhance the antitumor response in HCC when combined with ICI. These include combination of ICI with other immunotherapeutics such as adoptive cell therapies, vaccines, and oncolytic viruses. ICI can also be combined with systemic therapies and locoregional therapies. Abbreviations: CAR, chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GPC3, glypican 3; LAG-3, lymphocyte-activation gene 3; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TIM3, T-cell immunoglobulin and mucin domain containing-3; TKI, tyrosine kinase inhibitor

Monotherapies with ICIs

Nivolumab, a monoclonal antibody directed against PD-1, was first tested in HCC in the phase 1/2 CheckMate 040 study, which included 262 patients with HCC with or without previous exposure to sorafenib. Nivolumab produced an ORR of 14% by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (18% by modified RECIST) with a median response duration of 17 months (95% CI: 6–24).^[68] The study reported a median OS of 15.6 months and a safety profile similar to previous trials with nivolumab. As a consequence, the FDA granted accelerated approval to nivolumab for patients with advanced-stage HCC previously treated with sorafenib (Table 1). The following phase 3 CheckMate 459 study tested nivolumab as first-line treatment against sorafenib in patients with advanced HCC who had not received systemic treatment before.^[69] They were randomized to receive either nivolumab at 240 mg IV once every 2 weeks ($n = 371$) or sorafenib with the standard dose of 400 mg bid ($n = 372$). Surprisingly, the study did not meet its primary endpoint of improving OS, although patients treated with nivolumab had a numerically superior OS compared with sorafenib (median OS for nivolumab 16.4 months vs. 14.7 months for sorafenib; HR = 0.85 [95% CI: 0.72–1.02]; $p = 0.0752$). Correspondingly, the median OS rates at 12 months and 24 months were higher for nivolumab than for sorafenib (60% vs. 55% and 37% vs. 33%). The observed benefit was independent of the PD-L1 status and present across most predefined subgroups. Although the ORR was higher in the nivolumab (15%) than in the sorafenib arm (7%), the median progression-free survival (PFS) was similar between both arms (3.7 months for nivolumab and 3.8 months for sorafenib). In terms of safety, nivolumab showed a less toxic profile than sorafenib with fewer grade 3/4 treatment-related adverse events (trAEs) and fewer trAEs leading to discontinuation. Following an assessment of accelerated approvals for ICIs by the FDA, which recommended against upholding the approval of nivolumab, the manufacturer of nivolumab (Bristol Myers Squibb) decided to withdraw its indication as post-sorafenib monotherapy in HCC from the US market.^[70]

Pembrolizumab, another anti-PD-1 monoclonal antibody, suffered a similar fate: After a successful Keynote-224 phase 2 trial,^[71] it was approved by the FDA for advanced-stage HCC previously treated with sorafenib (Table 1). However, the subsequent Keynote-240 phase 3 trial failed to meet its primary endpoints.^[72] Keynote-224 tested pembrolizumab in 104 patients with advanced HCC who had progressed on sorafenib. It reported an ORR of 17% (RECIST v1.1), a PFS of 4.9 months, and a median OS of 12.9 months. There were no new safety signals. Unlike CheckMate 459, Keynote-240 evaluated pembrolizumab in the second-line setting, randomizing

TABLE 1 Past clinical trials on systemic immunotherapy in HCC that resulted in regulatory approval

Trial name	Treatment arms	Line of therapy	Primary endpoint	ORR	PFS	OS
CHECKMATE 040	Nivolumab ^a single arm	Second	ORR	15%	N/A	N/A
CHECKMATE 040	Nivolumab + ipilimumab ^b single arm	Second	ORR	32%	N/A	N/A
IMbrave150	Atezolizumab + bevacizumab vs. sorafenib	First	OS and PFS	29.8 vs. 11.3%	6.8 vs. 4.3 months	19.2 vs. 13.4 months (HR 0.66)
KEYNOTE 224	Pembrolizumab ^b single arm	Second	ORR	17%	N/A	N/A

Abbreviations: N/A, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

^aInitial regulatory approval by the U.S. Food and Drug Administration (FDA) has been withdrawn by the manufacturer. No approval by the European Medicines Agency.

^bRegulatory approval by the FDA but not the European Medicines Agency.

413 patients 2:1 to receive either pembrolizumab at 200 mg IV once every 3 weeks ($n = 278$) or placebo ($n = 135$). The study was designed to measure both OS and PFS as primary endpoints and reported a median OS of 13.9 months (95% CI: 11.6–16.0) for pembrolizumab versus 10.6 months (95% CI: 8.3–13.5) for placebo (HR = 0.781 [95% CI: 0.611–0.998]; $p = 0.0238$) and a median PFS of 3.0 months for pembrolizumab (95% CI: 2.8–4.1) versus 2.8 months for placebo (95% CI: 1.6–3.0) at final analysis (HR = 0.718 [95% CI: 0.570–0.904]; $p = 0.0022$). These co-primary endpoints just missed the predefined threshold for statistical significance ($p = 0.0174$ for OS and $p = 0.002$ for PFS), resulting in a formally negative study and no approval for pembrolizumab monotherapy outside the USA. Regarding safety, the known side effects were recorded with grade 3 or higher adverse events being slightly more frequent in the pembrolizumab than in the placebo group (147 [52.7%] vs. 62 [46.3%]; treatment-related 52 [18.6%] vs. 10 patients [7.5%]). KEYNOTE-394 was a phase 3 trial evaluating pembrolizumab against placebo in Asia in 453 patients with advanced HCC previously treated with sorafenib (randomized 2:1). Recently, the study reported a significantly improved OS (HR = 0.79 [95% CI: 0.63–0.99]; $p = 0.0180$), PFS (HR = 0.74 [95% CI: 0.60–0.92]; $p = 0.0032$), and ORR (estimated difference 11.4% [95% CI: 6.7–16.0]; $p = 0.00004$) for pembrolizumab versus placebo. The median OS was 14.6 versus 13.0 months, PFS 2.6 versus 2.3 months, and ORR 13.7% versus 1.3%.^[73]

Although the phase 3 studies CheckMate 459 and KEYNOTE-240 did not yield the required proof that single-agent use of either nivolumab or pembrolizumab provides a benefit in advanced HCC, they showed that these agents appear to have some antitumor activity in a subgroup of patients reflected in an ORR of 14%–17% and response durations of >1 year. Therefore, they remain a later line treatment option in patients with advanced HCC who have progressed on the available TKIs and have not received a PD1/PD-L1 inhibitor previously.

Further proof that single-agent PD1/PD-L1 inhibition has antitumor activity has been provided by the HIMALAYA phase 3 trial, which has tested a single, high-priming dose of tremelimumab, an anti-CTLA-4 antibody, added to durvalumab, an anti-PD-L1 antibody (STRIDE), or durvalumab alone in comparison to sorafenib as first-line treatment in 1171 patients with advanced HCC (NCT03298451). Monotherapy with durvalumab met the objective of OS noninferiority to sorafenib (HR = 0.86 [96% CI: 0.73–1.03]) while being less toxic (12.9% grade 3/4 trAEs with durvalumab vs. 36.9% with sorafenib).^[74]

Regarding anti-CTLA-4 monotherapy, the study 22 (phase 1/2) found a median OS of 15.1 months (95% CI: 7.7–24.6) and a median PFS of 2.0 months (95% CI: 1.8–5.4) with a manageable safety profile for tremelimumab monotherapy in patients previously treated

with sorafenib after intolerable toxicity or rejection of sorafenib. However, the combination of tremelimumab with durvalumab showed an overall better benefit–risk ratio.^[75] Moreover, early expansion of Ki67⁺CD8⁺ T cells was associated with response to either treatment alone or the combination.

Tislelizumab is another anti-PD1-antibody that is currently tested as first-line in unresectable HCC against sorafenib in the RATIONALE 301 phase 3 trial^[76] (NCT03412773) (Table 2). This is currently the last trial that could bring a single-agent checkpoint inhibitor regimen toward global regulatory approval. Overall, the attention and expectations have shifted to combination treatments.

Dual therapies combining ICIs with anti-VEGF antibodies

Following the positive outcome of the IMbrave150 phase 3 trial,^[15] a landmark study, the strategy of combining a PD1/PD-L1 inhibitor with a VEGF inhibition has been established as a new paradigm for the treatment of advanced HCC. Initially, a phase 1b study of atezolizumab plus bevacizumab in patients with untreated advanced HCC had demonstrated good safety and promising antitumor activity with an ORR of 36% and a median PFS of 7.3 months by RECIST 1.1 (95% CI: 5.4–9.9 months).^[77] The IMbrave150 trial then tested the combination of atezolizumab and bevacizumab versus sorafenib in 501 patients with advanced HCC who had not received systemic treatment previously and who were randomly assigned (2:1) to either study arm.^[15] Patients received either atezolizumab at 1200 mg IV plus bevacizumab at 15 mg/kg IV once every 3 weeks ($n = 336$) or sorafenib at 400 mg bid ($n = 165$) until unacceptable toxicity or loss of clinical benefit. The study assessed the co-primary endpoints OS and PFS by independent review and RECIST 1.1 in the intention-to-treat population. At the data cutoff for the first analysis on August 29, 2019, and a median follow-up duration of 8.6 months (8.9 months in the combination arm and 8.1 months in the sorafenib arm), treatment with atezolizumab and bevacizumab reduced the risk of death by 42% in comparison with sorafenib (HR = 0.58 [95% CI: 0.42–0.79]; $p < 0.001$). The median OS was not reached for atezolizumab plus bevacizumab, and was 13.2 months for sorafenib (95% CI: 10.4 months to not reached). The median PFS per RECIST 1.1 with 6.8 months was significantly longer for atezolizumab plus bevacizumab (95% CI: 5.7–8.3) than for sorafenib with 4.3 months (95% CI: 4.0–5.6; HR = 0.59 [95% CI: 0.47–0.76]; $p < 0.001$). The ORRs were 27.3% (95% CI: 22.5%–32.5%) for atezolizumab and bevacizumab versus 11.9% for sorafenib (95% CI: 7.4%–18%; $p < 0.001$). The frequency of grade 3–4 adverse events was similar with 56.5% for atezolizumab and bevacizumab versus 55.1% for sorafenib. Importantly, the

TABLE 2 Current clinicals trials on systemic immunotherapy in advanced HCC

Trial	Identifier	Phase	BCLC stage	Treatment arms	Primary endpoint(s)	Setting
CheckMate 9DW	NCT04039607	Phase 3	C	Nivolumab + ipilimumab Sorafenib or lenvatinib	OS	First-line
COSMIC-312	NCT03755791	Phase 3	B or C	Cabozantinib + atezolizumab Sorafenib Cabozantinib	PFS per RECIST 1.1 OS	First-line
HIMALAYA	NCT03298451	Phase 3	B or C	Durvalumab Durvalumab + trevelimumab 2 regimens Sorafenib	OS	First-line
LEAP-002	NCT03713593	Phase 3	B or C	Lenvatinib + pembrolizumab Lenvatinib	PFS per RECIST 1.1 OS	First-line
RATIONALE-301	NCT03412773	Phase 3	B or C	Tislelizumab Sorafenib	OS	First-line
N/A	NCT03764293	Phase 3	B or C	Camrelizumab (SHR-1210) + apatinib Sorafenib	PFS OS	First-line
Bayer 19497	NCT03347292	Phase 1b/2	B or C	Regorafenib + pembrolizumab	Safety	First-line
GOING	NCT04170556	Phase 1/2	BCLC C	Regorafenib (monotherapy for the first 8 weeks) + nivolumab	Safety	Second-line
ORIENT-32	NCT03794440	Phase 2/3	B or C	Sintilimab + IBI305 Sorafenib	PFS per RECIST 1.1 OS	First-line
RENOBATE	NCT04310709	Phase 2	B or C	Regorafenib + nivolumab	ORR per RECIST 1.1	First-line
N/A	NCT04183088	Phase 2	B or C	Part 1: Regorafenib + tislelizumab Part 2: Regorafenib + tislelizumab Regorafenib	Part 1: Safety Part 2: PFS per RECIST 1.1 ORR per RECIST 1.1	First-line
N/A	NCT04442581	Phase 2	B or C	Cabozantinib + pembrolizumab	ORR per RECIST 1.1	First-line
N/A	NCT03941873	Phase 1/2	B or C	Phase 1: Sitravatinib Sitravatinib + tislelizumab Phase 2: Sitravatinib Sitravatinib + tislelizumab	Phase 1: Safety Phase 2: ORR per RECIST 1.1	First- and later line

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.

IMbrave150 trial excluded patients with complications due to portal hypertension, such as esophageal/gastric varices at high risk of bleeding, moderate to severe ascites, or a previous episode of HE.

The IMbrave150 trial has led to the approval of the combination of atezolizumab and bevacizumab as first-line treatment for unresectable HCC in the USA and Europe (Table 1), which has become the new standard of care replacing the TKIs sorafenib and lenvatinib. The reason behind its success lies in the likely synergistic antitumor activity of PD-L1 inhibition, which activates the immune

response (particularly T-effector cells), and VEGF inhibition, which reduces VEGF-mediated immunosuppression and promotes T-cell infiltration in the TME.^[78]

Similar to the IMbrave150 trial, the ORIENT-32 phase 2/3 trial tested sintilimab (anti-PD1 antibody) plus IBI305 (a bevacizumab biosimilar) versus sorafenib in systemic treatment-naïve Chinese patients (NCT03794440). Sintilimab/IBI305 showed both an improved median OS and PFS relative to sorafenib (median OS: not reached vs. 10.4 months; median PFS: 4.6 vs. 2.8 months) with acceptable toxicity.^[79]

Dual therapies combining PD-1 and CTLA-4 inhibitors

Having been established in other cancer entities such as melanoma, the strategy of combining inhibitors of different immune checkpoints such as PD-1 and CTLA-4 is currently being explored in advanced HCC. The first clinical data came from the CheckMate 040 trial, which tested nivolumab and ipilimumab, an anti-CTLA-4 antibody, in 148 patients with advanced HCC who had progressed on sorafenib.^[80] The study had three arms: arm A with nivolumab at 1 mg/kg IV and ipilimumab at 3 mg/kg IV once every 3 weeks for four doses followed by nivolumab 240 mg IV once every 2 weeks ($n = 50$), arm B with nivolumab at 3 mg/kg IV and ipilimumab at 1 mg/kg IV once every 3 weeks for four doses followed by nivolumab 240 mg IV once every 2 weeks ($n = 49$), or arm C with nivolumab 3 mg/kg IV once every 2 weeks and ipilimumab 1 mg/kg IV once every 6 weeks ($n = 49$). The trial reported an ORR of 31% with a median duration of response (DOR) of 17 months, a disease control rate (DCR) of 49%, and a 24-month OS rate of 40%. Patients in arm A experienced the longest median OS with 23 months. The side-effect profile was acceptable with 37% of patients having grade 3/4 treatment-related adverse events. However, more than half of patients needed systemic steroids to manage side effects. Overall, the trial's results were regarded as a success and led to the approval of the combination of nivolumab and ipilimumab by the FDA (as used in the regimen of arm A; Table 1). Furthermore, the combination is currently being tested in the CheckMate 9DW phase 3 trial in the first line against sorafenib or lenvatinib in advanced HCC (CheckMate 9DW, NCT04039607).

Similarly, the combination of durvalumab and tremelimumab showed robust activity with an ORR of 17.5% in unresectable HCC.^[81] In the HIMALAYA trial, STRIDE achieved a significantly improved OS over sorafenib (HR = 0.78 [96% CI: 0.65–0.92]; $p = 0.0035$), while offering better tolerability (25.8% grade 3/4 trAEs with STRIDE vs. 36.9% with sorafenib).^[74]

Dual therapies combining checkpoint with multikinase inhibitors

Combining ICIs with TKIs instead of anti-VEGF antibodies may present an alternative to antibody-mediated VEGF inhibition. Several such combinations are currently being explored (Table 2).

The combination of cabozantinib and atezolizumab is being evaluated in the multicohort COSMIC-021 phase 1b trial in advanced solid tumors, including HCC (cohort 14; NCT03170960). In addition, it is being tested in the first-line setting in patients with advanced HCC against sorafenib in the COSMIC-312 phase 3 trial^[82] (NCT03755791). Here, cabozantinib monotherapy is additionally compared with sorafenib as a secondary

outcome measure. Patients are randomized 6:3:1 to cabozantinib 40 mg qd and atezolizumab 1200 mg IV q3w, sorafenib 400 mg bid, or cabozantinib 60 mg qd. OS and PFS are measured as co-primary endpoints. Pending peer-reviewed publication, the study's sponsor communicated in a press release that the trial demonstrated a significantly improved PFS for the combination treatment (HR = 0.63 [99% CI: 0.44–0.91]; $p = 0.0012$). However, a prespecified interim analysis for OS did not reach statistical significance. Results from its final analysis are expected in early 2022.^[83]

The combination of lenvatinib and pembrolizumab was studied in a phase 1b trial and produced respectable results in 104 patients with unresectable HCC who had not received systemic treatment previously.^[84] The ORRs by independent imaging review were 46.0% per mRECIST (95% CI: 36.0%–56.3%) and 36.0% per RECIST 1.1 (95% CI: 26.6%–46.2%). The median DORs were 8.6 months per mRECIST (95% CI: 6.9 to not estimable) and 12.6 months per RECIST 1.1 (95% CI: 6.9 to not estimable). Median PFS was 9.3 months per mRECIST and 8.6 months per RECIST 1.1. Median OS was 22 months. A total of 67% of patients experienced grade ≥ 3 trAEs (3% grade 5). The LEAP-002 phase 3 trial is currently testing this combination against lenvatinib monotherapy^[85] (NCT03713593).

Finally, the combination of apatinib (rivoceranib, TKI) and camrelizumab (SHR1210), an anti-PD-1 antibody, is under clinical development. A phase 1 study in patients with advanced HCC reported an ORR of 50%.^[86] The combination is also currently being evaluated in a phase 3 study in comparison with sorafenib in the first-line setting in patients with advanced HCC (NCT03764293).

Further currently ongoing clinical trials are mentioned in Table 2.

Systemic treatment beyond immune checkpoint inhibition

Inhibition of the immune checkpoints PD1/PD-L1 and CTLA-4 is currently the most popular form of cancer immunotherapy. An alternative immune checkpoint is LAG-3, which inhibits T-cell activity making it a marker of T-cell exhaustion.^[14] Relatlimab is an antibody-blocking LAG-3 and it is being evaluated in combination with nivolumab in the phase 2 RELATIVITY-073 trial (NCT04567615) in advanced, ICI-naïve HCC after progression on prior TKI therapy.^[87] Furthermore, an increasing number of alternative immunotherapeutic approaches are being explored. Such interventions may prove to be efficacious where today's ICIs fail. For example, adoptive transfer of NK or T cells to boost infiltration of tumors is an approach that may benefit patients whose tumors are not infiltrated by effector immune cells.

Most immune interventions beyond classic checkpoint inhibition are still at a preclinical or early clinical

stage and include chimeric antigen receptor (CAR)-T cells, allogeneic NK cells, and oncolytic viruses (Table 3). One of the first phase 1 studies targeting glypican 3 (GPC3) reported no dose-limiting toxicity, an ORR of 16.7%, and a DCR of 50% in 6 evaluable patients with advanced GPC3+ HCC who had received at least two lines of prior systemic therapy including the combination of TKIs and PD1/PD-L1 ICI^[88] (NCT03980288). Four more phase 1 studies with CAR-T cells targeting GPC3 are currently ongoing (NCT04121273, NCT02905188, NCT03884751, and NCT05003895).

The first phase 1 trial targeting AFP is evaluating the safety and antitumor activity of autologous T cells expressing enhanced TCRs specific for AFP (AFP^{c332}T) in HLA-A2-positive subjects with advanced HCC (NCT03132792). According to a recent conference presentation, the DCR in cohort 3 was 64% (7 of 11 patients, 1 CR [complete response] and 6 SD [stable disease]) with an acceptable toxicity profile.^[89]

One phase 2 study is testing treatment with invariant NKT cells and TACE against TACE alone (NCT04011033). Furthermore, there are phase 1 trials that evaluate FT500, an allogeneic NK cell line, and FATE-NK100, donor-derived NK cells, in various cancer entities including HCC (NCT03319459, NCT04106167, and NCT03841110). In the field of oncolytic viruses, pexastimogene devacirepvec (Pexa-Vec) failed as second-line monotherapy in advanced HCC in the TRAVERSE phase 2b trial^[90] and in combination with sorafenib in the PHOCUS trial^[91] (NCT02562755; phase 3). A phase 1/2a trial is now testing Pexa-Vec in combination with nivolumab (NCT03071094).

Novel immunotherapeutic approaches hold the promise of bringing the benefits of immunotherapy to a growing number of patients. However, at this stage, success is not guaranteed, and it is open as to which strategies will supplement or even replace the current systemic agents.

IMMUNOTHERAPY FOR INTERMEDIATE-STAGE HCC

The standard of care for intermediate-stage Barcelona Clinic Liver Cancer (BCLC) B HCC is TACE with a demonstrated improvement in OS.^[92,93] TACE also appears to modulate the tumor immune response.^[94–96] TACE can enhance the antitumor immune response by decreasing Tregs and exhausted effector T cells in the tumor core, and can enhance the pro-inflammatory tumor response.^[95] The safety and feasibility of tremelimumab and ablation was assessed in patients with HCC who were ineligible for liver transplantation or surgical resection ($n = 32$).^[97] Patients received tremelimumab every 4 weeks for six doses. On day 36 they underwent subtotal radiofrequency ablation or TACE. Confirmed partial response was noted in 5 of 19 evaluable patients, and median OS was 19.4 months. In those patients who had a clinical benefit, 6-week tumor biopsies demonstrated an increase in CD8⁺ T cells. Hence, there is mechanistic rationale for the combination of immunotherapy and locoregional therapy for intermediate-stage HCC.

Combination treatments

The IMbrave 150 trial also provided some data on patients with intermediate stage HCC, as it enrolled those with unresectable HCC.^[15] However, the proportion of patients with intermediate stage was fairly small (~15%). Thus, it does not suffice for a final assessment of the efficacy of atezolizumab and bevacizumab in this subgroup, particularly in comparison to TACE. To address this open question, the ABC-HCC trial, a large investigator-initiated phase 3b trial, is testing atezolizumab and bevacizumab against TACE in patients with intermediate HCC (NCT04803994; Table 4).^[98] Another large investigator-initiated phase 3 trial in this patient

TABLE 3 Current clinical trials on gene and cell-based systemic treatments

Identifier	Phase	BCLC stage	Treatment arms	Primary Endpoint(s)	Setting
NCT02905188	Phase 1	C	• CAR-GPC3 T cells	• Safety	Advanced stage
NCT03980288	Phase 1	C	• CAR-GPC3 T cells	• Safety	Advanced stage
NCT05003895	Phase 1	C	• CAR-GPC3 T cells	• Safety	Advanced stage
NCT03132792	Phase 1	C	• Autologous genetically modified AFP ^{c332} T cells	• Safety	Advanced stage
NCT04011033	Phase 2	C	• iNKT cells + TACE	• OS • PFS • DCR	Advanced stage
NCT03319459	Phase 1	C	• FATE-NK100	• Safety	Advanced stage
NCT03841110	Phase 1	C	• FT500 (allogeneic NK cells)	• Safety	Advanced stage
NCT03071094	Phase 1/2	C	• Pexastimogene devacirepvec + nivolumab	• Safety • ORR	Advanced stage

Abbreviations: DCR, disease control rate; iNKT cells, invariant natural killer T cells.

population is RENOTACE, which will test the combination of regorafenib and nivolumab against TACE (NCT04777851; Table 4). Both trials have the potential to be practice-changing and to establish systemic treatment in the intermediate stage. However, they face the challenge of comparing two different treatment modalities with different criteria for evaluating therapeutic success. In this regard, the ABC-HCC trial is proposing a novel kind of primary endpoint coined time-to-failure of treatment strategy, which measures the time until either treatment strategy (systemic treatment or TACE) is discontinued by the investigator due to failure.^[98] RENOTACE, in contrast, measures PFS per mRECIST as primary endpoint, which is established as a surrogate endpoint for OS and accounts for devascularized tumor tissue.

Rather than being exclusive, another option is to add systemic therapy to TACE in the intermediate stage (Figure 3). Four phase 3 trials are currently exploring this approach (Table 4): TALENTACE is testing the combination of atezolizumab, bevacizumab and TACE (NCT047126430)^[99]; LEAP-012 is testing the combination of lenvatinib, pembrolizumab, and TACE^[100] (NCT04246177); EMERALD-1 is testing the combination of durvalumab with or without bevacizumab and TACE^[101] (NCT03778957); and CheckMate 74W is testing the combination of nivolumab with or without ipilimumab and TACE^[102] (NCT04340193)—all in comparison to TACE as the standard of care. In addition, the TACE-3 trial is comparing the combination of nivolumab and TACE/transarterial embolization (TAE) with TACE/TAE (NCT04268888).

IMMUNOTHERAPY FOR EARLY-STAGE HCC

The current treatment options for patients with very early-stage (BCLC 0) and early-stage (BCLC A) HCC are surgical resection, ablation, and transplantation.^[54] The primary objective of these therapies in very early and early-BCLC stage HCC is cure. The 5-year survival with surgical treatments is approximately 70%–80%.^[3] However, recurrence following surgical resection remains a significant challenge. The 5-year rate of recurrence following surgical resection can be as high as 70%.^[103] Presence of satellite lesions, cirrhosis, and thrombocytopenia are associated with recurrence.^[103] Moreover, several immune factors are associated with poor outcomes following resection. Accumulation of immunosuppressive elements such as Tregs and MDSCs or attenuation of cytotoxic elements such as INF- γ , high PD-L1 expression is associated with a higher risk of recurrence.^[29,104–106] High density of CD3+ and CD8+ T cells in the tumor core and margin and the corresponding Immunoscores, a score based on numeration of CD3+ and CD8+ lymphocytes in the tumor core and margin,^[107] are associated with a significantly low rate

TABLE 4 Ongoing and planned clinical trials combining or comparing systemic immunotherapy with TACE

Trial/Identifier	Phase	BCLC stage	Treatment arms	Primary endpoint(s)	Setting
ABC-HCC/NCT04803994	Phase 3	B	• Atezolizumab + bevacizumab • TACE	• Time to failure of treatment strategy	First-line
CheckMate 74W/NCT04340193 (not yet recruiting)	Phase 3	B	• Nivolumab + ipilimumab + TACE • Nivolumab + TACE • TACE	• Time to TACE progression • OS	First-line
EMERALD-1/NCT03778957	Phase 3	B	• Durvalumab + TACE • Durvalumab + bevacizumab + TACE • TACE	• PFS per RECIST 1.1	First-line
LEAP-012/NCT04246177	Phase 3	B	• Lenvatinib + pembrolizumab + TACE • TACE	• PFS per RECIST 1.1 • OS	First-line
RENOTACE/NCT04777851 (not yet recruiting)	Phase 3	B	• Regorafenib + nivolumab • TACE	• PFS per mRECIST	First-line
TACE-3/NCT04268888	Phase 2/3	B	• Nivolumab + TACE/TAE • TACE/TAE	• Time to TACE progression • OS	First-line
TALENTACE	Phase 3	B	• Atezolizumab + bevacizumab + TACE • TACE	• TACE-PFS • OS	First-line

Abbreviation: TAE, transarterial embolization.

HCC	Stage	Locoregional/Surgical Treatment	ICI-based Combination
	Very early stage (BCLC 0) or Early stage (BCLC A)	Adjuvant - Ablation - Resection Neoadjuvant - Ablation - Resection	Nivolumab Pembrolizumab Atezolizumab + Bevacizumab Durvalumab ± Bevacizumab Nivolumab + Cabozantinib Pembrolizumab Ipilimumab + Nivolumab Nivolumab ± CCR2/5 inhibitor or Anti-IL-8 Cemiplimab
	Intermediate stage (BCLC B)	Neoadjuvant - Liver transplantation Locoregional Therapy - TACE	Lenvatinib + Pembrolizumab Lenvatinib + Pembrolizumab Durvalumab ± Bevacizumab Ipilimumab + Nivolumab Atezolizumab + Bevacizumab Nivolumab Regorafenib + Nivolumab Atezolizumab + Bevacizumab VS
	Advanced stage (BCLC C)		VEGF Inhibitors + ICI Atezolizumab + Bevacizumab* Sintilimab + IBI305 Multi-tyrosine kinase inhibitors + ICI Atezolizumab + Cabozantinib Pembrolizumab + Cabozantinib Pembrolizumab + Lenvatinib Camrelizumab + Apatinib Tislelizumab + Regorafenib Nivolumab + Regorafenib Pembrolizumab + Regorafenib Sitravatinib + Tislelizumab ICI Durvalumab + Tremelimumab** Nivolumab + Ipilimumab Tislelizumab

FIGURE 3 Strategies integrating ICI based on HCC stage currently under investigation. Combination strategies integrating ICI with surgical, locoregional, or other systemic therapies across HCC stages are depicted. *Regulatory approval in the first-line setting for advanced stage HCC. **Met primary endpoint of OS in the first-line setting for advanced-stage HCC. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CCR2, chemokine (C-C motif) receptor 2 [Correction added April 7, 2022 after first online publication: An earlier version of Figure 3 was mistakenly published in the article and was corrected. We apologize to the authors and our readers for this error.]

of recurrence following surgical resection for HCC.^[108] Hence, there is a rationale to integrate immunotherapy in the adjuvant and neoadjuvant setting to increase the chance of cure following surgical treatments for HCC.

Adjuvant treatment

Many adjuvant approaches using systemic treatment have failed to provide benefit after curative hepatic resection or ablation of HCC. Notably, sorafenib failed in this regard in the STORM trial.^[109] CIK cells are a mixture of T lymphocytes that are expanded *ex vivo* with cytokines. In an open-label, phase 3 trial that included 230 patients with HCC treated by surgical resection or ablation, the median survival in patients who received CIK was 44 months compared with 30 months for placebo (HR = 0.63; 95% CI 0.43–0.94; $p = 0.010$). Four phase 3 trials in patients who have

undergone curative surgery or ablation are currently ongoing (Table 5 and Figure 3): CheckMate 9DX with nivolumab^[110] (NCT03383458), KEYNOTE-937 with pembrolizumab^[111] (NCT03867084), IMbrave 050 with atezolizumab and bevacizumab^[112] (NCT04102098), and EMERALD-2 with durvalumab with or without bevacizumab^[113] (NCT03847428).

Neoadjuvant treatment

Theoretically, in the neoadjuvant setting, ICI can leverage the higher levels of tumor antigens present in the primary tumor and can promote expansion of clones of tumor-specific T lymphocytes that are already present in the TME.^[114] In preclinical models of triple-negative breast cancer, mice that underwent neoadjuvant regulatory T-cell depletion using diphtheria toxin or anti-CD25 had a significantly improved long-term survival

TABLE 5 Current clinical trials on adjuvant systemic immunotherapy after surgery or ablation

Trial	Identifier	Phase	BCLC stage	Treatment arms	Primary endpoint(s)	Setting
CheckMate 9DX	NCT03383458	Phase 3	0 or A	• Nivolumab • Placebo	• RFS	Adjuvant
EMERALD-2	NCT03847428	Phase 3	0 or A	• Durvalumab + bevacizumab • Durvalumab • Placebo	• RFS	Adjuvant
IMbrave050	NCT04102098	Phase 3	0 or A	• Atezolizumab + bevacizumab • Active surveillance	• RFS	Adjuvant
KEYNOTE-937	NCT03867084	Phase 3	0 or A	• Pembrolizumab • Placebo	• RFS • OS	Adjuvant

(> 250 days) compared with control ($\leq$ 100 days).^[115] In a subsequent study, the same investigators demonstrated that a short duration between first administration of neoadjuvant immunotherapy and resection of the primary tumor was necessary for optimal efficacy, while a longer duration abrogated the efficacy of immunotherapy in the neoadjuvant setting.^[116] In a single-arm phase 1b study, the feasibility of neoadjuvant cabozantinib and nivolumab in HCC was assessed.^[117] The study enrolled 15 patients who were unresectable, and 12 of these had successful margin-negative resection following neoadjuvant therapy with cabozantinib and nivolumab. Moreover, this combination appeared to modulate the TIME, as responders had an enrichment of CD138⁺ plasma cells and a distinct spatial rearrangement of B cells, with B cells being in close proximity to other B cells. These results suggest a role for a coordinated B-cell antitumor immune response.

Although this is still a nascent topic, there are several early-phase clinical trials being conducted (Table 6 and Figure 3). The NIVOLEP trial is assessing nivolumab before and after electroporation (NCT03630640). There are several trials investigating immunotherapy in neoadjuvant setting for potentially resectable HCC: CaboNivo, the combination of cabozantinib and nivolumab before hepatic resection in locally advanced/borderline resectable HCC^[118] (NCT03299946); a phase 2 trial investigating pembrolizumab before and after curative ablation or resection (NCT03337841); and multiple trials assessing the combination of ipilimumab and nivolumab (NCT03222076, NCT0351087, and NCT03682276).

Immunotherapy is also being evaluated in the neoadjuvant setting in liver transplantation. PLENTY202001 is testing the combination of lenvatinib and pembrolizumab before liver transplantation in patients with HCC exceeding the Milan criteria (NCT04425226; Figure 3). The use of ICIs in the transplant setting carries significant safety risks, as it may cause allograft rejection with potentially fatal consequences.^[119] Therefore, clinical trials involving ICIs typically exclude solid organ recipients. The PLENTY202001 is a rare exception and will gather highly relevant safety information in this respect.

MANAGEMENT OF IMMUNOTHERAPY TOXICITIES

Immune-related adverse events

Immune checkpoint molecules play a key role in the context of immune homeostasis. In particular, inhibitory immune checkpoint molecules such as PD-1 or CTL-4 are essential for balancing T-cell activation and self-tolerance.^[120,121] Thus, ICIs targeting PD-1 (or its ligand PD-L1) or CTL-4 may cause a variety of immune-related adverse events (irAEs) by enhancing self-immunity. IrAEs can potentially affect every organ system and range from low-grade rash to life-threatening complications.

The risk of irAEs driven by PD-1/PD-L1 inhibition is dose-independent.^[122] A meta-analysis consisting of 12,808 patients treated with anti-PD-1/PD-L1 drugs, reported an overall incidence of irAEs of 26.82% (95% CI: 21.73–32.61) regardless of grade, 6.10% (95% CI: 4.85–7.64) grade $\geq$ 3 events, and 0.17% lethal events. In contrast to anti-PD-1/PD-L1 agents, the risk of anti-CTL-4-related irAEs is dose-dependent.^[123] According to a meta-analysis including 1265 patients, the overall incidence of anti-CTL-4-related irAEs of any grade was 72% (95% CI: 65–79). Grade $\geq$ 3 events occurred in 24% (95% CI: 18–30), lethal events in 0.86%.^[123] Regarding both anti-CTLA-4 and PD-1/PD-L1 inhibitors, the most frequently affected organ systems were the skin and the gastrointestinal tract, whereas the liver and endocrine systems were less frequently affected.^[122,123] Another meta-analysis including 21 randomized controlled phase 2/3 trials with a total of 6528 patients treated with ICIs reported rash as the most frequent all-grade irAE (13.9%; 95% CI: 10.6–18.0), and both colitis and aspartate aminotransferase (AST) elevation as the most common high-grade irAEs (1.5%; 95% CI: 0.9–2.5 and 1.5%; 95% CI: 0.7–3.4).^[124] Compared with anti-PD-1/PD-L1 agents, ipilimumab was associated with a significant higher risk of rash (all grades, relative risk [RR] = 3.94 [95% CI: 3.02–5.14] vs. RR = 1.59 [95% CI: 0.90–2.82]) and colitis (high grade, RR = 22.5 [95% CI: 6.37–79.4] vs. RR

TABLE 6 Current clinical trials on neoadjuvant systemic immunotherapy

Trial/identifier	Phase	Patient population	Treatment arms	Primary endpoint(s)	Setting
AURORA/ NCT03337841	Phase 2	<i>n</i> = 50; curative resection/ablation possible; Child-Pugh A; ECOG PS	Pembrolizumab	1-year RFS rate	Neoadjuvant & adjuvant
CaboNivo/ NCT03299946	Phase 1b	Locally advanced/borderline resectable HCC; BCLC A or B; ECOG 0-1	Cabozantinib + nivolumab	Safety	Neoadjuvant
NCT03222076	Phase 2	<i>n</i> = 30; resectable HCC; prior therapy allowed; Child-Pugh A; ECOG PS 0-1	Nivolumab + Ipilimumab	Safety	Neoadjuvant
NCT0351087	Phase 2	<i>n</i> = 40; resectable HCC; Child-Pugh A; ECOG 0-1	Nivolumab + Ipilimumab	Objective response	Neoadjuvant
NCT04123379	Phase 2	<i>n</i> = 50; resectable HCC; ECOG 0-1	Nivolumab ± CCR2/5 inhibitor or anti-IL-8	<10% viable tumor at time of surgery	Neoadjuvant
NCT03916627	Phase 2	<i>n</i> = 94; resectable HCC; ECOG 0-1	Cemiplimab	Significant tumor necrosis	Neoadjuvant
NIVOLEP/ NCT03630640	Phase 2	<i>n</i> = 50; advanced HCC treated by electroporation; BCLC A or B; ECOG ≤ 2	Nivolumab	Local RFS	Neoadjuvant & adjuvant
PLENTY202001	Phase 2	HCC beyond Milan; Child-Pugh A-B7; ECOG 0-1	Pembrolizumab + Lenvatinib No intervention	RFS	Neoadjuvant
Prime-HCC/ NCT03682276	Phase 1/2	<i>n</i> = 32; HCC ineligible for liver transplantation; Child-Pugh A; ECOG PS 0-1	Nivolumab + Ipilimumab	Safety; delay to surgery	Neoadjuvant

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

2.47 [95% CI: 0.90–6.72]).^[124] The overall incidence of lethal irAEs was 0.64%.^[124] Importantly, no HCC trials were included in these large meta-analyses. To give an overview of the safety of ICIs in patients with HCC, frequencies of irAEs reported from major clinical trials in this patient population are listed in Table 7.

Management of irAEs

Hepatologists face several challenges in diagnosing and managing irAEs, since they are associated with a broad range of complicating factors in the context of HCC. First, liver cirrhosis itself leads to progressive immune dysfunction including both immune deficiency and systemic inflammation.^[125] Thus, the liver-related immune homeostasis is already severely compromised in these patients. Second, cirrhosis-driven hepatic and extra-hepatic complications may overlap with or exacerbate symptoms caused by irAEs, thereby hampering their early and rapid diagnosis, which is mandatory regarding the outcome of potentially life-threatening events.^[126] Thus, careful selection and evaluation of patients with HCC before ICI therapy should be performed.^[126]

In general, the management of irAEs is based on three pillars. First, close monitoring is mandatory, including weekly clinical controls up to hospitalization depending on the severity of events. Importantly, patients with high-grade irAEs should be referred to a specialized center already at an early stage. This is particularly important in patients with liver cirrhosis, as the differential diagnosis between cirrhosis-associated complications and irAEs can be challenging, and premature termination of an effective antitumor therapy or initiation of a steroid therapy in patients with cirrhosis may have severe consequences.^[126]

Second, temporary interruption or permanent discontinuation of ICI therapy depending on the type and severity of irAEs may be necessary. In general, permanent discontinuation of ICI therapy should be considered for irAEs of grade ≥ 3 , apart from PD-1/PD-L1-driven rash, nephritis, adrenal insufficiency and hypothyroidism, which resolve within 1 month after discontinuation.^[126] However, re-exposure to ICI therapy after discontinuation is associated with a relevant risk of recurrence of irAEs: In a cohort study consisting of 93 patients treated with anti-PD-1/PD-L1 agents presenting with irAEs of grade ≥ 2 , recurrence of irAEs occurred in 22 (55%) of 40 patients, who received the same agent after discontinuation.^[127] Although recurrence of irAEs was associated with a more rapid onset of the initial irAE, the recurrent irAEs did not differ in terms of severity.^[127]

Third, administration of glucocorticoids for irAEs of grade ≥ 2 may be indicated (0.5 up to 2 mg/kg/day prednisone PO or IV depending on the type and severity of irAEs).

Cutaneous irAEs, ranging from frequently observed rash or pruritus to very less common but more severe disorders such as Stevens-Johnson syndrome, are treated with topical, oral, or intravenous glucocorticoids and topical or oral antihistamines, depending on the severity of clinical presentation.^[126] Steroids should be continued until clinical signs resolve (at least 3 days) and tapered over 1–4 weeks.^[128,129]

Regarding gastrointestinal irAEs, including particularly colitis and/or diarrhea, differential diagnosis is mandatory, especially to exclude infectious diseases and drug side effects (in particular new administration or dosage adjustments of lactulose due to HE).^[126] For grade 2, glucocorticoids can be administered; and for grade ≥ 3 , glucocorticoids should be started, and hospitalization including sigmoidoscopy/colonoscopy should be considered. In case of glucocorticoid failure, immunosuppressive therapy (such as with infliximab or vedolizumab) should be added early.^[126,130] Tapering should be done over 2–8 weeks depending on steroid response and severity of clinical presentation.^[128,129]

The diagnosis and management of immune-related hepatitis in patients with HCC undergoing ICI therapy is particularly challenging. Importantly, up to 20% of placebo-treated patients present with any grade AST elevation.^[126] Thus, early consultation of an experienced hepatologist is strongly recommended. Before diagnosing immune-related hepatitis, intrahepatic tumor progression, HBV, and/or HCV flares or newly acquired viral hepatitis, CMV (cytomegalovirus) reactivation, hepatotoxic drug side effects, cholestasis, and ascites should be excluded.^[126] In addition, a liver biopsy should be considered before steroid administration. Following diagnosis of immune-related hepatitis, oral or intravenous steroids may be administered for grade 2 and should be administered for grade ≥ 3 .^[126] After toxicity resolves, tapering should be done over 4–6 weeks.^[126,128,129]

Pneumonitis represents a potential life-threatening irAE. Therefore, the suspicion of pneumonitis should be followed by a rapid and comprehensive differential diagnosis, including exclusion of infectious etiologies, porto-pulmonary hypertension, and hepatopulmonary syndrome.^[126] For grade 2, steroids should be initiated, and tapering should be performed over 4–6 weeks.^[128] Infliximab or mycophenolate mofetil may be used after glucocorticoid failure.^[126]

Thyroid-associated irAEs include hypothyroidism and hyperthyroidism as a consequence of thyroiditis. A progressive decrease of thyroid-stimulating hormone (TSH) in combination with normal or decreased levels of thyroxine (T4) should prompt regular cortisol measurements to rule out immune-related hypopituitarism.^[129] Regarding hypothyroidism, T4 substitution is indicated only in symptomatic patients.^[129] In symptomatic hyperthyroid patients, thyroid antibodies and uptake should be measured, and administration of beta-blockers and/or carbimazole should be considered.^[129]

TABLE 7 Immune-related adverse events reported from clinical trials with ICIs in HCC

	IMbrave 150 ^[15]	CheckMate 040 ^[68]	CheckMate 040 ^[80]	KEYNOTE 224 ^[74]	KEYNOTE-240 ^[72]	NCT02519348 ^[75]
	Atezolizumab + bevacizumab	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab	Pembrolizumab	Durvalumab + tremelimumab
	Phase 3	Phase 1/2	Phase 1/2	Phase 2	Phase 3	Phase 1/2
No. of patients (intervention arm)	329	48	49	48	104	74
Dosing	1200 mg atezolizumab + 15 mg/kg bevacizumab q3w	All doses tested in the dose-escalation phase	arm A ^a	arm C ^c	200 mg pembrolizumab q3w	200 mg pembrolizumab T300 + D ^g
n (%)						
irAEs						
Any grade	226 (68.7)	N/A	N/A	N/A	15 (14.4)	51 (18.3)
Grade ≥ 3	85 (25.8)	N/A	N/A	N/A	4 y	20 (7.2)
irAEs leading to discontinuation of treatment	N/A	N/A	N/A	N/A	N/A	9 (12.2) ^h
Skin						
rash						
Any grade	64 (19.5)	15 (31)	17 (35) ^d /0 ^f	14 (29) ^a /1 (2) ^c	8 (17) ^a /0 ^c	10 (10) ⁱ
Grade ≥ 3	2 (0.6)	0	3 (6) ^d /0 ^f	2 (4) ^d /1 (2) ^c	0 ^d /0 ^f	0 ⁱ
Pruritus						
Any grade	43 (13.1) ^j	13 (27)	22 (45) ⁱ	16 (33) ⁱ	14 (29) ^j	12 (12) ^j
Grade ≥ 3	0 ^j	0	2 (4) ^j	0 ⁱ	0 ⁱ	0 ⁱ
GI tract						
Colitis						
Any grade	6 (1.8)	N/A	5 (10) ^{d,e} /2 (4) ^{b,c}	1 (2) ^{d,e} /0 ^{e,f}	1 (2) ^e /0 ^{e,f}	2 (2) ^k
Grade ≥ 3	2 (0.6)	N/A	3 (6) ^{d,e} /2 (4) ^{e,f}	1 (2) ^{d,e} /0 ^{e,f}	1 (2) ^{d,e} /0 ^{b,c}	0
Diarrhea						
Any grade	34 (10.3) ^j	15 (31)				11 (11) ^j
Grade ≥ 3	1 (0.3) ^j	1 (2)				0 ⁱ
Liver						
Hepatitis						
Any grade	43 (13.1) ^j	2 (4)	10 (20) ^d /3 (6) ^f	6 (12) ^d /2 (4) ^c	3 (6) ^d /0 ^f	3 (3)
Grade ≥ 3	23 (7.0) ^j	2 (4)	10 (20) ^d /2 (4) ^c	5 (10) ^d /2 (4) ^f	3 (6) ^d /0 ^f	3 (3)
					5 (1.9)	0
					4 (1.4)	0

TABLE 7 (Continued)

	IMbrave 150 ^[15]		CheckMate 040 ^[68]		CheckMate 040 ^[80]		KEYNOTE 224 ^[71]		KEYNOTE-240 ^[72]		NCT02519348 ^[75]	
	Atezolizumab + bevacizumab		Nivolumab		Nivolumab + ipilimumab		Pembrolizumab		Pembrolizumab		Durvalumab + tremelimumab	
	Phase 3		Phase 1/2		Phase 1/2		Phase 2		Phase 3		Phase 1/2	
Endocrine organs												
Adrenal insufficiency												
Any grade	1 (0.3)		1 (2)		9 (18) ^d /0 ^f	3 (6) ^d /0 ^f	3 (6) ^d /0 ^f	3 (3)	2 (0.7)		N/A	
Grade ≥ 3	0		1 (2)		2 (4) ^d /0 ^f	0 ^d /0 ^f	0 ^d /0 ^f	2 (2)	0 (0)		N/A	
Hypothyroidism												
Any grade	36 (10.9)		2 (4)		10 (20) ^d /0 ^f	5 (10) ^d /0 ^f	6 (13) ^d /1 (2) ^f	8 (8)	14 (5.0)		4 (5.4)	
Grade ≥ 3	0		0		0 ^d /0 ^f	0 ^d /0 ^f	0 ^d /0 ^f	0	1 (0.4)		0	
Hyperthyroidism												
Any grade	15 (4.6)		N/A		5 (10) ^d /0 ^f	4 (8) ^d /0 ^f	3 (6) ^d /0 ^f	1 (1)	9 (3.2)		3 (4.1)	
Grade ≥ 3	1 (0.3)		N/A		0 ^d /0 ^f	0 ^d /0 ^f	0 ^d /0 ^f	0	0 (0)		0	
Hypophysitis												
Any grade	N/A		N/A		2 (4) ^d /0 ^f	1 (2) ^d /0 ^f	1 (2) ^d /0 ^f	N/A	2 (0.7)		0	
Grade ≥ 3	N/A		N/A		0 ^d /0 ^f	1 (2) ^d /0 ^f	1 (2) ^d /0 ^f	N/A	1 (0.4)		0	
Lung												
Pneumonitis												
Any grade	4 (1.2)		0		5 (10) ^d /3 (6) ^f	0 ^d /0 ^f	0 ^d /0 ^f	N/A	10 (3.6)		1 (1.4)	
Grade ≥ 3	0		0		3 (6) ^d /2 (4) ^d	0 ^d /0 ^f	0 ^d /0 ^f	N/A	4 (1.4)		1 (1.4)	

Abbreviation: GI, gastrointestinal; irAE, immune-related adverse event.

^aArm A: 1 mg/kg nivolumab + 3 mg/kg ipilimumab q3w (four doses), followed by 240 mg nivolumab q2w.^bArm B: 3 mg/kg nivolumab plus 1 mg/kg ipilimumab q3w (4 doses), followed by 240 mg nivolumab q2w.^cArm C: 3 mg/kg nivolumab q2w plus 1 mg/kg ipilimumab q6w.^dirAEs that required immunosuppressive treatment.^eDiarrhea/colitis combined.^firAEs leading to discontinuation.^gT300 + D: 300 mg tremelimumab + 1500 mg durvalumab (one dose), followed by 1500 mg durvalumab q4w (this dosing regimen showed the best risk-benefit profile).^hAny adverse event resulting in discontinuation of treatment.ⁱListed as treatment-related adverse event.^jIncludes only hepatitis (diagnosis), not hepatitis (laboratory abnormality).^kIncludes autoimmune colitis and colitis.^lIncludes colitis, enterocolitis, and autoimmune colitis.

Asymptomatic patients require no specific therapy and ICI treatment should be continued.

Patients undergoing ICI therapy should receive regular testing of both TSH and free T4. Each pituitary hormone axis should be screened if central hypothyroidism is suspected.^[126] This includes cortisol (drawn at 9 a.m.), adrenocorticotropic hormone, corticotropin-releasing hormone, TSH, free T4, luteinizing hormone, follicle-stimulating hormone, oestradiol (premenopausal women), testosterone (men), insulin-like growth factor 1, and electrolytes.^[126,128,129] In addition, cranial MRI should be considered. Treatment of symptomatic patients consists of initiation of steroids (1–2 mg/kg/day of prednisone oral or intravenous depending on severity) with a tapering regimen of 1–4 weeks and hormone replacement (e.g., starting with 100 mg hydrocortisone IV and levothyroxine 0.5–1.5 µg/kg/day).^[128,129] Regarding primary adrenal insufficiency, management includes administration of hydrocortisone and, if necessary, fludrocortisone (dosage depends on severity), followed by tapering over 5–14 days depending on symptoms.^[128]

UNMET NEEDS/FUTURE DIRECTIONS

The approval and therapeutic success of the first ICIs in advanced HCC has heralded in a new era of cancer immunotherapy for this disease. Three main questions remain to be solved by the field:

1. Does immunotherapy provide a benefit in earlier disease stages?
2. Which immune interventions other than PD-1/PD-L1/CTLA-4 inhibition have antitumor activity in HCC?
3. What are the treatment options for patients who do not respond to the currently available ICIs?

Regarding the first question, several clinical trials are exploring the use of ICIs in the intermediate and early stage. In the former, it is unclear whether checkpoint inhibitor-containing regimens represent an alternative or an addition to TACE, the standard of care. The ABC-HCC and RENOTACE trials will evaluate the combinations of atezolizumab plus bevacizumab and regorafenib plus nivolumab as an alternative. ABC-HCC recruits the whole spectrum of intermediate stage disease, whereas RENOTACE focuses on patients exceeding the up-to-seven criteria (i.e., the subgroup that has a higher tumor burden and is therefore more advanced). The LEAP-012, EMERALD-1, and CheckMate 74W trials will test lenvatinib plus pembrolizumab, durvalumab (plus bevacizumab), and nivolumab (plus ipilimumab) in addition to TACE. In addition, nivolumab, pembrolizumab, atezolizumab plus bevacizumab, and durvalumab plus bevacizumab are being evaluated as adjuvant treatment after surgery or ablation. Furthermore, the first trials evaluating ICIs for neoadjuvant strategies are being conducted.

Taken together, this set of trials will investigate the efficacy and safety of immunotherapy in the early and intermediate stage from different angles and provide high-quality data that will certainly help to clarify the role of checkpoint inhibition in these settings.

Regarding the second question, the targeting of other immune checkpoints such as LAG-3, the use of engineered immune cells such as CAR-T/-NK cells and the use of oncolytic viruses are under clinical development and may produce meaningful responses in patients who are unresponsive or have stopped responding to treatment with the established ICIs.

These novel immunotherapeutic approaches may also be part of the answer to the third question. However, it is likely that a subgroup of patients such as those with an immune desert TME will benefit less from immunotherapy. For such patients, the current and future targeted agents will be highly relevant, and exploration of novel therapeutic targets should not be neglected despite the impressive achievements by immunotherapy.

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AUTHOR CONTRIBUTIONS

All authors performed the research, writing, and review of all of the drafts of this paper and approved the final version.

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