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Title: Advances in the Management of Hepatocellular Carcinoma: Evolving Systemic Therapy, Perioperative Strategies, and Care for Special Populations

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Clinical Question Box

What are the most important recent practice-changing developments in hepatocellular carcinoma management?

Hepatocellular carcinoma management is increasingly shaped by immune-based combinations, with nivolumab plus ipilimumab, atezolizumab plus bevacizumab, and the STRIDE regimen representing key first-line standards for appropriately selected patients. Treatment selection remains driven not only by tumor burden, but also by hepatic reserve, bleeding risk, transplantation history, autoimmune comorbidity, and the likelihood of maintaining liver function through sequential therapy. Neoadjuvant systemic therapy is emerging as a promising strategy in selected resectable disease, whereas updated IMbrave050 results do not currently support routine adjuvant atezolizumab plus bevacizumab after curative-intent treatment outside clinical trials after longer follow-up. After progression on first-line immunotherapy, tyrosine kinase inhibitors remain the backbone of subsequent therapy. Overall, modern HCC care requires individualized, multidisciplinary decision-making that integrates disease stage, liver function, and patient phenotype.

Abstract

Hepatocellular carcinoma (HCC) remains the dominant histologic subtype of primary liver cancer and a major cause of cancer mortality worldwide. Its epidemiology continues to evolve, with metabolic dysfunction-associated steatotic liver disease and steatohepatitis becoming increasingly important drivers in Western populations, while chronic hepatitis B virus infection remains a dominant cause in endemic regions. Management requires integration of tumor burden, liver functional reserve, and patient-specific clinical constraints. Diagnosis in at-risk patients increasingly relies on noninvasive imaging criteria, and prognostic assessment is refined by objective tools such as the Albumin-Bilirubin grade. For advanced disease, first-line treatment has shifted decisively toward immune checkpoint inhibitor-based combinations, including nivolumab plus ipilimumab, atezolizumab plus bevacizumab, and tremelimumab plus durvalumab, with emerging tyrosine kinase inhibitor-immunotherapy combinations further broadening the landscape. At the same time, perioperative strategies are moving earlier in the disease course, with encouraging neoadjuvant data in selected resectable tumors, although routine adjuvant immunotherapy remains unestablished after updated follow-up. In the post-immunotherapy setting, optimal sequencing is still evolving, but tyrosine kinase inhibitors remain the principal evidence-based option after progression on frontline immune-based therapy. Important management challenges persist in special populations, particularly patients with Child-Pugh B liver dysfunction, post-transplant recurrence, untreated high-risk varices, viral hepatitis at risk of reactivation, and rare actionable genomic alterations. Overall, the current HCC treatment landscape is characterized by growing therapeutic complexity, persistent evidence gaps in real-world fragile populations, and an increasing emphasis on individualized sequencing, preservation of hepatic reserve, and biomarker development beyond α-fetoprotein.

Keywords: Hepatocellular carcinoma; immunotherapy; systemic therapy; tyrosine kinase inhibitors; neoadjuvant therapy; liver cancer

1. Introduction and Epidemiology

Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer, accounting for approximately 85%–90% of cases, and liver cancer remains one of the leading causes of cancer-related mortality worldwide.[1,2] As a highly aggressive malignancy that typically arises in the setting of chronic liver disease, HCC poses a major global health burden. In 2022, liver cancer was associated with approximately 866,000 new cases and 759,000 deaths worldwide, ranking sixth in incidence and third among causes of cancer-related mortality globally.[3]

The epidemiologic landscape of HCC is currently undergoing a rapid shift. While the incidence in regions such as Asia and Africa has historically been driven by endemic hepatitis B virus (HBV) infection and dietary aflatoxin B1 exposure,[4] Western nations are witnessing a rise in cases attributed to metabolic factors. Specifically, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) have emerged as the fastest-growing etiologies for primary liver malignancies in these regions.[5] In the United States, patients with MASLD/MASH-related cirrhosis face an annual HCC incidence of approximately 2% to 2.4%.[6]

A primary clinical hurdle remains the late-stage presentation of the disease. HCC is frequently diagnosed late in its course due to an absence of symptoms during early-stage hepatocarcinogenesis and suboptimal surveillance rates among high-risk populations in the West.[7] Consequently, many patients present with advanced disease, significantly limiting the availability of potentially curative therapeutic interventions.

2. Diagnosis and Precise Clinical Staging

The diagnostic paradigm for HCC is unique among solid organ malignancies, as a definitive diagnosis can frequently be established in high-risk patients through non-invasive imaging alone, thereby obviating the need for histologic confirmation. Under the Liver Imaging Reporting and Data System (LI-RADS) framework, a lesion categorized as LR-5 is considered definitely HCC.[8] This categorization relies on radiographic hallmarks such as non-rim arterial phase hyperenhancement and subsequent washout in the portal venous or delayed phases.[9] When these criteria are strictly applied, the specificity for HCC exceeds 95%.[9] For sub-centimeter lesions detected during surveillance, AASLD guidance recommends close monitoring with ultrasound at short intervals of three to six months to assess for growth or the development of malignant features, rather than immediate transition to more intensive diagnostic imaging.[10]

2.1 Prognostic Stratification and the ALBI Grade

Effective management of HCC requires a delicate balance between assessing the oncologic tumor burden and the severity of the underlying hepatic dysfunction. While the Barcelona Clinic Liver Cancer (BCLC) system remains the global standard for treatment allocation, there is increasing reliance on more objective measures of liver reserve.[11] The albumin-bilirubin (ALBI) score has emerged as an objective alternative to the Child-Pugh classification for assessing hepatic reserve in patients with hepatocellular carcinoma (HCC), because it is based solely on serum albumin and bilirubin and avoids the subjective variables included in Child-Pugh scoring. Originally developed and internationally validated in HCC cohorts, the ALBI score is calculated as: ALBI = (log10 bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.085).[12]

The resulting grade provides a highly discriminatory method for assessing liver function: ALBI Grade I (≤−2.60) represents well-preserved function, while Grade III (>−1.39) indicates significant compromise.[12] Objective liver function assessment is increasingly used when identifying patients who may be unsuitable for repeated TACE. In particular, ALBI grade 2 or worse and tumor burden beyond the up-to-seven criteria have been proposed as markers of poorer candidacy for TACE, because these features are associated with higher risk of liver function deterioration and lower likelihood of sustained benefit from repeated locoregional therapy.[13] For these individuals, earlier transition to systemic regimens is recommended to preserve liver function and optimize overall survival outcomes.

3. First-Line Systemic Therapy: The New Standards

The first-line therapeutic landscape for advanced HCC has shifted away from tyrosine kinase inhibitor (TKI) monotherapy toward immune checkpoint inhibitor (ICI)-based combination regimens, which are now preferred for many eligible patients.[11] For patients with preserved liver function, typically Child-Pugh class A, first-line therapy for advanced HCC is increasingly selected using an evidence-based approach centered on ICI-based combinations, particularly either dual-ICI blockade or ICI plus antiangiogenic therapy (Figure 1).[14]

3.1 Dual Checkpoint Blockade: Nivolumab plus Ipilimumab

A milestone in the frontline management of unresectable or metastatic HCC was the April 2025 regulatory approval of the nivolumab plus ipilimumab combination.[15] This approval was predicated on the results of the Phase III CheckMate 9DW trial, which demonstrated the superior efficacy of dual programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition. The regimen achieved a median overall survival (OS) of 23.7 months, a statistically significant improvement over the 20.6 months observed in patients receiving investigator's choice of TKI (sorafenib or lenvatinib).[16]

Nivolumab plus ipilimumab is increasingly preferred for selected patients in whom achieving a high objective response rate and durable long-term survival is the principal therapeutic goal. In CheckMate 9DW, the regimen achieved an objective response rate of 36%, with durable responses that support its role as a high-efficacy first-line option. This benefit must be balanced against toxicity: grade 3/4 treatment-related adverse events occurred in 41% of patients, and serious grade 3/4 treatment-related adverse events occurred in 25%, underscoring the need for vigilant monitoring and early management of immune-mediated adverse events.[16] In parallel, a recent

model-based cost-effectiveness analysis informed by CheckMate 9DW reported that nivolumab plus ipilimumab was cost-effective compared with lenvatinib or sorafenib in the United States, with an incremental cost-effectiveness ratio of $127,063.87 per quality-adjusted life-year, below the prespecified willingness-to-pay threshold of $150,000.[17]

3.2 Anti-PD-L1 plus Anti-VEGF Synergy: Atezolizumab plus Bevacizumab

The combination of atezolizumab and bevacizumab remains a foundational standard for frontline HCC based on the landmark IMbrave150 trial.[18] In this study, the combination demonstrated a median OS of 19.2 months compared to 13.4 months for sorafenib, representing the first regimen to significantly outperform the historical TKI benchmark on both OS and progression-free survival (PFS).[19] Real-world analyses have confirmed that the survival benefit of atezolizumab plus bevacizumab is reproducible in routine clinical practice, although safe implementation depends on rigorous pretreatment screening and ongoing monitoring, particularly for bleeding risk and portal hypertension.[20] The most critical safety consideration is bevacizumab-associated hemorrhage, particularly in patients with portal hypertension. Because bevacizumab increases bleeding risk, pretreatment esophagogastroduodenoscopy (EGD) is widely recommended before atezolizumab-bevacizumab, ideally based on a recent examination within the prior 6 months, to identify and treat high-risk esophagogastric varices and reduce major bleeding risk.[21]

3.3 The STRIDE Regimen: Tremelimumab plus Durvalumab

The phase III HIMALAYA trial established an overall survival benefit for the STRIDE regimen (Single Tremelimumab with regular interval Durvalumab), which consists of a single priming dose of tremelimumab combined with durvalumab followed by durvalumab maintenance monotherapy.[22] The STRIDE regimen achieved a median overall survival of 16.4 months in

HIMALAYA, and long-term follow-up demonstrated a 5-year overall survival rate of 19.6%. In current practice, STRIDE is an important frontline option for patients in whom anti-VEGF therapy is unsuitable, including those with clinically significant bleeding risk, portal hypertension, or other contraindications to bevacizumab.[22] By avoiding bevacizumab, this regimen offers a durable immune-mediated response with a toxicity profile that is manageable for a broad segment of the HCC population.

3.4 Emerging TKI/ICI Combinations: CARES-310

Camrelizumab plus rivoceranib (apatinib) has emerged as a highly active first-line option for unresectable HCC. In the global phase III CARES-310 study, the combination improved overall survival compared with sorafenib, and the final overall survival analysis reported a median OS of 23.8 months versus 15.2 months, representing one of the longest median overall survivals reported in a first-line phase III trial in unresectable HCC.[23] Although CARES-310 was conducted predominantly in HBV-associated HCC, camrelizumab plus rivoceranib has emerged as a high-activity first-line option for patients with substantial tumor burden, given its comparatively high objective response rate and broad efficacy across key clinical subgroups. The robust OS benefit (HR 0.64) underscores the potency of combining next-generation anti-angiogenic TKIs with PD-1 blockade in this disease space.[23]

3.5 Antiviral Management During ICI-Based Therapy

In newly diagnosed hepatitis-associated HCC, antiviral management should be integrated early into multidisciplinary oncologic care, particularly for patients being considered for neoadjuvant or first-line ICI-based therapy.[24] Baseline viral assessment should include HBsAg, anti-HBc, anti-HCV, HBV DNA in patients with current or prior HBV exposure, and HCV RNA when HCV

infection is suspected.[25] For HBV-associated HCC, prophylactic or therapeutic nucleos(t)ide analogue therapy with a high-genetic-barrier agent, such as entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide, should be initiated before or at the start of ICI therapy and continued during treatment to reduce HBV reactivation risk and preserve hepatic reserve.[26] Updated HBV reactivation guidance supports HBV screening and antiviral prophylaxis before or at the start of systemic anticancer therapy in patients at risk for HBV reactivation, including those receiving immunomodulatory anticancer therapies; AASLD HCC guidance also recommends antiviral therapy for patients who meet HBV or HCV treatment criteria.[10,25] For HCV-associated HCC, direct-acting antiviral therapy should be individualized in coordination with hepatology and oncology, considering tumor burden, liver function, urgency of systemic therapy, and expected prognosis.[24] Antiviral therapy should generally not delay clinically indicated neoadjuvant or first-line ICI therapy; rather, viral suppression and serial monitoring of liver enzymes and viral load should proceed concurrently throughout treatment.

4. The Perioperative and Locoregional Frontier

A major recent shift in HCC management has been the integration of systemic therapy into the perioperative setting, motivated by the historically high recurrence rate after curative-intent partial hepatectomy, which often exceeds 50% and may approach 70% at 5 years.[27] While potentially curative resection remains a cornerstone of management for patients with adequate liver reserve, the frequent emergence of local recurrence from preexisting microscopic tumor foci has driven the clinical community toward neoadjuvant and adjuvant systemic strategies.

4.1 Neoadjuvant Progress: Lessons from the CARES-009 Trial

The neoadjuvant landscape has been advanced by the phase 2/3 CARES-009 trial, a multicentre, open-label, randomised study in 294 patients with resectable HCC at intermediate or high risk of recurrence. The trial evaluated perioperative camrelizumab plus rivoceranib, consisting of 2 preoperative cycles followed by surgery and up to 15 postoperative cycles.[28] The findings represent a critical milestone: perioperative systemic therapy significantly improved median event-free survival to 42.1 months, compared with 19.4 months with surgery alone (HR 0.59; 95% CI 0.41-0.85). Similarly, median disease-free survival was prolonged to 40.8 months versus 19.4 months, respectively (HR 0.59; 95% CI 0.40-0.86).[28] Despite these efficacy gains, clinical implementation requires careful patient selection because treatment-related toxicity was substantial. In CARES-009, grade 3 or worse treatment-related adverse events occurred in 38% of patients receiving perioperative camrelizumab plus rivoceranib, and 2 treatment-related deaths were reported during neoadjuvant therapy. In addition, because the study population was predominantly enrolled in China and largely had HBV–related HCC (77%), further data are needed to determine the generalizability of these results to broader global populations and to nonviral etiologies of HCC.[29]

4.2 Adjuvant Therapy Challenges and the Evidence Gap

In contrast to the neoadjuvant successes, the role of adjuvant ICIs remains fraught with challenges and is currently considered investigational. The foundational IMbrave050 trial, which evaluated adjuvant atezolizumab plus bevacizumab for treated patients at high risk of recurrence, initially generated significant enthusiasm by meeting its primary endpoint of improved recurrence-free survival (RFS) at the first interim analysis.[30]

However, with extended follow-up, the initial recurrence-free survival benefit was not sustained, and overall survival remained immature, with no demonstrated overall survival advantage.[31] Given the increased toxicity burden and the lack of a demonstrated survival benefit, current evidence does not support the routine use of adjuvant atezolizumab plus bevacizumab in clinical practice. In contrast, antiviral therapy remains recommended in patients with HBV- or HCV-related HCC when indicated for the underlying viral hepatitis, as it is associated with improved survival and reduced late recurrence after curative treatment. The search for an effective systemic adjuvant or secondary chemopreventive strategy continues in ongoing clinical trials.[32]

5. Sequential Therapy and the Post-Immunotherapy Landscape

5.1 Sequencing Paradigms Following Frontline ICI Progression

The rapid adoption of ICI-based combinations as first-line therapy has created a significant evidence gap regarding optimal second-line sequencing. Most currently approved second-line agents were originally validated in patients after sorafenib failure, necessitating reliance on recent real-world analyses and contemporary reviews to guide practice after first-line immunotherapy.[33,34] Current evidence generally favors a transition to a tyrosine kinase inhibitor rather than sequential dual-immunotherapy after progression on atezolizumab plus bevacizumab.[35] In a multicenter, registry-based 2026 study, second-line lenvatinib was associated with longer overall survival and higher disease control than durvalumab plus tremelimumab, although these findings remain preliminary because they derive from retrospective, non-randomized data. In that cohort, median overall survival was 14.0 months with lenvatinib versus 5.3 months with durvalumab plus tremelimumab ($p=0.047$), and disease control rates were 76.7% versus 15.4%, respectively.[36]

Furthermore, the success of sequential therapy is closely linked to preservation of hepatic reserve. Objective measures of liver function, particularly the ALBI score, are independent prognostic factors for outcomes with second-line lenvatinib after atezolizumab plus bevacizumab. In a 2026 multicenter study, a lower pre-atezolizumab/bevacizumab ALBI score and a cumulative lenvatinib dose ≥400 mg were independently associated with better survival, underscoring the importance of maintaining liver function and adequate treatment exposure.[37]

5.2 Evidence-Based TKIs and Biomarker-Selected Therapy

TKIs continue to serve as the backbone of second- and later-line therapy in advanced hepatocellular carcinoma. Evidence-based options include regorafenib and cabozantinib, both

supported by phase III data in previously treated patients, while sorafenib remains a commonly used later-line option in contemporary practice, particularly after first-line immunotherapy.[38,39] Indirect matching-adjusted comparison analyses found no significant overall survival difference between regorafenib and cabozantinib, with median OS of 11.1 and 11.3 months, respectively. However, cabozantinib was associated with longer progression-free survival than regorafenib (5.5 vs 3.0 months), suggesting a potential advantage when delaying radiographic progression is a priority, although these findings derive from indirect rather than head-to-head evidence.[40]

Precision medicine in HCC remains limited, with ramucirumab representing the only approved biomarker-selected systemic option. In patients with a baseline Alpha-fetoprotein (AFP) ≥400 ng/mL, ramucirumab has demonstrated a survival benefit, although contemporary real-world outcomes vary across cohorts.[41]

5.3 Emerging Therapeutic Strategies and Novel Mechanisms

An important therapeutic frontier in HCC is the evaluation of immune continuation strategies and cellular therapies. The phase III IMbrave251 trial is assessing whether continuing atezolizumab in combination with lenvatinib or sorafenib improves outcomes compared with lenvatinib or sorafenib alone after progression on first-line atezolizumab plus bevacizumab.[42] This strategy aims to determine if sustained PD-L1 inhibition can overcome acquired resistance when paired with anti-angiogenic multi-kinase inhibition.

Adoptive T-cell therapies represent a step toward personalized oncology. In the first-in-human ADP-A2AFP study, preliminary activity was observed in heavily pretreated patients, with early reports showing disease control in approximately two-thirds of treated patients.[43] These advances are supported by investigation of high-accuracy biomarkers such as FGF-19, which in one study

achieved an AUC of 0.98 for HCC detection.[44] The FGF19-FGFR4 axis is also under active clinical investigation as a biomarker and therapeutic target.[45]

5.4 Clinical Barriers to Later-Line Delivery

Despite the expanding armamentarium of systemic agents, the attrition rate between treatment lines remains a formidable challenge. Only about 38% of patients successfully transitioned from first-line to second-line therapy in a 2026 real-world cohort (50 of 131 patients). The most commonly reported barriers were patient choice (26.7%) and poor performance status (25.2%).[46] These findings underscore that proactive toxicity management and preservation of liver function during frontline therapy are not simply supportive measures, but fundamental prerequisites for maintaining eligibility for subsequent therapy and maximizing cumulative survival.[47]

6. Special Populations and Management Challenges

6.1 Therapeutic Strategies for Patients with Impaired Hepatic Reserve (Child-Pugh B)

A primary challenge in the management of advanced HCC remains the limited evidence for patients with Child-Pugh B liver function, as most pivotal phase III trials have strictly restricted enrollment to the Child-Pugh A population.[48] For these fragile patients, overall survival is frequently governed more by the degree of underlying hepatic dysfunction than the malignancy itself.

For patients with an Eastern Cooperative Oncology Group (ECOG) performance status <2 and minimal comorbidities, single-agent ICI therapy (durvalumab, tislelizumab, or pembrolizumab) is the preferred approach. While these agents appear generally safe and do not demonstrate increased rates of grade ≥3 immune-related adverse events compared to Child-Pugh A populations, their efficacy is notably more modest.[14] A systematic review and meta-analysis of clinical trial and real-world data found that, in Child-Pugh B advanced HCC treated with ICIs, the pooled ORR was 14% overall, with a pooled median OS of 5.49 months; in the ICI monotherapy subgroup, the pooled ORR was 12%.[49]

Anti-angiogenic TKIs remain a viable alternative, though they are often more difficult to tolerate in this setting (Table 1). Sorafenib has the most established safety experience in Child-Pugh B HCC, but outcomes remain substantially worse than in patients with preserved liver function. Recent reviews summarizing contemporary clinical and real-world data report median overall survival of about 5.2 months in Child-Pugh B versus 13.6 months in Child-Pugh A patients.[50] For patients with severe hyperbilirubinemia or Child-Pugh C status, systemic therapy is typically

deferred in favor of best supportive care due to a lack of demonstrable benefit and the high risk of treatment-induced decompensation.[51]

6.2 Systemic Management in the Post-Liver Transplantation Setting

The management of HCC recurrence following orthotopic liver transplantation presents a unique immunological hurdle. ICIs are generally avoided and remain highly controversial in the post-transplant setting because of the substantial risk of allograft rejection and graft loss.[52] Data suggest that ICI-induced activation of the host immune response may lead to liver allograft rejection rates of up to 39% in reported post-transplant series.[53] Consequently, patients requiring systemic therapy for post-transplant recurrence should be managed in close consultation with transplant hepatology and ideally within the context of specialized clinical trials.

For patients with advanced or multifocal HCC recurrence after liver transplantation, systemic therapy with TKIs remains the mainstay of treatment. Sorafenib is the most extensively studied agent in this setting, and newer real-world data support lenvatinib as a valid, and possibly preferred, first-line option in selected patients.[54] These agents are used in conjunction with post-transplant immunosuppression, typically with calcineurin-inhibitor minimization and selective incorporation of mammalian target of rapamycin inhibitors.[55] However, vigilant monitoring is essential, as these patients may experience higher rates of treatment-related toxicities, including hand-foot skin reactions and acute hepatitis, requiring prompt dose modifications.

6.3 Rare Genomic Alterations and Viral Reactivation Risks

Universal screening for HBV and HCV is mandatory for all patients initiating systemic therapy for HCC. The risk of viral reactivation remains a significant concern during active treatment with ICIs or molecularly targeted agents. Patients with evidence of chronic or past HBV infection

require continuous monitoring and, in most cases, antiviral prophylaxis for at least 12 months after the cessation of anticancer therapy.[25]

While HCC is rarely driven by actionable genomic fusions, precision oncology has provided a lifeline for a small subset of patients. For the rare patient whose tumor harbors an NTRK fusion, treatment with a TRK inhibitor is recommended. Larotrectinib and entrectinib are established tumor-agnostic options, while repotrectinib is also FDA-approved and may be considered in appropriate patients. These agents can produce high response rates and durable benefit across NTRK fusion–positive solid tumors, representing an important precision-oncology strategy in hepatobiliary malignancies.[56-58]

7. Biomarkers and Precision Oncology

7.1 The Actionability Gap: AFP and Beyond

Despite the rapid expansion of the systemic armamentarium, biomarker development in advanced HCC continues to lag behind other solid tumors, such as non-small cell lung cancer or melanoma. AFP remains the only routinely actionable biomarker in clinical practice.[59] While highly useful as a prognostic indicator, correlating with tumor size, vascular invasion, and poor histologic differentiation, its predictive utility is primarily confined to determining eligibility for ramucirumab. Under the REACH-2 framework, ramucirumab is restricted to patients with a baseline AFP ≥400 ng/mL and remains the clearest successful example of biomarker-driven phase III drug development in HCC.[60]

Established immunotherapy biomarkers utilized in other malignancies, such as PD-L1 expression and tumor mutational burden, have failed to emerge as robust decision-making tools in HCC.[61] PD-L1 status, in particular, does not consistently correlate with objective response or OS across pivotal Phase III trials, and TMB in HCC is generally low, limiting its practical value for most patients.[62]

7.2 Emerging Molecular Signatures and Liquid Biopsy

The current research frontier is focused on moving beyond single-protein markers to define molecular subclasses and immune microenvironment signatures. Recent integrative genomic analyses have reclassified HCC into major metabolism-based and signaling-based subclasses, such as the fatty acid degradation subtype, which may eventually guide personalized treatment algorithms.[63]

A critical molecular determinant in HCC is activation of the WNT/β-catenin pathway. CTNNB1 mutations, present in roughly 20–30% of tumors, define a molecular subclass associated with immune exclusion and relative resistance to immune checkpoint blockade.[64] These tumors are typically immunologically "cold," with reduced immune-cell infiltration and relative insensitivity to immune checkpoint inhibitor monotherapy. In contrast, a pre-existing immune-activated tumor microenvironment, including higher intratumoral CD8+ T-cell density, has been associated with better clinical outcomes with atezolizumab plus bevacizumab.[65,66]

Liquid biopsy, particularly circulating tumor DNA (ctDNA) analysis, has strong potential to improve post-treatment surveillance in HCC and may help refine later-line treatment selection, but it has not yet become routine standard-of-care for either use.[67] Emerging data suggest that lower, or undetectable, ctDNA levels after treatment initiation are associated with improved outcomes, and that serial ctDNA profiling may provide a real-time, non-invasive means of monitoring tumor evolution and the emergence of resistance-associated genomic alterations. However, in HCC this approach remains promising rather than fully established.[68]

7.3 Phenotype-Driven Personalization and Clinical Constraints

In the absence of a universally implemented genomic roadmap, clinical personalization in HCC still relies heavily on tumor burden and host factors, especially liver functional reserve and performance status. Key variables that shape treatment selection and prognosis include ALBI grade, Child-Pugh class, the presence and extent of portal vein tumor thrombus, extrahepatic spread, and the etiology of the underlying liver disease.[69]

Patient safety remains a major determinant of treatment selection. In particular, patients with untreated or high-risk gastroesophageal varices are poor candidates for bevacizumab-containing

regimens because of the increased risk of serious gastrointestinal and variceal bleeding.[11] Similarly, patients with a history of liver transplantation face major challenges with ICIs because liver allograft rejection rates of up to 39% have been reported after checkpoint inhibitor exposure. Patients with severe or active autoimmune disease also require particular caution, as ICIs can trigger disease flares and immune-related toxicities.[70] In these scenarios, phenotypic constraints often shift treatment toward TKIs, particularly sorafenib and lenvatinib. In post-transplant recurrence, TKIs remain the principal systemic option, and in patients for whom ICIs are unsuitable because of prior transplantation or severe active autoimmune disease, TKIs are commonly relied upon because of their broader clinical experience and lower risk of immune-mediated complications.[54]

7.4 Addressing the External Validity Gap

The external validity of modern systemic trials remains a concern for the oncology community. Most pivotal Phase III data were derived from highly selected cohorts with Child-Pugh A liver function and ECOG performance status 0–1. In real-world practice, many patients present with impaired hepatic reserve, particularly Child-Pugh B cirrhosis. In this population, the survival benefit of aggressive systemic combinations is less well defined than in trial-eligible Child-Pugh A patients, while the risk of hepatic decompensation is substantially higher.[49]

Bridging this evidence gap remains an urgent priority. In Child-Pugh B HCC, single-agent ICIs have shown manageable safety and modest activity, with an ORR of about 12% in prospective nivolumab data and 12% in the monotherapy subgroup of a meta-analysis.[71] However, prospective studies specifically designed to stratify these fragile patients into individualized therapeutic pathways remain limited. The field is still moving from empiric treatment selection toward a more

integrated model that combines molecular profiling with phenotypic and hepatic-reserve optimization.[72]

8. Conclusion

The management of hepatocellular carcinoma is increasingly complex and requires coordinated multidisciplinary care that integrates oncologic stage, liver functional reserve, and patient phenotype. Immune-based combination therapy now defines the first-line standard for many patients, neoadjuvant strategies are expanding the perioperative frontier, and tyrosine kinase inhibitors remain essential for post-immunotherapy sequencing and for selected populations in whom immunotherapy is unsuitable. At the same time, major external-validity gaps persist because many pivotal data sets were generated in highly selected trial populations with preserved liver function and limited comorbidity. Closing these gaps will require prospective studies in fragile real-world populations and the continued development of biomarkers and sequencing strategies that align tumor biology with hepatic reserve and clinical phenotype.

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Table 1. Phenotype-Driven Systemic Therapy Selection in Hepatocellular Carcinoma

Clinical situation	Preferred approach	Avoid/caution	Rationale
Child-Pugh B	Individualized; single-agent ICI or cautious TKI in selected patients	Aggressive combinations	Limited evidence and decompensation risk
High-risk varices	Treat varices before bevacizumab; consider STRIDE/TKI	Atezolizumab plus bevacizumab until bleeding risk addressed	Bleeding risk
Prior liver transplant	TKI preferred	ICI generally avoided	Rejection or graft loss risk
Severe autoimmune disease	TKI favored	ICI caution/avoidance	Flare risk
AFP ≥400 after prior therapy	Consider ramucirumab if otherwise eligible		Biomarker-selected option

664 **Figure Legend**

665 Figure 1 Algorithm for Drug Therapy for Hepatocellular Carcinoma