The Role of Immunotherapy in Hepatocellular Carcinoma (HCC)

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ABSTRACT

Hepatocellular carcinoma (HCC) is an aggressive primary liver malignancy with a historically poor prognosis and limited treatment options. It accounts for approximately 75–85% of all liver cancer cases worldwide, with an estimated global incidence of about 9.5 per 100,000 person-years. According to GLOBOCAN 2022, the liver cancer mortality-to-incidence ratio in Indonesia is 0.99, indicating that nearly all patients diagnosed with HCC die from the disease. Systemic therapy, primarily sorafenib, a targeted therapy approved since 2007, has long been the mainstay for advanced cases, but it offers limited clinical benefit. In recent years, immunotherapy, particularly immune checkpoint inhibitors (ICIs), has significantly altered the therapeutic approach to HCC. These agents function by inhibiting regulatory pathways such as PD-1/PD-L1 and CTLA-4, thereby enhancing immune-mediated tumor clearance. Clinical trials, such as IMbrave150, have shown that combining atezolizumab and bevacizumab leads to notable improvements in both overall and progression-free survival compared to sorafenib, resulting in its approval as a first-line treatment. Similarly, combinations like durvalumab with tremelimumab have shown encouraging efficacy. Nonetheless, therapeutic resistance remains a challenge, often driven by the immunosuppressive tumor microenvironment. Emerging strategies, such as next-generation checkpoint blockades, adoptive cell therapy, therapeutic cancer vaccines, and oncolytic virotherapy, are under investigation to improve response rates. This review discusses current progress in immunotherapy for HCC, addresses clinical limitations, and explores potential future directions to enhance treatment success.

Keywords: *Immunotherapy, Immune Checkpoint Inhibitor, Hepatocellular Carcinoma*

ABSTRAK

Karsinoma hepatoseluler merupakan bentuk kanker hati yang bersifat agresif, dengan prognosis buruk dan pilihan terapi yang terbatas. HCC mencakup sekitar 75–85% dari seluruh kasus kanker hati di dunia. Menurut laporan GLOBOCAN 2022, rasio kematian terhadap kejadian kanker hati di Indonesia mencapai 0,99 yang menunjukkan bahwa hampir semua pasien HCC yang terdiagnosis meninggal akibat penyakit ini. Terapi sistemik, terutama sorafenib yaitu suatu terapi target yang disetujui sejak 2007, telah lama menjadi pengobatan utama untuk kasus stadium lanjut, meskipun manfaat klinisnya terbatas. Dalam beberapa tahun terakhir, imunoterapi, khususnya dengan immune checkpoint inhibitors (ICIs), telah secara signifikan mengubah pendekatan terapi pada HCC. Agen ini bekerja dengan menghambat jalur regulasi seperti PD-1/PD-L1 dan CTLA-4 sehingga meningkatkan respons imun dalam menghancurkan sel tumor. Uji klinis seperti IMbrave150 menunjukkan bahwa kombinasi atezolizumab dan bevacizumab menghasilkan peningkatan bermakna dalam lama waktu hidup dan waktu perburukan dibandingkan dengan sorafenib, yang kemudian disetujui sebagai terapi lini pertama.

Kombinasi lain seperti durvalumab dan tremelimumab juga menunjukkan hasil yang menjanjikan. Meskipun demikian, resistensi terapi tetap menjadi tantangan, yang sebagian besar dipicu oleh lingkungan mikro tumor yang imunosupresif. Berbagai strategi baru, seperti checkpoint inhibitor generasi berikutnya, terapi sel adoptif, vaksin kanker terapeutik, dan viroterapi onkolitik sedang diteliti untuk meningkatkan respons terapi. Artikel ini membahas perkembangan terkini imunoterapi pada HCC, tantangan dalam aplikasi klinis, serta prospek masa depan untuk meningkatkan keberhasilan pengobatan.

Kata kunci: *Imunoterapi, Penghambat Checkpoint Imun, Hepatoseluler Karsinoma*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer, accounting for approximately 75–85% of liver cancer cases worldwide. Based on GLOBOCAN 2022, Indonesia reports a mortality-to-incidence ratio of 0.99, indicating that nearly all diagnosed cases result in death. Chronic liver injury and inflammation caused by chronic hepatitis B and C infections, excessive alcohol consumption, and nonalcoholic steatohepatitis (NASH) are the predominant risk factors for HCC. These conditions lead to cumulative hepatocyte damage, fibrosis, and cirrhosis, creating a microenvironment that promotes carcinogenesis.[1,2,3]

The absence of early clinical signs in HCC often leads to late detection, leaving many individuals unsuitable for definitive therapies such as hepatectomy or transplant. As a result, **systemic therapy** becomes the mainstay of treatment. Recent advances in cancer immunotherapy, particularly through immune checkpoint inhibitors (ICIs), have shifted the treatment landscape in HCC. ICIs work by blocking inhibitory pathways such as PD-1/PD-L1 and CTLA-4, thereby reactivating T-cell–mediated antitumor immunity. The IMbrave150 clinical trial demonstrated that the combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) significantly improved both overall survival (OS) and progression-free survival (PFS) compared to sorafenib, which had long been the standard first-line therapy.[5,6,7]

This superior efficacy, along with a more favorable safety profile, has made immunotherapy a promising and preferred systemic treatment option. However, challenges remain, including immune resistance, patient variability, and the immunosuppressive tumor microenvironment. HCC remains associated with poor survival outcomes, and the optimal integration of immunotherapy into clinical practice continues to face significant biological and clinical challenges. Therefore, this review aims to explore the immunological basis of HCC, evaluate recent advances in immunotherapy, and examine emerging strategies to overcome therapeutic resistance and improve clinical outcomes. This review integrates recent clinical trial data with emerging immunological mechanisms and resistance pathways to provide an updated and clinically relevant perspective on immunotherapy in HCC. [8]

This article is a narrative review that summarizes current evidence regarding immunotherapy in HCC. Literature searches were conducted using PubMed, Scopus, and Google Scholar databases. Relevant articles published between 2019 and 2025 were identified using keywords including “hepatocellular carcinoma,” “immunotherapy,” “immune checkpoint inhibitors,” “PD-1,” “PD-L1,” “CTLA-4,” and “combination therapy”. Original research articles, clinical trials, meta-analyses, and relevant review articles published in English were included. Studies focusing on non-hepatocellular liver malignancies or lacking clinical relevance were excluded. Selected articles were critically reviewed and synthesized narratively to highlight current evidence, limitations, and future directions.

HEPATOCELULLAR CARCINOMA

Definition and Etiopathogenesis

HCC is a primary liver malignancy originating from hepatocytes, the main functional cells of the liver. This type of cancer usually develops in the context of chronic liver disease, particularly liver cirrhosis caused by persistent hepatitis B or C infection, prolonged alcohol use, or nonalcoholic steatohepatitis (NASH). Persistent environmental stress on the liver induces repeated hepatocyte injury, inflammation, and fibrosis, culminating in cirrhosis. Once cirrhosis develops, hepatocytes become prone to genetic instability, which can trigger mutations, epigenetic modifications, and other genetic changes. These alterations result in aberrant activation of intracellular signaling pathways. In HCC, four major signaling pathways are frequently dysregulated: the Wnt/β-catenin pathway, the receptor tyrosine kinase pathway, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, and the transforming growth factor-β (TGF-β) pathway. The Wnt/

β-catenin pathway regulates cell growth and proliferation. Mutations in this pathway, which are hyperactivated, result in uncontrolled tumor growth. A disrupted JAK/STAT pathway contributes to a tumor-tolerant microenvironment. The TGF-β pathway, normally a tumor suppressor, can support cancer progression through immunosuppression in the context of malignancy. Together, these pathological mechanisms lead to hepatocellular injury, liver cirrhosis, and, ultimately, the development of HCC. While viral hepatitis–associated HCC is mediated by chronic inflammation and direct viral oncogenic effects, metabolic or NASH-related HCC is driven by metabolic dysfunction and oxidative stress, with both entities ultimately converging on shared oncogenic signaling pathways.[9,10,11]

Diagnosis and Management of HCC

The clinical manifestations of HCC may include fatigue, weight loss, abdominal pain, fever, ascites, and jaundice. Due to its non-specific symptoms in the early stages, only 10–20% of HCC cases are diagnosed early enough to be amenable to curative surgical intervention. Abnormal liver function tests are often observed, particularly in patients with liver cirrhosis. Diagnosis can be initiated with abdominal ultrasonography (US). According to Omata et al. (2023), combining US with alpha-fetoprotein (AFP) testing increases diagnostic sensitivity to 63%, compared to 53% with US alone. AFP is an important diagnostic and prognostic biomarker. Regular AFP and ultrasound screening every six months is recommended for high-risk individuals, such as those with cirrhosis or chronic hepatitis B/C infection. Combining AFP with other biomarkers, such as protein induced by vitamin K absence or antagonists-II (PIVKA-II), can improve diagnostic accuracy, especially in AFP-negative HCC cases.[11,12]

When a liver nodule >1 cm or an AFP level ≥200 ng/mL is detected on US, further evaluation using multiphasic computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) is indicated. These imaging modalities are considered the gold standard for HCC diagnosis. The diagnosis of HCC was established according to AASLD and EASL guidelines, based on characteristic imaging findings on multiphase contrast-enhanced CT or MRI, including arterial-phase hyperenhancement, washout in the portal venous or delayed phases, and an enhancing capsule. Biopsy should be considered if imaging is uncertain, if there are no predisposing conditions (e.g., cirrhosis, chronic hepatitis), or when a tissue diagnosis is needed for therapy planning.[13,14]

Treatment strategies are increasingly personalized, considering both tumor progression and liver function, in line with the updated 2022 Barcelona Clinic Liver Cancer (BCLC) classification. Patients with early-stage HCC may undergo curative treatments such as surgical resection, local ablation, or liver transplantation. For intermediate-stage HCC (BCLC B), options include transarterial therapies and downstaging procedures to qualify for transplantation. Advanced-stage HCC (BCLC C) is defined by macrovascular invasion, extrahepatic spread, or an Eastern Cooperative Oncology Group (ECOG) performance status of 1–2, for which systemic therapy is the standard approach.[10,15]

In Indonesia, the 2022 National Clinical Practice Guidelines (Pedoman Nasional Pelayanan Kedokteran/ PNPK) recommend assessing liver function using the Child-Pugh classification before initiating treatment. This approach accounts for the high proportion of patients who present at advanced stages, who would otherwise only qualify for supportive care under strict BCLC criteria. As shown in **Figure 1,**

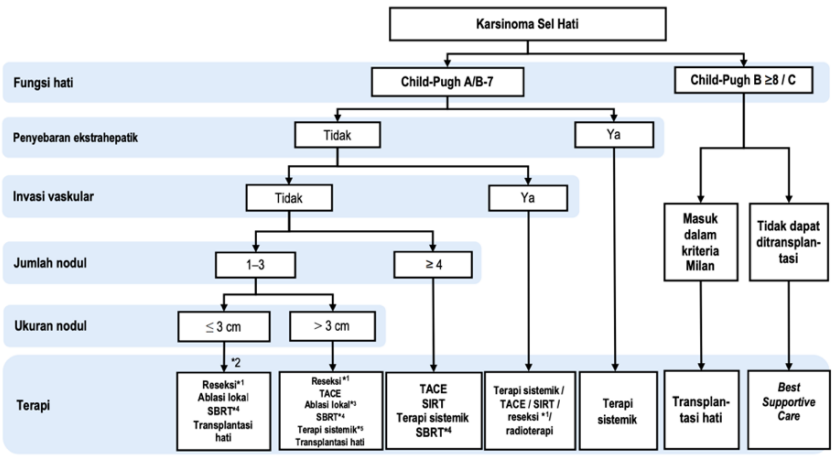

Figure 1. Management Algorithm for HCC[16]

patients with a Child-Pugh score ≥8 are limited to supportive care or, if eligible, transplantation. Those with better liver function (Child-Pugh <8) and radiologic evidence of vascular invasion, extrahepatic spread, or multiple large nodules (≥4 nodules or >3 cm) may be considered for systemic therapy.[16]

Over the past five years, the range of systemic therapies for HCC has broadened considerably. Sorafenib, introduced in 2007, served as the sole effective systemic therapy for more than ten years, followed later by lenvatinib. In recent years, ICIs have emerged as a novel therapeutic option for HCC and other solid tumors. These drugs target regulatory pathways, such as PD-L1, PD-1, and CTLA-4, which tumors exploit to evade immune surveillance. Combinations of monoclonal antibodies, including atezolizumab plus bevacizumab and durvalumab plus tremelimumab, are now approved for use as first-line therapy in advanced HCC.[4,13]

THE ROLE OF IMMUNOTHERAPY IN HCC

Immunological Mechanism of HCC

In HCC, the liver immune system plays a dual role in tumor surveillance and tumor promotion, shaped by chronic inflammation and immune dysregulation. Innate immunity, mediated by Kupffer cells, dendritic cells, and natural killer (NK) cells, provides the first line of defense against malignant transformation. While NK cells exert direct cytotoxic effects and secrete interferon-γ (IFN-γ), chronic liver injury promotes macrophage polarization toward an immunosuppressive, tumor-promoting phenotype. Dendritic cell dysfunction further impairs effective antigen presentation, limiting the initiation of robust adaptive immune responses and fostering immune tolerance within the tumor microenvironment. Adaptive immunity contributes through both cellular and humoral components, with cell-mediated immunity playing a dominant role in antitumor . Tumor antigens are presented to $CD8^+$ cytotoxic T lymphocytes via MHC class I molecules, supported by $CD4^+$ helper T cells through cytokine signaling and co-stimulatory interactions, as seen in **Figure 2.** However, persistent antigen exposure leads to T-cell exhaustion characterized by upregulation of inhibitory checkpoints such as PD-1 and CTLA-4, facilitating immune escape. Humoral immunity, mediated by B cells, plays a more limited role and may become immunosuppressive through regulatory B-cell subsets that secrete IL-10 and TGF-β, further contributing to HCC progression.[17]

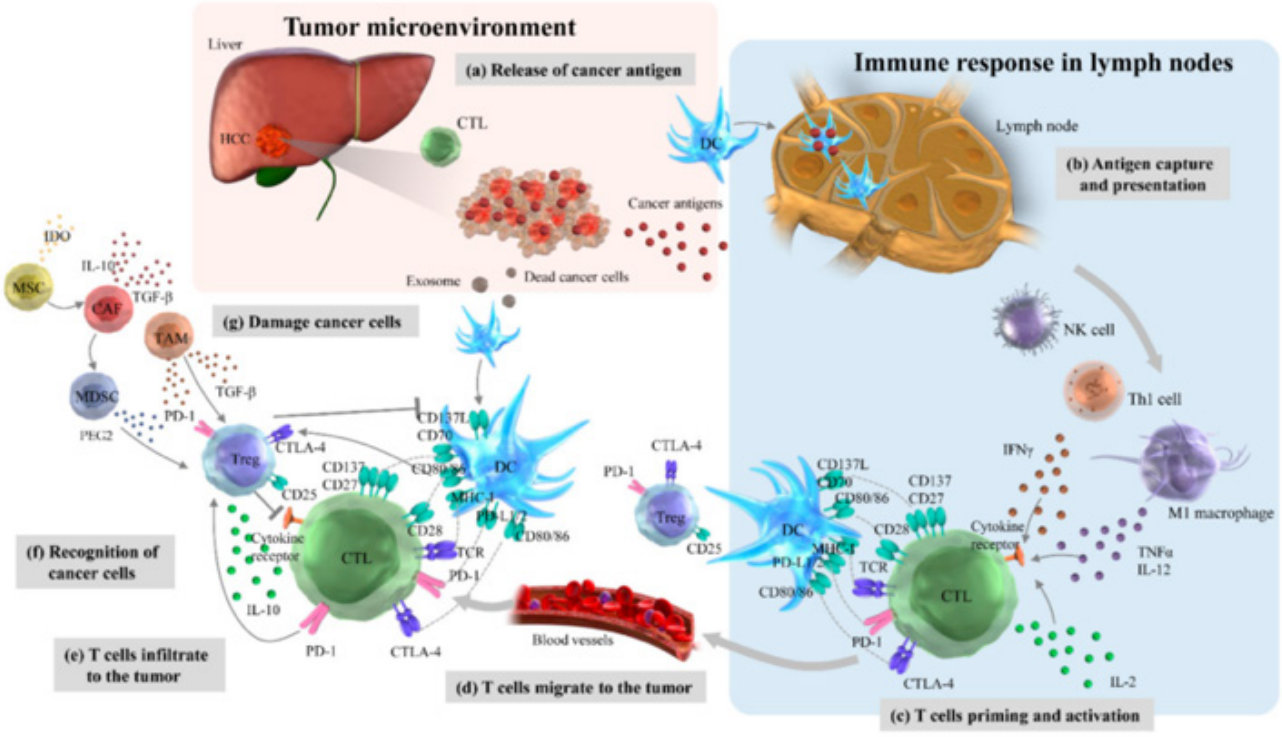

Figure 2. Steps of the Cancer-Immunity Cycle in HCC[17]

Although the immune system is capable, its activity can be dampened by tumor-induced immune checkpoints that function as inhibitory regulators **(Figure 3).** T cells express inhibitory receptors, including PD-1, CTLA-4, LAG-3, TIM-3, and TIGIT, to limit overactivation. Persistent exposure to tumor antigens promotes overexpression of these checkpoints, reducing T-cell effectiveness. The tumor microenvironment in HCC contains a high number of immunosuppressive cells, including tumor-associated macrophages, regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). In addition, cytokines such as TGF-β and IL-10, produced by both tumor and immune cells, inhibit the activity of effector T cells and promote the proliferation of immunosuppressive populations, allowing the tumor to escape immune surveillance. Tumor cells can reprogram their metabolism by increasing glucose uptake, utilizing lipids, and enhancing adenosine production, all contributing to immune suppression. They may also downregulate MHC class I expression, reducing recognition by cytotoxic T cells. Additionally, activation of VEGF and TGF-β promotes angiogenesis and alters antigen presentation, facilitating immune evasion. These complex mechanisms offer promising targets for combination therapies to enhance immunotherapy efficacy.[7,18]

TYPES OF IMMUNOTHERAPY

Immunotherapy has demonstrated safety and long-term efficacy in solid tumors, including HCC. Currently, several ICIs targeting CTLA-4, PD-1, or PD-L1 pathways have received FDA approval for treating various malignancies, including HCC. In addition, other innovative immunotherapeutic approaches, as shown in Table 1, such as adoptive cell transfer, CAR-engineered immune cells, cytokines, and therapeutic cancer vaccines, have progressed into clinical trials, offering promising prospects for patients with HCC.[18]

Table 1. Types of Immunotherapy for HCC[18]

Category	Type of Immunotherapy
Antibody-based therapy	Immune checkpoint inhibitors (ICIs) Bispecific antibodies Antibody–drug conjugates (ADCs)
Adoptive cell therapy	Cytokine-induced killer (CIK) cells Tumor-infiltrating lymphocytes (TILs) Chimeric antigen receptor T-cell (CAR-T) therapy T-cell receptor (TCR)-engineered T cells
Therapeutic vaccines	Peptide-based vaccines Dendritic cell (DC) vaccines Recombinant protein vaccines Oncolytic virus vaccines
Cytokine-based therapy	Interferon-α (IFN-α) Pegylated interferon Interleukin-2 (IL-2)

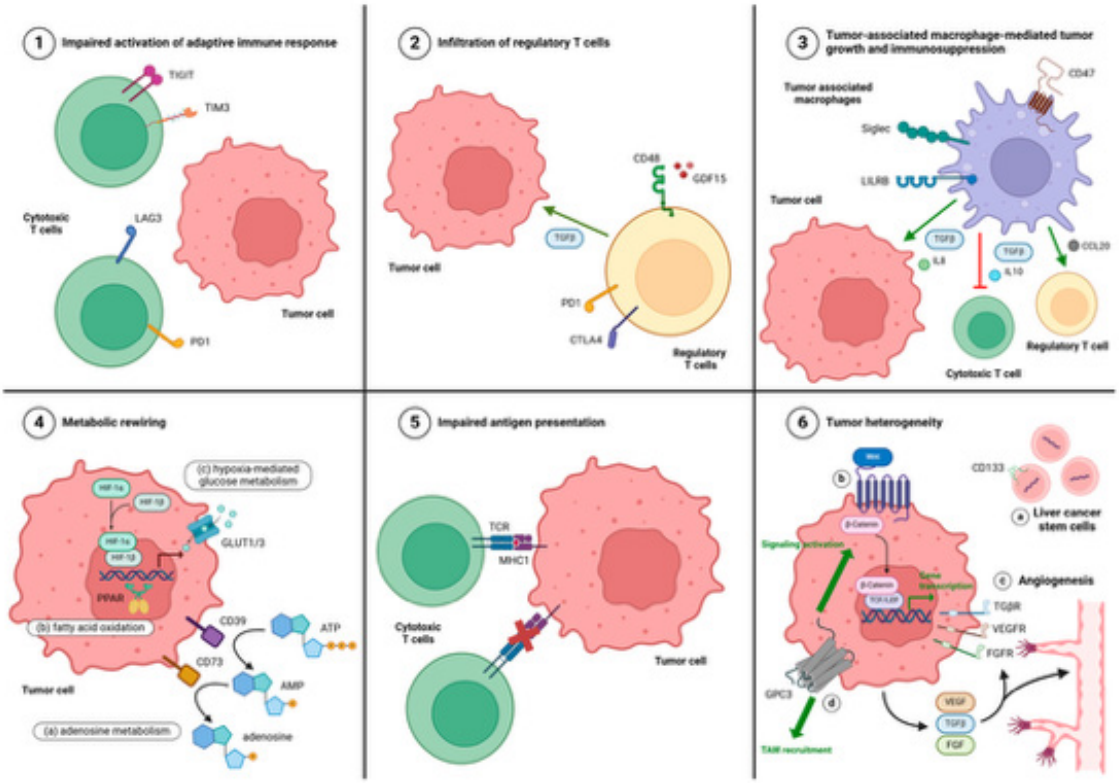

Figure 3 Mechanisms of Tumor Cell Immune Evasion[7]

Antibody-Based Therapy

ICIs are antibody-based therapies that block interactions between checkpoint proteins and their ligands, preventing T-cell suppression. Key targets include PD-1, PD-L1, and CTLA-4. PD-1, expressed on activated T cells, NK cells, Tregs, MDSCs, monocytes, and dendritic cells, binds to PD-L1 and PD-L2 on tumor cells, including HCC, to dampen T-cell activity and enable immune evasion. ICIs targeting these pathways have become central in treating solid tumors such as HCC. Considering the liver's tolerogenic nature and the immunosuppressive tumor microenvironment in HCC, ICIs offer a promising therapeutic approach.[7,8]

These therapies are indicated for patients with advanced-stage HCC who are ineligible for curative treatment, have preserved liver function (Child-Pugh class A), an ECOG performance status of 0–1, and adequate organ function.[12]

1. Atezolizumab + Bevacizumab

For more than ten years, sorafenib was the cornerstone of first-line therapy for advanced HCC. The IMbrave150 trial shifted this paradigm by revealing that atezolizumab plus bevacizumab significantly prolonged OS compared to sorafenib. Atezolizumab targets programmed death-ligand 1 (PD-L1), while bevacizumab inhibits vascular endothelial growth factor-A (VEGF-A), as seen in **Figure 4.** VEGF is frequently overexpressed in HCC and contributes to immune suppression within the tumor microenvironment. Anti-VEGF therapy helps overcome immunosuppressive mechanisms, facilitates T-cell penetration, and augments the efficacy of immune checkpoint therapy.[8]

In a Phase III study including 501 patients with unresectable and previously untreated HCC, administration of atezolizumab (1200 mg) combined with bevacizumab (15 mg/kg) every three weeks led to a significant improvement in 12-month: OS 67.2% versus 54.6% compared with sorafenib, and PFS 6.8 versus 4.3 months with sorafenib. The combination therapy also achieved an objective response rate over twice that of sorafenib.[8,18]

Treatment-related adverse events occurred in 38% of patients, primarily hypertension and proteinuria. Due to the bleeding risk linked to bevacizumab, patients underwent upper endoscopy before enrollment to assess and manage esophageal varices. The positive findings from IMbrave150 led the US FDA to approve atezolizumab–bevacizumab as a first-line therapy for advanced HCC in patients with Child-Pugh A liver function and good performance status. For patients with contraindications to bevacizumab, the combination of tremelimumab and durvalumab was an alternative. In Child-Pugh B patients with a score of 7, dual monotherapy is not recommended; sorafenib or lenvatinib may be preferred in those with poor clinical status, comorbidities, or limited immunotherapy tolerance **(Figure 5).**[4]

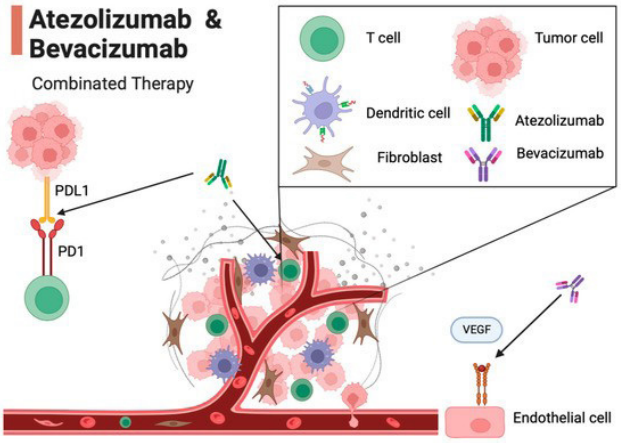

Figure 4. Mechanism of Action of Atezolizumab and Bevacizumab[18]

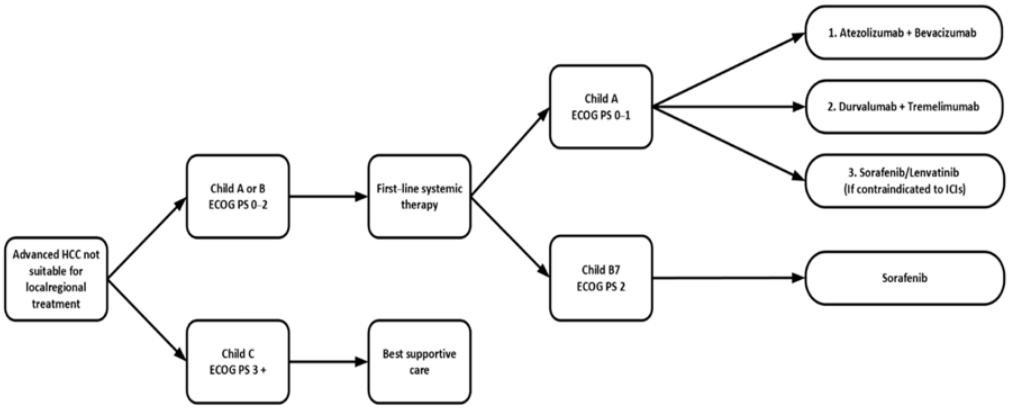

Figure 5. First-line Systemic Therapy for HCC[4]

2. Durvalumab + Tremelimumab

The durvalumab (anti-PD-L1) and tremelimumab (anti–CTLA-4) combination has demonstrated effectiveness as a first-line therapy for patients with unresectable HCC. In the Phase III HIMALAYA trial, the STRIDE regimen—consisting of a single dose of tremelimumab 300 mg followed by durvalumab 1500 mg every four weeks—led to a notable increase in OS compared to sorafenib. After four years, 25.2% of patients treated with STRIDE were still alive, versus 15.1% in the sorafenib arm, highlighting a survival outcome previously unseen in HCC. Patients treated with STRIDE had a median OS of 16.4 months, compared with 13.8 months in the sorafenib group, while durvalumab alone yielded a median OS of 16.6 months.[20]

Common adverse effects in the STRIDE cohort included rash, fatigue, diarrhea, pruritus, musculoskeletal discomfort, and abdominal pain, all of which were generally manageable. These results led to the FDA's 2022 approval of durvalumab–tremelimumab as a first-line treatment for adults with unresectable HCC who had not received previous systemic therapy. This immunotherapy provides an alternative for patients having intact liver function (Child-Pugh A) who are ineligible for curative procedures such as resection or transplantation, especially for those who cannot receive atezolizumab–bevacizumab.[20]

3. Ipilimumab + Nivolumab

As a monoclonal antibody targeting CTLA-4, ipilimumab increases T-cell activation and proliferation, strengthening the immune response against cancer cells. This immune activation, however, may cause immune-related adverse events (irAEs) such as diarrhea, colitis, hepatotoxicity, autoimmune hepatitis, rash, and pruritus. Management of irAEs typically involves temporary discontinuation of therapy and systemic corticosteroids.[21]

Ipilimumab has been studied in combination with nivolumab (an anti-PD-1 antibody) for the treatment of advanced HCC, particularly in patients previously treated with sorafenib. This dual immune checkpoint blockade aims to synergistically enhance antitumor immunity. In the Phase I/II CheckMate 040 trial, combining nivolumab and ipilimumab resulted in an objective response rate (ORR) of 32%, a median response duration of 51.2 months, a median OS of 22.2 months, and a five-year survival rate of 29%. Subsequently, the Phase III CheckMate 9DW study reported a median OS of 23.7 months for the combination therapy, compared to 20.6 months for patients receiving tyrosine kinase inhibitors (TKIs), with a median duration of response of 30.4 months versus 12.9 months for TKIs. These findings supported the FDA's April 2025 authorization of nivolumab–ipilimumab as a first-line option for advanced HCC, with nivolumab 1 mg/kg and ipilimumab 3 mg/kg administered every three weeks for four cycles, followed by nivolumab 480 mg every four weeks. Eligible patients required preserved liver function (Child-Pugh A), ECOG 0–1, and no previous systemic treatment.[21,22]

Antibody-based immunotherapies for HCC primarily include anti-PD-1, anti-PD-L1, and anti–CTLA-4 agents, which differ in their mechanisms of action, clinical roles, and safety profiles. Anti–PD-1 antibodies act by blocking the PD-1 receptor on T cells, thereby restoring exhausted T-cell function, and are commonly used as monotherapy or in combination regimens. Anti-PD-L1 antibodies inhibit the interaction between PD-L1 on tumor or immune cells and PD-1 on T cells, and are often combined with anti-angiogenic agents to enhance antitumor efficacy with a relatively favorable safety profile. In contrast, anti-CTLA-4 antibodies promote T-cell priming and activation at an earlier stage of the immune response, resulting in stronger immune stimulation but also a higher risk of immune-related adverse events, which limits their use mainly to selected patients or combination strategies.[18,23]

Adoptive Cell Therapy

Adoptive cell therapy (ACT) is an immunotherapeutic approach that employs immune cells obtained from the patient or a healthy donor to recognize and destroy cancer cells. Unlike passive immunotherapy, ACT involves isolating, activating, expanding, or genetically engineering effector cells ex vivo before reinfusion, enabling them to exert durable antitumor effects. It is often referred to as a "living therapy" because the transferred immune cells retain their functionality and persist in the host. Compared to chemotherapy, ACT offers greater specificity by targeting tumor-associated antigens.[18]

Several ACT modalities are being explored for HCC. Cytokine-induced killer cells (CIKs) are cytotoxic immune cells that can recognize and kill tumor cells in an MHC-unrestricted manner through adhesion molecules. These cells are created by exposing

a patient's peripheral blood mononuclear cells to a combination of cytokines. Liu et al. (2021) reported that autologous CIKs improved clinical outcomes in patients with primary HCC without causing significant side effects, suggesting their potential to boost immune function. TILs, extracted directly from tumor tissues, consist of diverse immune cells, including T cells, NK cells, B cells, and regulatory T cells (Tregs), and play a central role in antitumor immunity. A Phase I study has shown that TIL therapy in HCC is feasible and can recognize multiple tumor antigens, providing stronger cytotoxic activity compared to single-antigen therapies. Nonetheless, the need to obtain tumor tissue remains a practical limitation of this approach.[18,23]

Chimeric antigen receptor (CAR) therapies involve genetically engineering T cells or NK cells to express synthetic receptors that specifically recognize tumor-associated antigens. CAR-NK cells offer several advantages, including a reduced likelihood of cytokine release syndrome and the potential to use allogeneic off-the-shelf products. Another form of immunotherapy, T-cell receptor-engineered (TCR-T) therapy, modifies T cells to recognize intracellular tumor peptides presented by MHC class I molecules. This method requires compatibility with the patient's HLA type and is currently being evaluated in early-phase clinical trials for HCC.[23,24]

Therapeutic Vaccines

Therapeutic vaccines are a type of immunotherapy aimed at introducing tumor-associated antigens to trigger an effective anti-cancer immune response. In HCC, immunotherapeutic research has targeted peptides, dendritic cells (DC), and oncolytic virus vaccines. Peptide vaccines induce cytotoxic T-cell responses against antigens such as GPC3 and AFP, while DC vaccines stimulate $CD8^+$ T cells and boost serum IFN-γ, leading to improved patient outcomes.[23]

Meta-analyses support that DC-based vaccines boost antitumor immunity, extend survival, and reduce recurrence with low toxicity. Pairing TAE with DC infusion enhances the activation of tumor-targeted T cells. Oncolytic viruses, such as JX-594 (Pexa-Vec), replicate preferentially in tumor cells, causing destruction and activating the immune system. However, the effectiveness of these vaccines is limited by the immunosuppressive microenvironment, and a Phase III study of Pexa-Vec plus sorafenib showed no substantial clinical benefit.[23,25]

Cytokines

Cytokines play a key role in the immune system's antitumor activity, acting as signaling molecules secreted by various immune cells, including interferons, interleukins, colony-stimulating factors, and tumor necrosis factors. Interferons possess antiviral, immunoregulatory, anti-angiogenic, and pro-apoptotic effects, making them valuable in cancer treatment. Studies have shown that PEGylated interferons can lower recurrence rates after surgery in HCC patients with hepatitis. Interleukin-2 (IL-2) supports the expansion of T cells and other effector immune cells, improving survival outcomes in patients with unresectable HCC, underscoring the therapeutic potential of cytokines in liver cancer. Nevertheless, cytokine monotherapy is limited by insufficient accumulation in tumor tissue, high systemic toxicity, and the risk of activating immune checkpoints, which reduces clinical efficacy.[18]

Adverse Effects of Immunotherapy in HCC

Treatment with ICIs can induce irAEs due to heightened immune activity. The severity of these events is rated I through V using the CTCAE guidelines. Grade I involves mild symptoms; immunotherapy can continue with monitoring. Symptomatic treatments may include antihypertensives, topical agents for rash/pruritus, and loperamide for mild diarrhea. Grade II covers moderate symptoms that begin to limit daily activities; temporary cessation of ICI therapy and initiation of prednisone 0.5–1 mg/kg/day is advised. Grade III–IV include severe symptoms requiring medical intervention; initiate IV methylprednisolone 1–2 mg/kg/day. If no response in 48–72 hours, additional immunosuppressive agents such as infliximab, vedolizumab, or tocilizumab may be considered. Steroids should be tapered gradually to avoid flares. Once irAEs improve to ≤ Grade I, re-challenge with reduced dose or a switch to anti-PD-1 monotherapy may be considered. In Grade V, ICI therapy should be permanently discontinued. Palliative care or multidisciplinary consultation should be pursued as needed.[26]

Challenges in the Development of Immunotherapy

HCC is a highly malignant liver tumor with historically restricted therapeutic choices. Over the past decade, immunotherapy—especially in combination regimens—has redefined treatment strategies. The atezolizumab–bevacizumab combination, by

concurrently targeting immune checkpoints and angiogenesis, has demonstrated superior clinical outcomes over sorafenib in the IMbrave150 trial. However, the immunosuppressive environment within HCC tumors often limits the therapeutic efficacy of ICIs. Patients with smaller tumors (<5 cm), AFP decline ≥20% within eight weeks, minimal extrahepatic metastases, and lower leukocyte counts show more favorable responses. Although patients with non-viral etiologies like metabolic steatohepatitis also benefit from ICIs, responses are generally less robust than those with HBV- or HCV-associated HCC. In IMbrave150, non-viral HCC—particularly NASH—was associated with lower OS, likely due to preexisting T-cell exhaustion in the liver.[27,28]

Emerging strategies include personalized therapeutic cancer vaccines, such as Geneos Therapeutics' DNA vaccine combined with pembrolizumab, which showed tumor shrinkage in one-third of patients—double that of pembrolizumab alone. Promising directions involve triplet combinations of second-generation ICIs (e.g., TIGIT, LAG3, TIM3) with anti-PD-1/PD-L1 and anti-VEGF agents. Specific tumor-associated antigens like glypican-3 (GPC3) are also being investigated. Ongoing innovations focus on overcoming therapeutic resistance through second-generation ICIs, tumor microenvironment remodeling, precision delivery systems, and locoregional interventions. To ensure efficacy and minimize irAEs, validated biomarkers for patient selection are crucial. These efforts will support the development of personalized immunotherapy strategies and guide future clinical trials in HCC.[7,18,29]

Emerging immunotherapeutic strategies in HCC are increasingly focused on optimizing immune checkpoint inhibitor combinations with anti-angiogenic agents and locoregional treatments to enhance antitumor immunity and overcome resistance, while novel agents, such as bispecific antibodies, adoptive cell therapies, and cancer vaccines, are under active investigation. The identification of reliable predictive biomarkers is expected to refine patient selection and improve treatment efficacy. These converging efforts mark a shift toward personalized immunotherapy and are anticipated to broaden the clinical applicability and long-term outcomes of HCC immunotherapy.[30]

CONCLUSION

HCC remains a highly aggressive primary liver malignancy with considerable clinical challenges. Traditional therapies often provide limited, durable benefits. Immunotherapy using monoclonal antibodies, particularly ICIs, has emerged as a promising treatment strategy, capable of enhancing antitumor immune activity by targeting PD-L1, CTLA-4, and PD-1 pathways. Atezolizumab plus bevacizumab, which blocks PD-L1 and VEGF, has received FDA approval for use as a first-line systemic treatment in individuals with unresectable HCC. For those unable to receive this regimen, alternative ICI combinations, including durvalumab with tremelimumab or nivolumab with ipilimumab, are also FDA-approved for patients with preserved liver function. Despite their clinical benefits, ICIs may trigger immune-related adverse events (irAEs); therefore, **close monitoring during treatment is highly recommended**, with timely management based on toxicity severity.

CONFLICT OF INTEREST

The authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

All authors contributed substantially to the conception and design of the study, literature review, manuscript preparation, critical revision, and final approval of the manuscript.

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