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Research Article

Research Progress and Real-World Research Perspectives of Immunity-Based Combination Regimens for Hepatocellular Carcinoma in the Chinese Population

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Abstract

China bears the world's heaviest disease burden of hepatocellular carcinoma (HCC), with hepatitis B virus (HBV) infection as the predominant aetiology. Most patients are diagnosed at intermediate-to-advanced stages, achieving only limited benefit with conventional systemic therapy. Combination therapies centring on programmed death-1 (PD-1)/programmed death ligand-1(PD-L1) immune checkpoint inhibitors have reshaped the diagnostic and therapeutic landscape of HCC, establishing four mainstream modalities: immunotherapy combined with anti-angiogenic targeted agents, dual immunotherapy, immunotherapy plus locoregional therapy, and perioperative targeted-immunotherapy with comprehensive management. While phase III clinical trials and updated domestic guidelines have confirmed that these combination regimens significantly improve objective response rates and prolong overall survival, the stringent eligibility criteria of randomised controlled trials (RCTs) limit their generalisability. These criteria make it difficult to reflect real-world treatment outcomes in Chinese patients, who frequently present with coexisting liver cirrhosis, hepatic impairment, and multiple comorbidities—resulting in a notable gap in stratified, real-world evidence generated from local populations. This review systematically summarises the mechanisms of action, clinical evidence, and evolving guideline recommendations for immune-based combinations in Chinese patients with HCC, and analyses current bottlenecks in clinical research. Based on the design of a national multicentre real-world registry study, we further discuss the value of real-world research for optimising individualised immunotherapy for HCC in China, so as to provide evidence-based references for clinical practice and scientific exploration.

Keywords

Hepatocellular Carcinoma, Immune Checkpoint Inhibitors, Combination Therapy, Real-world Study, Clinical Guidelines, Hepatitis B Virus

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1. Introduction

Globally, 841,000 new HCC cases and 782,000 HCC-related deaths occur annually. Of these, 466,000 new cases and 422,000 deaths are reported in China, accounting for over 55% of the global burden [1]. The 5-year survival rate of HCC in China is only 12.1%, substantially lower than the 15%–19% reported in Europe and North America. HBV-associated HCC, portal vein tumour thrombus, multifocal tumours, and decompensated cirrhosis are highly prevalent among Chinese patients, representing distinctive clinical features that preclude the direct extrapolation of findings from overseas clinical trials to domestic clinical practice.

The IMbrave150 trial in 2020 ushered in the era of targeted-immunotherapy combination for HCC. Subsequently[2], domestic PD-1 inhibitor-based regimens—including combinations with targeted agents, immunotherapy plus interventional therapy, and perioperative neoadjuvant/adjuvant immunotherapy—have been successively approved and incorporated into clinical guidelines, formally ushering in the "Comprehensive Immunotherapy 3.0 Era" for HCC. However, RCTs routinely exclude patients with Child-Pugh B hepatic dysfunction, active infection, high risk of gastrointestinal haemorrhage, or concomitant autoimmune diseases. Given that more than 40% of Chinese patients with intermediate-advanced HCC present with such comorbidities, substantial bias is inevitably introduced into the efficacy data generated from clinical trials. Drawing upon recent clinical studies and the 2022–2026 editions of Chinese HCC clinical guidelines[3,4], this review elaborates on advances in immune-combination therapies for Chinese patients with HCC. Furthermore, with reference to a national multicentre real-world registry study in which Baotou Cancer Hospital participated, we illustrate the critical role of real-world studies in bridging the gap in local clinical evidence.

2.Synergistic Mechanisms of Combination Immunotherapy for Hepatocellular Carcinoma

HCC is a typical "cold tumour", with its tumour microenvironment predominantly infiltrated by immunosuppressive cells. Monotherapy with PD-1/PD-L1 immune checkpoint inhibitors yields an objective response rate of only 10%–20% [5], which falls short of clinical requirements for therapeutic conversion and long-term survival. Multimodal combination therapy thus constitutes a core strategy to overcome therapeutic bottlenecks.

2.1. Immunotherapy Combined with Anti-angiogenic Targeted Therapy

Tumour-derived overexpression of vascular endothelial growth factor (VEGF) induces aberrant angiogenesis, suppresses effector T-cell infiltration, and upregulates immunosuppressive molecules. Anti-angiogenic agents normalise tumour vasculature, enhance CD8+ T-cell infiltration into tumour tissues, and downregulate regulatory T cells as well as PD-L1 expression. These agents exert bidirectional synergy with immune checkpoint inhibitors, forming the mechanistic cornerstone of current first-line standard regimens for advanced HCC.

2.2. Dual Immunotherapy

Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitors prime naive T cells within lymph nodes, whereas PD-1 inhibitors relieve local tumour-associated immune suppression. Dual blockade of immune checkpoints broadens the repertoire of anti-tumour immune responses. Free from the bleeding and proteinuria risks associated with anti-angiogenic agents, dual immunotherapy is particularly favourable for patients with Child-Pugh B hepatic function or high-risk oesophagogastric varices.

2.3. Immunotherapy Combined with Locoregional Interventional Therapy

Transarterial chemoembolisation (TACE) and hepatic arterial infusion chemotherapy (HAIC) induce tumour cell necrosis and release abundant neoantigens, thereby activating systemic anti-tumour immunity. Concurrently, local hypoxia further elevates VEGF expression, providing a theoretical rationale for triple therapy integrating immunotherapy, targeted agents, and locoregional intervention. This strategy substantially increases the likelihood of tumour downstaging and subsequent curative resection for patients with intermediate-stage HCC.

2.4. Perioperative Combination Immunotherapy

Preoperative targeted-immunotherapy can induce tumour regression, eradicate micrometastases, and reduce the risk of postoperative recurrence. Postoperative adjuvant immunotherapy persistently suppresses circulating tumour cells and has been shown to significantly prolong event-free survival in patients at high recurrence risk, including those with microvascular invasion or multifocal tumours.

3. Clinical Evidence of Combination Immunotherapy in Chinese Patients with Hepatocellular Carcinoma

3.1. Immunotherapy Plus Anti-angiogenic Targeted Therapy: Standard First-line Regimen for Advanced Disease

The IMbrave150 trial demonstrated that atezolizumab plus bevacizumab (T+A) significantly prolonged overall survival compared with sorafenib (19.2 months vs 13.4 months) [2]. Survival benefits in the Chinese HBV-infected subgroup were consistent with the global cohort; however, a higher incidence of haemorrhagic adverse events was observed, necessitating baseline gastroscopic screening in clinical practice.

Two domestic targeted-immunotherapy regimens have been evaluated in phase III trials enrolling predominantly Chinese patients with HBV-related HCC, making them better suited to local clinical practice. The ORIENT-32 trial (sintilimab plus bevacizumab biosimilar) enrolled exclusively patients with HBV-associated advanced HCC, achieving a median overall survival of 21.2 months with a 34% reduction in mortality risk; this regimen has been covered by national medical insurance [6]. In the SHR-1210-III-310 trial (camrelizumab plus apatinib, the "Double-Ai" regimen), the objective response rate reached 33.1% per mRECIST criteria, with particularly notable benefits in subgroups with portal vein tumour thrombus and extrahepatic metastasis. This regimen received first-line approval in 2023 and has since been updated with perioperative recommendations [7]. In addition, multiple domestic real-world studies have reported that lenvatinib combined with various PD-1 inhibitors achieved a median overall survival of up to 26 months [8], with favourable surgical conversion rates. Adverse events were predominantly hypertension and hypothyroidism, which were generally manageable throughout treatment.

3.2. Dual Immunotherapy: Preferred Option for Patients Intolerant to Anti-angiogenic Agents

In the HIMALAYA trial, the STRIDE regimen (single-dose tremelimumab plus durvalumab) achieved a 3-year survival rate of 30.7% without requiring continuous anti-angiogenic treatment [9], and received a Grade I recommendation in the 2024 Chinese Society of Clinical Oncology (CSCO) guidelines for first-line treatment of advanced HCC in patients with Child-Pugh B hepatic function [10]. In the CheckMate-040 trial, nivolumab plus ipilimumab (O+Y) achieved an objective response rate of 32% in the post-first-line setting, with complete remission observed in 8% of patients; this combination is frequently adopted as a salvage regimen upon progression after targeted-immunotherapy [11]. The 2025 CheckMate-9DW study further validated that first-line nivolumab plus ipilimumab (O+Y) significantly improved overall survival (OS) compared with lenvatinib or sorafenib in patients with advanced hepatocellular carcinoma, with a median OS of 23.7 months versus 20.6 months [12].

3.3. Immuno-Interventional Combination: Core Strategy for Converting Unresectable Intermediate-Stage HCC

A substantial proportion of Chinese patients present with China Liver Cancer Staging (CNLC) stage IIb/IIIa intermediate-stage HCC. TACE monotherapy yields limited long-term efficacy, making triple therapy combining targeted-immunotherapy with TACE a focus of recent research. The global phase III EMERALD-1 trial confirmed that triple therapy significantly prolonged progression-free survival [13]. A Chinese multicenter prospective study demonstrated that triplet conversion therapy with TACE plus lenvatinib and camrelizumab yielded an objective response rate (ORR) of 76.4% and a conversion resection rate of 52.7% [14]. For patients with multifocal intrahepatic tumors, HAIC combined with targeted-immunotherapy demonstrated superior efficacy compared with TACE-based triple therapy, without obvious additive toxicity [15].

3.4. Perioperative Targeted-immunotherapy: Reducing Recurrence Risk After Curative Resection

CARES-009 is the world's first positive phase III trial on perioperative therapy for HCC. Among patients with resectable HCC at intermediate-high recurrence risk, neoadjuvant plus adjuvant camrelizumab plus apatinib yielded a median event-free survival of 42.1 months versus 19.4 months with surgery alone, achieving a marked reduction in recurrence risk. These findings have been incorporated into the Multidisciplinary Expert Consensus on Perioperative Immunotherapy for HCC (2025)[16,17]. In parallel, the IMbrave050 trial validated that adjuvant T+A prolonged recurrence-free survival in postoperative high-risk patients [18], and this regimen is particularly suitable for those intolerant to small-molecule anti-angiogenic tyrosine kinase inhibitors.

4. Evolution of Recommendations for Immune-Combination Regimens in Domestic Guidelines (2022–2026)

Drawing on well-documented domestic phase III and real-world data, the Chinese Guidelines for Diagnosis and Treatment of Primary Liver Cancer and the CSCO HCC Guidelines have established a stratified recommendation system distinct from European and American guidelines[3,4,10]:

1) First-line therapy for unresectable advanced HCC (Grade I, Category 1A evidence): targeted-immunotherapy combinations (T+A [atezolizumab plus bevacizumab], sintilimab/camrelizumab plus anti-angiogenic agents, lenvatinib plus PD-1 inhibitors), and dual-immunotherapy regimens including STRIDE and O+Y [3, 4, 10].
2) Intermediate-stage CNLC IIb HCC: triple therapy comprising TACE combined with targeted-immunotherapy (newly added as a Grade I recommendation in the 2026 edition) [4, 13].
3) Perioperative setting: for resectable HCC with intermediate-high recurrence risk, full-course neoadjuvant plus adjuvant camrelizumab plus apatinib is recommended [16, 17]; adjuvant maintenance with T+A may be adopted for patients at high postoperative recurrence risk [18].
4) Stratified management according to liver function: targeted-immunotherapy is preferred for Child-Pugh A patients; dual-immunotherapy is the first choice for Child-Pugh B patients to avoid bleeding and hepatic and renal toxicities induced by anti-angiogenic agents; only best supportive care is delivered for Child-Pugh C patients, and combination immunotherapy is not recommended [4, 10].

By contrast, while the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO)guidelines from Europe and North America regard perioperative therapy and TACE-based triple therapy only as investigational options within clinical trials, domestic guidelines routinely recommend these comprehensive modalities based on the distinctive characteristics of HBV-related HCC in local populations, thereby establishing a distinctive Chinese paradigm for HCC immunotherapy.

5. Current Bottlenecks in Clinical Research

5.1. Substantial Discrepancies Between RCTs and Real-world Clinical Practice

Stringent enrolment criteria of RCTs routinely exclude numerous patients with liver cirrhosis, ascites, active hepatitis, or geriatric frailty. Consequently, RCT outcomes cannot adequately reflect the efficacy and safety profiles of patients managed in primary-level hospitals, and long-term surveillance data for special adverse events—such as immune-mediated hepatitis and gastrointestinal haemorrhage—remain scarce.

5.2. Insufficient Large-sample Stratified Real-world Data from Chinese Populations

Existing domestic real-world studies are mostly single-centre, small-sample retrospective analyses, which suffer from three major limitations: failure to stratify HBV-positive versus non-viral HCC subgroups; lack of stratified comparisons across perioperative, first-line, and post-progression treatment phases; and absence of head-to-head real-world efficacy comparisons among different combination immunotherapy regimens.

5.3. Lack of Clinical Translation for Individualised Efficacy Prediction Systems

Biomarkers including PD-L1, tumour mutational burden (TMB), peripheral inflammatory indices, and tertiary lymphoid structures (TLS) have demonstrated predictive value in solid tumours [19, 20]. Nevertheless, combined predictive models remain unavailable for HBV-associated HCC, hindering precise patient stratification for immune-combination regimens and the development of individualised efficacy prediction systems.

5.4. Absence of Unified Criteria for Clinical Regimen Selection

More than ten first-line options are currently available, including targeted-immunotherapy, dual-immunotherapy, and locoregional-based triple therapy. However, no standardised stratified selection framework based on liver function, tumour burden, viral status, and bleeding risk has been established. Consequently, decisions on treatment sequencing and post-progression switching strategies largely depend on clinicians' empirical judgment.

6. Design and Clinical Value of a Multicentre Real-World Registry Study

To fill gaps in local evidence, Academician Wang Xuehao initiated a national multicentre real-world registry study on combination immunotherapy for HCC. As one of the participating sub-centres, Baotou Cancer Hospital plans to enrol 30 patients. This study adopts a bidirectional design combining retrospective and prospective cohorts, spanning from January 2025 to December 2026.

6.1. Study Design

The retrospective cohort enrols patients previously treated with immune-combination regimens for HCC, with comprehensive collection of medical records, laboratory results, pathological findings, efficacy outcomes, and adverse event data. The prospective cohort consecutively recruits treatment-naïve patients eligible for immune-combination therapy, with standardised follow-up until disease progression, death, or study termination. Stratification dimensions cover treatment

phase (perioperative, first-line for advanced disease, post-progression), aetiology (HBV-related versus non-HBV-related), combination modality (targeted-immunotherapy, dual-immunotherapy, immunotherapy plus locoregional triple therapy), and Child-Pugh liver function classification.

Primary endpoints are categorised into efficacy and safety. Efficacy endpoints include objective response rate, disease control rate, progression-free survival, overall survival, and tumour conversion-resection rate. Safety endpoints encompass all treatment-related adverse events, grade ≥3 adverse events, and specific events of special interest, including immune-related hepatitis and gastrointestinal haemorrhage. In addition, this study explores the impacts of baseline alpha-fetoprotein (AFP), vascular invasion, and Eastern Cooperative Oncology Group (ECOG) performance status on therapeutic efficacy, and systematically documents real-world medication patterns, dose modifications, and reasons for treatment discontinuation.

6.2. Clinical Application Value of Real-world Research

First, this study fills the data gap on immunotherapy for HBV-related HCC in northern border regions. By enrolling special populations excluded from RCTs, it objectively evaluates the real-world benefits of domestic and imported immune-combination regimens among local patients, thereby supplying native evidence to inform future guideline updates.

Second, stratified subgroup analyses enable regimen recommendations tailored to liver function, tumour stage, and viral status, thereby guiding individualised clinical decision-making.

Third, it systematically characterises the patterns of immune-related adverse events in real-world settings and establishes a whole-course adverse event management workflow adapted for Chinese HCC patients.

Fourth, built upon the standardised clinical database, further extended research can develop combinatorial efficacy prediction models incorporating circulating inflammatory markers and immunopathological biomarkers, facilitating the implementation of precision immunotherapy for HCC.

7. Summary and Perspectives

Multimodal combination therapies centred on immune checkpoint inhibitors have fundamentally reshaped the diagnostic and therapeutic landscape of HCC in China. The four major strategies—targeted-immunotherapy, dual-immunotherapy, immunotherapy combined with locoregional intervention, and full-course perioperative immunotherapy—have obtained high-level evidence from clinical trials and recommendations in domestic guidelines, and have substantially improved response rates and long-term survival for patients with intermediate-advanced HCC. Nevertheless, patient selection bias in RCTs, scarcity of stratified local real-world data, and delayed clinical translation of individualised predictive biomarkers remain core obstacles constraining precise clinical practice.

Multicentre bidirectional-cohort real-world registries can reconstruct the full picture of routine clinical practice in China, objectively assess the efficacy and safety of diverse immune-combination regimens in special populations characterised by HBV predominance, liver cirrhosis, and hepatic impairment, and compensate for the inherent limitations of trial-derived evidence. Leveraging the well-established research team and complete clinical case resources of the Gastrointestinal Oncology Department at Baotou Cancer Hospital, this project standardises data collection and stratified analyses for Chinese HCC patients receiving immune-combination therapy. It is expected to generate high-quality real-world evidence, optimise comprehensive immunotherapy pathways for HCC in northern China, and offer practical references for the standardised implementation of immune-combination therapy in grassroots hospitals.

Future research on HCC immunotherapy should prioritise three directions: first, constructing efficacy-prediction biomarker models tailored for Chinese patients with HBV-related HCC based on large-scale real-world datasets; second, performing real-world head-to-head comparisons to establish unified stratified selection criteria for immune-combination regimens; and third, exploring the synergistic potential of novel immune targets—such as regulatory T cells (Tregs) and other emerging checkpoints—as well as cell-based therapies combined with existing immune-combination strategies, to further overcome the survival bottlenecks of advanced HCC.

Abbreviations

HCC	Hepatocellular Carcinoma
HBV	Hepatitis B Virus
PD-1/PD-L1	Programmed Death-1/Programmed Death Ligand-1
RCTs	Randomised Controlled Trials
VEGF	Vascular Endothelial Growth Factor
CTLA-4	Cytotoxic T-lymphocyte-Associated Antigen-4
TACE	Transarterial Chemoembolisation
HAIC	Hepatic Arterial Infusion Chemotherapy
OS	Overall Survival
CNLC	China Liver Cancer Staging
ORR	Objective Response Rate
CSCO	Chinese Society of Clinical Oncology
TMB	Tumour Mutational Burden
TLS	Tertiary Lymphoid Structures
AFP	Alpha-Fetoprotein
ECOG	Eastern Cooperative Oncology Group
NCCN	National Comprehensive Cancer Network
ESMO	European Society for Medical Oncology
Tregs	Regulatory T Cells

Author Contributions

Wang Yuanfang: Conceptualization,Investigation, Writing-original draft

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Gao Yuqian: Conceptualization, Supervision, Writing-review & editing, Funding acquisition

Conflicts of Interest

The authors declare no potential conflicts of interest.

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