A Paradigm Shift in Hepatocellular Carcinoma Treatment: An In-Depth Analysis of Etiology-Stratified First-Line Immunotherapy and Targeted Regimens

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Abstract. Hepatocellular carcinoma (HCC) represents a significant global health burden, with its pathogenesis intricately linked to underlying etiologies such as Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and non-viral factors like non-alcoholic steatohepatitis (NASH). For over a decade, the multi-targeted tyrosine kinase inhibitor (TKI) sorafenib remained the standard first-line systemic therapy, despite offering modest survival benefits and substantial toxicities. The recent introduction of immune checkpoint inhibitors (ICIs) and next-generation TKIs has revolutionized the therapeutic landscape. This paper explores the efficacy and safety of these novel first-line regimens, drawing heavily upon a comprehensive network meta-analysis of 24 randomized controlled trials (RCTs). By examining overall survival (OS), progression-free survival (PFS), objective response rates (ORR), and adverse events, this analysis highlights the superiority of ICI-based combinations over traditional TKIs. Furthermore, it underscores the critical importance of viral etiology in guiding personalized treatment, demonstrating that HBV-related HCC benefits most from specific ICI plus anti-angiogenic combinations (e.g., sintilimab plus bevacizumab biosimilar), HCV-related HCC uniquely favors atezolizumab plus bevacizumab, and non-viral HCC requires dual checkpoint blockade (the STRIDE regimen) to overcome unique metabolic and immunological barriers.

Keywords: HCC

1. Introduction: The Global Burden and Etiological Complexity of HCC

Hepatocellular carcinoma (HCC) is the predominant histologic subtype of primary liver cancer, accounting for more than 80% of all cases globally. It stands as the sixth most common malignancy and the third leading cause of cancer-related mortality worldwide, imposing a devastating human and economic toll (Bray et al., 2024). The incidence of HCC exhibits profound geographic heterogeneity, which is intrinsically linked to the regional prevalence of its primary risk factors. In East Asia and sub-Saharan Africa, hyperendemic foci of HCC are largely driven by the high prevalence of chronic Hepatitis B (HBV) and Hepatitis C (HCV) infections. Conversely, in Western nations, the rising incidence of HCC is increasingly attributed to non-viral etiologies, particularly metabolic dysfunction-associated steatotic liver disease (MASLD) and non-alcoholic steatohepatitis (NASH).

The etiology of HCC is not merely a historical footnote in a patient's medical record; it is a fundamental driver of hepatocarcinogenesis that shapes the tumor's molecular architecture, the baseline hepatic reserve, and the tumor immune microenvironment (TIME) (Llovet et al., 2022). Viral and non-viral HCCs rely on vastly different immune-evasion programs. For instance, chronic HBV infection typically results in a "hot" immune microenvironment characterized by dense intrahepatic inflammatory infiltrates but marked T-cell exhaustion. HCV, on the other hand, manipulates angiogenesis and specific signaling pathways to evade immune surveillance. Non-viral HCC, particularly driven by NASH, creates a unique metabolic environment that can lead to aberrant T-cell activation, which may actively impair tumor surveillance (Pfister et al., 2021). Consequently, understanding these etiologic nuances is paramount for optimizing systemic therapy, as the efficacy of immunotherapies and targeted agents is heavily modulated by the TIME.

2. The Evolution of Systemic Therapies: From Sorafenib to Combination Immunotherapy

For patients presenting with advanced or unresectable HCC, systemic therapy serves as the cornerstone of clinical management. The historical benchmark was established by the seminal SHARP trial in 2008, which demonstrated that sorafenib, a first-in-class multi-targeted tyrosine kinase inhibitor (TKI), significantly improved overall survival (OS) compared to placebo (10.7 months versus 7.9 months) (Llovet et al., 2008). While a landmark achievement, the clinical benefits of sorafenib were undeniably modest. The objective response rate (ORR) hovered at a mere 2% to 3%, and the drug was associated with a high burden of treatment-related adverse events, including severe hand-foot skin reactions, diarrhea, and hypertension. These toxicities frequently necessitated dose reductions or complete discontinuation, severely limiting the drug's real-world effectiveness outside the stringent confines of clinical trials.

The therapeutic landscape has recently undergone a profound transformation driven by breakthroughs in tumor immunology and molecular targeting. Immune checkpoint inhibitors (ICIs), specifically targeting the programmed cell death protein 1 (PD-1), its ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have demonstrated the ability to restore T-cell-mediated antitumor immunity. Concurrently, next-generation TKIs (e.g., lenvatinib, cabozantinib) and monoclonal antibodies targeting vascular endothelial growth factor (VEGF) (e.g., bevacizumab) have shown potent suppression of the angiogenic and proliferative signaling cascades that fuel HCC progression (Finn et al., 2020).

The paradigm shifted definitively with the IMbrave150 trial, which paired the PD-L1 inhibitor atezolizumab with the anti-VEGF antibody bevacizumab. This combination yielded superior OS and PFS compared to sorafenib, establishing a new standard of care (Cheng et al., 2022). Subsequently, the HIMALAYA

trial validated the use of dual-checkpoint blockade (tremelimumab plus durvalumab, known as the STRIDE regimen) (Sangro et al., 2024), while other trials like COSMIC-312 evaluated combinations like cabozantinib plus atezolizumab (Yau et al., 2024). Despite this rapid proliferation of effective regimens, a critical clinical dilemma has emerged: because the majority of these pivotal phase III trials utilized sorafenib as the sole comparator arm, there is a profound lack of direct, head-to-head evidence comparing these novel combinations against one another. This absence of comparative efficacy data leaves oncologists without definitive guidance on treatment sequencing and optimal regimen selection.

3. Methodological Rigor in Network Meta-Analysis

To bridge the gap left by the lack of head-to-head trials, researchers employ network meta-analysis (NMA), a sophisticated statistical framework that synthesizes both direct and indirect evidence across a network of comparative trials. Following the PRISMA extension for network meta-analyses, a recent comprehensive evaluation systematically searched databases (PubMed, Embase, Cochrane Library, and Web of Science) to aggregate data from 24 randomized controlled trials encompassing 13,572 participants.

This NMA utilized a Bayesian fixed-effects model to generate probabilistic treatment rankings. The use of a Bayesian framework allows for the calculation of surface under the cumulative ranking curve (SUCRA) values, which provide a quantitative hierarchy indicating the probability of a treatment being the best for a specific outcome. By mapping a connected evidence network that includes 26 different first-line regimens—ranging from single-agent TKIs (sorafenib, lenvatinib) to ICI monotherapies (tislelizumab, nivolumab) and diverse combinations (e.g., lenvatinib plus pembrolizumab, camrelizumab plus rivoceranib)—the NMA provides the most robust synthesis of currently available clinical data.

4. Overall Efficacy: Survival Outcomes in the General Population

In analyzing the overall population of patients with advanced HCC, the NMA reveals a clear dominance of ICI-based combinations over traditional TKIs in extending overall survival. Five specific regimens demonstrated a statistically significant reduction in the risk of death compared to sorafenib. Leading this hierarchy is the combination of sintilimab (a PD-1 inhibitor) plus a bevacizumab biosimilar (IBI305), which yielded a remarkable hazard ratio (HR) of 0.57, representing a 43% reduction in the risk of mortality. This was closely followed by camrelizumab plus rivoceranib (HR 0.62) and the established standard, atezolizumab plus bevacizumab (HR 0.66). These data unequivocally confirm that combining immune checkpoint blockade with anti-angiogenic therapy provides a profound survival advantage over single-agent targeted therapy.

When assessing progression-free survival (PFS)—a measure of the time during which the disease is controlled without worsening—the rankings shift slightly, though the theme of combination superiority remains. The top-ranked regimen for PFS was camrelizumab plus rivoceranib (HR 0.52), indicating a 48% reduction in the risk of disease progression or death compared to sorafenib. Other highly effective combinations for delaying progression included anlotinib plus penpulimab (HR 0.53), lenvatinib plus pembrolizumab (HR 0.55), and sintilimab plus bevacizumab biosimilar (HR 0.56). Notably, while most immunotherapy-based regimens demonstrated robust OS benefits, not all significantly improved PFS, underscoring the complex dynamics of immune responses, where survival benefits may outpace radiographic markers of progression.

5. Evaluating Tumor Response and Tolerability

Survival metrics must be balanced against the likelihood of shrinking the tumor (Objective Response Rate, ORR) and the patient's quality of life, dictated by the safety profile of the drug.

In terms of tumor shrinkage, lenvatinib combined with pembrolizumab (Lenva-Pembro) demonstrated unprecedented efficacy, achieving a risk ratio (RR) of 8.00 compared to sorafenib. This signifies that patients receiving Lenva-Pembro are eight times more likely to experience a significant reduction in tumor size. Other regimens providing exceptional ORR included durvalumab monotherapy (RR 6.13) and sintilimab plus bevacizumab biosimilar (RR 6.10). High ORR is particularly critical for patients with highly symptomatic tumors or those being considered for potential downstaging to curative-intent therapies like surgical resection or liver transplantation.

However, the safety profiles of these potent regimens diverge significantly. Combinations that pair ICIs with TKIs or anti-angiogenic agents inevitably carry cumulative, class-specific toxicities. For instance, VEGF inhibition is notoriously associated with hypertension, proteinuria, and an increased risk of severe bleeding, while TKIs frequently cause diarrhea, fatigue, and dermatological toxicities. Consequently, combinations generally have higher rates of Grade 3 or greater adverse events (AEs).

Conversely, ICI monotherapies emerged as the safest options in the network. Tislelizumab and nivolumab were associated with the lowest incidence of severe AEs (RR 0.42 and 0.45, respectively, compared to sorafenib). PD-1 inhibitors possess a more focused mechanism of action; while they introduce the risk of immune-related adverse events (irAEs) such as pneumonitis or colitis, they spare the patient from the systemic, off-target toxicities inherent to continuous TKI exposure. Therefore, for fragile patients who may not tolerate aggressive combination therapies, ICI monotherapy represents a highly viable, tolerable alternative.

6. The Etiology-Stratified Framework: A Roadmap to Personalized Medicine

The most groundbreaking revelation of contemporary HCC research is the profound impact of viral etiology on treatment efficacy. The immune microenvironment of the liver is deeply sculpted by the underlying disease driving the cirrhosis and subsequent carcinogenesis. The Bayesian network meta-analysis highlights these distinct etiology-specific optima, paving the way for truly individualized oncological care.

6.1. Hepatitis B Virus (HBV) and the "Hot" Tumor Microenvironment

Chronic HBV infection subjects the liver to persistent antigenic and inflammatory stimulation. Over time, this chronic exposure drives intrahepatic T cells into an "exhausted" state, characterized by high expression of the PD-1 receptor and a severe impairment of cytotoxic effector function (Llovet et al., 2022). Consequently, HBV-associated HCCs frequently exhibit a "hot" immune microenvironment; they are heavily infiltrated with PD-1-positive tumor-infiltrating lymphocytes (TILs) and demonstrate high expression of PD-L1.

While this dense inflammatory infiltrate often correlates with aggressive disease features—such as portal vein tumor thrombosis (PVTT)—it paradoxically renders the tumor highly susceptible to pharmacological PD-1/PD-L1 blockade. Furthermore, the incorporation of VEGF inhibition in these patients is highly synergistic. VEGF acts as a potent immunosuppressant within the TIME, mobilizing regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) while suppressing dendritic cell maturation (Kudo, 2020). By combining a PD-1 inhibitor with an anti-VEGF agent, therapies can simultaneously lift VEGF-mediated immune suppression, normalize the aberrant tumor vasculature to improve T-cell infiltration, and release the brakes on the exhausted T cells.

This biological rationale perfectly aligns with the NMA findings for the HBV-infected subgroup. The combinations of sintilimab plus bevacizumab biosimilar (HR 0.58) and atezolizumab plus bevacizumab (HR 0.58) emerged as the absolute top performers for overall survival. For progression-free survival in this cohort,

cabozantinib plus atezolizumab (HR 0.50) provided the greatest benefit.

6.2. Hepatitis C Virus (HCV) and VEGF-Driven Pathogenesis

The oncogenesis of HCV-related HCC relies on entirely different molecular machinery. The HCV core protein has been shown to directly upregulate the expression of VEGF via pathways including hypoxia-inducible factor 1-alpha (HIF-1α) and STAT3 (Shao et al., 2017; Goto et al., 2020). Histological analyses confirm that HCV-driven tumors exhibit significantly higher baseline VEGF expression and microvessel density compared to their HBV-driven counterparts.

In this context, the tumor microenvironment is dominated by VEGF-driven angiogenesis and immunosuppression. VEGF creates a physical and immunologic barrier, restricting the infiltration of cytotoxic CD8+ T cells while expanding immunosuppressive populations. Because the pathology is so heavily dependent on the VEGF axis, the clinical data reflects a narrow window of efficacy for systemic therapies.

In the NMA's HCV-infected subgroup, atezolizumab plus bevacizumab was the only regimen to confer a statistically significant overall survival advantage (HR 0.43) compared to sorafenib. No other combination achieved a significant OS benefit. For PFS, cabozantinib plus atezolizumab was the sole regimen to achieve statistical superiority (HR 0.73). This highly specific efficacy profile underscores the absolute necessity of robust anti-VEGF targeting in HCV-related HCC to dismantle both the vascular and immunologic barriers protecting the tumor.

6.3. Non-Viral HCC: Overcoming NASH-Induced Immune Dysfunction

The rising incidence of HCC in Western populations is primarily driven by metabolic syndrome, obesity, and NASH. The immunology of non-viral HCC presents a unique and formidable challenge. Unlike viral HCC, which features T cells exhausted by viral antigens, NASH-associated HCC is characterized by a specific type of immune dysfunction.

Preclinical and translational studies have demonstrated that the metabolic environment of a NASH-afflicted liver causes aberrant T-cell activation. Specifically, a unique population of CD8+ T cells accumulates in the liver, contributing to tissue damage while simultaneously failing to conduct proper tumor surveillance (Pfister et al., 2021). Critically, blocking the PD-1/PD-L1 axis alone does not reverse this specific dysfunction; in fact, there is concern that it may inadvertently exacerbate immune-mediated tissue damage without generating an effective anti-tumor response.

This mechanistic insight explains the historically poor performance of single-agent ICIs and standard PD-L1/VEGF combinations in NASH-HCC patients. Strikingly, the NMA revealed that in the non-viral subgroup, the STRIDE regimen (tremelimumab plus durvalumab) was the only therapy to achieve a significant OS benefit (HR 0.75)

The success of the STRIDE regimen lies in its dual-checkpoint blockade. Tremelimumab targets CTLA-4, an immune checkpoint that operates upstream in the lymph nodes during the initial "priming" phase of the immune response (Wei et al., 2018). By inhibiting CTLA-4, tremelimumab promotes the proliferation of new, naive T cells and diversifies the peripheral T-cell repertoire. This priming effect is essential in non-viral HCC; it recruits novel, high-avidity T-cell clones that have not been corrupted by the NASH metabolic environment. Once these fresh T cells migrate to the tumor, the durvalumab (anti-PD-L1) prevents them from being suppressed by the local TIME (Abou-Alfa et al., 2022). Thus, dual blockade overcomes the unique resistance mechanisms inherent to metabolic hepatocarcinogenesis.

7. Addressing Complexities and Special Populations

While aggregate data and etiology-stratified networks provide a powerful decision-making framework, the clinical application of these findings must account for the heterogeneous reality of HCC patient populations.

A primary limitation of the current clinical trial landscape is the strict exclusion of patients with impaired liver function. The vast majority of phase III RCTs (including IMbrave150, HIMALAYA, and LEAP-002) mandated that enrolled patients possess Child-Pugh class A liver function. This is done to minimize the confounding risk of mortality from hepatic decompensation. However, in routine clinical practice, a substantial proportion of HCC patients present with Child-Pugh class B cirrhosis. These patients have inherently lower tolerance for systemic toxicities, particularly the bleeding risks associated with bevacizumab or the hepatic toxicity of high-dose TKIs. Consequently, the efficacy hierarchies established in NMAs cannot be directly extrapolated to Child-Pugh B patients, who require highly individualized risk-benefit assessments and a reliance on emerging real-world evidence.

Furthermore, macrovascular invasion—specifically portal vein tumor thrombosis (PVTT)—represents a high-risk phenotype that drastically alters prognosis. Tumors extending into the main portal vein, hepatic vein, or inferior vena cava are associated with rapid disease progression and a higher risk of systemic spread. While anti-angiogenic combinations (e.g., lenvatinib-based therapies) have shown promise in patients with high tumor burdens, variations in how trials report PVTT subsets make it difficult to ascertain which precise combination is optimal for the highest-risk vascular phenotypes.

Finally, the emerging concept of PANoptosis—a multifaceted inflammatory programmed cell death pathway involving pyroptosis, apoptosis, and necroptosis—offers a new frontier in understanding HCC biology. Modulating PANoptosis networks may explain the variable responses to immunotherapies and represents a critical area for future drug development and biomarker discovery (Xiang et al., 2025).

8. Future Directions and Unanswered Questions

The rapid establishment of combination therapies as the first-line standard of care introduces new clinical dilemmas regarding sequencing. As patients inevitably progress on first-line ICI plus anti-angiogenic combinations, the optimal second-line strategy remains highly debated. The traditional second-line TKIs (e.g., regorafenib, cabozantinib, ramucirumab) were largely validated in patients who had previously progressed on sorafenib, not on ICIs.

A critical area of ongoing investigation is the potential for ICI rechallenge. For patients who progress on a PD-L1/VEGF combination, is there a benefit to introducing a CTLA-4 inhibitor in the second line? Or does a switch to a potent, multi-targeted TKI like lenvatinib offer better disease control? High-quality, prospective real-world registries and pragmatic clinical trials are urgently required to map out these sequencing strategies and establish a "full-course" management framework for advanced HCC (Li et al., 2025).

Additionally, while network meta-analyses provide the highest tier of synthesized evidence currently available, they rely heavily on indirect comparisons. To definitively confirm these findings, the oncology community requires dedicated, head-to-head phase III trials comparing the top-performing regimens against each other (e.g., atezolizumab plus bevacizumab versus sintilimab plus bevacizumab biosimilar, or STRIDE versus lenvatinib plus pembrolizumab).

9. Conclusion

The management of advanced hepatocellular carcinoma has entered an era of unprecedented efficacy and complexity. The transition from the era of sorafenib monotherapy to a landscape dominated by immune checkpoint inhibitors and next-generation targeted agents has yielded profound improvements in patient survival and objective tumor responses. As demonstrated by comprehensive network meta-analyses, ICI-based combinations paired with anti-angiogenic agents generally outperform traditional TKIs.

Crucially, the monolithic approach to treating HCC is obsolete. The data compellingly demonstrate that therapeutic efficacy is deeply intertwined with the underlying viral or metabolic etiology of the disease. By stratifying treatment decisions—utilizing sintilimab or atezolizumab-based combinations for HBV-related HCC, reserving atezolizumab plus bevacizumab for HCV-related disease, and deploying the dual-checkpoint STRIDE regimen for non-viral, metabolically driven HCC—clinicians can leverage the specific immunological vulnerabilities of the tumor. This etiology-stratified framework represents a monumental leap toward precision oncology in hepatology, ensuring that patients receive not just a highly effective therapy, but the exact therapy most likely to overcome their specific biological disease drivers.

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