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Review Article

Treatment Options for Hepatocellular Carcinoma Using Immunotherapy: Present and Future

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Abstract

Hepatocellular carcinoma (HCC) is a common cancer, and the body's immune responses greatly affect its progression and the prognosis of patients. Immunological suppression and the maintenance of self-tolerance in the tumor microenvironment are essential responses, and these form part of the theoretical foundations of immunotherapy. In this review, we first discuss the tumor microenvironment of HCC, describe immunosuppression in HCC, and review the major biomarkers used to track HCC progression and response to treatment. We then examine antibody-based therapies, with a focus on immune checkpoint inhibitors (ICIs), monoclonal antibodies that target key proteins in the immune response (programmed cell death protein 1, anti-cytotoxic T-lymphocyte associated protein 4, and programmed death-ligand 1) which have transformed the treatment of HCC and other cancers. ICIs may be used alone or in conjunction with various targeted therapies for patients with advanced HCC who are receiving first-line treatments or subsequent treatments. We also discuss the use of different cellular immunotherapies, including T cell receptor (TCR) T cell therapy and chimeric antigen receptor (CAR) T cell therapy. We then review the use of HCC vaccines, adjuvant immunotherapy, and oncolytic virotherapy, and describe the goals of future research in the development of treatments for HCC.

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Introduction

Liver cancer is among the most common cancers worldwide, and is becoming increasingly prevalent in Western nations.[1,2] Hepatocellular carcinoma (HCC) is the main type of liver cancer, and it usually occurs due to persistent liver damage from infection by the hepatitis B virus (HBV) or hepatitis C virus (HCV), alcoholism, or metabolic syndrome.[3] The most common serum biomarker for HCC is α-fetoprotein (AFP). Tumor load, location, and comorbidities influence the choice of treatment, which may consist of transplantation, resection with percutaneous ablation, trans-arterial chemoembolization (TACE), and radio-embolization.[4]

Effective anticancer immune surveillance occurs due to the interplay between the adaptive and innate immune responses. Immune evasion occurs when there are dysfunctional interactions between the body's defense system and a tumor. More specifically, the immune system may have weakened detection of tumor-associated antigens (TAAs) or there may be an immune-suppressive tumor microenvironment (TME).[5,6] Alterations in peptide or antigen processing, post-transcriptional inactivation, epigenetics, and other changes can impair the identification of TAAs by different components of the immune system.[7] Deficient immune regulation by regulatory T cells (T_{regs}), myeloid-derived suppressor cells (MDSCs), inhibitory B cells, and M2-polarized tumor-associated macrophages (TAMs) can stimulate cancer progression. Increased regulation of co-inhibitory lymphocyte signals and increased levels of tolerogenic enzymes also contribute to cancer development and progression.[8] Targeting the body's defense system by immunotherapy is therefore a potentially effective general strategy for the treatment of many malignancies.

Liver tumors use specific ligands and receptors to enable communication of tumor cells with stromal cells, and to bypass anti-tumor immune responses.[9] Effector lymphocytes

Keywords: Hepatocellular carcinoma; Liver cancer; Immunotherapy; Vaccines.
Abbreviations: AFP, α-fetoprotein; APC, antigen-presenting cell; BsAbs, bispecific antibodies; CAR, chimeric antigen receptor; CIKs, cytokine-induced killer cells; CMs, Co-stimulatory molecules; CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DCs, dendritic cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; GPC3, glypican 3; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLA, human leukocyte antigens; HSCs, hepatic stellate cells; ICIs, immune checkpoint inhibitors; LAG3, lymphocyte-activation gene 3; LSECs, liver sinusoidal endothelial cells; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility; NK, natural killer; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; RFA, radiofrequency ablation; SPEAR, specific peptide enhanced affinity receptor; TAAs, tumor-associated antigens; TACE, trans-arterial chemoembolization; TAMs, tumor-associated macrophages; TCR, T cell receptor; TILs, tumor-infiltrating lymphocytes; TIM3, T cell immunoglobulin, and mucin domain containing-3; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden; TME, tumor microenvironment; Tregs, regulatory T cells; TSAs, tumor-specific antigens; VEGF, vascular endothelial growth factor.

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generate several co-inhibitory compounds at immune checkpoints, such as lymphocyte-activation gene 3 (LAG3), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), PD-1, T cell immunoglobulin, and mucin domain containing-3 (TIM3), and this prevents over-activation of the immune response.[10] Activated T cells and T_{regs} express high levels of CTLA-4, and this down-regulates the immune response and blocks the activation of effector T cells.[11] Activated T cells, T_{regs}, monocytes, natural killer (NK) cells, dendritic cells (DCs), and MDSCs all express programmed cell death protein-1 (PD-1), and a variety of stromal and cancer cells express programmed cell death-ligand 1 (PD-L1). PD-1 decreases the activity of effector T cells, leading to suppression of effector functions. Many studies that used specific monoclonal antibodies (mAbs) as immune checkpoint inhibitors (ICIs) demonstrated the benefits of an efficient immune response that eliminates different types of cancerous cells. ICIs can prevent the deactivation of T cells by blocking the binding of checkpoint proteins with their ligands.[12] and are the first immunotherapy drugs with demonstrated efficacy against HCC.

Tumor immunotherapy has become a promising strategy for preventing the spread, recurrence, and development of many different tumors.[13] Immunotherapy agents trigger tumor-specific immune responses and prevent immunological tolerance. Cancer immunotherapy has the potential to provide systemic and long-term anti-tumor activities, making it an appealing treatment option for metachronous and multicentric HCC. The US Food and Drug Administration (FDA) has licensed eight different ICIs that target PD-1, CTLA-4, or PD-L1 for the treatment of a variety of malignancies, including HCC.[14,15] Other immunotherapeutic methods (such as the administration of immune cells with chimeric antigen receptors, cancer vaccines, adoptive cell therapy, and specially formulated cytokines) are currently under development and offer fresh optimism for the treatment of patients with HCC.[16,17]

Immune microenvironment of HCC

Antigenicity

Antigen expression is the first event in the establishment of a T cell response to a tumor. Uncontrolled expression of cancer testis antigens and oncofetal antigens during hepatocarcinogenesis can trigger a spontaneous immune response.[18] Blood and tumor samples from HCC patients exhibit tumor-specific T-cell reactions, such as the production of $CD8^+$ T lymphocytes, and these can target AFP, melanoma-associated gene 1 (MAGE-A1), glypican 3 (GPC3), and New York esophageal squamous cell carcinoma 1 (NY-ESO1). Genetic changes during hepatocarcinogenesis may lead to amino acid modifications of proteins and the formation of cancer neoantigens.[19] These amino acid modifications may improve the peptide's ability to bind to human leukocyte antigens (HLA), attract T cells toward the novel epitope, or create novel structures with T cell receptors (TCRs), and this allows T cells to recognize the novel epitope without being blocked by immunological tolerance.[20] Many neoantigens derive from mutations of tumor suppressor proteins, such as tumor protein p53 (TP53), and are present in a variety of tumors. However, most of these novel epitopes are private neoepitopes (on a single HLA) caused by somatic mutations, and are considered to be passenger mutations.[21,22]

Next-generation sequencing (NGS) technology has allowed researchers to identify the mutational landscapes of numerous tumors.[23] The tumor mutational burden (TMB, somatic mutations per Mb) is widely employed as a proxy for neoantigens due to its correlation with the number of T cells specific for neoantigens.[24] The TMB varies widely among different types of tumors, and is low in pancreatic tumors (<1 mut/Mb) but high in many other tumors (>20 mut/Mb).[25] HCC often has a low-to-moderate TMB compared to other tumors, with a mean TMB of about 5 mut/Mb, corresponding to about 60 non-synonymous changes.[26] Theoretically, a tumor is more likely to become antigenic in the presence of a high TMB. Neoantigens are common in HCC, but their pathological significance is uncertain.

Immunological profile

The liver performs a variety of functions, such as blood transportation *via* the hepatic artery and portal vein, filtration of intestinal infectious agents, and excretion of harmful substances, and is therefore exposed to numerous foreign antigens.[27,28] The hepatic reticulo-endothelial system is comprised of sinusoids, liver sinusoidal endothelial cells (LSECs), and Kupffer cells, which present antigens to innate T-cells. This system induces an immunological reaction that is tolerogenic in healthy individuals.[29] Liver inflammation due to infection by HBV or HCV leads to the recruitment of cytokines and other immune molecules that can promote cancer proliferation.[30] Innate and adaptive immune cells in the TME and TAMs stimulate PD-1 and CTLA-4.[31] CTLA-4 blocks T-cell activation by competing with CD28 in its binding to CD80/86 on antigen-presenting cells (APC); PD-1 regulates T-cell collapse and hinders T-cell stimulation.[32] The different components of the TME function in several complex processes, such as decreasing the detection of TAAs, interacting with immunological checkpoints, and forming immune suppressive cells that provide a balanced and immunotolerant status.[33] The immunotolerance of HCC is also associated with the production of numerous cytokines and other regulatory molecules, including the immunosuppressive transforming growth factor beta (TGF-β).[34]

Immune cell microenvironment

The liver also down-regulates immune system activity, and this promotes tolerance to foreign antigens that are benign, such as those in the diet.[35,36] The maintenance of a tolerogenic environment in humans requires interactions of non-parenchymal liver cells, such as Kupffer cells, LSECs, and hepatic stellate cells (HSCs). Kupffer cells can function as APCs in conjunction with LSECs and HSCs.[37] Kupffer cells also produce inhibitory molecules, including indoleamine 2,3-dioxygenase (IDO), prostaglandins, and interleukin 10 (IL-10),[38] and increase the activation of T_{regs}.[39] PD-L1 has high expression in LSECs, and is responsible for the TGF-β-mediated initiation of T_{regs}. HSCs secrete hepatocyte growth factor (HGF), and this leads to the accumulation of MDSCs and T_{regs} in the liver, followed by PD-L1-mediated T cell death.[40–42]

The TME of HCC contains a mixture of cancer cells, cancer-associated fibroblasts, and non-parenchymal hepatic cells. Activation of the TME and the presence of defective tumor-infiltrating lymphocytes (TILs) are manifestations of a muted adaptive immune response to HCC.[18] Suppression of the innate immune response, expression of inhibitory receptors.[43,44] MDSC-mediated immune suppression,[45] and an increase in the number of defective NK cells contribute to the activation of the TME.[46] TGF-β controls immune cells in the liver, and promotes a balance between immune adaptability and stimulation under normal conditions.[47] However, the production of excessive TGF-β within the TME can disrupt this balance and promote cancer growth, because of its pathological effects on a range of important cell types that control innate and adaptive immunity (Fig. 1).

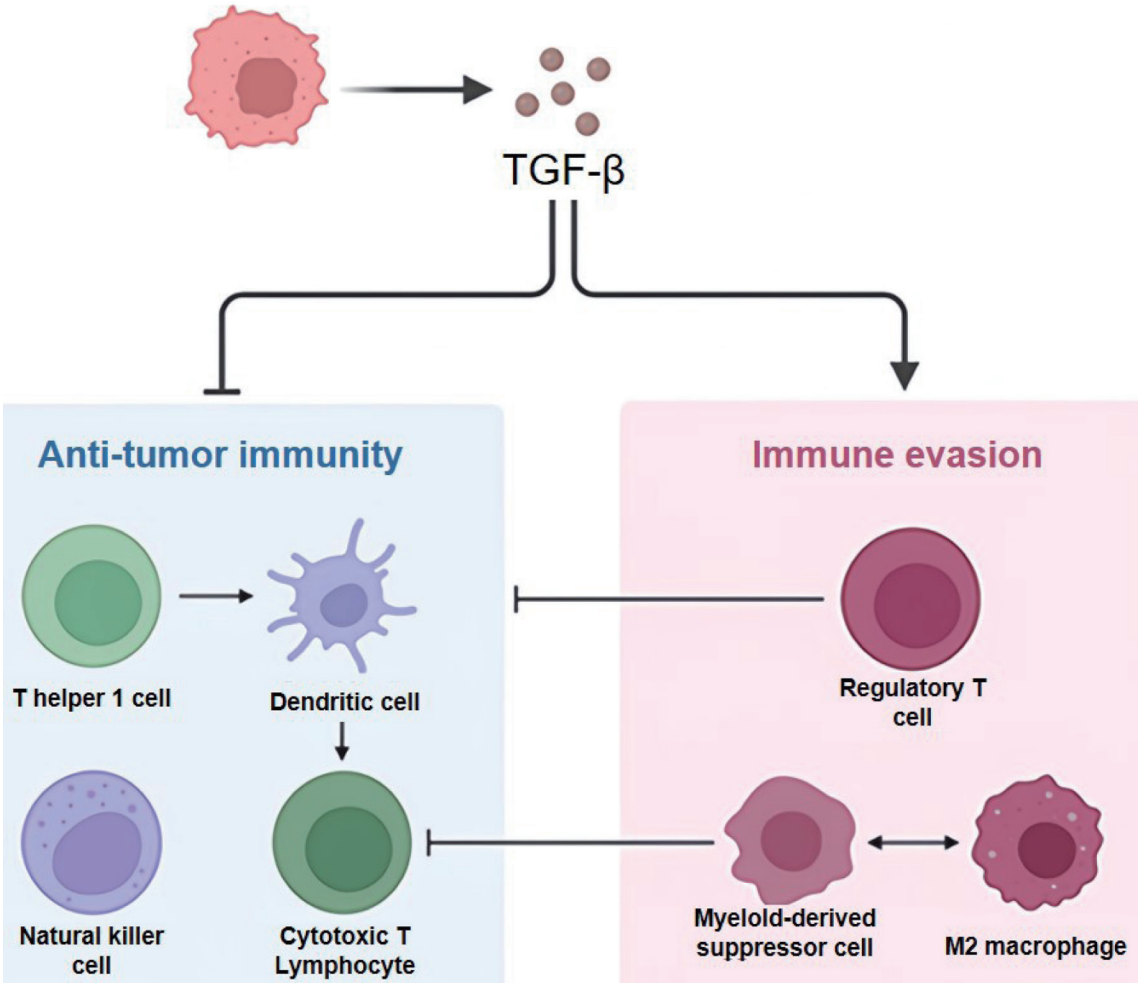

Fig. 1. Schematic illustration of the various approaches targeting TGF-β pathways for Hepatocellular carcinoma (HCC). The effect of TGF-β controls both immune evasion and antitumor immunity. TGF-β, transforming growth factor beta.

Mechanism of immunosuppression in HCC

Co-stimulatory molecules (CMs) must be produced on T cells and APCs for TCRs to bind the major histocompatibility (MHC) peptides on APCs. The downregulation of MHC class I on cancer cells hampers antigen conversion.[48,49] Additionally, the decreased development of CMs, such as B7-1 and B7-2, in HCC can cause T cell anergy.[50] In healthy humans, immune checkpoints defend against unchecked autologous immunity by blocking excessive T-cell activation. However, tumor cells can overexpress immune checkpoint compounds that bind to TCRs and prevent T cell stimulation. Thus, activation of immune checkpoint pathways in HCC compromises the effector function of cellular immune reactions.[51,52]

The impaired $CD4^+$ T cells in HCC patients can also suppress the body's defense system.[53] In the absence of appropriate CMs, expansion of MHC class II leads to inactive $CD4^+$ T cells.[54] Additionally, immunosuppressive components, such as T_{regs}.[55] MDSCs, and regulatory DCs,[56] have significant immunosuppressive effects in cancer patients. An increase in the number of immunosuppressive cells (such as T_{regs}), may promote cancer progression and lead to a poor prognosis. For example, previous research showed that HCC patients with venous metastases experienced changes in the Th1/Th2 balance in the hepatic microenvironment.[57] More specifically, abnormal immune responses in the TME are an important indicator of HCC metastasis, and these manifest as the up-regulation of Th2-like cytokines (which are immunosuppressive and anti-inflammatory) and the down-regulation of Th1-like cytokines (which are pro-inflammatory and immunogenic) in adjacent non-cancerous hepatic tissues.[58,59] Figure 2 summarizes the bidirectional interactions between HCC tumor cells and the immunosuppressive component of the TME.

Immunotherapies for HCC

The liver collects blood from the hepatic artery and portal vein, and blood from the portal vein contains nutrients and gut bacteria that are exposed to Kupffer cells (macrophages), NK cells, and innate T lymphocytes in the hepatic sinusoids.[60,61] Immune adaptability in the liver, coordinated by T_{regs} and immunosuppressive inflammatory mediators, is essential because there is a need to prevent excessive immune responses against harmless antigens and bacteria.[62] Immunotherapeutic approaches to hepatic cancer can be especially effective because the liver's defense system promotes an immunosuppressive landscape that can encourage the development and impede the immune capture of cancerous hepatic cells.

Various factors that increase liver inflammation (e.g., tox-

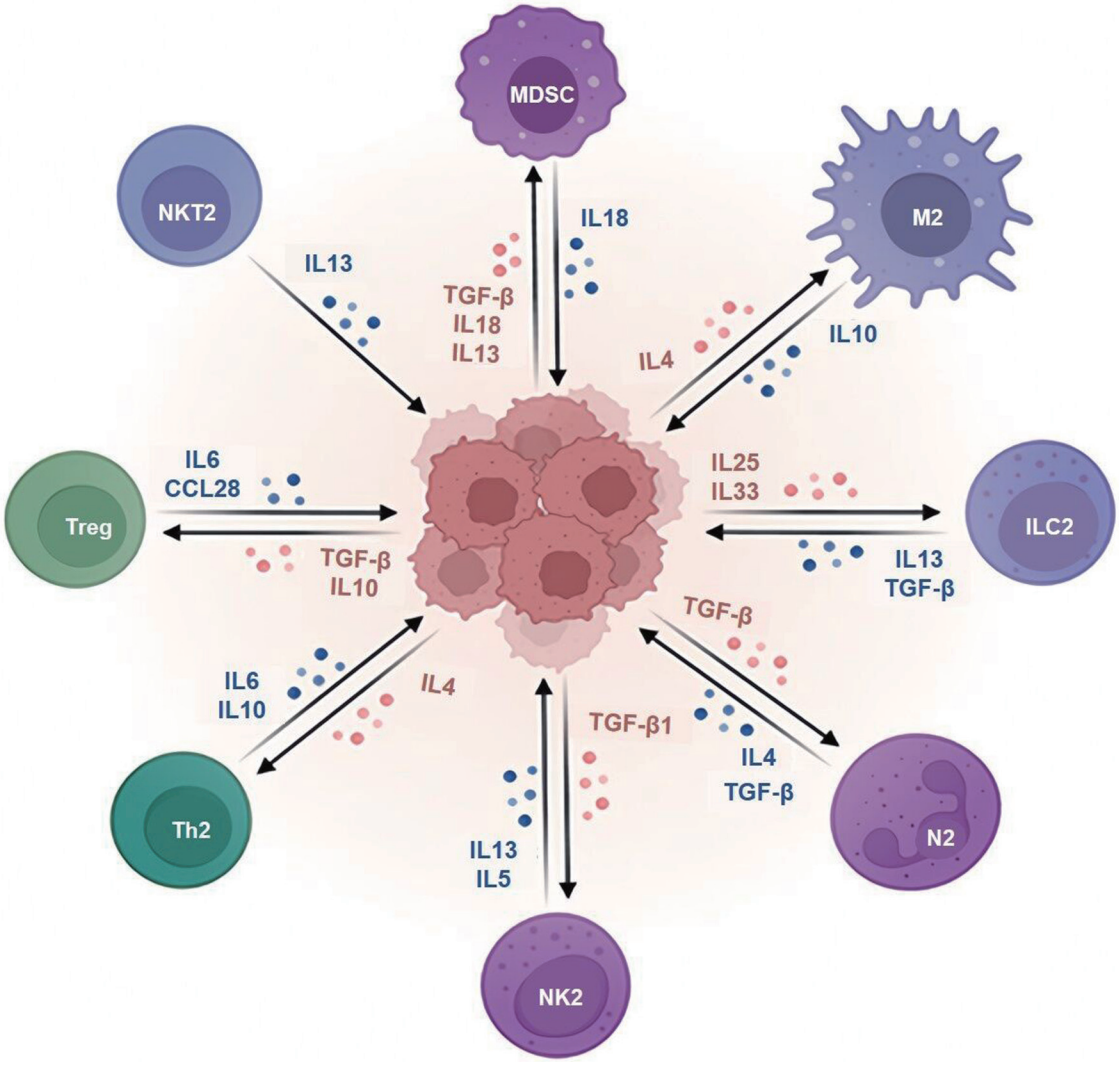

Fig. 2. The bidirectional interactions between Hepatocellular carcinoma (HCC) tumor cells (image drawn in the center) and the immunosuppressive component including MDSCs, M2 macrophages, ILCs, N2 cells, NK2, Th2, Treg, NKT of the tumor microenvironment. MDSCs, myeloid-derived suppressor cells; ILCs, Innate lymphoid cells; NK2, Natural killer; Th2, T helper 2; Treg, regulatory T cells; NKT, natural killer T.

ins, non-alcoholic hepatic steatosis, and viruses such as HBV and HCV) are also risk factors for the onset and progression of HCC. HCC can occur as a consequence of cirrhosis, which is characterized by abnormal interactions among angiogenic cells, fibroblasts, and defense cells.[63] HCC is mostly influenced by disruptions in the balance of immune-suppressive and immune-activating cells, and these alterations in the tissue microenvironment can affect prognosis. For example, *in vitro* studies showed that increased expression of T_{regs} was linked to more advanced stages of HCC.[64] Additionally, clinical studies showed that increased expression of T_{regs} was associated with a worse prognosis and an increased risk of metastasis.[65,66] T_{regs} impede the invasion of $CD8^+$ effector T cells and decrease the activities of granzyme and perforin.[64] Thus, increasing the level of checkpoint blockers (PD-1, PD-L1, T_{regs}, and MDSCs) decreases antiviral immune reactions.[67,68] In particular, PD-L1 overexpression decreases cytokine production, increases the growth of T_{regs}, and decreases effector T cell cytotoxicity.[69] PD-L1 expression is associated with a worse prognosis, a more advanced tumor stage, and an increased likelihood of tumor recurrence.[67,70] Several *in vitro* studies demonstrated that PD-L1 blockade decreased viral density, halted cancer-derived immunosuppression, and prevented cancer growth.[71]

Biomarkers for tracking responses to immunotherapies in HCC

Many ongoing clinical trials are examining the application of immune therapy for HCC (Table 1).[72–74] Some of these studies focused on PD-L1 expression as an indicator of the response to immunotherapy, and examined the effects of novel combinations of ICIs. Early studies found that PD-L1 production is associated with poor prognosis in patients with advanced HCC.[75–77] In the ORIENT-32 trial, sintilimab combined with IBI305 showed significant overall survival and progression-free survival benefits compared with first-line treatment with sorafenib in patients with unresectable HBV-related hepatocellular carcinoma.[72] Early studies found that the OS benefit of tislelizumab is non-inferior to that of sorafenib, with a higher objective response rate and more durable response, while

Table 1. Significant immunotherapy trials are still being conducted to treat advanced hepatocellular carcinoma

Trial name	Phase	Setting	Target	Intervention	References
LEAP-002	Phase III	Lenvatinib vs. the initial therapy for patients who have not received treatment	TKI, PD-1 inhibitor	Lenvatinib+pembrolizumab	74
ORIENT-32	Phase II/III	Comparison of sorafenib and first-line therapy for treatment-naive patients	PD-1 inhibitor, VEGF	Sintilimab+IBI308	72
RATIONALE-301	Phase III	Comparison of sorafenib and first-line therapy for treatment-naive patients	PD-1 inhibitor	Tislelizumab	73

CAR-T, chimeric antigen receptor-modified T cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-L1, programmed death ligand 1; TKI, a tyrosine kinase inhibitor; PD-1, programmed cell death protein.

the median progression-free survival of sorafenib is longer.[73] There are also considerable inter-institutional variations in the techniques used to assess PD-L1 production, and this may explain the disparate results of multicenter clinical trials. Ideally, cooperating institutions should establish standardized methods for defining PD-L1 production. It is also crucial to analyze sub-groups of patients with advanced HCC who have similar tumor loads, because PD-L1 expression changes as the disease progresses. The best time for immunohistochemical analysis of HCC tissue specimens and measurement of PD-L1 production is unknown; it is also unknown whether PD-L1 should be measured in stromal tissues, tumor tissues, or both. The inconsistent immuno-histochemical methods used to measure PD-L1 expression make it more difficult to interpret results that assess responses to immunotherapy.[78]

High intra-tumoral concentrations of $CD3^+$ and $CD8^+$ T cells are associated with longer recurrence-free survival, and the clinical outcomes following treatment with nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) are associated with the penetration of $CD8^+$ cells.[79] However, this relationship might not apply to patients with chronic hepatitis C, because T-cell entry generally increases in the presence of chronic viral disease. Thus, more research is required to assess the beneficial effects of ICIs in patients with HCC.[79] The TMB can also indicate a tumor's immunogenic potential.[80,81] The generally low TMB in HCC (average of 5 mut/Mb) may mean that this metric has limited application for HCC, although TMB is increasingly used as a biomarker in a variety of other malignancies. A thorough genomic profile analysis of 755 patients with late-stage HCC showed that the median overall TMB was only about 4 mut/Mb, and that there was no link between TMB and response to treatment, disease progression, or stable disease (SD). This underlines the limited usefulness of TMB as a biomarker for HCC.[82]

The organization of cancers into molecular features is contrary to individual types of indicators, because HCC tumors are variable and have unique TMEs. A study of HCC found that the most prevalent genetic "clusters" were for interferon predominance, lymphocyte deficiency, inflammation, and wound healing. An improved understanding of the role of different gene clusters in the development of particular immune escape mechanisms may help to develop more effective combination therapies.[83] This may allow researchers to specify patient groups that would benefit most from specific combination therapies according to their genetic profiles.

Antibody-based therapies for HCC

Treatments with a single ICI

Effector immune cells express different immunological checkpoints, and activation of these checkpoints prevents an overactive immune response. There are numerous endogenous inhibitors of these checkpoints, including the T cell immunoreceptor with Ig and ITIM domains (TIGIT), B and T lymphocyte attenuator, LAG3, and TIM3.[84,85] HCC exploits this checkpoint system to prevent anti-tumor immune responses.[86] ICIs are mAbs that block these checkpoints and restore immune responses. The immune response against tumors can also be enhanced by preventing the deactivation of T cells and the reactivation of immune targets. PD-1, CTLA-4, and PD-L1 are currently the main targets of approved ICIs.[87] The vast majority of immune cells (including MDSCs) mainly stimulated T-cells, T_{reg}, DCs, NK cells, and monocytes, express PD-1, which is a member of the CD28 family. PD-1, PD-L1, and PD-L2 inhibit T cells, and this activates HCC and allows it to evade the immune system.[88]

The US FDA approved nivolumab (PD-1 inhibitor) in 2017 for use as a second-line therapy for patients with severe HCC after the receipt of sorafenib, a tyrosine kinase inhibitor (TKI).[89] Several trials have also examined the use of other ICIs as treatments for HCC, and pembrolizumab (PD-1 inhibitor) and atezolizumab (PD-L1 inhibitor) were approved as clinical treatments for HCC in various countries. Nivolumab and pembrolizumab can provide an objective remission rate of 15 to 20%, and a complete recovery rate of 1 to 5%. More specifically, for the 48 patients in the CheckMate 040 trial, nivolumab treatment led to a median response duration of 17 months, and 80% of responders had a survival time of 2 years or more.[90] The KEYNOTE-240 study, a phase III trial of 413 patients that compared pembrolizumab after sorafenib with placebo after sorafenib, found a significantly longer survival time in the pembrolizumab group. Based on overall survival (OS) and progression-free survival (PFS), pembrolizumab appears to provide long-term benefit for some patients.[91] The phase III CheckMate 459 trial of 743 patients who had not used systemic medicines also evaluated nivolumab and sorafenib. In comparison with the sorafenib group, the nivolumab group had a longer median survival time.[92] The extended continuation period in the CheckMate 459 trial supported the superiority of nivolumab over sorafenib in terms of long-term survival.[93]

Tislelizumab (PD-1 inhibitor) also provided long-term benefits and was readily accepted by patients who received prior systemic treatment for unresectable HCC. Tislelizumab and sorafenib were used as a first-line treatment in a large, randomized phase III trial of adults with unresectable HCC (NCT03412773).[94] The majority of CD28 family member CTLA-4-expressing T cells and DCs that have been stimulated do so. CTLA-4 (which is related to CD28) downregulates the immune response after binding to B7.[95] Ipilimumab (CTLA-4 inhibitor) was approved in 2011 and was the first ICI ap-

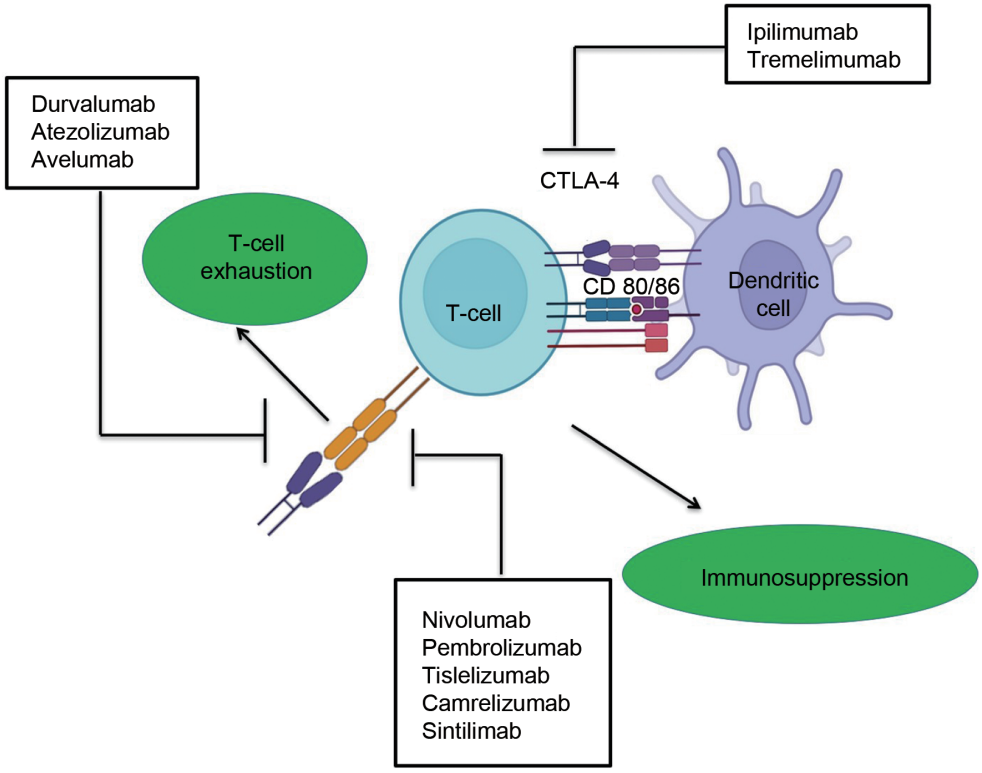

Fig. 3. Inhibitors of immune checkpoints in hepatocellular carcinoma. CTLA-4, Cytotoxic T-lymphocyte antigen 4.

proved by the US FDA for the treatment of advanced skin tumors. Tremelimumab (CTLA-4 inhibitor) was approved in 2022, and is the most recently approved ICI.[96]

Ipilimumab (CTLA-4 inhibitor and an IgG1 mAb) and tremelimumab (CTLA-4 inhibitor and an IgG2 mAb) have distinct antibody-dependent cell-mediated cytotoxicities and complement-dependent cytotoxicities.[97] Clinical trials showed that tremelimumab had potent anti-HCC effects, with a 17.6% partial response (PR) rate and a 76.4% illness control rate.[98] Some research suggests that the efficacy of CTLA-4 inhibitors can be attributed to the targeted removal of T_{regs} from cancers.[99] HCC impairs the ability of T cells to function as effector cells due to the occurrence of TIM3 on TAMs and TILs, and there is a corresponding increased expression of tumor suppressor genes by T_{regs}.[100] The excess production of TIM3 is related to a less distinguished HCC.[101] Compared to other immune system components, LAG3 is considerably more abundant on tumor-specific $CD4^+$ and $CD8^+$ TILs in individuals with HCC. Fibrinogen-like protein 1, which is produced by hepatocytes, is another soluble ligand for LAG3.[102] There is evidence that Siglec-15 (a lectin that binds to sialic acid) prevents the lysosomal destruction of CD44, leading to increased migration of liver cancer cells.[102,103] TIGIT is also affected by T-cell immunoreceptors that have immunoglobulin and ITIM domains.[104] To prevent the activation of T cells, DCs produce more IL-10 and less IL-12 by the activation of the TIGIT/CD155 pathway.[105] Recent clinical trials showed that individuals who received ICIs alone had inadequate responses. Hence, future trials should examine combinations of different ICIs with other treatments.

The combination of atezolizumab (PD-L1 inhibitor) with bevacizumab (anti-angiogenic antibody) significantly decreased the risk of death in patients with unresectable HCC.[106] The overall response rate of 46% was achieved by combining pembrolizumab with lenvatinib (TKI), and patients with unresectable HCC had a complete response (CR) rate of 11% and a partial response (PR) rate of 35%.[107] Other recent preclinical and clinical studies showed that co-administration of ICIs with radiation, radiofrequency ablation (RFA), or TACE improved therapeutic efficacy.[108,109] A phase Ib/II clinical study of patients with advanced HCC is examining the effect of camrelizumab (investigational PD-1 inhibitor) with FOLFOX4 chemotherapy.[110]

The HIMALAYA phase III trial showed that treatment with a single PD-1 inhibitor or a single PD-L1 inhibitor led to significant antitumor activity.[111] A study that administered tremelimumab (CTLA-4 inhibitor) monotherapy to patients who previously received sorafenib and experienced intolerable toxic effects or who rejected sorafenib, showed that this ICI provided demonstrable protection; however, the combination of tremelimumab with durvalumab (PD-L1 inhibitor) led to greater benefit.[112] Figure 3 lists the numerous ICIs that have been used to treat HCC and Table 2 summarizes the clinical studies that examined the use of ICIs for the treatment of HCC during the past three years.[75,90,105,112–115]

Combination treatments with two ICIs

PD-1 with CTLA-4 blockers: Treatments for advanced HCC are currently focusing on the use of CTLA-4 inhibitors and PD-1 inhibitors together. For example, the CheckMate 040 study examined the effect of ipilimumab (CTLA-4 inhibitor) with nivolumab (PD-1 inhibitor) in 148 individuals who developed advanced HCC after sorafenib treatment.[75,116] This trial found that the median response time was 17 months, the overall response rate was 31%, and the disease control rate was 49%. These results led the US FDA to approve the com-

Table 2. Hepatocellular carcinoma immune therapy with immune checkpoint blockers: A reported clinical trial

Treatment	Patients, n	ORR%	OS in mo	References
Camrelizumab	217	15 (0)	13.8	115
Pembrolizumab	278	18 (2)	13.9	105
Durvalumab	104	11 (0)	13.6	113
Tremelimumab	69	7 (0)	15.1	113
Durvalumab and tremelimumab	159	9.5–24.0 (1–2)	11.3–18.7	113
Pembrolizumab and lenvatinib	100	36 (1)	22	112
Nivolumab and ipilimumab	148	31–32 (0–8)	12.5–22.8	75
Atezolizumab and bevacizumab	336	27 (6)	NE	112
Nivolumab and cabozantinib	36	14 (3)	21.5	75
Nivolumab, ipilimumab and cabozantinib	35	31 (6)	NE	75
Atezolizumab	59	17 (5)	NA	115
Nivolumab	371	15(4)	16.4	90

NE, Not evaluable; NA, Not available; OS, Overall survival; ORR, Overall response rate.

bination of ipilimumab and nivolumab for these patients. The CheckMate 9DW phase III trial (NCT04039607) is currently assessing this combination treatment as first-line therapy for advanced HCC.

ICIs with vascular endothelial growth factor inhibitors: The IMbrave150 phase III study examined the combination of a PD-1 inhibitor (atezolizumab) with a vascular endothelial growth factor (VEGF) inhibitor that inhibits angiogenesis (bevacizumab) as a unique approach for the treatment of advanced HCC.[117,118] This treatment provided good protection and antitumor efficacy in individuals with untreated late-stage HCC.[119] In particular, relative to sorafenib, this combination reduced the risk of death by 42%. The IMbrave150 trial led to the approval of treatment that combined atezolizumab and bevacizumab, instead of TKIs (sorafenib or lenvatinib), as a first-line therapy for unresectable HCC in the United States and Europe. The efficacy of this new treatment is most likely due to the synergistic effects of these two drugs, which inhibit PD-L1 (stimulating the immune system, chiefly T-effector cells) and also inhibit VEGF (promoting T-cell infiltration, reducing VEGF-mediated immunosuppression, and inhibiting angiogenesis).[113]

ICIs with tyrosine kinase inhibitors: The combination of ICIs with TKIs (rather than an anti-VEGF antibody) is an alternative approach. The multi-cohort COSMIC-021 phase Ib trial (NCT03170960) examined the effect of cabozantinib (TKI) and atezolizumab (PD-L1 inhibitor) for the treatment of HCC.[120,121] This study also compared the effect of cabozantinib monotherapy to sorafenib as a secondary outcome. A planned interim analysis demonstrated no significant difference in OS. However, a phase Ib trial showed that the combination of lenvatinib (TKI) with pembrolizumab (PD-1 inhibitor) led to acceptable outcomes in 104 patients with unresectable HCC who did not receive a previous systemic therapy.[107] The LEAP002 phase III trial (NCT03713593) compared this combination with lenvatinib monotherapy.[122] Another study examined the effect of camrelizumab (investigational PD-1 inhibitor) with apatinib (TKI) and reported the overall response rate was 50%.[123] Moreover, an ongoing phase III study (NCT03764293) is evaluating camrelizumab with apatinib *vs.* sorafenib as a first-line treatment for advanced HCC.

Recent research indicated that ICI combination therapies, including those with TKIs, have increased anticancer efficacy due to their immunomodulatory effects on the TME and their pro-angiogenic effects on certain pro-tumor immune cells. Before the IMbrave150 trial, there were promising response rates to TKI+ICI combinations compared to individual therapies. In particular, lenvatinib decreased the level of tumor-associated macrophages and increased the level of $CD8^+$ T cells.[124] Regorafenib (TKI), which targets VEGFR, EGFR, PDGFR, and FGFR, promoted antitumor immunity by regulating macrophages and enhancing $CD8^+$ T cell proliferation. Preclinical and clinical studies of cabozantinib showed it had synergistic effects when combined with an ICI; the effect on tumor antigens (such as TAMs) reduced tumor vascularity, and bevacizumab significantly restored an immune-supportive TME.[125] The use of PD-1 inhibitors with TKIs and TACE was also an effective treatment for patients with unresectable HCC, and the ORR surpassed that achieved by the monotherapies.[126,127] Thus, combining an ICI with anti-angiogenic drugs can reverse the immunosuppressive character of the TME, but the most effective and safe TKI to be used with an ICI has not yet been established.

Cellular therapies for HCC

Therapies with non-genetically altered cells

Cytokine-induced killer cells: Cytokine-induced killer cells (CIKs) are $CD3^+CD56^+$ NK-like T-cells that develop from peripheral blood mononuclear cells or cord blood following *ex vivo* incubation with anti-CD3 mAb, IL-2, IFN-γ, and IL-1α.[128,129] CIKs have non-MHC-restricted cytotoxic and anti-proliferation effects.[130] A phase I clinical study with adjuvant CIKs found there was decreased tumor recurrence of graft-versus-host disease (GvHD) after surgery in patients with stage A/B liver cancer (staging based on the Barcelona Clinic Liver Cancer system).[131,132] Three of these 13 patients had good tolerance to the CIKs, and this treatment reduced the HBV burden and slowed tumor development.[133] A second phase I basket study examined 12 patients who received 3 cycles of CIKs over 3 weeks (median dosage: 28×10^9 cells, range: 6 to 61×10^9 cells) for the treatment of late-stage HCC, resistant renal cell carcinoma, or lymphoma. After an average follow-up time of 33 months, the CIKs were well tolerated, 3 patients attained CR, and 2 patients had SD.[134]

Another study of patients with unresectable HCC assessed the effect of CIKs paired with TACE.[135] The CIK+TACE group had a PFS of 6 months in 72.2% of patients, 1 year in 40.4% of patients, and 2 years in 25.3% of patients, and these numbers were better than in the TACE-alone group (34.8%, 7.7%, and 2.6%, respectively). The median OS in the CIK+TACE group was 31 months (95% CI: 27–35), but was only 10 months (95% CI: 7–13) in the TACE-alone group. These findings indicate the potential benefits of combining an immunotherapy strategy with TACE for treating HCC.[135] A subsequent clinical study of 64 patients with HCC applied TACE and RFA sequentially in patients who did (n=33) or did not (n=31) receive prior CIK treatment.[129] These researchers administered 8 doses of CIKs into the hepatic artery or a peripheral vein at intervals of 4 weeks. After 1 year, 68% of the control group and 88% of the CIK group were free of recurrence.[129] Another study evaluated a DC+CIK combination therapy in a basket trial, and showed that DCs enhanced the activation of CIKs.[136] There is also evidence that a DC+CIK regimen can control tumor development and increase OS.[136,137] An *in vitro* study of HCC cells (BEL27402) compared to DC+CIK alone, sorafenib alone, and CIK alone, and DC+CIK with sorafenib, showed the greatest efficacy in the DC+CIK with sorafenib group.[138]

Tumor infiltrating lymphocytes: TILs are also used in autologous therapies. In particular, TILs are developed *ex vivo* from polyclonal, tumor-targeting T-cells that are generated against a patient's tumor. In patients with immunogenic tumors, such as metastatic melanoma, these treatments led to an overall response rate (ORR) of 49 to 72%, a CR rate of 10 to 20%, and persistent responses in 40% of all patients.[139,140] Terminally differentiated TILs, with a predominance of immune-suppressive components (T_{regs}), can result from protracted *ex vivo* processing. To prevent this, tumor-reactive/neoantigen-responsive cytotoxic T-cells are now grown non-selectively in large quantities of TILs,[141] and clinical investigations of these treatments are currently being conducted for patients with non-small cell lung cancer and melanoma. HCC TILs, by phenotype worn out in preclinical models, have increased production of TIM-3 and LAG-3, but reduced production of inflammatory mediators.[142,143] Preclinical studies demonstrated that TIGIT and PD-1 co-blockade enhanced the proliferation of these cells and the release of cytokines.[143]

Therapies with genetically altered cells

The capacity of the immune system to identify TAAs is a prerequisite for effective anti-tumor responses in immunotherapeutic cancer treatments. A functional immune system has self-tolerance, and because all tumors consist of self-tissues, it is difficult to induce a strong anti-tumor response. Therapies that use chimeric antigen receptor (CAR) engineered T cells and T cell receptor (TCR) engineered T cells use synthetic receptors developed by genetic engineering to alter immune cells and increase the detection of TAAs and tumor-specific antigens (TSAs).[144]

Chimeric antigen receptor T cells: Immune cells can be genetically reprogrammed to recognize and attack cells that express specific TAAs using artificial cell surface receptors (CARs) that are independent of the MHC system.[145,146] A typical CAR structure consists of an external, antibody-derived single-chain variable fragment (scFv) antigen-binding domain that is linked to an intracellular signaling endodomain, which has (at a minimum) CD3ζ signaling capabilities.[147] First-generation CARs with isolated CD3ζ signaling were mostly replaced by CARs with CD28 or 4-1BB receptors, leading to enhanced CAR-T cell growth and increased cancer cell death *in vitro* and *in vivo*.[148,149] The most significant development in hematological malignancies during the past ten years was the development of CARs that target CD19 in the subsequent phase, and have 4-1BB[150] and CD28[151] co-stimulatory endodomains. There is now global approval of autologous CD19-targeting CAR-T cells for relapsed and refractory B-cell lymphoma. Notably, third-generation CARs, which contain two intracellular signaling domains, such as 4-1BB and CD28, are also under development.[152–155] Ongoing research is examining the effect of CAR-T cell therapies for HCC, and there are several promising CAR-T cell tumor targets, including AFP, c-MET, GPC3, Mucin 1, and NK group 2D ligand (NKG2DL).

Glypican-3 biological system and CAR-T cells: The placenta contains GPC3, a 65 kD (580 amino acid) heparin sulfate proteoglycan that is anchored to glycosylphosphatidylinositol and normally functions in morphogenesis by activating the Wnt pathway.[129,156,157] Several solid tumors, including 72% of HCCs, carries a negative prediction.[158,159] Crucially, GPC3 is only weakly expressed in noncancerous tissues, such as healthy tissues and cirrhotic liver tissues.[160,161] About 53% of HCC patients have soluble GPC3, and this protein is therefore under investigation as a disease biomarker.[159] GPC3 appears to affect the onset and progression of HCC.[162,163] Studies of primary HCC cells reported that siRNA-mediated GPC3 silencing reduced proliferation, increased apoptosis, and impaired the migration of tumor cells.[164]

Just like central- or stem-cell memory T-cells, GPC3-CAR-T item characterization showed advancement for final differentiation, $CD45RA^+$ re-expressing effector memory T-cells (78.2%) and effector memory T-cells (14.1%).[165] Several studies showed that CD19-CAR-T activity was negatively affected by terminally differentiated T-cells, and this was likely to occur in HCC.[166,167] Leukapheresis could possibly improve the efficacy of GPC3-CAR-T cell therapy.[168]

Even the responses to these therapies were inadequate, the toxicities were generally manageable, and this trial laid the groundwork for future GPC3-CAR-T strategies. For example, current trials are examining 'armored' GPC3-CAR-T models, with components designed for 41BBL and IL-15/IL-21 (NCT02932956),[169] a combination of techniques using TKIs or IPIs (NCT03980288), and administration *via* hepatic artery perfusion (NCT03993743). It is not yet clear how soluble GPC3 can affect GPC3-CAR-T function. However, soluble GPC3 might prevent accessibility to cell-surface GPC3.[170] Future studies should consider this when creating and testing the preclinical versions of the next-generation GPC3-CAR-T cell therapies.

Others: AFP can occur as a serum protein or an intracellular protein, and a modified version can occur as a cell surface protein on MHC class I molecules. AFP is a biomarker for HCC, its release into the serum stimulates the growth of tumors, and a high serum level is associated with poor prognosis.[171,172] A phase I clinical trial, whose results have not yet been published, is examining the effect of intravenous and intrahepatic arterial administration of AFP-CAR-T cells in AFP+ patients with HCC (NCT03349255).

After processing and presenting short antigenic peptide fragments on HLA class I and II molecules, engineered TCRs can recognize intracellular TAAs and TSAs.[173] The ability of TCR-T cells to recognize and connect intracellular antigens encoded on HLA, despite a low target density, can provide a significant benefit.[174,175] Two disadvantages of this approach are that this treatment is limited to a small percentage of patients, primarily those who are HLA-A*0201 positive,[174] and it is difficult to engineer high-affinity, synthetic αβ-TCR for TAA-specific targeting, while avoiding the challenges of

TCR chain mispairing and low TCR production.[176] Additionally, there is a chance that production in normal and cancerous tissues will overlap at low antigen densities. TCR-T cell binder development could be advanced by adjusting TCR affinity with physiochemical and *in silico* approaches to facilitate discrimination of cancerous and non-cancerous cells.[177] There are now seven phase I/II TCR-T cell clinical studies of HCC that are accepting participants.[153] Additional trials listed on clinicaltrials.gov that have 'status unknown' or 'not yet recruiting' include three studies of patients with HCC relapse following liver transplantation (NCT02686372, NCT04677088, and NCT02719782).

Clinical studies utilizing an AFP epitope ($AFP_{158–166}$, [NCT03132792]), AFP is managed and displayed on HLA and reflects a useful seek for TCR-T methods.[178] Studies that performed *in vitro* testing described three novel HLA class I epitopes ($AFP_{542–550}$, $AFP_{137–145}$, and $AFP_{325–354}$) that were cytotoxic and induced IFN- production against in HLA-A*0201+/AFP+ tumor cells. Other research used a transgenic mouse model to investigate the immunogenicity of different AFP epitopes.[179,180] Altogether, these results of these studies demonstrate the presence of four immunogenic AFP epitopes that could be used as targets of TCR-T cells.

The initial clinical findings of a study that used affinity-boosted autologous specific peptide enhanced affinity receptor (SPEAR) T-cells targeting AFP (NCT 03132792) were released in 2019.[129] This study examined patients with the HLA-A*02:01 or HLA-A*02:642 haplotypes who had serum AFP levels of 400 ng/mL or more or had positive immunohistochemical staining for AFP (≥1+ in 20% or more HCC cells). Following a fludarabine/cyclophosphamide chemotherapy regimen, SPEAR T cells (10^2 to 10^3 million) were given to cohort-one (n=5) to determine the maximum tolerated dose (MTD). All five patients had SD as the optimal reaction. The MTD for cohort two (n=3) was set at 5×10^9 SPEAR T- cells (range: 5.0 to 5.6×10^9). One patient achieved PR, and the other 2 experienced progressive disease, and the treatment was well-tolerated.[178]

HBV is responsible for about 80% of all cases of HCC in Asia because of persistent hepatic inflammation, and the virus is incorporated into the hepatic cell genome.[181,182] Because the likelihood of on-target, off-tumor toxic effects decreases and the low rate of target production lends itself to TCR-T targeting, attacking viral, non-self-antigens is an appealing approach for TCR-T cell treatments. HBV infections typically induce high-affinity TCRs, which have significant therapeutic potential because they can lyse HBV-infected cells. However, the main disadvantage of this approach is that non-malignant liver tissues are also likely to have HBV antigens, raising the possibility of life-threatening liver injury.[183]

Gehring *et al*. presented a liver transplant patient who had extra-hepatic HCC, and HBV-DNA integration resulted in surface HBV (HBsAg), but there was no detectable HBV-DNA in the blood.[183,184] The HCC cells displayed HLAA0201/HBV peptide complexes, and their expression was uniform across the tumor. To produce autologous, patient-derived HBV-TCR-T cells, these researchers identified a specific TCR that targeted the HLA-A-*0201/HBs183-91 mixture and cloned this gene. Without lympho-depletion, the individual received only one dosage of 1.2×10^4 HBV-TCR-T cells/kg. These cells multiplied and decreased the blood levels of HbsAg, and there was no evidence of harm to healthy tissues.[183] However, the recurrence rate from hepatitis B is substantial (50% within five years)[13] and the blood HbsAg level is linked to recurrence. An important question raised by this instance is if HBV-TCR-T might be utilized greater frequently for HCC patients who relapse after liver transplantation.[185] In particular, after liver transplantation in HbsAg+ patients, TCR-T cells could be administered as prophylactic to avert relapse.

Bispecific antibodies (BsAbs), produced using recombinant DNA technologies, can precisely and simultaneously bind two antigens or epitopes.[186,187] To alter immune-suppression in the tumor environment, a BsAb can be used to target immune checkpoints and TAAs, thereby enhancing the function of immune cells. Therefore, because BsAbs have two effects, they are potentially more effective than mAbs. BsAbs typically function as a "bridge"; they can recruit and activate immune cells to target cancer cells.[188] Solitomab (AMG110, MT110) is one example of a humanized EpCAM/CD3 BsAb. The *in vitro* binding of Gamma-Delta T cells with the bispecific T-cell engager (BITE) leads to the nearly complete lysis of HCC cells. This treatment is characterized by the attachment of the anti-epithelial cell adhesion molecule (EpCAM), single-chain variable fragment (scFv), and the anti-CD3 single-chain variable fragment (scFv) by a Gly4Ser linker.[189] A distinct BsAb named GPC3/CD3 BITE was designed to attract CTL and target GPC3+ HCC cells. This BsAb used flexible linker peptides to unite two anti-GPC3 Fab fragments to an asymmetric Fab-sized binding module, leading to an IgG-shaped Tri-Fab that activated two antigens sequentially, so that it could be used for the targeted delivery of different payloads.[190]

HCC vaccines

Antigenic compounds can elicit tumor-specific immune responses, leading to a reduced tumor load and prevention of tumor reversion. HCC vaccines can be developed from cancer cells, DCs, peptides, and DNA, and some of these vaccines have successfully prevented tumor spread and recurrence. Peptides are widely used as cancer vaccines, and the most appropriate peptide for generating a cancer vaccine is determined by the type of tumor and the immunologic characteristics of the patient.[191,192] The search for "HCC vaccines" identified six general types of research (Table 3).[193]

Cellular vaccines

Autologous or allogenic HCC cells or extracts that have been physically or chemically killed or damaged so that they are not pathogenic can be used as antigens to induce tumor-specific defense reactions. A phase I trial examined 8 patients with advanced HCC that tested bi-shRNA/granulocyte-macrophage colony-stimulating factor (GM-CSF) boosted autologous tumor cells. The long-term follow-up showed that 3 patients had clear immune responses to the reinfused cancer cells, and the long-term follow-up demonstrated survival times were 319, 729, 784, 931+, and 1,043+ days after treatment. However, the effectiveness of HCC vaccines remains unknown due to their poor immunogenicity.[194]

Antigen peptide vaccines

Several studies used peptide-based vaccines to treat HCC, and these vaccines utilized AFP, GPC3, SSX-2, NY-ESO-1, human telomerase reverse transcriptase (hTERT), human carcinoma-associated antigen (HCA587), and melanoma antigen gene-A (MAGE-A) as TAAs.[195,196] Embryonic liver cells normally produce AFP, but this protein is also overexpressed on the surface of HCC cells. However, the development of acquired immunological tolerance during development limits immune responses to this excess AFP in patients with HCC. A recent study used recombinant rat AFP to trigger cross-reactions between xenografts and endogenous molecules in

Table 3. The clinical trial of cancer vaccines targeting HCC[193]

Target	Phase	Start	End	Peptide	Methods/ combination	Descriptions
DNAJB1-PRKACA	1	Apr., 20	–	DNAJB1-PRKACA	Nivolumab and Ipilimumab	The trial's main goal is to determine the vaccine's safety and tolerability.
16 common cancer antigens	1 and 2	Sep., 17	Dec., 19	16 newly identified, excessively expressed tumor-related peptides	Novel RNA	For the treatment of (hepatocellular carcinoma), a new adjuvant called CV8102 is paired with a new cancer vaccination called IMA970A.
VEGFR1, VEGFR2	1	2007	2013	VEGFR1, VEGFR2		This study aims to evaluate the side effects of angiogenic peptide vaccine therapy in patients with advanced hepatocellular carcinoma who are HLA-A*2402 restricted.
AFP	1 and 2	Jan., 01	Oct., 08	Four HLA-A*0201-restricted immunodominant AFP peptides [hAFP137-145 (PLFQVPEPV), hAFP158-166 (FMNKFIYEI), hAFP325-334 (GLSPNLNRFL), and hAFP542-550 (GVALQTMKQ)]	Dendritic cells	Phase I/II study to examine the efficacy of vaccination treatment in the management of patients with liver cancer.
AFP	1 and 2	Jul., 09	Jun., 02	4- HLA-A*0201-restricted immunodominant AFP peptides [hAFP137-145 (PLFQVPEPV), hAFP158-166 (FMNKFIYEI), hAFP325-334 (GLSPNLNRFL), and hAFP542-550 (GVALQTMKQ)]	Intradermal	Phase I/II study to examine the efficacy of vaccination treatment in the management of patients with liver cancer.
Ras mutation	2	Oct., 07	May., 07	Mutated Ras Peptides Specific for Tumors	IL2 or GM- CSF	Adults with metastatic solid tumors will be treated in a phase II trial to see whether vaccination therapy combined with interleukin-2 and/ or sargramostim is beneficial.

GM-CSF, Granulocyte-macrophage colony-stimulating factor; VEGFR, Vascular endothelial growth factor receptor.

mice to overcome this immunological tolerance and reported minor cellular and humoral immune responses.[197] A phase II trial examined 25 patients who received a GPC3-derived peptide vaccine for HCC. The treatment consisted of 10 injections over a 1-year period following surgery. Relapse was less common in patients who received surgery and vaccination relative to those who received surgery alone (24% *vs.* 48% at 1 year [p=0.047] and 52.4% vs. 61.9% at 2 years [p=0.387]), demonstrating the effectiveness of this vaccine.[198]

Many other clinical investigations have investigated the use of HCC vaccines (Fig. 4).[193] The outcomes of one trial that examined a peptide vaccine developed using GPC3 (which typically has elevated expression in HCC) were published in 2011.[199] These patients had advanced HCC, were from the National Cancer Center Hospital East (Kashiwa, Japan), and were recruited into this phase I trial to assess the protection and immunogenic response elicited by the vaccine.[200] This study demonstrated a relationship between the peptide-specific cytotoxic T lymphocyte level and patient privacy concerns regarding the GPC3 peptide vaccine utilization because RFA influences a specific T cell's improvement against HCC-related antigens or GPC3. The same team conducted a single-arm Phase II trial in which some patients received adjuvant treatment with a GPC3-derived peptide vaccine.[201] This GPC3 peptide vaccine induced a CTL response that efficiently destroyed cancer cells that expressed GPC3, so that GPC3-negative cells proliferated. This proof-of-concept utilizing the GPC3 peptide and additional peptides was effective, and hence opened the door for studies of other peptide and antigen treatments.

DC vaccines

DCs are the most potent APCs, and function in the absorption, digestion, and presentation of tumor antigens. These cells have significant levels of MHC and Cas ligands with multiple Src homology (SH) 3 domains (CMS), such as B7-1 and B7-2. They also induce primary T cells and release IFN-γ, a cytokine that inhibits tumor angiogenesis and creates immunological memory. Altogether, DCs therefore have many anticancer effects.[202,203]

During the creation of a vaccine against HCC, DCs were first stimulated by specific mediators (e.g., rhGM-CSF and rhIL-4) then developed in the existence of TNF-α, and eventually became activated by autologous tumor cells or antigens.[196] DCs with gene transfections continue to express cytokines or tumor antigens that enhance their function. A recent study of mice with HCC administered nifuroxazide (which blocks signal transduction mediated by stimulation of transcription 3 [STAT3]), together with DCs that were loaded with tumor cell lysate (TCL). This combination increased the antitumor immune response, slowed tumor development, and increased the survival time.[204] A phase I/IIa trial examined the effect of tumor antigen-pulsed DCs for HCC patients who received primary treatment and showed that DC immunization was an efficient adjuvant therapy.[205] Another study reported the safety and tolerability of DC vaccinations in HCC patients.[206]

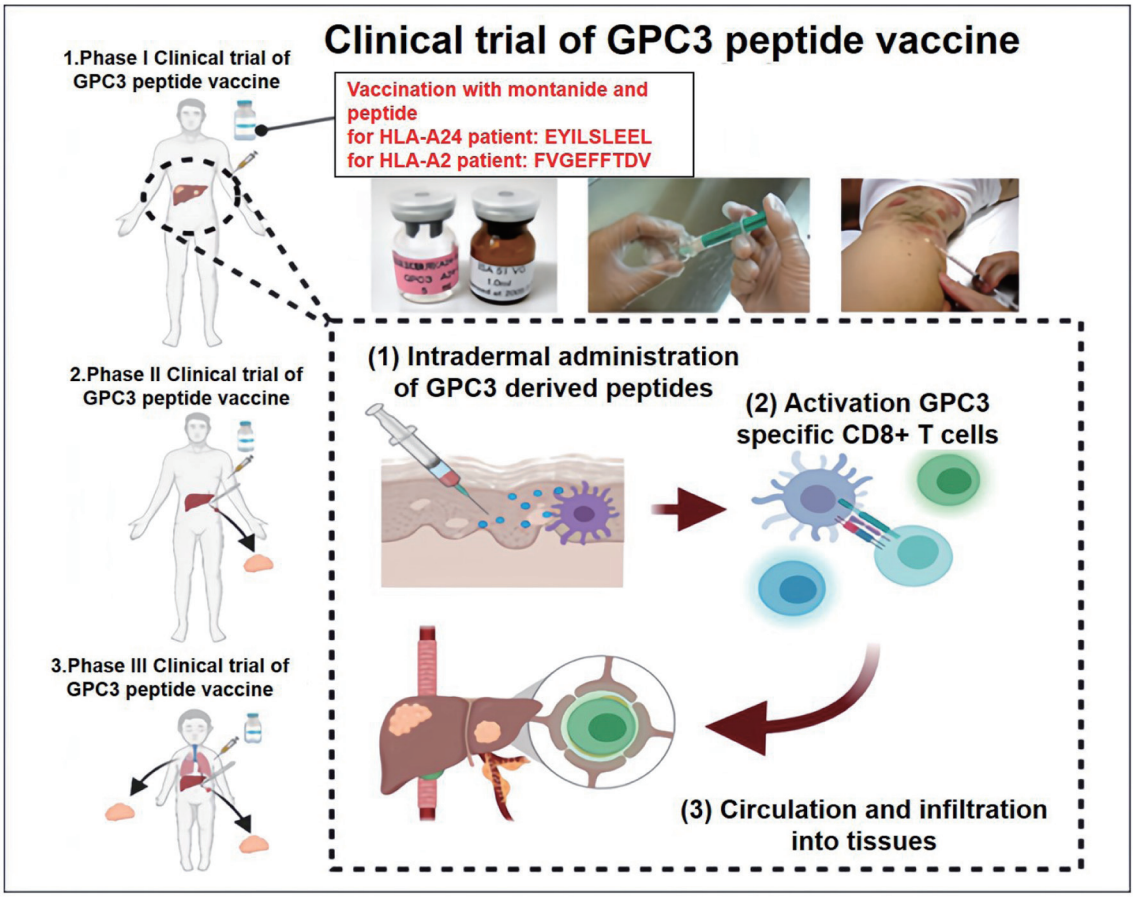

Fig. 4. Diagram illustrating the GPC3-targeting peptide vaccination. The picture shows the various steps involved in creating the vaccine. GPC3, glypican 3.[193]

Adjuvant immunotherapies for HCC

Numerous clinical studies are examining the use of adjuvant immunotherapies for patients with intermediate-stage HCC. The preliminary results suggest that tremelimumab with TACE or RFA has the potential for use in patients with early-stage HCC.[109,207] This approach was also examined in the IMbrave150 trial, a randomized, open-label, phase III study that examined HCC patients after curative resection or RFA and compared atezolizumab with bevacizumab to active monitoring.[208] Additionally, the phase III EMERALD-1 and EMERALD-2 trials are comparing durvalumab with or without bevacizumab to placebo for patients with intermediate-stage HCC who received TACE or RFA.[93,209]

Unlike many other cancers, HCC can be treated using locoregional therapies (LRTs), including TACE or RFA. Consequently, complementary therapies administered after an LRT may improve clinical outcomes. Sorafenib was approved in 2007, and it remains the only treatment option for advanced HCC. Additional systemic medications for advanced HCC have recently been examined, including new TKIs (e.g., lenvatinib) as a front-line therapy and regorafenib or cabozantinib as a second-line therapy. In an effort to improve clinical outcomes, several researchers are now examining a combination of TKIs and LRTs. Nevertheless, sorafenib followed by resection or ablation (STORM study)[210] failed to increase recurrence-free survival compared to placebo. Likewise, multiple earlier trials showed that TKIs following TACE failed to improve clinical outcomes.[211] For unresectable HCC, an ICI such as nivolumab is now recommended, although recent trials demonstrated that ICI monotherapies did not significantly improve survival in HCC (in contrast to other tumors).[212] As a result, other studies have investigated different strategies for overcoming the inadequate response to ICIs. As a first-line treatment, a combined regimen of atezolizumab with bevacizumab provided significantly greater clinical benefit than sorafenib.[107] Additionally, another combination treatment—pembrolizumab with lenvatinib—was recently tested in clinical studies and has shown good clinical efficacy during the early stages of treatment.[117] Combining LRTs with ICIs could be an important development in the treatment of HCC, and could also significantly improve the prognosis of these patients.

Oncolytic virotherapy

Therapeutic oncolytic viruses are engineered viruses or wild-type viruses that reproduce and destroy cancer tissues or other pathological tissues without adversely affecting healthy tissues.[213,214] Because a tumor's defenses against viral infection are compromised, most viruses can easily spread to cancer cells.[215] Furthermore, the stimulation of immune responses against neighboring cancer cells can be facilitated by the presence of tumor antigens and viruses within cell lysates.[216,217] One advantage of oncolytic virotherapy is that it may not be subject to some of the limitations of conventional cancer therapies, such as chemotherapy and radia-

tion therapy. For example, certain cancer cells can become resistant to chemotherapy or radiotherapy, but viruses can persist over time and still infect and kill tumor cells.[218] In addition to directly killing cancer cells, oncolytic viruses can also stimulate the immune system to target the cancer cells because lysed cancer cells release TSAs that can stimulate an immune response. This approach therefore enhances the body's ability to detect and eliminate tumor cells,[219] and is particularly suitable for treating HCC because the liver has a high degree of immune surveillance.[60]

Oncolytic viruses can target cancer cells through several different mechanisms. First, several wild-type viruses can infect tumors by different mechanisms that evolved in nature, such as Sindbis viruses, reoviruses, and varicella viruses.[220] Second, genetic engineering can also be used to create oncolytic viruses by eliminating viral genes that are essential for replication in healthy cells but have no functionality in cancerous cells.[221] Third, the targeted transcription of viruses in cancer cells can be achieved by inserting tumor-specific promoters, including the human telomerase reverse transcriptase promoter, upstream of essential viral genes.[222] Finally, viruses can target tumor cells after alteration by TAA-specific receptors. For instance, the tumor-specific inhibition of tumor angiogenesis can be achieved using an oncolytic vaccinia virus that is engineered with anti-angiogenic genes.[223]

Previous research examined the effectiveness of a progressive tumor-favoring modified vaccinia virus (CVV) in an animal model of metastatic HCC. In this study, groups of rats were randomly given sorafenib, the CVV, or sorafenib plus the CVV. In comparison to the sorafenib-only group, the other two groups had smaller metastatic areas. These findings indicate the potential use of CVV as a treatment for metastatic HCC.[224] JX-594 is a modified vaccinia virus that is particularly hazardous to cancer cells, but is stable and safe for people. This virus has a mutated TK gene (which regulates cancer cell-specific reproduction) and an insertion in the human GM-CSF gene (which boosts antitumor immune reactions).[225] A phase II randomized open-label trial of patients with HCC examined the effectiveness and safety of oncolytic virotherapy using JX-594. The results showed that the intrahepatic reaction rate was 62%, 1 patient achieved CR, the therapy was well tolerated at high and low dosages, and the OS was greater in the high-dose group than in the low-dose group.[226] Numerous other studies have investigated other oncolytic viruses for the treatment of HCC, including GLV-1h68 and G47delta.[227] Important safety considerations related to this approach are the risk of viral disease and the development of insertional mutations that stimulate oncogenes or disrupt tumor suppressor genes.

Conclusions and future prospects

HCC is a complex disease that can escape immune responses by various mechanisms, suggesting great potential for treatments that use different or multiple immunotherapy approaches. The range of immunotherapy treatments for HCC has expanded significantly during the past 10 years, and ICIs are now widely used for patients with advanced-stage HCC. The development of novel medicines and combination therapies is being shaped by the greater understanding of the molecular pathways responsible for cancer initiation and termination of the body's anti-tumor immune responses in the TME. Although many trials have demonstrated the possible efficacy of different immunotherapies for HCC, only a few have been formally licensed. The identification of more focused immunological targets (such as TAAs/TSAs and new immune checkpoints) and the use of oncolytic viruses require further research. It is also important to accelerate the enrollment of patients in these clinical studies and to consider the effectiveness and safety of novel medications. The development of more individualized treatment programs may also increase the effectiveness of immune therapies.

HCC immunotherapy has progressed greatly, and although ICIs were initially used to treat other cancers, they are now commonly used to treat HCC. Our update on the use of immunotherapy in HCC primarily describes developments in the methodologies used in clinical trials.[74] It is likely that the recently developed neoadjuvant treatments for patients with resectable or non-resectable HCC will soon provide benefits to patients, in terms of decreased cancer progression and mortality. ICI-based therapies may also boost the efficiency of locoregional and radical treatments for HCC. The expansion of novel immunotherapies, such as immunostimulatory mAbs, BsAbs, tailored cytokines, antibody-drug conjugates, adoptive T cell therapies, and vaccination with neoantigens, will be important future developments. It is crucial to consider the molecular aspects of the responses to these treatments and the development of tolerance to specific drugs or mixtures, and to use relevant biomarkers to monitor patient responses to personalized immunotherapies. Clinical studies and other research should aim to incorporate the correlative findings from other investigations, and provide the results to other researchers while safeguarding the concerns and rights of patients and organizations.[74]

The various mechanisms that contribute to resistance to different ICI treatments may be overcome by the use of novel immunotherapies and targeted combination treatments. In addition to the results that were published at the time of the current review, the results of other ongoing clinical studies of HCC will be available soon. It is likely that patients who received more advanced ICI regimens will respond favorably to these new combination treatments. Certain combinations of VEGF inhibitors, ICIs, and TKIs are effective in patients with other types of tumors who previously received ICIs, and these approaches may be extended to HCC.[114] For example, a phase Ib/II trials of lenvatinib (a TKI that inhibits angiogenesis) with pembrolizumab appears to have great potential for the treatment of patients with metastatic HCC.[115]

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

HW and XL designed the study and HW drafted the manuscript. HW and CD reviewed and edited the manuscript. All authors revised and approved the final manuscript.

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