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Current Status and Future Perspectives of Systemic Therapy for Advanced Hepatocellular Carcinoma: From Mechanistic Paradox to Precision Oncology

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Abstract: The therapeutic landscape for advanced HCC has expanded with ICI combinations, yet durable survival remains limited—an efficacy paradox from regimen proliferation without consistent long-term benefit, reflecting persistent biological constraints. We replace the trial-chronology approach with a mechanism-driven framework integrating the immunological basis of the HCC 'cold' microenvironment, liver immune tolerance and immune-privileged regulation, ICI–TKI-induced microenvironment remodeling, and how etiologic heterogeneity and dynamic resistance shape durability. This synthesis reveals three key limitations: First, low intrinsic immunogenicity and constrained de novo immune generation restrict sustained checkpoint blockade-induced anti-tumor immunity. Second, ICI–TKI synergy is target-mediated rather than serendipitous: TKIs remodel the microenvironment to create a time-limited window for ICI action, not merely potentiating pre-existing immunity. Third, the biomarker void and etiology-related differences prevent reliable patient matching, fostering an illusion of choice, while regimen-specific, evolving resistance complicates treatment sequencing and safety under liver-function constraints. Precision oncology for advanced HCC should therefore shift from regimen accumulation to implementation guidance: deploy multi-omic and dynamic biomarkers for patient stratification and risk-aware sequencing; target beyond PD-1/PD-L1 and VEGF axes to address oncogenic drivers and immune escape; and advance cure-oriented perioperative pathways with standardized definitions and evidence-based endpoints. Future work must focus on these three core directions: multi-omic biomarkers, novel therapeutic targets, and cure-oriented strategies.

Keywords: Hepatocellular carcinoma; Immunotherapy; Tumor microenvironment; Multi-omics biomarkers; Novel therapeutic targets; Cure-oriented strategies.

Introduction

In 2022, there were approximately 870,000 new cases of and 760,000 deaths from HCC[1–4]. Over the past decade, systemic therapy for advanced HCC has transitioned from sorafenib-based regimens to immune checkpoint inhibitor (ICI) combinations, thereby expanding treatment options[5,6]. The advent of regimens such as ICIs plus bevacizumab or durvalumab plus tremelimumab has displaced the long-standing dominance of tyrosine kinase inhibitors (TKIs), thereby establishing a new standard of care and having broken previously insurmountable survival barriers[7,8]. HCC remains a lethal disease with limited opportunities for curative interventions at diagnosis, and hepatic functional reserve often constrains the intensity and tolerability of systemic therapy. Over the past decade, systemic regimens have expanded rapidly, yet responses are frequently non-durable, suggesting that mechanistic barriers within the tumor microenvironment and host immune context still govern clinical outcomes.

However, this rapid expansion of regimens has not yielded durable survival benefits for most patients. Primary or acquired resistance emerges within months[7–9]. This disparity constitutes a core paradox: treatment options continue to multiply, yet long-term benefit remains limited. We therefore address three research questions: Why have existing combination therapies failed to achieve breakthrough survival benefits? What is the root cause of the 'illusion of choice' in clinical decision-making? And how can we shift from palliative-intent toward cure-oriented strategies?

Accordingly, this review first dissects the immunological and molecular mechanisms underlying treatment failure, then examines the evidence gaps that constrain clinical decision-making, and finally prospects cure-oriented therapeutic strategies while proposing an implementation pathway for precision oncology in HCC.

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The Immunological Landscape of HCC

Three characteristics of the HCC "cold tumor" phenotype

A foundational misconception fueling the current therapeutic plateau is the implicit assumption that HCC is an immunologically responsive "hot" tumor, amenable to the same ICI strategies that have revolutionized malignancies like melanoma or non-small cell lung cancer. A diverse array of hepatic immune cells, most notably resident Kupffer cells, dendritic cells, and NK cells, underpin liver homeostasis and drive effective anti-tumor immunity[10]. The stark reality is that the majority of HCCs are intrinsically "cold," characterized by a triad of immunological inertia: low T-cell infiltration, a low tumor mutational burden (TMB), and a near-universal absence of microsatellite instability (MSI)[11,12]. The median TMB in HCC is approximately 3–5 mutations per megabase, far below the threshold of 10 mutations per megabase that has been associated with ICI responsiveness in other cancers[11]. MSI-high status, which predicts robust responses to pembrolizumab in colorectal cancer, is found in less than 1% of HCC cases[11].

The assertion that HCC is predominantly ‘cold’ is not merely conceptual. Single-cell RNA sequencing analyses of treatment-naïve HCC have objectively classified a large proportion of tumors into an ‘immune-excluded’ or ‘immune-desert’ subtype, characterized by sparse $CD8^+$ T-cell infiltrates and a stromal barrier, which directly correlated with a lack of response to anti-PD-1 therapy in early-phase trials[13]. This provides the empirical basis for our framework’s first pillar: that successful immunotherapies must generate, not just enhance, anti-tumor immunity.

Regulatory mechanisms of the liver's immune-privileged microenvironment

Compounding this is the unique, tolerogenic microenvironment of the liver itself—an organ evolutionarily designed to suppress immune responses against a constant barrage of antigens from the gut. The liver's inherent immune privilege, mediated by specialized antigen-presenting cells and regulatory T cells (Tregs), creates a baseline state of immune suppression that tumors can readily exploit[12].

Therefore, single-agent ICI exhibits limited efficacy in HCC because it only relieves immune checkpoint inhibition and cannot induce de novo anti-tumor immune responses in a microenvironment lacking intrinsic anti-tumor immunity. The failure of nivolumab monotherapy to demonstrate superiority over sorafenib in the CheckMate 459 trial[14]. In that trial, nivolumab achieved a median OS of 16.4 months versus 14.7 months with sorafenib—a numerical improvement that failed to reach statistical significance, underscoring the limited efficacy of single-agent ICI in unselected HCC patients. We argue that the field's slow progress is a direct consequence of this conceptual error. Instead of persisting with strategies that attempt to reinvigorate a non-existent immune response, the focus must shift to fundamentally transforming the "cold" HCC microenvironment into a "hot" one—a process of *de novo* immune induction rather than mere potentiation. The partial success of ICI-TKI combinations should not be misinterpreted as proof of HCC's inherent immunogenicity; rather, it is a hint that the non-immunological component (the TKI) is likely acting as the primary driver by remodeling the tumor microenvironment, creating a window of opportunity for the ICI to act. This distinction is critical, as it reframes the entire therapeutic challenge from one of immune reactivation to one of immune generation.

Impact of HCC etiological heterogeneity on the immune microenvironment

A further layer of complexity that is systematically ignored in clinical trial design and treatment guidelines is the profound etiological heterogeneity of HCC. Unlike many solid tumors with a dominant driver mutation, HCC arises from diverse causes—chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol-related liver disease, and increasingly, metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH)—each creating a distinct immunological and molecular landscape (Fig. 1)[12,15]. Despite these fundamental differences, clinical trials lump all HCC patients together, and treatment recommendations are uniform regardless of etiology. This is a critical oversight. Emerging evidence suggests that the response to immunotherapy may indeed vary by etiology, with some studies hinting at differential efficacy of ICIs in viral versus non-viral HCC[15]. The failure to stratify by etiology in trial design and to develop etiology-specific treatment strategies is a major missed opportunity and a likely contributor to the modest overall efficacy of current therapies.

Translational studies suggest that HBV-associated HCC often exhibits a distinct immunologic infiltration pattern characterized by higher baseline activation/exhaustion of cytotoxic T cells (e.g., increased PD-1– and/or TIM-3–associated $CD8^+$ phenotypes) together with expanded regulatory immune cell fractions and an immunosuppressive cytokine milieu, including IL-10/TGF-β–related signatures[10,12]. In contrast, MASH-associated HCC tends to develop within a metabolically inflamed setting, where immune composition and myeloid polarization differ from viral etiologies—reflected in altered frequencies of macrophage/TAM subsets (e.g., $CD68^+$/$CD163^+$ phenotypes) and distinct cytokine patterns[12]. These etiology-linked differences in immune architecture provide a plausible mechanistic basis for variable immunotherapy responsiveness and durability across viral versus metabolic HCC[12].

Etiology stratification is rarely implemented in current clinical trials primarily due to practical constraints: etiologic status (viral burden, history of non-alcoholic fatty liver disease (NAFLD)/MASH, and mixed etiologies) is not consistently collected with sufficient granularity; subgroup enrichment would substantially reduce sample size and statistical power; and baseline liver-function and metabolic inflammation act as major confounders that influence both efficacy interpretation and safety/tolerability endpoints. Consequently, most trials enroll heterogeneous cohorts to preserve accrual and maintain feasible trial design, which can mask etiology-specific immune mechanisms and reduce the clinical translatability of immunotherapy findings.

A nuanced understanding requires transcending etiology alone. Modern multi-omics profiling has converged on an immunological classification that cuts across viral and metabolic etiologies. Approximately 30% of HCCs, disproportionately enriched with activating CTNNB1 (β-catenin) mutations, exhibit an ‘immune-

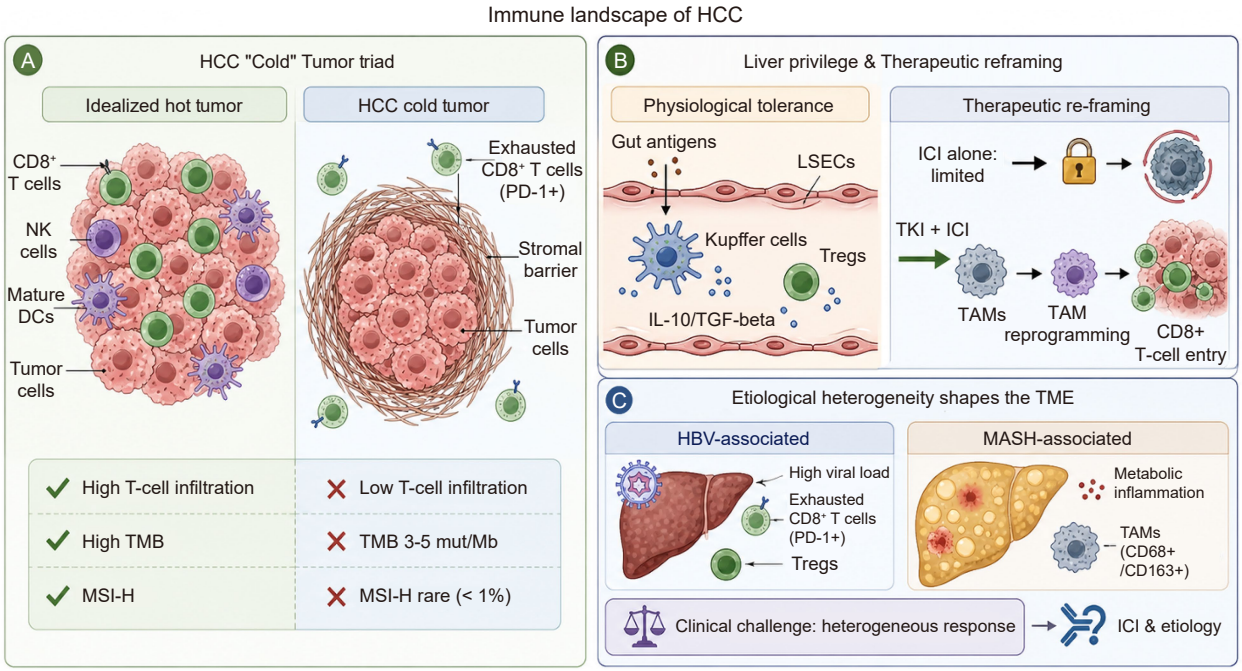


Fig. 1. Immune Landscape of HCC.
A. HCC "Cold" Tumor Triad.
B. Liver Privilege & Therapeutic Re-framing.
C. Impact of Etiological Heterogeneity on the TME.

desert' phenotype. These tumors are characterized by a near-complete absence of T-cell infiltration and CD103$^+$ dendritic cells. Crucially, resistance to PD-1 blockade in this subset is not a matter of degree but an intrinsic biological exclusion, as demonstrated by their null objective response rates even to potent ICI-TKI combinations in retrospective series.

A second, 'immune-excluded' subtype, often associated with high TGF-β signaling and dense fibrotic stroma, traps T cells in the peritumoral rim. This subtype might benefit from stromal-disrupting agents (e.g., TGF-β inhibitors) to facilitate T-cell entry. The third, 'immune-inflamed' subtype, which constitutes a minority of HCCs, bears the hallmarks of an ongoing but exhaustible immune response (high PD-L1, high CD8$^+$ T-cell infiltration). This group is most likely to derive benefit from standard ICI combinations. Our framework thus moves from a general 'cold-to-hot' narrative to a precise, subtype-adapted strategy: stromal de-barrier for the excluded phenotype, de novo immune induction for the desert phenotype, and immune reinvigoration for the inflamed phenotype. Acknowledging this granularity is critical to dismantling the illusion of uniform treatment efficacy."

Synergy or Serendipity? Dissecting ICI-TKI Combination Mechanisms

The current standard of care, combining ICIs with multi-targeted TKIs, is built on a compelling biological rationale: TKIs remodel the tumor microenvironment (TME) to be more permissive for an anti-tumor immune response, which is then unleashed by ICIs[12]. For instance, Lenvatinib has been shown to elevate NAD$^+$ levels by modulating TET2 synthesis, enhance inosine secretion, and inhibit the secretion of nicotinamide, 5-hydroxy-L-tryptophan, and quinolinic acid—thereby driving macrophage proliferation, migration, and M1 polarization. Additionally, it promotes the infiltration of GZMK$^+$CD8 T cells by suppressing VEGFR signaling, a process mediated by macrophage-derived CXCL9. Through these signaling pathways, Lenvatinib remodels the tumor microenvironment, effectively converting "cold" tumors into "hot" tumors[16]. Similarly, bevacizumab-mediated VEGF-A neutralization blocks VEGFR2/VEGFR1 signaling on endothelial cells, promoting pericyte coverage and suppressing Ang2-driven vessel destabilization to normalize tumor vasculature, alleviate hypoxia, and enhance T-cell trafficking[17]. Bevacizumab, in particular, has been shown to enhance the maturation of dendritic cells and promote T-cell priming, creating a more favorable immune landscape[17]. This synergy is undeniable and represents a cornerstone of modern HCC therapy. The IMbrave150 trial provided the first Level 1 evidence that this combination strategy is superior to TKI monotherapy, achieving a hazard ratio for death of 0.58 (95% CI 0.42–0.79) compared to sorafenib[7].

However, it is our contention that the current understanding of this synergy is superficial and potentially misleading. The narrative of "TKI primes, ICI strikes" is an oversimplification that ignores the complex, and often contradictory, roles of the signaling pathways involved. For example, in bevacizumab-containing regimens, VEGF-A neutralization blocks VEGFR2/VEGFR1 signaling, which normalizes abnormal tumor vessels by improving pericyte coverage and suppressing Ang2-driven vessel destabilization, thereby facilitating T-cell trafficking. In parallel, promiscuous TKIs may exert immune off-target effects: sorafenib inhibits LCK phosphorylation, leading to dose- and time-dependent suppression of CD25/CD69 expression and IL-2 production in vitro, and reduces T-cell-mediated contact dermatitis responses in mice, collectively implying that net synergy depends on balancing vascular normalization with immune T-cell receptor (TCR) inhibi-

tion (Fig. 2)[16]. The intricate crosstalk between key signaling pathways—such as the MAPK, PI3K/AKT, and particularly the WNT/β-catenin pathway (activated in ~ 30% of HCCs and strongly associated with an immune-excluded phenotype) —is poorly understood in the context of combination therapy[12,18]. Tumors with activated WNT/β-catenin signaling exhibit a paucity of T-cell infiltration and are inherently resistant to ICIs, yet there is no clear strategy for how to overcome this resistance in the setting of ICI-TKI combinations[18]. Overall, drug-drug interactions reflect a systems-level balance between agonistic and antagonistic signaling effects rather than a single deterministic mechanism. A deeper, systems-level understanding of this network is imperative to move from empirically derived combinations to rationally designed combinations. To overcome the current limited mechanistic understanding of synergy and potential immune off-target suppression, future research could employ a range of advanced preclinical models. One promising approach involves the construction of patient-derived organoid (PDO) models with immune-compatible co-culture systems to dissect drug-drug interactions between immune checkpoint inhibitors and TKIs, quantifying pathway-level effects on TCR signaling, T-cell activation, and vascular normalization. However, given that many PDOs lack a functional endothelial component, vascularized microtumor models that incorporate a functional endothelium represent another powerful platform to study these interactions in a more physiologically relevant context.

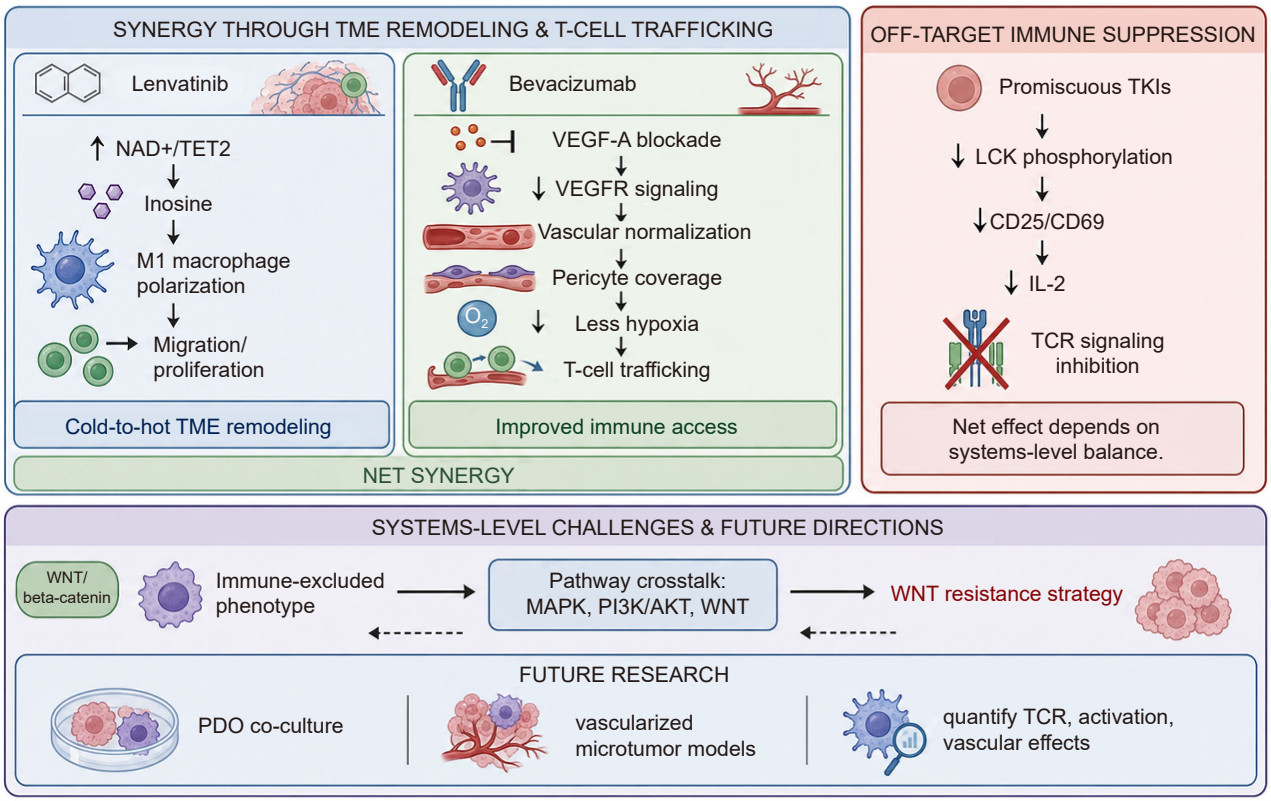


Fig. 2. Molecular mechanisms underlying synergy and off-target effects in ICI–TKI combination therapy: bevacizumab-mediated VEGF-A/VEGFR2 blockade normalizes tumor vasculature via pericyte and Ang2 regulation, while sorafenib inhibits TCR signaling through LCK phosphorylation suppression (reduced CD25/CD69 and IL-2), and the net clinical effect depends on the balance between vascular normalization and immune off-target inhibition.

The Resistance Conundrum: Why Responses Are Rarely Durable

The initial enthusiasm for combination immunotherapy is invariably tempered by the clinical challenge of treatment resistance. The majority of patients either fail to respond from the outset (primary resistance) or, more critically, respond initially only to relapse later (acquired resistance). In the IMbrave150 trial, while the ORR was 27%, this means that 73% of patients did not achieve an objective response, and even among responders, the median duration of response was 18.1 months, indicating that many eventually progressed[7]. The mechanisms underpinning this failure represent the most critical knowledge gap in the field.

Primary Resistance: Intrinsic Barriers to Immune Attack

Primary resistance is often rooted in the intrinsic biology of the tumor and its microenvironment. As discussed, the WNT/β-catenin signaling pathway is a major culprit, creating a physical barrier that prevents T-cell infiltration[18]. Other factors include the loss of antigen presentation machinery (e.g., B2M mutations), an overwhelming density of immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and a hostile cytokine milieu dominated by IL-10 and TGF-β[11,19]. The tumor-associated macrophages (TAMs) in HCC are often polarized toward an M2, immunosuppressive phenotype, secreting factors that inhibit T-cell function and promote an-

giogenesis[19]. These tumors are not just "cold"; they are resistant to current immunotherapeutic approaches. Furthermore, the chronic inflammation and fibrosis associated with underlying liver cirrhosis create a systemically immunosuppressive environment that extends beyond the tumor itself, making it even more difficult to mount an effective anti-tumor response[12]. Mechanistically, primary resistance can be parsed into three mechanistic axes: (1) WNT/β-catenin (CTNNB1) activation, occurring in a substantial fraction of HCC. In a large genomic dataset (n = 1,306), CTNNB1 mutations were more prevalent in PD-L1-negative tumors (35%) than in PD-L1-high tumors (21%), and CTNNB1-high expression was associated with a shorter duration of ICI treatment in PD-L1-negative patients (P = 0.04). These findings support a role for WNT/β-catenin signaling in limiting response durability to immune checkpoint blockade[15,17]. (2) Antigen-presentation defects, including B2M loss, impair MHC-I presentation and blunt $CD8^+$ recognition, enabling immune escape[7]. (3) Immunosuppressive infiltration—enriched Tregs and myeloid-derived suppressor populations (e.g., MDSC/TAM programs) —creates an IL-10/TGF-β–dominated cytokine milieu. Beyond cytokines, metabolic licensing also reinforces Treg-mediated resistance: in anti-PD-1–treated HCC, resistant patients show higher monocarboxylate transporter (MCT1/2) expression in induced Tregs, and higher MCT1 expression associates with worse clinical outcomes[7,16,18].

Acquired Resistance: Tumor Evolution Under Therapeutic Pressure

Acquired resistance, on the other hand, is a dynamic process of tumor evolution under therapeutic pressure. This can involve the immunoediting and subsequent loss of recognizable tumor antigens, the upregulation of alternative immune checkpoints (e.g., TIM-3, LAG-3, TIGIT), or the metabolic reprogramming of tumor cells to create a nutrient-deprived microenvironment that starves infiltrating T cells[19,20]. A recent study identified the transforming acidic coiled-coil containing protein 3 (TACC3) as a key mediator of acquired resistance, showing that it promotes lipid metabolism reprogramming in tumor cells, leading to the depletion of docosahexaenoic acid (docosahexaenoic acid (DHA)) in the tumor microenvironment, which in turn impairs $CD8^+$ T-cell function[21]. This highlights the emerging importance of metabolic interactions between tumor cells and immune cells as a mechanism of resistance. Critically, the mechanisms of resistance are likely regimen-specific. Resistance to Atezo + Bev, which involves VEGF blockade, may differ fundamentally from resistance to Durva + Treme, a pure dual-ICI regimen. Yet, this crucial distinction is largely ignored in current clinical practice and trial design. There is an urgent need for serial tumor biopsies and liquid biopsies during treatment to track the evolution of resistance mechanisms in real-time, which can then inform the development of adaptive, resistance-directed therapies.

This leads to the ultimate bottleneck: the biomarker void. In the absence of reliable predictive biomarkers, patient selection for these expensive and potentially toxic therapies is highly uncertain due to incomplete predictive information. Unlike in other cancers, PD-L1 expression, TMB, and MSI status have all proven to be poor predictors of response in HCC[11]. A meta-analysis of ICI trials in HCC found no significant association between PD-L1 expression and treatment outcomes, in stark contrast to lung cancer where PD-L1 is an established biomarker[11]. While promising candidates are emerging from multi-omics analyses — including transcriptomic signatures (e.g., immune cell infiltration scores), the gut microbiome composition, circulating tumor cells (CTCs) expressing PD-L1, and radiomics features from baseline imaging—they remain investigational and have not been validated in prospective trials[11,22]. In practice, patient selection relies on incomplete predictive information, committing all patients to a course of treatment from which only a minority will derive profound benefit. This is not only scientifically inefficient but also economically unsustainable and ethically questionable. The development and validation of predictive biomarkers must be a top priority for the HCC research community, alongside other critical priorities such as prevention and early detection. The absence of reliable predictive biomarkers leads to medical resource waste and patient overtreatment, exposing patients to prolonged cost and toxicity with limited probability of durable benefit. Emerging candidates are progressing from discovery to early clinical validation: (i) circulating tumor DNA (ctDNA) dynamics are being evaluated as liquid-biopsy surrogates for early response and resistance monitoring in prospective settings. (ii) Gut microbiome signatures are being tested in validation cohorts to refine response prediction to anti–PD-1–based therapy. (iii) Imaging-based radiomics scores provide non-invasive stratification and have reached multicenter external evaluation in some studies, although robust prospective decision thresholds remain under development. Overall, clinical utility will require standardized assays, predefined endpoints, and external validation beyond single-institution cohorts.

Exploration of therapy strategies

The explosion of treatment options has paradoxically complicated, rather than simplified, clinical decision-making. Clinicians and patients are faced with a bewildering array of choices, guided by clinical trials with different designs, control arms, and patient populations, and a near-complete absence of head-to-head comparisons. This section critically appraises the evidence for current first- and second-line therapies, exposing the "illusion of choice" and the precarious foundation upon which many treatment recommendations are built.

The RATIONALE-301 trial (Level I—RCT) established the non-inferiority of tislelizumab to sorafenib in terms of OS (15.9 vs. 14.1 months). Tislelizumab yielded a superior ORR (14.3% vs. 5.4%) and a tripled median DOR (36.1 vs. 11.0 months). Safety outcomes also favored tislelizumab, which was associated with fewer Grade 3^+ TRAEs compared to sorafenib[23]. In 2020, the pivotal IMbrave150 trial (Level I—RCT) evaluated atezolizumab plus bevacizumab versus sorafenib in patients with unresectable HCC. The combination therapy demonstrated marked superiority across all primary endpoints: overall survival (OS:19.2 vs.13.4 months; HR = 0.66; $P < 0.001$), progression-free survival (PFS: 6.9 vs. 4.3 months; HR = 0.65; $P < 0.001$), and objective response rate (ORR: 30% vs. 11%; $P < 0.001$)[7,24]. Following these landmark results, the FDA approved the combination in 2020, establishing it as the global standard of care for first-line unresectable HCC[5]. Results from the ORIENT-32 study (Level I—RCT) showed that sintilimab-bevacizumab biosimilar signific-

antly outperformed sorafenib in patients with unresectable HCC. Median PFS was 4.6 months vs. 2.8 months (HR = 0.56, 95% CI 0.46–0.70; $P < 0.0001$), while median OS was not reached for the combination group compared to 10.4 months for sorafenib (HR = 0.57, 95% CI 0.43–0.75; $P < 0.0001$). These findings also underscore the superior efficacy of this combination regimen over traditional tyrosine kinase inhibitor (TKI) monotherapy[25].

Multikinase inhibitors (MKIs), such as sorafenib and lenvatinib, remain cornerstone therapies in HCC due to their inhibition of angiogenesis and tumor proliferation. The integration of MKIs and ICIs in HCC treatment leverages mechanistic synergy, where MKIs enhance ICI-mediated T-cell function by remodeling the immunosuppressive microenvironment[26]. However, translating early-phase success into Phase III results has proven challenging. While KEYNOTE-524 (Level III—phase II) showed promising activity, the LEAP-002 study (Level I—RCT) of pembrolizumab and lenvatinib failed to achieve statistically significant improvements in OS or PFS over lenvatinib monotherapy[27,28]. Conversely, the CARES-310 trial (Level I —RCT) successfully demonstrated the superiority of camrelizumab plus rivoceranib over sorafenib, yielding a median OS of 22.1 months[29]. This combination now provides a highly effective first-line alternative, notwithstanding its distinct safety profile. More recently, the CheckMate 9DW trial (Level I —RCT) showed that nivolumab plus ipilimumab improved OS compared to sorafenib or lenvatinib in the first-line setting, suggesting that dual ICI combinations may also be effective in the second-line setting after TKI failure, although prospective data in this specific sequence are still lacking[30].

CTLA-4 and PD-L1 inhibitor combinations have shown additive antitumor activity associated with complementary immunostimulatory effects[31]. In the phase III HIMALAYA (Level I—phase III RCT) study, the Single Tremelimumab Regular Interval Durvalumab (STRIDE) regimen significantly improved overall survival versus sorafenib (16.43 vs 13.77 months), and durvalumab monotherapy was noninferior to sorafenib (hazard ratio, 0.86; 95.67% CI, 0.73 to 1.03; noninferiority margin, 1.08)[8,32,33]. While, the dual-ICI nature of Durva + Treme carries a higher risk of immune-related adverse events (irAEs), with Grade 3–4 irAEs occurring in 25.8% of patients in the HIMALAYA (Level I—phase III RCT) trial compared to 15.5% with Atezo + Bev in IMbrave150[7,8]. This makes Durva + Treme less suitable for patients at higher risk of irAEs. The comparative efficacy, safety, and evidence levels of these first- and second-line regimens are summarized in Table 1 and Fig. 3. However, this creates a false dichotomy where the choice is driven more by avoidance of toxicity than by maximization of efficacy. Furthermore, the elevation of these combinations to "standard of care" obscures the fact that they are unsuitable for a large proportion of the real-world HCC population. Patients with Child-Pugh B liver function, who may constitute up to 30–40% of the advanced HCC population, were largely excluded from the pivotal trials, leaving their treatment an evidence-free zone[34]. The IMbrave150 trial enrolled only 15% Child-Pugh B patients, and the HIMALAYA (Level I —phase III RCT) trial excluded them entirely[7,8]. The current guidelines offer a weak recommendation for a "cautious approach" in these patients, a euphemism for clinical uncertainty[5]. This is not a minor detail; it is a major ethical and clinical failure of the current research paradigm, which prioritizes pristine trial populations over the clinical reality of clinical practice. Real-world studies are beginning to fill this gap, but the evidence remains limited and of lower quality than prospective RCTs[34]. Child-Pugh B liver dysfunction represents a critical evidence gap in advanced HCC, because this subgroup is markedly underrepresented or excluded from pivotal Level I RCTs. In first-line settings, IMbrave150 includes only a limited proportion of Child-Pugh B patients[3,4], whereas HIMALAYA excludes them entirely[3,4], resulting in cautious, evidence-limited guideline recommendations[31]. Therefore, real-world experience and smaller datasets provide the main practical basis for treatment selection[32], but comparative prospective evidence remains insufficient and heterogeneous with respect to efficacy and toxicity; accordingly, Child-Pugh B management currently relies largely on Level II–III evidence and warrants prospective stratified studies and liver-function–aware dosing strategies.

Table 1. Comparison of first-line therapies for advanced liver cancer.

Category	Regimen	N	Study Design	ORR (%)	mPFS (95% CI)	mOS (95% CI)
TKI Monotherapy	Sorafenib	299	Phase III (SHARP)[9]	2.0	5.5months (NR)	10.7months (NR)
	Lenvatinib	478	Phase III (REFLECT)[35]	24.1	7.4months (6.9–8.8)	13.6months (12.1–14.9)
	Donafenib	328	Phase III (ZGDH3)[36]	4.6	3.7months (NR)	12.1months (NR)
ICI Monotherapy	Tislelizumab	342	Phase III (RATIONALE-301)[23]	14.3	2.1months (2.1–3.5)	15.9months (13.2–19.7)
	Nivolumab	262	Ib/II Phase (CheckMate-040)[37]	20.0	NR	NR
	Pembrolizumab	104	Phase II (KEYNOTE-224)[38]	17.0	4.9months (3.4–7.2) (2nd-line)	12.9months (9.7 –15.5) (2nd-line)
ICI + TKI	Pembrolizumab + Lenvatinib	104	Phase I b Study[28]	36.0	8.6months (7.1–9.7)	22.0months (20.4– not reached)
	Apatinib + Camrelizumab	272	Phase III (CARES-310)[29]	25.0	5.6months (5.5–6.3)	22.1months (19.1–27.2)
ICI + Anti-VEGF	Atezolizumab + Bevacizumab	336	Phase III (IMbrave150)[24]	27.3	6.9months (5.7–8.3)	median not reached
	Sintilimab + IBI305	380	Phase II-III (ORIENT-32)[25]	25.0	2.8months (2.7–3.2)	median not reached
Dual ICI	Durvalumab + Tremelimumab	103	Phase III (HIMALAYA)[33]	51.5	NR	NR
	Nivolumab + Ipilimumab	335	Phase III (CheckMate-9DW)[30]	36.0	9.2months (7.9–11.1)	23.7months (18.8–29.4)

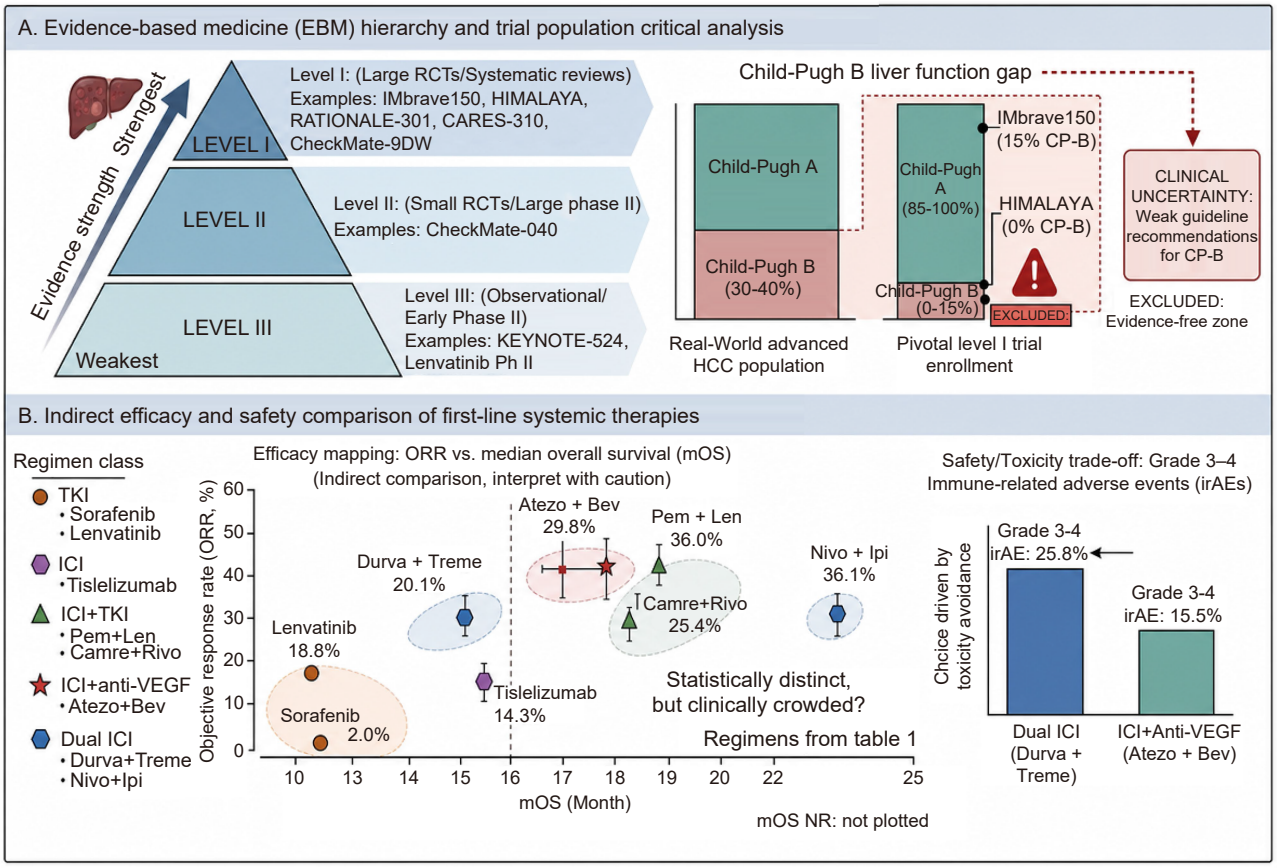


Fig. 3. Evidence-based medicine levels and indirect efficacy/safety comparisons of first- and second-line therapies for advanced HCC.
A. Evidence-Based Medicine Hierarchy and Trial Population Critical Analysis.
B. Indirect Efficacy and Safety Comparison of First-Line Systemic Therapies.
This scatter plot maps the efficacy of different treatments, with Median Overall Survival (mOS) on the X-axis and Objective Response Rate (ORR %) on the Y-axis. Different treatment categories are represented by specific color and symbol codes: TKI Monotherapy (Brown Circle); ICI Monotherapy (Purple Hexagon); ICI + TKI (Green Triangle); ICI + Anti-VEGF (Red Star); Dual ICI (Blue Hexagon). The plot illustrates the "illusion of choice" and clinical crowding of competing treatments. The smaller bar chart on the right compares safety profiles, highlighting how treatment choices are often driven by safety avoidance.

Immunotherapy is recommended for patients who experience disease progression following first-line TKI monotherapy. Nivolumab was the first PD-1 inhibitor to demonstrate clinical efficacy in HCC through the landmark CheckMate 040 (Level III—phase I/II) study. This Phase 1/2 trial reported an objective response rate (ORR) of 15–20% across diverse patient cohorts, including those with HBV/HCV infections and those previously treated with sorafenib. Beyond its efficacy, nivolumab exhibited a manageable safety profile and maintained stable patient-reported quality of life, supporting its clinical utility even in patients with underlying chronic viral hepatitis[37,39]. The situation is also somewhat better understood for patients who progress on first-line TKI monotherapy. For these patients, cabozantinib, regorafenib (for those who tolerated sorafenib), and ramucirumab (for AFP ≥ 400 ng/mL) have all demonstrated survival benefits in placebo-controlled RCTs (Level I—RCT)[40–42]. For example, the CELESTIAL trial (Level I—RCT) showed that cabozantinib improved overall survival compared with placebo in patients who had progressed on sorafenib; however, the trial predated the first-line immunotherapy era[40].

However, the transition of immunotherapy to first-line treatment has created a clinical dilemma: how to effectively treat patients who progress on these agents in the second-line setting. For patients who progress after first-line immunotherapy, multiple retrospective studies (Level II—real-world) have shown that subsequent multi-targeted TKI therapy (such as lenvatinib or sorafenib) following progression on the first-line "T + A" regimen can still provide clinical benefit, with an ORR reaching 6.1% and a median OS of up to 14.7 months. Among these, patients treated with lenvatinib achieved longer PFS (6.1 months vs. 2.5 months) and also achieved a median overall survival of 9.8 months[43]. The recent prospective Phase II (Level III—small-sample) KCSG HB23-04 study[44] also confirmed that for patients progressing on first-line "T + A", second-line lenvatinib resulted in a median PFS of 5.4 months, an ORR of 14%, and a manageable safety profile. Another prospective Phase II (Level III—small-sample) study by Ryoo et al.[45] showed that after progression on first-line "T + A", second-line regorafenib yielded a median PFS of 3.5 months, a median OS of 10.5 months, and an ORR of 10.0%. A comprehensive comparison of available second-line regimens is provided in Table 2.

Whether immunotherapy can be continued beyond progression is another clinically relevant question. Exploratory analysis (Level II—secondary evidence) from the IMbrave150 study[7] suggested that patients who continued with "T + A" or other immunotherapies after progression on first-line "T + A" appeared to

Table 2. Comparison of second-line therapies for advanced liver cancer.

First-Line Therapy	Second-Line Therapy Regimen	N	Study Design	ORR (%)	mPFS (95%CI)	mOS (95%CI)
Sorafenib	Nivolumab + Ipilimumab (NIVO 1 mg/kg + IPI 3 mg/kg Q3W)	50	Phase I/II[39]	32	NR	22.8 (9.4–not reached)
Sorafenib	Apatinib	267	Phase III, RCT[46]	11	4.5months (3.9–4.7)	8.7months (7.5–9.8)
Atezolizumab + Bevacizumab ("T + A")	Sorafenib, Lenvatinib, or Cabozantinib	49	Retrospective[43]	6.1	3.4months (1.8–4.9)	14.7months (8.1–21.2)
Atezolizumab + Bevacizumab ("T + A")	Regorafenib	40	Phase II[45]	10.0	3.5months (3.0–3.9)	10.5months (7.1–13.8)
Atezolizumab + Bevacizumab ("T + A")	Lenvatinib	50	Phase II[44]	14.0	5.4months (4.2–7.1)	9.8months (8.1–not reached)

have better OS compared to those who received other treatments or no treatment. However, this still requires confirmation from prospective studies. Trials such as IMbrave251 (Level I—phase III RCT) are currently underway to address the critical question of whether immunotherapy can be used "beyond progression".

The most profound impact of modern systemic therapy may not be the incremental survival gains in the palliative setting, but its potential to completely reshape the treatment paradigm for earlier-stage disease. The high response rates achieved by potent combination therapies are challenging the traditional, rigid boundaries between unresectable and resectable disease, and between local and systemic treatments. This is driving a paradigm shift away from a purely palliative mindset towards cure-oriented strategies, including conversion therapy for initially unresectable patients and perioperative therapy to reduce recurrence in those undergoing curative-intent procedures.

For the first time, a subset of patients with locally advanced, unresectable HCC can be successfully "downstaged" by systemic therapy to a point where curative resection or ablation becomes feasible. This concept, known as conversion therapy, represents a tangible path to a potential cure for patients previously deemed incurable. The high ORR of regimens like lenvatinib-based combinations or Atezo + Bev provides the biological premise for this strategy, with studies reporting successful conversion rates ranging from 10% to over 25% in selected patient cohorts[47,48]. A real-world study from China reported that 25.3% of patients with initially unresectable or advanced HCC achieved resectable disease after combination therapy with systemic agents and locoregional treatments. All 20 patients underwent successful R0 resection, among whom 12 experienced tumor recurrence, yielding a median recurrence-free survival (RFS) of 15.0 months; the 12- and 24-month RFS rates were 43.3% and 37.1%, respectively[47]. The integration of systemic therapy with aggressive locoregional treatments, such as transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC), appears to further enhance this potential, creating a powerful synergistic effect[49]. The rationale is that locoregional therapy induces immunogenic cell death, releasing tumor antigens and creating an inflamed microenvironment that is more susceptible to systemic immunotherapy[49].

However, the path of conversion therapy is fraught with challenges that temper its promise. A major obstacle is the lack of standardized criteria for defining both "unresectable" disease and successful "conversion." These definitions vary widely between institutions and studies, making it difficult to compare results and establish clear guidelines. The Chinese consensus on conversion therapy proposed criteria based on tumor burden, vascular invasion, and liver function, but these have not been universally adopted[48]. The optimal strategy and timing also remain elusive. Should systemic therapy be given alone or in combination with locoregional therapy? How many cycles should be administered before reassessing for surgery? The surgical timing dilemma is particularly critical: operating too early may miss the window of maximal tumor response, while waiting too long risks tumor progression or the loss of a surgical window due to deteriorating liver function.

To address this clinical dilemma, it may be essential for future researchers to define the criteria for a "window for maximizing therapeutic efficacy". This window aims to identify the optimal time point at which the best balance between tumor shrinkage and systemic disease control is achieved. Its determination should not rely on a single static image but rather integrate continuous dynamic assessments: radiologically, the trend and speed of tumor burden reduction should be tracked according to the Response Evaluation Criteria in Solid Tumors (RECIST), while remaining vigilant for signs of a "mixed response" or early progression—such as the appearance of new lesions or an inflection of tumor markers (e.g., alpha-fetoprotein) from a declining to a rising trend—even when partial response criteria are met. Furthermore, in the future, the integration of dynamic biomarkers such as radiomics and circulating tumor DNA (ctDNA) holds promise for defining this optimal surgical window with greater precision, thereby truly advancing the decision-making process from "if" to "when" to pursue conversion. Without standardized pathological response criteria and validated radiological surrogates, these decisions remain highly subjective, hindering the widespread, effective adoption of this promising strategy. There is an urgent need for prospective, multicenter trials with standardized definitions and endpoints to establish evidence-based guidelines for conversion therapy.

The high risk of recurrence after surgical resection or ablation, which can be as high as 70% at 5 years, is the major limitation of curative-intent treatment for HCC[50]. The advent of effective systemic therapies has logically led to their investigation in the perioperative setting to eradicate micrometastatic disease and reduce this risk.

Neoadjuvant therapy, administered before surgery, is particularly attractive. It provides an *in vivo* assessment of tumor biology and treatment sensitivity, and the presence of the primary tumor may serve as a source of antigens to prime a more robust systemic immune response. Early-phase trials of neoadjuvant ICIs have yielded encouraging results, with major pathological response (MPR, defined as ≤ 10% viable tumor) rates of 30–50% and pathological complete response (pCR, defined as 0% viable

tumor) rates approaching 30% in some studies[51,52]. These pathological responses appear to correlate strongly with improved recurrence-free survival (RFS). A meta-analysis of neoadjuvant immunotherapy trials in HCC found that patients achieving MPR had a significantly lower risk of recurrence compared to those who did not[51]. Several recent studies[53] have further confirmed this association and provided specific data on different combination regimens. For instance, in the nivolumab plus ipilimumab regimen, the major pathological response (MPR) rate reached 33%, with estimated 2-year progression-free survival (PFS) and overall survival (OS) rates of 47.1% and 72.0%, respectively. This suggests that patients achieving a pathological response derive significant long-term survival benefits. Another study investigating tislelizumab combined with lenvatinib and transarterial chemoembolization (TACE) reported an MPR rate as high as 76.9%, with 15.4% of patients achieving a pathological complete response (pCR), corresponding to a 12-month recurrence-free survival (RFS) rate of 82.5%. Similarly, in the triple therapy consisting of lenvatinib plus an anti-PD-1 antibody and TACE, the 3-year RFS rate was significantly higher in the treatment group (52% vs. 30%), further supporting the notion that enhanced pathological response rates through combination therapy can translate into long-term survival benefits. Additionally, a study on lenvatinib monotherapy for advanced HCC observed that among patients achieving an objective response (ORR 37.5%), 76.2% successfully underwent surgical resection, with a median RFS of 7.2 months. Collectively, these data indicate that deeper pathological responses (particularly MPR and pCR) achieved during neoadjuvant therapy—whether with immunotherapy, targeted therapy, or their combination with TACE—are closely associated with lower postoperative recurrence rates and prolonged survival. However, neoadjuvant therapy is not without risks. There is a theoretical concern that it may delay surgery and potentially lead to disease progression in non-responders, although most studies have not reported significant delays or increases in surgical complications[52].

In the adjuvant setting, the landscape has been transformed by the results of the IMbrave050 trial, which showed that one year of adjuvant Atezo + Bev significantly improved RFS compared to active surveillance in patients at high risk of recurrence after resection or ablation[54]. The trial classified patients based on whether they underwent resection or ablation. For patients who underwent resection, high risk was defined as meeting any of the following criteria: (i) up to three tumors, with the largest tumor > 5 cm in diameter (regardless of vascular invasion or poor tumor differentiation); (ii) up to three tumors, with the largest tumor ≤ 5 cm in diameter but accompanied by vascular invasion (regardless of tumor differentiation); or (iii) four or more tumors, with the largest tumor ≤ 5 cm in diameter (regardless of vascular invasion or poor tumor differentiation). For patients who underwent ablation, high risk was defined as: (i) a single tumor > 2 cm but ≤ 5 cm in diameter; or (ii) multiple tumors (up to four tumors), all ≤ 5 cm in diameter. The trial enrolled patients with these high-risk features and demonstrated a hazard ratio for recurrence or death of 0.72 (95% CI 0.56–0.93), representing a 28% reduction in risk[54]. This marks the first time an adjuvant regimen has succeeded where numerous previous trials with sorafenib and other TKIs have failed, establishing a new standard of care. However, critical questions remain. The long-term impact on overall survival is not yet known, as the trial was not powered for OS and the follow-up is still ongoing. Furthermore, the optimal duration of adjuvant therapy is still a matter of debate. The IMbrave050 trial used one year of treatment, but whether shorter or longer durations would be equally effective or more tolerable is unknown. The applicability of these findings to patients who received neoadjuvant therapy is also unclear, as the trial did not include such patients. The perioperative space is rapidly evolving, but we must exercise caution to avoid the premature adoption of these strategies outside of well-defined high-risk populations until more mature data on long-term outcomes and cost-effectiveness become available. The overall clinical pathway integrating conversion, surgical, and adjuvant strategies for unresectable HCC is illustrated in the Clinical Application Flow Chart (Fig. 4).

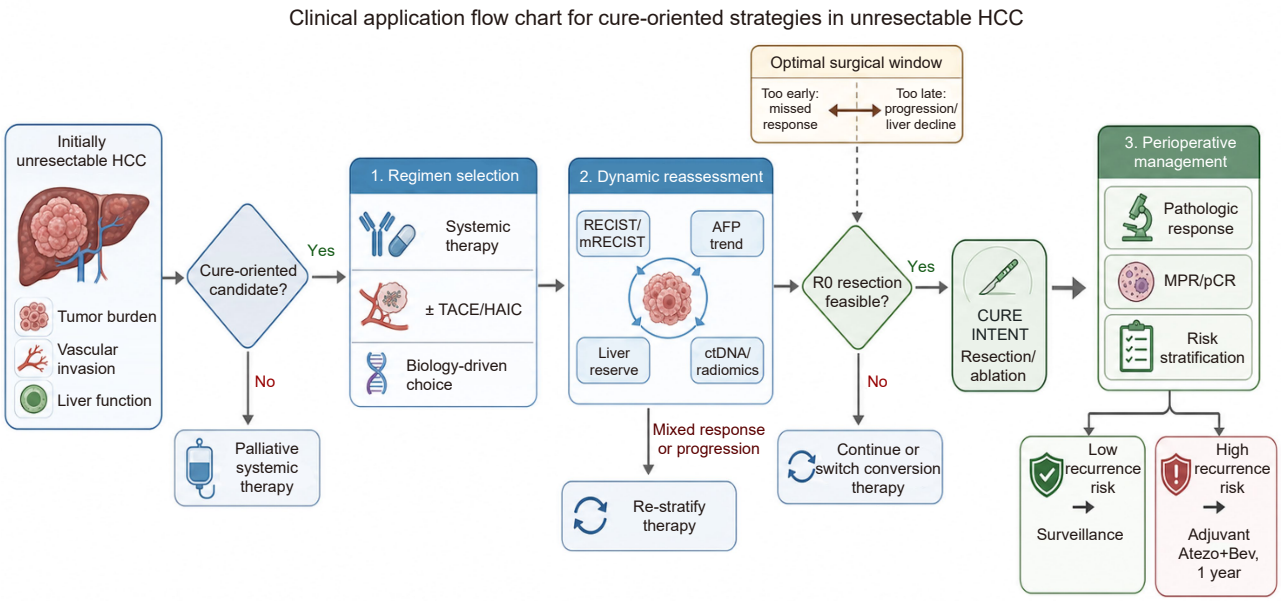


Fig. 4. Clinical application flow chart for cure-oriented strategies in unresectable HCC.

Future Directions: Toward Precision and Personalized HCC Therapy

The path forward requires a fundamental shift from the current trial-and-error approach to a paradigm of precision oncology. Breaking the current therapeutic plateau will not come from simply adding more drugs to the cocktail, but from a deeper biological understanding that enables the selection of the right treatment for the right patient at the right time. We envision the next five years will be defined by disruptive breakthroughs in three key areas: predictive biomarkers, novel therapeutic targets, and next-generation combination strategies.

The most urgent unmet need in HCC is the development of robust, validated predictive biomarkers. The future lies in moving beyond single-analyte, static measurements towards integrated, multi-omic, and dynamic approaches. Considerable progress has already been made in leveraging artificial intelligence within individual data domains; for instance, radiomic models applied to baseline imaging have shown promise in capturing tumor heterogeneity and vascular patterns[18], and machine learning classifiers built on transcriptomic signatures have been used to infer immune cell infiltration or interferon-γ pathway activity. However, these pioneering studies have largely focused on a single modality and lack the integrative, multi-omic perspective required to fully capture the complex determinants of immunotherapy response. These models will be developed through a structured, multi-step process. First, they will integrate multi-omic data—including genomic alterations (e.g., WNT/β-catenin pathway mutations, TERT promoter mutations), transcriptomic signatures (e.g., immune cell infiltration scores, interferon-gamma signatures), proteomic markers (e.g., circulating cytokines, soluble PD-L1), and radiomic features from baseline imaging (e.g., tumor heterogeneity indices, vascular patterns) —to construct a composite "Immunotherapy Response Score" using machine learning algorithms trained on large-scale, well-annotated cohorts. Subsequently, this score will undergo rigorous clinical validation in prospective, biomarker-driven platform trials. Ultimately, it is anticipated to guide first-line treatment selection by distinguishing likely responders to Atezo + Bev versus Durva + Treme versus TKI monotherapy with greater than 80% accuracy[11,22]. Furthermore, liquid biopsy monitoring of circulating tumor DNA (ctDNA) will become the standard of care for detecting minimal residual disease after curative-intent therapy and for the early identification of acquired resistance, allowing for adaptive, real-time changes in treatment strategy long before radiological progression is evident[22]. The integration of machine learning algorithms trained on large, multi-institutional datasets will be key to unlocking the predictive power of these complex, high-dimensional data.

The current therapeutic arsenal is narrowly focused on the PD-1/PD-L1 and VEGF axes. Long-term progress requires expanding our target portfolio to address the core drivers of HCC biology and immune evasion. We foresee a breakthrough in targeting previously "intractable" drivers of HCC. Within five years, clinical data will emerge for novel agents that indirectly target TERT promoter mutations (present in 60–70% of HCCs) or effectively disrupt the WNT/β-catenin signaling pathway, thereby converting the immune-excluded phenotype into an inflamed one and sensitizing a large, resistant patient population to ICIs[12,18]. Strategies under investigation include inhibitors of downstream effectors of WNT signaling, such as tankyrase inhibitors, and agents that target the transcriptional machinery activated by β-catenin. In hepatocellular carcinoma (HCC), the clinical development of WNT/β-catenin pathway inhibitors remains in early stages, with no agents currently approved. The anti-DKK1 monoclonal antibody DKN-01 was investigated in a monotherapy trial for HCC (NCT03645980); however, the trial status is unknown and no efficacy data have been disclosed. The Fzd8-Fc fusion protein OMP-54F28 was evaluated in a Phase I trial combining with sorafenib in HCC (NCT02069145), but results have not been reported, and its development has been hindered by dose-limiting bone toxicity observed in other solid tumor trials. The first-generation CBP/β-catenin inhibitor PRI-724 was explored in HCC-related settings but did not yield desirable outcomes. Currently, the most notable candidate in the HCC landscape is the third-generation CBP/β-catenin inhibitor E7386, which is being evaluated in active Phase I/II combination trials (e.g., with pembrolizumab) that include an HCC cohort (NCT05091346). Overall, while early exploration in HCC has been limited and several candidates have faced challenges related to toxicity or lack of efficacy, E7386 represents a promising avenue warranting further clinical investigation[18].

Concurrently, the concept of "metabolic checkpoint inhibitors" will mature into clinical reality. Agents that target key metabolic dependencies of tumor cells (e.g., glutamine metabolism, fatty acid synthesis) or reprogram the metabolic fitness of T cells (e.g., by enhancing glucose or lipid uptake) will enter Phase II/III trials in combination with ICIs[20]. The recent identification of TACC3 as a mediator of metabolic resistance provides a concrete target for such strategies[20]. We also predict that the first GPC3-targeting T-cell engager bispecific antibody will demonstrate compelling efficacy in Phase II trials, offering a potent, off-the-shelf cellular immunotherapy-like option and challenging the dominance of traditional ICI combinations[55]. Glypican-3 (GPC3) is overexpressed in 70–80% of HCCs and is an attractive target for bispecific antibodies that can redirect T cells to kill tumor cells.

Simultaneously, Chimeric Antigen Receptor T-cell (CAR-T) therapy represents another frontier in targeting GPC3. Unlike ICIs which rely on endogenous T-cells, CAR-T therapy adopts a cellular therapeutic approach by infusing engineered T-cells to directly recognize and eliminate tumor cells, theoretically overcoming the barrier of the immunologically 'cold' microenvironment described earlier. Early-phase trials of GPC3-CAR-T cells have demonstrated manageable safety and encouraging preliminary efficacy, with objective response rates (ORR) ranging from 10% to 20% in heavily pre-treated populations, and select patients achieving durable complete remission significantly exceeding historical expectations.

Glypican-3 (GPC3)-targeted therapy has demonstrated potential in hepatocellular carcinoma (HCC); however, its clinical translation remains constrained by multiple challenges. Regarding solid tumor penetration, the heterogeneous expression of GPC3 facilitates immune evasion by antigen-negative clones, while the clinical efficacy of monoclonal antibodies (e.g., codrituzumab) is limited by insufficient intratumoral penetration and incomplete target saturation. Furthermore, CAR-T therapy is prone to functional exhaustion within the suppressive hepatic microenvironment, and the low-level expression of GPC3 in nor-

mal tissues may induce on-target/off-tumor toxicity (e.g., cytokine release syndrome). To overcome these obstacles, future optimization strategies should integrate multi-dimensional innovations. To address inadequate tumor infiltration, strategies include optimizing the pharmacokinetic properties of antibodies to enhance intratumoral penetration, or employing localized delivery techniques in CAR-T design (such as hepatic arterial infusion) to enrich effector cells at the tumor site. At the engineering level, the development of multi-antigen or tandem CARs (e.g., co-targeting AFP or EGFR) can counteract antigen heterogeneity, while affinity-optimized CAR designs can enhance solid tumor penetration while discriminating between tumor and normal tissues. By integrating localized delivery techniques with logic-gated systems (e.g., "AND" logic gates), immune activation can be further restricted to the tumor site. Through the integration of these strategies, a synergistic therapeutic framework that balances efficacy and safety may be established in the future[56]. Thus, the future may witness a competition or perhaps a synergy between 'off-the-shelf' bispecific antibodies and autologous CAR-T therapies, with the choice guided by patient-specific biomarker profiles.

The future of combination therapy depends less on empirically adding agents than on prespecified, mechanism-anchored regimens that integrate systemic therapy with locoregional treatment and biomarker-informed decision rules. This framework prioritizes complementary immunomodulation and rational sequencing between local and systemic modalities.Triplet and quadruplet strategies are increasingly defined by concrete trial architectures and early efficacy readouts rather than qualitative promises of "smarter" combinations. Expert reviews of TKI–immune checkpoint inhibitor combinations in HCC provide complementary synthesis for how multiagent regimens are evolving[53]. As an example of TGF-β–directed therapy combined with PD-1 inhibition, a multicenter phase Ib/II study (NCT02423343) of galunisertib plus nivolumab met its primary safety objectives; efficacy analyses in the phase II NSCLC cohort reported a 24% confirmed objective response rate and survival estimates such as median progression-free survival of 5.26 months and median overall survival of 11.99 months[54]. In advanced HCC, TGF-β receptor I inhibition combined with multi-kinase inhibition was evaluated in a phase II trial of galunisertib plus sorafenib, which reported clinically meaningful survival signals in dose cohorts (including median overall survival of 18.8 months in the 150 mg twice-daily cohort)[55]. These observations conceptually inform ICI–TKI–TGF-β–axis regimens, which are further supported by a multinational phase Ib trial of lenvatinib plus pembrolizumab in unresectable HCC (NCT03006926) demonstrating objective response rates of 36.0–46.0% and median overall survival of 22 months in treatment-naïve expansion patients[56]. For locoregional integration, a multicenter cohort study of TACE plus lenvatinib plus tislelizumab in intermediate-stage HCC showed higher objective response and longer survival than TACE-based comparators (e.g., median overall survival 31.5 vs. 18.5 months vs. TACE alone)[57]. Nationwide real-world data likewise indicate that TACE combined with PD-(L)1 inhibitors plus molecular targeted therapy improves progression-free and overall survival versus TACE monotherapy[58]. Epigenetic priming through HDAC pathway modulation alongside PD-1/PD-L1 blockade is supported by mechanistic HCC analyses[59]; prospective trials that explicitly combine TACE with an HDAC inhibitor and checkpoint blockade remain scarce, representing a key design gap for the next generation of locoregional–systemic triplets.

Adaptive platform trials are increasingly relevant to HCC because they can evaluate multiple regimens in parallel while updating allocation using prespecified statistical and safety rules. The I-SPY 2 neoadjuvant platform in breast cancer illustrates the operational logic: patients are stratified into biomarker signatures; experimental arms are adaptively randomized using Bayesian methods to enrich assignment toward regimens with higher early efficacy (e.g., pathologic complete response); arms can be "graduated" or dropped when posterior probabilities cross prespecified efficacy or futility thresholds; and serial imaging together with on-trial biopsies supports interim decision-making. Adaptive arm assignment within I-SPY 2 substudies provides concrete examples of how interim activity signals can reweight randomization during accrual[60], and contemporary reviews synthesize the platform's biomarker strata, Bayesian allocation, and graduation/futility rules in detail[61]. In HCC, multicenter phase Ib/II platform infrastructure is exemplified by neoadjuvant immunotherapy combination studies such as MORPHEUS-NeoHCC, a randomized platform protocol evaluating several perioperative immunotherapy combinations in surgically resectable disease (NCT05908786). Complementary large cohort analyses—including CHANCE001 —benchmark TACE combined with PD-(L)1 inhibition and molecular targeted therapy against locoregional monotherapy at population scale[58]. Finally, we predict that the success of adjuvant immunotherapy will spur the development of truly curative-intent trials aiming to eradicate disease in intermediate stages, where systemic therapy plus aggressive locoregional therapy will be investigated not for downstaging, but for complete pathological remission, potentially obviating the need for surgery in a subset of patients. This "watch-and-wait" strategy, already employed in rectal cancer after chemoradiotherapy, could be transformative for HCC if pathological complete responses can be reliably achieved and maintained.

Conclusion

The core paradox of advanced HCC therapy is the proliferation of regimens with inadequate mechanistic understanding. The cold tumor microenvironment and etiological heterogeneity constitute key barriers. Resistance is inevitable and dynamically evolving across regimens, requiring real-time monitoring and individualized intervention strategies. Cure-oriented strategies depend on standardized definitions and evidence-based guidance for conversion and perioperative therapy. Research gaps and prospects: Three unresolved issues remain - biomarker deficiency, insufficient evidence for special populations (notably Child-Pugh B), and a superficial understanding of synergistic mechanisms. The field should prioritize etiology-stratified randomized trials, establish a global multicenter biobank, and develop an AI-driven clinical decision support system for mechanism-based patient matching. Through multidisciplinary collaboration and mechanism-driven research, the management of HCC can evolve decisively from incremental benefits toward genuine cure, realizing the long-awaited clinical implementation of individualized precision therapy.

Abbreviations

Ang2, Angiopoietin-2; B2M, Beta-2 microglobulin; CAR-T, Chimeric antigen receptor T-cell; CTCs, Circulating tumor cells; ctDNA, Circulating tumor DNA; CTNNB1, Catenin beta 1; DHA, Docosahexaenoic acid; GPC3, Glypican-3; HAIC, Hepatic arterial infusion chemotherapy; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; HDAC, Histone deacetylase; HR, Hazard ratio; ICI, Immune checkpoint inhibitor; irAEs, Immune-related adverse events; MASH, Metabolic dysfunction-associated steatohepatitis; MCT, Monocarboxylate transporter; MDSCs, Myeloid-derived suppressor cells; MPR, Major pathological response; MSI, Microsatellite instability; NAFLD, Non-alcoholic fatty liver disease; ORR, Objective response rate; OS, Overall survival; pCR, Pathological complete response; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PFS, Progression-free survival; RCT, Randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; RFS, Recurrence-free survival; TACC3, Transforming acidic coiled-coil containing protein 3; TACE, Transarterial chemoembolization; TAMs, Tumor-associated macrophages; TCR, T-cell receptor; TGF-β, Transforming growth factor beta; TKI, Tyrosine kinase inhibitor; TMB, Tumor mutational burden; Tregs, Regulatory T cells; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

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Conflicts of interest

The authors declare no competing interests.

Authors' contributions

Conceptualization: YHK. Methodology: YTZ, QY. Writing-Original Draft: YTZ, QY. Writing-Review & Editing: YHK. Funding Acquisition: YHK. Literature search: ZZZ.

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