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From Viral Oncogenesis to Dual Checkpoint Blockade: A Comprehensive Review of Hepatocellular Carcinoma Biology, Treatment and Guideline Evolution

Ziming Qiao

School of Science, Engineering, and Technology, Pennsylvania State University, Harrisburg, USA
zpq5037@psu.edu

Abstract. Hepatocellular carcinoma (HCC) is the leading primary liver cancer and remains one of the deadliest malignancies globally. Its incidence continues to rise, driven by chronic viral hepatitis in the Eastern countries and metabolic liver disease in the Western countries. Landmark phase III trials have transformed the landscape of systemic therapy: atezolizumab–bevacizumab, durvalumab–tremelimumab, and nivolumab–ipilimumab each deliver superior survival over sorafenib and are now first-line standards. Parallel studies are testing these agents in adjuvant, neoadjuvant, and locoregional combinations, signalling a shift toward earlier immunologic intervention. Yet the field still lacks validated biomarkers and globally harmonised treatment algorithms. This review compiles current evidence on worldwide epidemiology of HCC, key risk factors such as HBV, aflatoxin exposure and NAFLD, and the molecular pathways that drive hepatocarcinogenesis. It critically compares the design, efficacy and safety of major immunotherapy trials and summarises ongoing studies that combine systemic agents with surgery, ablation or transarterial chemo-embolisation. By mapping existing data to current unmet needs, this analysis highlights key opportunities for advancing biomarker-guided precision therapy and expanding access to novel treatments in resource-limited settings.

Keywords: Hepatocellular carcinoma, Tremelimumab, Malignancies, Embolisation.

1. Introduction

Hepatocellular carcinoma (HCC) represents the dominant histological subtype of primary liver cancer and is the fifth most commonly diagnosed cancer globally [1,2]. In 2020 alone, more than 900,000 new cases and over 800,000 deaths were attributed to liver cancer, with HCC accounting for 75–85% of cases [1]. The global distribution of HCC is notably heterogeneous, with East Asia and sub-Saharan Africa disproportionately affected due to endemic HBV infection and dietary exposure to aflatoxin B1, which induces characteristic R249S TP53 mutations [3,4].

Conversely, in Western countries like the United States and United Kingdom, the increasing burden of HCC is largely driven by NAFLD and metabolic syndrome, often in the absence of cirrhosis [2,5]. Marked regional differences in access to early detection, antiviral therapy, liver

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transplantation, and advanced systemic therapies contribute to significant disparities in clinical outcomes and overall survival [6,7].

The etiology of HCC is multifactorial. Chronic HBV and HCV infections remain the leading risk factors worldwide, although metabolic conditions such as obesity and type 2 diabetes, as well as environmental exposures like aflatoxins, alcohol, and industrial toxins (e.g., vinyl chloride), play significant roles [3,4,8]. Inherited disorders including hereditary hemochromatosis and Wilson's disease, though less common, represent important genetic risk factors [2].

Systemic therapy for advanced HCC has evolved significantly in recent years. The multikinase inhibitor sorafenib remained the only approved first-line agent for over a decade, offering limited efficacy and significant toxicity [6]. The introduction of ICIs, beginning with early trials of PD-1/PD-L1 inhibitors, led to mixed results, spurring further investigation into combination regimens that could improve antitumor immunity and overcome the immune-suppressive tumor microenvironment (TME) [9].

A major breakthrough came with the IMbrave150 trial, which showed that atezolizumab plus bevacizumab significantly prolonged overall and progression-free survival compared to sorafenib, and improved quality of life metrics [6]. The HIMALAYA trial introduced a chemotherapy-free immune checkpoint blockade strategy using durvalumab and tremelimumab (STRIDE regimen), while CheckMate-9DW revealed strong clinical efficacy of nivolumab and ipilimumab as dual checkpoint blockade [10-13] . Collectively, these landmark studies represent a paradigm shift in systemic therapy and are now reflected in international clinical guidelines [8].

This review examines the latest evidence surrounding HCC epidemiology, risk stratification, pathogenesis, and treatment evolution. Emphasis will be placed on integrating immunotherapy into clinical practice and addressing regional disparities in outcomes and drug access.

2. Epidemiology and global distribution of HCC

HCC is the predominant histologic type of primary liver cancer and remains one of the leading causes of cancer-related death globally. According to the GLOBOCAN 2020 estimates, liver cancer was responsible for approximately 905,677 new cases and 830,180 deaths worldwide, placing it sixth in incidence and third in mortality among all cancers [6]. The overwhelming majority—75% to 85%—of these cases are HCC [1,6].

2.1. Global incidence patterns

HCC shows significant geographical disparity, with the highest incidence rates observed in East and Southeast Asia, as well as sub-Saharan Africa. These patterns reflect underlying etiological factors, including chronic hepatitis B virus (HBV) infection, which is endemic in these regions, and aflatoxin B1 exposure, a potent mycotoxin produced by Aspergillus flavus that contaminates food storage in tropical climates [1,3]. China alone accounts for over 50% of all global HCC cases [1]. The synergistic effect of chronic HBV infection and aflatoxin B1 exposure is particularly evident, especially in rural regions of Asia and Africa, where both exposures remains common [3].

In Western countries such as the United States and the United Kingdom, while HBV and HCV still contribute, the rising incidence of HCC is largely attributed to metabolic risk factors, including obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) [2,5]. These conditions can lead to non-alcoholic steatohepatitis (NASH), which in turn may progress to cirrhosis and liver cancer. Importantly, a growing proportion of HCC cases in the Western populations are being diagnosed in non-cirrhotic livers, a shift that complicates screening and early detection [1,2].

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2.2. Sex and age disparities

Globally, males are 2 to 4 times more likely than females to develop HCC [1]. This disparity is partly due to differences in lifestyle-related risk exposures—such as smoking and alcohol use—as well as potential biological influences, including hormonal and immune regulatory mechanisms [1]. Additionally, HCC tends to occur at a younger age in high-incidence regions such as sub-Saharan Africa and East Asia (often in the 40s to 50s) compared to Western countries, where the median age at diagnosis is typically in the 60s [1,2].

Even within a single high-income health system, pronounced regional inequities persist in how HCC is detected and treated. In England, an analysis of 15 468 patients diagnosed between 2010 and 2016 showed that 35.6 % first presented as an emergency, whereas only 31.1 % were referred by a general practitioner and 11.5 % entered care via the two-week-wait cancer pathway. Emergency presentation carried the worst prognosis: one-year net survival for this route was 38.2 % in Kent and Medway versus 53.0 % for patients in West Yorkshire who were more often diagnosed through planned outpatient channels. Access to potentially curative therapy also varied widely; overall, only 21.4 % of patients received resection, transplantation or ablation, but the proportion ranged from < 16 % in Kent and Medway, Lancashire and South Cumbria, and South-East London to ≥ 27 % in Cheshire and Merseyside and West Yorkshire. After adjustment for age, sex and socioeconomic deprivation, odds of emergency presentation rose by 1 % per year of age and 10 % per deprivation quintile, while the likelihood of curative treatment fell by roughly 5 % for each year increase in age and 11 % per deprivation quintile. These findings demonstrate that inequalities in surveillance uptake, specialist referral and socioeconomic status translate directly into differences in treatment opportunity and survival, even under a universal-coverage model [2].

The World Health Organization projects that the global burden of liver cancer will increase by over 55% by 2040, potentially reaching 1.4 million deaths per year without stronger efforts in prevention and early detection [6]. Primary prevention strategies—such as universal HBV vaccination, screening and treatment of viral hepatitis, and dietary aflatoxin control—are therefore critical in high-burden regions [1,8]. In contrast, in Western countries, addressing metabolic risk profiles and implementing surveillance protocols for NAFLD-related cirrhosis are key emerging challenges [1,8,9].

3. Etiology and risk factors of HCC

HCC arises from a complex interplay between viral, metabolic, toxic, genetic, and immunological factors. While the etiologic spectrum varies by geography and socioeconomic context, a consistent core of major risk factors has been identified globally. Understanding these factors is critical for guiding effective prevention strategies and optimizing individualized approaches to disease management.

3.1. Chronic hepatitis B and C infections

Chronic infection with HBV remains the most important global risk factor for HCC, especially in East Asia and sub-Saharan Africa, where it accounts for 50% to 80% of all cases [1]. The oncogenic potential of HBV stems from both indirect mechanisms—such as chronic inflammation and liver fibrosis—and direct effects, including integration of HBV DNA into the host genome and expression of viral proteins like HBx, which promotes genomic instability [4].

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Hepatitis C virus (HCV) infection is a leading cause of HCC in Western countries. Unlike HBV, HCV does not integrate into host DNA but causes persistent hepatic inflammation, leading to fibrosis and cirrhosis. Patients with advanced fibrosis or cirrhosis remain at increased risk for HCC even after viral eradication by direct-acting antivirals (DAAs) therapy [4].

3.2. Aflatoxin B1 exposure

Aflatoxin B1 (AFB1), a mycotoxin produced by Aspergillus species, is a potent hepatocarcinogen found in inadequately stored grains and nuts, especially in warm, humid regions. AFB1 induces the TP53 R249S mutation, a well-established driver mutation in HCC [3]. Experimental and epidemiological evidence shows a synergistic carcinogenic effect between chronic HBV infection and aflatoxin exposure, markedly elevating HCC risk in affected populations [3]. Excessive alcohol consumption contributes hepatocarcinogenesis through multiple mechanisms including oxidative stress, lipid peroxidation, acetaldehyde toxicity, and chronic inflammation. Long-term alcohol abuse can result in alcoholic steatohepatitis (ASH), fibrosis, cirrhosis, and ultimately, HCC [1]. Alcohol remains a major risk factor to HCC in many regions of Europe and the Americas.

3.3. Metabolic syndrome, NAFLD, and NASH

NAFLD and its progressive form, NASH, have emerged as dominant risk factors for HCC in high-income countries [2,5]. NAFLD is strongly associated with obesity, type 2 diabetes mellitus, dyslipidemia, and insulin resistance—collectively termed metabolic syndrome. More importantly, HCC can develop in NAFLD patients even in the absence of cirrhosis, posing challenges for surveillance [1,2].

The pro-inflammatory microenvironment in NASH promotes hepatocyte injury, regenerative hyperplasia, and fibrosis, setting the stage for malignant transformation. With the global obesity epidemic worsening, NAFLD-related HCC is projected to become the leading cause of liver cancer in the United States by 2030 [1].

3.4. Genetic and rare disorders

A small subset of HCCs develops on the background of inherited metabolic disorders that disrupt hepatic homeostasis from an early age. In hereditary hemochromatosis, excessive intestinal iron absorption leads to parenchymal iron overload, resulting in oxidative DNA damage, and progressive fibrosis. Wilson's disease causes toxic copper accumulation, provoking chronic necro-inflammatory injury and cirrhosis. Alpha-1 antitrypsin deficiency results in polymerised protein inclusions within hepatocytes, predisposing the liver to steatohepatitis and scarring, while tyrosinaemia type I produces fumarylacetoacetate accumulation, triggering early-onset hepatocellular injury and malignant transformation. Although each disorder is individually rare, they warrant consideration in younger patients or in those who lack the more common viral, metabolic, or toxic risk factors for HCC [1].

Recent evidence reveal that immune dysregulation also plays a key role in HCC progression. Chronic inflammation, T-cell exhaustion, immunosuppressive cytokines (e.g., IL-10, TGF-β), and regulatory T cell infiltration create a permissive TME [5,14]. These immune characteristics not only facilitate carcinogenesis but also inform the rationale for immune checkpoint inhibitor (ICI) therapy in advanced HCC [5,15].

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4. Pathogenesis and molecular mechanisms of HCC

HCC arises through a multistep process of chronic hepatic injury, inflammation, regeneration, and eventual malignant transformation. The pathogenesis of HCC is underpinned by both extrinsic etiologic insults—such as viral hepatitis, toxins, and metabolic disease—and intrinsic genetic and epigenetic alterations. In recent years, increasing clarity has emerged regarding the molecular pathways and cellular ecosystems that govern HCC development, offering critical implications for targeted and immune-based therapies.

4.1. Chronic injury, inflammation, and cirrhosis

The majority of HCC cases develop on a background of chronic liver disease, particularly cirrhosis, which provides a protumorigenic microenvironment. Repeated hepatocyte injury from viral infections (HBV, HCV), alcohol, or fatty liver disease results in cycles of cell death and compensatory regeneration, promoting DNA replication errors and mutations [1,4]. Kupffer cell activation and inflammatory cytokines (e.g., IL-6, TNF-α) drive oxidative stress, fibrosis, and remodeling of the extracellular matrix [5].

Cirrhosis itself is a precancerous state. Fibrotic nodules, impaired vasculature, and hypoxia create selective pressure favoring clonal evolution of dysplastic hepatocytes. Even after viral suppression (e.g., via direct-acting antivirals for HCV), cirrhotic patients remain at elevated risk for HCC due to irreversible architectural distortion and latent molecular damage [4].

4.2. Viral oncogenesis: HBV and HCV

HBV has direct oncogenic potential due to its integration into the host genome. This process leads to chromosomal instability, insertional mutagenesis, and expression of oncogenic viral proteins such as HBx, which interferes with tumor suppressors like p53 and retinoblastoma (Rb) proteins [4]. HBV integration also dysregulates genes involved in cell cycle progression and telomerase activation [1,4].

In contrast, HCV is an RNA virus that does not integrate into host DNA but induces persistent inflammation and immune-mediated injury. Viral proteins like core, NS3, and NS5A can modulate insulin signaling, Wnt/β-catenin signaling, and apoptosis, contributing indirectly to hepatocarcinogenesis [4].

4.3. Genomic instability and common mutations

Large-scale genomic profiling has revealed that HCC is driven by a limited set of recurrent, often overlapping lesions that converge on cell-cycle control, telomere maintenance, and oncogenic signalling. One of the earliest events is the reactivation of telomerase through promoter mutations in TERT, a change detected in roughly two-thirds of tumours and thought to confer a replicative advantage to premalignant hepatocytes [5]. In regions where dietary aflatoxin B1 is endemic, the canonical TP53-R249S hotspot predominates, providing strong molecular evidence of the toxin's mutagenic fingerprint [3]. Constitutive activation of the Wnt/β-catenin cascade arises from gain-of-function mutations in CTNNB1, promoting unchecked proliferation and immune exclusion of the tumour niche [7]. Additional loss- or gain-of-function alterations in AXIN1, ARID1A, PIK3CA and MTOR further deregulate chromatin structure, apoptotic signalling and metabolic homeostasis, collectively dismantling DNA-damage checkpoints and innate tumour-surveillance mechanisms [5]. These interrelated genetic programmes, amplified by an immunosuppressive micro-environment rich

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in regulatory T cells and myeloid-derived suppressor cells, laying the molecular foundation on which hepatocarcinogenesis and immune escape.

The tumour micro-environment in HCC is profoundly immunosuppressive. High densities of regulatory T cells and myeloid-derived suppressor cells accumulate around, and sometimes within, tumour nodules, curtailing cytotoxic T-cell priming and natural-killer-cell activity. At the same time, malignant hepatocytes and infiltrating immune cells up-regulate multiple checkpoint molecules—including PD-1, CTLA-4 and, in a sizeable subset, LAG-3—imposing redundant brakes on effector T-cell function. The cytokine milieu is dominated by interleukin-10 and transforming growth factor-β, both of which reinforce regulatory cell expansion and inhibit antigen presentation. Concomitantly, many tumours down-regulate major-histocompatibility-complex class I molecules, thereby blunting neo-antigen display and rendering the lesions less visible to the adaptive immune system. Together, these cellular, molecular and cytokine-driven mechanisms establish an immune-privileged niche that supports tumour growth and contributes to primary resistance against single-agent immune checkpoint blockade.

These features enable tumor immune evasion and foster progression [5,13]. Additionally, β-catenin activation is associated with "cold" tumors that resist immune checkpoint blockade due to poor T cell infiltration [7]. This has important implications for therapy selection and biomarker development in immuno-oncology.

4.4. Epigenetic and metabolic reprogramming

Beyond genetic mutations, HCC evolves through a layered epigenetic programme that remodels chromatin architecture and gene expression. Hypermethylation of CpG islands within the promoters of tumour-suppressor genes—including those governing cell-cycle arrest and DNA repair—silences their transcription and removes critical braking mechanisms on proliferation. These DNA-methylation changes are complemented by aberrant histone marks: widespread acetylation of histone H3 lysine-27 and trimethylation of lysine-4, for example, open chromatin domains that favour oncogene expression, whereas loss of acetylation at lysine-9 condenses chromatin around growth-inhibitory loci. Non-coding RNAs provide an additional layer of post-transcriptional regulation; in particular, down-regulation of the liver-specific microRNA-122 derepresses a network of pro-oncogenic targets involved in lipid metabolism and cell-cycle progression, while other dysregulated microRNAs modulate Wnt, PI3K/Akt and TGF-β pathways. Together, these DNA, histone and RNA modifications cooperate with somatic mutations to shift the transcriptomic landscape toward sustained proliferation, metabolic re-programming and immune evasion, thereby reinforcing every stage of hepatocarcinogenesis.

Moreover, tumors undergo metabolic reprogramming, with increased glycolysis (Warburg effect), altered lipid metabolism, and glutamine addiction—facilitating survival under hypoxia and nutrient stress [5].

5. Systemic therapy of HCC: from sorafenib to immune-based combinations

For over a decade, systemic therapy for advanced HCC was defined by the use of sorafenib, a multikinase inhibitor that targets VEGFR, PDGFR, and RAF kinases. Approved in 2007 following the SHARP trial, sorafenib was the first agent to demonstrate a statistically significant survival benefit in unresectable HCC, extending median overall survival (OS) by approximately 2.8 months compared to placebo (10.7 vs. 7.9 months) [16]. However, the response rate was low (<5%), and toxicity—primarily hand-foot skin reaction, diarrhea, and fatigue—often limited its tolerability [16].

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5.1. Emergence of immunotherapy and IMbrave150 trial

The advent of ICIs marked a transformative era in HCC treatment. Despite promising phase I/II data for PD-1 inhibitors such as nivolumab and pembrolizumab, these agents failed to meet primary endpoints in confirmatory phase III trials (CheckMate-459 and KEYNOTE-240), prompting the exploration of combination strategies to enhance efficacy [7].

The IMbrave150 trial (2020) was a pivotal phase III study that evaluated the efficacy of atezolizumab (anti–PD-L1) plus bevacizumab (anti–VEGF) compared to sorafenib in patients with unresectable HCC [15]. The combination demonstrated a median OS not reached at primary analysis vs. 13.2 months for sorafenib, with a hazard ratio (HR) of 0.58 (95% CI, 0.42–0.79; $p<0.001$). The progression-free survival (PFS) was also significantly longer (6.8 vs. 4.3 months), and the objective response rate (ORR) was nearly triple (27.3% vs. 11.9%) [15].

Importantly, the combination also delayed deterioration in quality of life, making it the first regimen to improve both survival and patient-reported outcomes in HCC. As a result, atezolizumab plus bevacizumab was rapidly adopted as the new first-line standard of care by global treatment guidelines [15].

5.2. The HIMALAYA study and STRIDE regimen

The HIMALAYA trial (2022) introduced a novel, chemotherapy-free immunotherapy regimen known as STRIDE—single tremelimumab regular interval durvalumab. Tremelimumab (anti–CTLA-4) was given as a single priming dose, followed by regular dosing of durvalumab (anti–PD-L1). This dual immune checkpoint blockade strategy aimed to achieve rapid immune activation while minimizing toxicity [10].

The trial demonstrated a median OS of 16.4 months with STRIDE versus 13.8 months with sorafenib, with a HR of 0.78 (95% CI, 0.66–0.92; $p = 0.0035$). Notably, the STRIDE regimen had a manageable safety profile, with grade ≥3 treatment-related adverse events in 25.8% of patients—lower than with most dual ICI therapies [10,16]. Durvalumab monotherapy was also shown to be non-inferior to sorafenib, providing a viable option for patients unsuitable for combination therapy. In 2024, an updated 4-year follow-up confirmed sustained OS benefit and long-term responders, particularly among patients with low tumor burden and non-viral etiologies [16].

5.3. CheckMate-9DW: nivolumab + ipilimumab as first-line therapy

The CheckMate-9DW trial further evaluated a dual checkpoint blockade approach using nivolumab (anti–PD-1) and ipilimumab (anti–CTLA-4). While full peer-reviewed publication is pending, early reports suggest that the combination yielded a significant OS benefit over sorafenib, with high objective response rates (~30%) and durable disease control in a meaningful proportion of patients [11].

This combination is modeled after the success of CheckMate 040, a phase I/II study that demonstrated high response rates and manageable toxicity in pretreated HCC patients [13]. The toxicity profile of nivolumab plus ipilimumab is more intense than STRIDE or atezo/bev regimens, requiring close monitoring and expertise in immune-related adverse event management.

5.4. Treatment selection and clinical implications

As of 2024, three major first-line systemic options have emerged for advanced HCC (Table 1). Treatment choice should be guided by patient comorbidities, bleeding risk (e.g., varices for

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bevacizumab), autoimmune status, tumor burden, and access to monitoring and follow-up [15,17].

Table 1. Treatment selection and clinical implications

Regimen	Composition	Median OS	Key Advantages
Atezo + Bev (IMbrave150)	Anti–PD-L1 + Anti–VEGF	Not reached (~19.2 mo)	High ORR, QoL benefit, anti-angiogenic synergy
STRIDE (HIMALAYA)	Tremelimumab (1 dose) + Durvalumab	16.4 mo	Chemo-free, low AE burden
Nivo + Ipi (CheckMate-9DW)	Dual ICI	~21 mo (est.)	Highest ORR, deep responses

6. Adjuvant, neoadjuvant, and guideline-based therapeutic strategies in HCC

The therapeutic landscape of HCC extends beyond systemic treatment for advanced disease. Increasingly, efforts are directed at early intervention, perioperative strategies, and evidence-based guideline harmonization to optimize long-term outcomes across the disease spectrum. This chapter outlines the roles of adjuvant, neoadjuvant, and guideline-directed therapies as defined by leading international and national frameworks, including the BCLC, EASL, AASLD, and CSCO guidelines.

6.1. Adjuvant therapy: addressing postoperative recurrence risk

HCC is characterized by a high recurrence rate even after curative-intent treatments such as surgical resection or ablation. Studies report that up to 70% of patients experience tumor recurrence within five years of resection [1,5]. Historically, no globally approved adjuvant therapy has been available for HCC; however, multiple strategies are currently under active investigation.

6.2. Tyrosine Kinase Inhibitors (TKIs)

The STORM trial evaluated sorafenib as adjuvant therapy in high-risk patients after resection or ablation, but it failed to demonstrate a significant benefit in recurrence-free survival (RFS) compared to placebo [6]. As a result, TKIs are not currently recommended as routine adjuvant therapy in international clinical guidelines.

6.3. Ongoing immunotherapy trials

Given the efficacy of ICIs in advanced disease, several ongoing trials (e.g., CheckMate-9DX, IMbrave050) are evaluating ICIs such as nivolumab, durvalumab, and atezolizumab as adjuvant therapies. Preliminary findings suggest potential in improving recurrence-free survival, especially in patients with residual microvascular invasion or high-risk molecular features [9].

6.4. Neoadjuvant approaches: immunomodulation before surgery

The rationale for neoadjuvant immunotherapy in HCC lies in the hypothesis that exposure to tumor antigens in the presence of intact vasculature may enhance T-cell priming and systemic immune activation. This approach also allows for early assessment of response and potentially facilitate tumors downstaging.

Several early-phase trials have investigated neoadjuvant nivolumab or durvalumab, either alone or without CTLA-4 inhibitors like tremelimumab. These studies have demonstrated acceptable

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safety profiles, tumor necrosis rates from 20 to 40%, and a potential to achieve pathological complete response (pCR) [16].

Although several phase II studies have reported encouraging pathological response rates, neoadjuvant immunotherapy for HCC remains investigational; to date no regimen has secured regulatory approval or been incorporated into routine practice. As a result, peri-operative strategies are guided more by expert consensus rather than by definitive level-I evidence.

6.5. Global treatment guidelines and the emerging consensus

The Barcelona Clinic Liver Cancer (BCLC) strategy, updated in 2022, continues to serve as the most widely adopted staging-and-treatment algorithm. In the revised version, atezolizumab combined with bevacizumab is explicitly endorsed as the preferred first-line systemic option for advanced (BCLC-C) disease, whereas trans-arterial chemo-embolisation (TACE) or surgical resection remains favoured for earlier stages with preserved liver function [5].

In Europe and North America, clinical societies have reached similar conclusions. Both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) now place atezolizumab + bevacizumab, the STRIDE regimen of tremelimumab single-dose priming plus durvalumab maintenance, and selected TKI/ICI combinations on an equal footing as first-line standards. These documents stress that therapy should be individualised according to Child–Pugh class, tumour burden, portal-hypertension status and extra-hepatic comorbidity [5,12].

In East Asia, the Chinese Society of Clinical Oncology (CSCO) tailors its recommendations to the uniquely high prevalence of HBV-related HCC. The 2022 guideline integrates long-term antiviral suppression with curative resection whenever feasible and lists atezolizumab + bevacizumab or durvalumab + tremelimumab as systemic first-line anchors. It also accords a prominent role to hepatic-arterial infusion chemotherapy (HAIC) and conformal radiotherapy for intermediate-stage tumours that are unsuitable for conventional TACE, thereby reflecting local practice patterns and resource availability [7].

Table 2. Treatment selection considerations

Parameter	Consideration
Liver function	Child–Pugh A is required for systemic therapy trials
Etiology (HBV, HCV, NAFLD)	HBV etiology may influence ICI efficacy; antiviral therapy is recommended
Bleeding risk	Variceal screening and management are essential before bevacizumab use
Autoimmune disorders	Caution with CTLA-4 or PD-1 blockade
Cost and access	Immunotherapy remains cost-prohibitive in many LMICs

Adjuvant and neoadjuvant strategies for HCC remain an evolving frontier, supported by emerging trials and growing evidence for immunotherapy's role in earlier disease settings (Table 2). Meanwhile, treatment guidelines continue to incorporate regional disease characteristics, resource availability, and molecular insights, pointing toward a future of precision-guided, multimodal care.

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7. Biomarkers and future directions in HCC

7.1. Challenges in biomarker discovery

Despite recent therapeutic advances, HCC still lacks validated biomarkers for predicting response to immunotherapy. Traditional markers such as alpha-fetoprotein (AFP) remain useful for surveillance and prognostication but have limited predictive value for treatment selection [1,8]. In the IMbrave150 trial, elevated AFP was associated with worse outcomes but was not predictive of benefit from atezolizumab plus bevacizumab [13]. Efforts to identify biomarkers of tumor immunogenicity, such as PD-L1 expression, tumor mutation burden (TMB), and immune cell infiltration, have produced inconsistent results in HCC [14,17].

7.2. TME and immune resistance

The TME in HCC is typically characterized by T-cell exhaustion, low PD-L1 expression, and immune exclusion. Genomic activation of the Wnt/β-catenin pathway has been associated with immune resistance, likely due to impaired T-cell recruitment [11]. This subgroup, often bearing CTNNB1 mutations, may not benefit from immune checkpoint blockade [7].

Other immunosuppressive factors include tumor-associated macrophages, myeloid-derived suppressor cells, and TGF-β signaling, all contributing to a non-inflamed tumor phenotype that limits response to immunotherapy [14,17]. Emerging work in tumor immunophenotyping—such as the identification of “immune-active” vs. “immune-desert” phenotypes—has shown potential in stratifying patients for ICI-based therapy [14]. In parallel, liquid biopsy platforms assessing circulating tumor DNA (ctDNA) and immunologic signatures are being explored to monitor dynamic response and resistance, though these remain investigational [15].

7.3. New immunotherapy combinations in development

Ongoing clinical development is steadily pushing immunotherapy into earlier disease stages and testing increasingly complex combinations with locoregional techniques. The phase-III LEAP-012 study is evaluating lenvatinib plus pembrolizumab in conjunction with TACE for intermediate-stage HCC, seeking to exploit the complementary anti-angiogenic, immunomodulatory and cytotoxic effects of this triplet regimen [12]. Similarly, EMERALD-1 is examining durvalumab with or without bevacizumab alongside TACE in an effort to embed checkpoint blockade at the time of first locoregional treatment and thus delay progression to a systemic-therapy setting [13]. For patients with unresectable disease, the IMbrave151 programme is adding cabozantinib to the established atezolizumab–bevacizumab backbone to determine whether vertical VEGF blockade plus multikinase inhibition can deepen and prolong responses beyond those achieved in IMbrave150 [15]. These trials signal a strategic pivot toward earlier and multi-modal immunotherapy that pairs systemic agents with TACE or HAIC, aiming to convert partial cytoreduction into durable immune control.

Parallel efforts in laboratory research and early-phase clinical trials are broadening the checkpoint repertoire beyond PD-1/PD-L1 and CTLA-4. In particular, inhibitors of LAG-3 and TIGIT are being explored for their capacity to reverse T-cell exhaustion and to synergise with established checkpoint blockade, offering new treatment avenues for patients with primary resistance to current immunotherapies [11,17].

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Beyond the canonical PD-1/PD-L1 and CTLA-4 axis, novel inhibitory receptors such as LAG-3 (lymphocyte activation gene 3) and TIGIT (T cell immunoreceptor with Ig and ITIM domains) have emerged as promising next-generation targets. These molecules contribute to T-cell exhaustion and immune escape which are now under investigation in HCC and other solid tumors. LAG-3 inhibitors, such as relatlimab, have shown efficacy in melanoma and are entering HCC trials in combination with anti–PD-1 agents. TIGIT inhibitors are similarly being evaluated for synergy with PD-1/PD-L1 blockade. These represent the next frontier in immune reprogramming strategies for HCC, potentially applicable across both early and advanced stages [11,17].

The future of HCC treatment lies in personalized immuno-oncology, integrating tumor biology, immune profiling, and genomic data. As newer agents and combinations enter clinical trials, rational treatment design and robust biomarker validation will be critical for maximizing benefit while minimizing toxicity and cost. The incorporation of immunotherapy in adjuvant, neoadjuvant, and intermediate-stage settings, along with exploration of novel immune targets, marks a decisive shift toward earlier and deeper intervention in HCC.

8. Conclusion

This review has synthesised current knowledge on HCC by mapping global epidemiology, clarifying the dominant viral, toxic and metabolic risk factors, and outlining the genomic and epigenetic events that drive malignant transformation. It has compared the pivotal immunotherapy trials that now underpin first-line systemic care, examined their extension into adjuvant and neoadjuvant settings, and collated the treatment algorithms of leading Western and Asian guidelines. In addition, emerging biomarker candidates, novel checkpoints such as LAG-3 and TIGIT, and combination studies that integrate immunotherapy with TACE or HAIC have been highlighted as the next frontier.

Taken together, these analyses underscore two key takeaways. First, a multi-modal strategy that couples early viral suppression or metabolic risk reduction with stage-appropriate locoregional and systemic therapy offers the best prospect of durable control. Second, the consistent survival gains achieved across IMbrave150, HIMALAYA and CheckMate-9DW demonstrate that rationally designed immune combinations can overcome much of the historical therapeutic inertia in advanced disease. By consolidating data on efficacy, safety and evolving guideline recommendations, this review provides a structured reference for clinicians selecting first-line regimens and for investigators designing peri-operative or biomarker-driven studies.

Several limitations should be acknowledged. Long-term data for dual-checkpoint and triplet regimens remain immature; heterogeneity in trial populations complicates cross-study comparisons; and real-world evidence from regions with restricted drug access is still sparse. Future research should prioritise prospective validation of immune-genomic biomarkers, optimise sequencing of systemic agents with surgery or ablative techniques, and expand access to curative treatments in resource-limited settings. Continued progress will depend on multinational collaboration that aligns basic science, clinical trials and public-health initiatives, ultimately translating molecular insight into equitable survival gains for patients with HCC.

References

[1] Yang, J. D., Hainaut, P., Gores, G. J., Amadou, A., Plymoth, A., and Roberts, L. R. A Global View of Hepatocellular Carcinoma: Trends, Risk, Prevention and Management. Nature Reviews Gastroenterology & Hepatology, vol. 16, no. 10, 2019, pp. 589–604.

[2] Burton, A., Balachandrakumar, V. K., Driver, R. J., et al. Regional Variations in Hepatocellular Carcinoma Incidence, Routes to Diagnosis, Treatment and Survival in England. British Journal of Cancer, vol. 126, no. 5,

DOI: 10.54254/2753-8818/2025.AU25990

2022, pp. 804–814.
[3] Han, C., Yu, T., Qin, W., et al. Genome-Wide Association Study of the TP53 R249S Mutation in Hepatocellular Carcinoma with Aflatoxin B1 Exposure and Infection with Hepatitis B Virus. Journal of Gastrointestinal Oncology, 2020. jgo.amegroups.org/article/view/47450/html.
[4] D'souza, S., Lau, K. C., Coffin, C. S., and Patel, T. R. Molecular Mechanisms of Viral Hepatitis-Induced Hepatocellular Carcinoma. World Journal of Gastroenterology, vol. 26, no. 38, 2020, pp. 5759–5787.
[5] Khemlina, G., Ikeda, S., and Kurzrock, R. The Biology of Hepatocellular Carcinoma: Implications for Genomic and Immune Therapies. Molecular Cancer, vol. 16, 2017, article 149.
[6] Liver and Intrahepatic Bile Ducts Fact Sheet. GLOBOCAN, gco.iarc.who.int/media/globocan/factsheets/cancers/11-liver-and-intrahepatic-bile-ducts-fact-sheet.pdf.
[7] Pai, S. G., Carneiro, B. A., Mota, J. M., et al. Wnt/β-Catenin Pathway: Modulating Anticancer Immune Response. Journal of Hematology & Oncology, vol. 10, 2017, article 101.
[8] Zhou, J., Sun, H., Wang, Z., et al. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition). Liver Cancer, vol. 12, no. 5, 2023, pp. 405–444.
[9] Reig, M., Forner, A., Rimola, J., et al. BCLC Strategy for Prognosis Prediction and Treatment Recommendation: The 2022 Update. Journal of Hepatology, vol. 76, no. 3, 2022, pp. 681–693.
[10] Sangro, B., et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. Annals of Oncology 35.5 (2024): 448-457.
[11] Sangro, B., Chan, S. L., Kelley, R. K., et al. Four-Year Overall Survival Update from the Phase III HIMALAYA Study of Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma. Annals of Oncology, vol. 35, no. 5, 2024, pp. 448–457.
[12] Pitton, M. B., Kloeckner, R., Ruckes, C., et al. Randomized Comparison of Selective Internal Radiotherapy Versus Drug-Eluting Bead Transarterial Chemoembolization for Hepatocellular Carcinoma. CardioVascular and Interventional Radiology, vol. 38, no. 2, 2015, pp. 352–360.
[13] Kudo, M. Immuno-Oncology Therapy for Hepatocellular Carcinoma: Current Status and Ongoing Trials. Liver Cancer, vol. 8, no. 4, 2019, pp. 221–238.
[14] Pan, Q., Zhou, R., Su, M., Wu, X., and Li, R. Clinical Biocharacterization of Immunophenotype in Hepatocellular Carcinoma Patients. International Journal of Clinical and Experimental Pathology, vol. 10, no. 7, 2017, pp. 7670–7673.
[15] Finn, Richard S., et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. New England Journal of Medicine 382.20 (2020): 1894-1905.
[16] Hui, W., Song, R., Tao, H., et al. Cost-Effectiveness of First-Line Immunotherapy Combinations with or Without Chemotherapy for Advanced Non-Small Cell Lung Cancer: A Modelling Approach. BMC Cancer, vol. 23, 2023, article 442.
[17] CheckMate-9DW: First-Line Nivolumab/Ipilimumab Prolongs Overall Survival, Yields High Objective Response Rate in Unresectable HCC. ASCO Daily News, dailynews.ascopubs.org/do/checkmate-9dw-first-line-nivolumab-ipilimumab-prolongs-overall-survival-yields-high.