Frontline Therapy in Advanced Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and a leading cause of cancer-related mortality worldwide. Despite advances in screening, most cases are diagnosed at advanced stages, requiring systemic therapies. The treatment landscape has evolved significantly over the past two decades, with the introduction of targeted therapies, tyrosine kinase inhibitors and immunotherapy. Combination regimens, particularly using immune checkpoint inhibitors, have demonstrated superior efficacy over sorafenib, the historical standard of care. However, challenges persist, including treatment resistance, biomarker-driven heterogeneity and the absence of biomarkers able to predict response. This article evaluates the current frontline therapies for advanced HCC, with a focus on their clinical efficacy, limitations and the potential role of predictive biomarkers in optimizing treatment selection. Additionally, we discuss emerging therapeutic approaches and ongoing research aiming to refine systemic treatment strategies for advanced-stage HCC.

Keywords

Biomarkers, drug therapy, hepatocellular carcinoma, immunotherapy, liver cancer, tyrosine kinase inhibitors

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Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, comprising approximately 85% of all primary liver cancers.[1] Globally, it ranks as the sixth-most common cancer and the third-leading cause of cancer-related mortality, with over 900,000 new cases and 830,000 deaths estimated in 2020.[1] The risk factors for HCC vary according to geographical and socioeconomic factors but generally include chronic infection with hepatitis B virus (HBV) and hepatitis C viruse (HCV), obesity, diabetes mellitus, alcohol consumption, tobacco use, ingestion of aflatoxin-contaminated food, α-1-antitrypsin deficiency, haemochromatosis and autoimmune diseases.[2,3]

The prognosis of HCC is often poor due to its aggressive nature and late diagnosis at advanced stages. Despite advances in screening protocols, most cases are diagnosed at intermediate or advanced stages, where curative treatments such as resection, transplantation or ablation are no longer feasible.[4] This highlights the need for effective systemic therapies developed for advanced-stage HCC.

Over the past two decades, significant progress has been made in the prevention and management of HCC, largely driven by antiviral treatments, targeted therapies and immunotherapy.[3,5]

This article aims to explore the latest evidence on advanced HCC, offering a detailed assessment of current approaches and emerging strategies.

Hepatocellular carcinoma aetiology

HCC is a complex and aggressive cancer with a poor prognosis, posing a significant global health burden. The aetiology of HCC is multifaceted, with various risk factors contributing to its development and progression. Chronic liver disease and cirrhosis are the primary underlying conditions in approximately 80% of cases with HCC, while 20% occur in non-cirrhotic livers.[6]

Viral hepatitis remains the most common cause of HCC worldwide.[7] HBV infection is associated with about half of all HCC cases, while HCV accounts for an additional 25%.[8] These viral infections lead to chronic liver inflammation and injury, significantly contributing to HCC development.[6] However, the landscape of viral hepatitis-related HCC is changing due to advancements in antiviral treatments. Nucleoside/nucleotide analogues for HBV and direct-acting antivirals for HCV have shown promise in slowing disease progression, reducing HCC risk and improving long-term survival in patients with or without HCC.[7] Non-viral aetiologies of HCC are becoming increasingly prevalent, particularly in countries with westernized lifestyles.[6] Alcoholic liver disease (ALD) is a significant risk factor and has become the second fastest-growing cause of HCC-related deaths, a trend that has accelerated since the coronavirus disease of 2019 (COVID-19) pandemic.[7,8] Non-alcoholic

Table 1: Description and prevalence/impact of the main aetiologies of hepatocellular carcinoma[6–10]

Aetiology	Description	Prevalence/impact
HBV	Chronic infection leading to liver inflammation and cirrhosis	Associated with approximately 50% of cases with HCC[8]
HCV	Chronic infection causing liver damage and cirrhosis	Accounts for about 25% of cases with HCC[8]
ALD	Excessive alcohol consumption leading to liver damage	Second fastest-growing cause of HCC-related deaths[7]
NAFLD	Associated with metabolic syndrome, obesity and type 2 diabetes	Rapidly increasing cause of HCC globally[7]
Cirrhosis	Characterized by decreased hepatocyte proliferation and increased fibrous tissue	Present in about 80% of HCC cases[6,8]
Aflatoxin exposure	Consumption of food contaminated with aflatoxin	Significant risk factor, especially in certain geographical regions[6,8]
Inherited diseases	Inherited disorders like hereditary haemochromatosis cause chronic inflammation, fibrosis and cirrhosis	In patients with hereditary haemochromatosis who developed cirrhosis, the annual incidence of HCC is 4%[9]
Tobacco smoking	Environmental carcinogen	Individuals who smoke ≥2 packs have 2.5 times higher odds of developing HCC[10]

ALD = alcoholic liver disease; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NAFLD = non-alcoholic fatty liver disease.

fatty liver disease (NAFLD), closely associated with metabolic syndrome, obesity and type 2 diabetes, is rapidly emerging as a major cause of HCC.[6,7] NAFLD-related HCC can occur in patients without cirrhosis and is associated with lower survival rates compared with viral hepatitis-related HCC.[7] Other risk factors include exposure to aflatoxin-contaminated food, tobacco smoking and certain inherited diseases.[6,8]

The aetiology of HCC significantly impacts patient characteristics, disease course and treatment outcomes.[8] Understanding these diverse aetiological factors is crucial for developing effective prevention strategies, optimizing surveillance methods and improving early detection and management of HCC.[6,8] As the distribution of major HCC aetiologies continues to evolve, further research is needed to elucidate the complex mechanisms involved in HCC pathogenesis and to develop targeted therapies for this deadly disease.[6,8]

Table 1 summarizes the main etiologies of HCC.[6–10] It is important to note that risk factors often interact and coexist in patients, contributing to the complex nature of HCC development.[6] The prevalence and impact of these aetiologies may vary geographically and are subject to change over time due to factors such as improved antiviral treatments and lifestyle changes.[7]

Barcelona classification and standard treatments

The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely adopted model for stratifying patients with HCC based on tumour burden, liver function (assessed by the Child–Pugh score) and performance status (PS; evaluated using Eastern Cooperative Oncology Group Performance Status).[11] This classification plays a crucial role in treatment decision-making and prognosis estimation.

BCLC stage 0 (very early stage):

- Characteristics: single tumour <2 cm, preserved liver function (Child–Pugh A), good PS (PS 0).
- Treatment: curative approaches like surgical resection, liver transplantation or ablation.

BCLC stage I (early stage):

- Characteristics: ingle or up to three nodules <3 cm, PS 0–1, preserved liver function.
- Treatment: esection (if feasible), liver transplantation or radiofrequency ablation.

BCLC stage II (intermediate stage):

- Characteristics: ultinodular HCC, preserved liver function, PS 0.
- Treatment: transarterial chemoembolization (TACE) remains the standard, with selective use of systemic therapy in certain patients.

BCLC stage III (advanced stage):

- Characteristics: ascular invasion, extrahepatic spread (EHS), PS 1–2.
- Treatment: Systemic therapy.

BCLC stage IV (terminal stage):

- Characteristics: PS >2, decompensated liver function.
- Treatment: best supportive care to maintain quality of life.

Multidisciplinary teams (MDTs), including hepatologists, oncologists, interventional radiologists and surgeons, are essential for managing HCC. They integrate expertise to tailor treatments based on tumour characteristics, liver function, PS and patient preferences, as recommended by the 2025 European Society of Medical Oncology (ESMO) guidelines.[12] MDTs guide therapy selection, such as TACE for BCLC stage II or systemic therapies like atezolizumab plus bevacizumab for BCLC stage III, and identify clinical trial candidates (e.g. EMERALD-Y90) [51]. Benefits include improved outcomes (10–15% survival increase), but challenges involve coordination delays and limited access in some regions.[13]

Having outlined the diverse aetiologies driving HCC, we now turn to systemic treatment options that have transformed the management of advanced disease, beginning with tyrosine kinase inhibitors (TKIs), followed by immunotherapy and combination approaches.

Tyrosine kinase inhibitors

In the landscape of HCC treatment, TKIs have emerged as a crucial therapeutic option, particularly for patients with advanced-stage disease. TKIs become necessary when HCC is diagnosed at advanced stages and the tumour is unresectable, making locoregional treatments ineffective.[14] Additionally, TKIs are increasingly being used as a bridging or downstaging strategy before liver transplantation, aiming to prevent tumour progression and reduce dropout risk.[15]

TKIs are primarily used in the following clinical scenarios:

1. Upfront therapy: TKIs are a critical first-line option for patients with advanced, unresectable HCC when immunotherapy is contraindicated. These contraindications often include a history of prior liver transplantation, where the risk of graft rejection precludes the use of immune checkpoint inhibitors (ICIs), and active autoimmune diseases, which may be exacerbated by immune activation. For such patients, TKIs such as sorafenib and lenvatinib offer a viable alternative by targeting tumour angiogenesis and proliferation without engaging the immune system.[14] The landmark SHARP trial (A Phase III Study of Sorafenib in Patients with Advanced Hepatocellular Carcinoma; ClinicalTrials.gov: NCT00105443) established sorafenib as the first TKI approved for advanced HCC. This phase III study demonstrated a median overall survival (OS) of 10.7 months with sorafenib compared with 7.9 months with placebo (HR: 0.69; 95% confidence interval [CI]: 0.55–0.87; p<0.001), setting a benchmark for systemic therapy in HCC.[16] Sorafenib inhibits multiple receptor tyrosine kinases, including vascular endothelial growth factor (VEGFR), platelet-derived growth factor receptor (PDGFR) and rapid accelerated fibrosarcoma (RAF) kinases, disrupting tumour growth and vascularization.[16] Subsequently, the REFLECT trial (A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib [E7080] Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma; ClinicalTrials.gov: NCT01761266) introduced lenvatinib as a non-inferior alternative to sorafenib in the first-line setting. In this phase III study, lenvatinib achieved a median OS of 13.6 months versus 12.3 months with sorafenib (HR: 0.92; 95% CI: 0.79–1.06), meeting its primary endpoint of non-inferiority.[16] Lenvatinib's broader inhibition profile, targeting VEGFR, fibroblast growth factor receptor (FGFR), PDGFR and proto-oncogene tyrosine-kinase receptor (RET), offers a distinct mechanism that may benefit patients with specific tumour characteristics, such as those with high fibroblast growth factor (FGF) signalling.[16] Notably, lenvatinib also showed improved progression-free survival (PFS) (7.4 months versus 3.7 months; HR: 0.66; 95% CI: 0.57–0.77; p<0.0001) and a higher objective response rate (ORR) (24% versus 9%) compared with sorafenib, highlighting its potential as a preferred upfront option in select cases.[16]
2. Post-immunotherapy progression: in patients who progress after first-line immunotherapy, TKIs are frequently considered for second-line treatment, though randomized controlled trials supporting this approach are lacking.[5] Clinicians may opt for TKIs like lenvatinib or cabozantinib based on their distinct mechanistic profiles, which target pathways (e.g. angiogenesis and tumour signalling) not directly addressed by ICIs.[5] For example, some practitioners favour lenvatinib for its broader kinase inhibition post-ICI failure, with the multicentre retrospective analysis of 464 patients by Persano et al. progressing after atezolizumab–bevacizumab showing longer median OS with lenvatinib (17.0 months) than sorafenib (14.2 months; HR: 0.45; p=0.01) and comparable safety, while others prefer cabozantinib, which has demonstrated efficacy in refractory HCC in the CELESTIAL trial (A Phase 3, Randomized, Double-blind, Controlled Study of Cabozantinib [XL184] vs Placebo in Subjects With Hepatocellular Carcinoma Who Have Received Prior Sorafenib; ClinicalTrials.gov: NCT01908426) (median OS: 10.2 versus 8.0 months with placebo; HR: 0.76; 95% CI: 0.63–0.92; p=0.005).[17] However, without robust randomized data, the choice of TKI in this setting remains individualized, guided by patient PS, prior treatment tolerance and clinician preference.[5]
3. Bridging or downstaging strategy: TKIs also play a role in preparing patients for liver transplantation by either downstaging tumours to meet transplant criteria or serving as a bridge to prevent progression during the waiting period. Sorafenib and lenvatinib have been explored in this context, with observational studies suggesting that they can stabilize the disease and reduce dropout risk from transplant waitlists.[15,18] While not a primary indication, this strategy underscores the versatility of TKIs in managing advanced HCC, particularly when curative options remain a long-term goal.[15,18]

Beyond their role in systemic therapy, TKIs offer an important alternative for patients who are not candidates for other forms of treatment, such as TACE or radioembolization, further highlighting their significance in managing advanced HCC.[19]

Sorafenib was the first TKI approved for advanced HCC and remains a widely used option. It exerts its effects by inhibiting multiple receptor tyrosine kinases, including VEGFR, PDGFR and RAF kinases, thereby disrupting tumour angiogenesis and proliferation.[18] Lenvatinib, another multi-targeted TKI, demonstrated non-inferiority to sorafenib in first-line treatment and offers an alternative with a distinct inhibition profile that affects VEGFR, FGFR, PDGFR and RET.[18,20] Regorafenib and cabozantinib have been preferred options for refractory patients due to their proven efficacy in clinical trials and their ability to target multiple pathways, offering potential benefits after progression on first-line treatment.[21]

Despite their clinical activity in HCC, TKIs have limited efficacy, with response rates around 30% and a modest survival benefit of approximately 3 months.[14] Resistance often develops within 6 months, posing a challenge to long-term disease control.[14]

Immunotherapy in hepatocellular carcinoma

Multikinase inhibitors such as sorafenib and lenvatinib have been widely adopted treatments for patients with unresectable HCC.[16,22] However, immunotherapy has emerged as a transformative strategy, addressing a critical limitation of traditional treatments: the ability of tumours to evade immune detection.[23] By targeting immune checkpoints such as programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), these therapies disrupt the molecular 'shields' used by cancer cells to suppress immune activity.[23] This reactivates T cells – mediators of antitumour responses – and restores the body's capacity to identify and destroy malignant cells through mechanisms like natural immune surveillance.[23]

IMbravel150 trial

The IMbravel150 trial (A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma; ClinicalTrials.gov identifier: NCT03434379), a phase III study, evaluated the combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-vascular endothelial growth factor) versus sorafenib as first-line therapy in 804 patients with unresectable or metastatic HCC.[24] Key inclusion criteria required Child–Pugh A liver function and PS 0–1. The cohort included predominantly viral hepatitis-related HCC (HBV: 49%; HCV: 21%), with non-viral aetiologies (alcohol-related: 19%; non-alcoholic steatohepatitis [NASH]: 8%; other: 3%) representing a smaller group.

This trial established a new standard of care for first-line treatment, showing superior OS, PFS and ORR compared with sorafenib. The median OS was 19.2 months for the combination group versus 13.4 months for sorafenib (HR: 0.66; 95% CI: 0.52–0.85; p<0.001). The median PFS was 6.8 months for the combination versus 4.3 months for sorafenib (HR: 0.65;

95% CI: 0.53–0.80; p<0.001). The ORR was 27.3% for the combination group versus 11.9% for sorafenib per RECIST v1.1, including complete responses in 5.5% of patients.

The multivariate analysis confirmed that the benefit persisted after adjusting for aetiology, geographic region and baseline alpha-fetoprotein (AFP) levels (adjusted HR for OS: 0.68; 95% CI: 0.54–0.85).

Grade ≥3 adverse events occurred in 56.5% of the combination group versus 55.1% with sorafenib. Notable risks with atezolizumab/bevacizumab included hypertension (15.2%), proteinuria (6.5%) and bleeding events (7%).

Obligatory pre-treatment endoscopy was mandated to screen for oesophageal/gastric varices, as bevacizumab increased the risk of life-threatening haemorrhage in patients with cirrhosis. Prophylactic variceal ligation or beta-blockers were required for high-risk lesions before initiating therapy.

HIMALAYA trial

The HIMALAYA trial (A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma; ClinicalTrials.gov identifier: NCT03298451), a phase III clinical trial, enrolled 1,171 patients globally with unresectable HCC to receive the STRIDE regimen (a single dose of tremelimumab – anti-CTLA-4 – plus durvalumab – anti-PD-L1), durvalumab monotherapy or sorafenib.[25,26] The cohort included Child–Pugh A cirrhosis (94%), with aetiologies distributed as hepatitis B (33%), hepatitis C (30%), alcohol-related (19%) and NASH/other causes (18%). The study demonstrated that the combination therapy significantly improved OS compared with sorafenib. The median OS for the combination group was 16.4 months, compared with 13.8 months for sorafenib (HR: 0.78; 95% CI: 0.65–0.93; p=0.0035), with 5-year OS rates of 15.2% versus 6.3% – the longest survival rate ever reported for an immunotherapy-based regimen in advanced HCC.[24] The PFS was 3.8 months for the combination group versus 4.1 months for sorafenib (HR: 0.90; 95% CI: 0.77–1.06; p=0.20), and the ORR was 20.1% for the combination group versus 5.1% for sorafenib (p<0.001), including complete responses in 3.1% of patients. The safety profile favoured STRIDE, with grade ≥3 adverse events occurring in 35.1% versus 43.5% with sorafenib, manageable immune-related toxicities (rash and colitis) and no mandatory pre-treatment endoscopy (unlike antiangiogenic therapies). The 2024 update of 5-year survival data highlights STRIDE's potential to induce durable immune-mediated disease control, establishing it as a promising first-line option, particularly for patients ineligible for vascular endothelial growth factor (VEGF)-targeted therapies.[26]

ORIENT-32 trial

The ORIENT-32 trial (A Randomized, Open-label, Multi-center Study to Evaluate the Efficacy and Safety of the Combination of Sintilimab and IBI305 Compared to Sorafenib in the First-Line Treatment of Patients With Advanced Hepatocellular Carcinoma. [ORIENT-32]; ClinicalTrials.gov identifier: NCT03794440) was a phase II/III study conducted in Chinese patients with advanced HCC, evaluating the combination of sintilimab (anti-PD-1) and IBI305 (a bevacizumab biosimilar) against sorafenib as first-line treatment.[27] Enrolling a cohort with predominantly HBV-related HCC (83%) and Child–Pugh A liver function (92%). The median OS was not reached in the combination group versus 10.4 months for sorafenib (HR: 0.57; 95% CI: 0.43–0.75; p<0.0001), and the median PFS was 4.6 months for the combination versus 2.8 months for sorafenib (HR: 0.56; 95% CI: 0.46–0.70; p<0.0001).

Safety aligned with expectations for PD-1/VEGF inhibition: Grade ≥3 adverse events occurred in 62% of the combination group (notably hypertension and elevated transaminases) versus 48% with sorafenib. Reflecting the risks of antiangiogenic therapy, mandatory pre-treatment endoscopy was required to exclude high-risk varices.

CheckMate 040 trial

The CheckMate 040 trial (A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination With Ipilimumab in Advanced Hepatocellular Carcinoma Subjects With or Without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects Who Are Naive to Systemic Therapy; ClinicalTrials.gov identifier: NCT01658878) was a phase I/II study evaluating nivolumab (anti-PD-1) both as monotherapy and in combination with ipilimumab (anti-CTLA-4) in patients with advanced HCC, most of whom had Child–Pugh A cirrhosis (86%) and prior sorafenib exposure (70%).[28] The combination therapy showed a promising ORR of 31% (95% CI: 20–45), with durable responses. The median OS for the combination group was 22.8 months (95% CI: 9.4–not reached), compared with 15.6 months for nivolumab monotherapy. The PFS was 4.6 months for the combination group (95% CI: 3.6–5.6). However, grade 3–4 immune-related adverse events occurred in 35% of patients (e.g. hepatitis, colitis), necessitating vigilant monitoring.

CheckMate 9DW trial

The CheckMate 9DW trial (A Randomized, Multi-center, Phase 3 Study of Nivolumab in Combination With Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants With Advanced Hepatocellular Carcinoma; ClinicalTrials.gov identifier: NCT04039607), a phase III study, evaluated the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) versus the investigator's choice of lenvatinib or sorafenib as first-line treatment for patients with unresectable HCC.[29] A total of 668 patients were randomized in a 1:1 ratio. Updated results presented at American Society of Clinical Oncology (ASCO) 2024 revealed survival benefits: median OS of 23.7 months for nivolumab/ipilimumab versus 20.6 months for sorafenib/lenvatinib (HR: 0.79; 95% CI: 0.65–0.96; p=0.012), with a 32% ORR (versus 14% for control), including a complete response of 8% versus 2% in the control group. While median PFS remained limited (5.8 versus 4.3 months; HR: 0.75; 95% CI: 0.63–0.90). The safety profile of the combination therapy was consistent with previous studies, with grade ≥3 treatment-related adverse events occurring in 41% of patients in the nivolumab/ipilimumab group and 46% in the control arm. The most common adverse effects from each trial are summarized in *Table 2*.[24–29]

Negative trials combining tyrosine kinase inhibitor and immunotherapy

Some clinical trials have evaluated the combination of TKIs and immunotherapy for treating advanced HCC but failed to demonstrate significant clinical benefits:

1. COSMIC-312 trial (A Randomized, Controlled Phase 3 Study of Cabozantinib [XL184] in Combination With Atezolizumab Versus Sorafenib in Subjects With Advanced Hepatocellular Carcinoma Who Have Not Received Previous Systemic Anticancer Therapy; ClinicalTrials.gov identifier: NCT03755791): this phase III trial evaluated cabozantinib in combination with atezolizumab versus sorafenib in patients with advanced HCC. While the combination improved PFS to 6.8 months (99% CI: 5.6–8.3) for the combination treatment group versus 4.2 months (2.8–7.0) for sorafenib group, it did not show an improvement in OS, 15.4 months (96% CI: 13.7–17.7)

Table 2: Most common adverse effects[24–29]

Trial (ClinicalTrials.gov identifier)	Treatment arms	Adverse effects	Grade ≥3 events
IMbrave150 (NCT03434379)[24]	Atezolizumab + bevacizumab versus sorafenib	Hypertension (15.2%), proteinuria (6.5%), bleeding events (7%)	56.5% (combination) versus 55.1% (sorafenib)
HIMALAYA (NCT03298451)[25,26]	STRIDE (tremelimumab + durvalumab) versus sorafenib	Rash (20%), colitis (7%), hepatitis (5%)	35.1% (STRIDE) versus 43.5% (sorafenib)
ORIENT-32 (NCT03794440)[27]	Sintilimab + IBI305 (bevacizumab biosimilar) versus sorafenib	Hypertension, elevated transaminases	62% (combination) versus 48% (sorafenib)
CheckMate 040 (NCT01658878)[28]	Nivolumab + ipilimumab versus nivolumab monotherapy	Hepatitis (14%), colitis (5%), rash (8%)	35% (combination)
CheckMate 9DW (NCT04039607)[29]	Nivolumab + ipilimumab versus sorafenib/lenvatinib	Hepatitis (18%), pneumonitis (3%), colitis (7%)	41% (nivo/ipi) versus 46% (sorafenib/lenvatinib)

HIMALAYA = Study of Durvalumab and Tremelimumab as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma; NCT = National Clinical Trial; ORIENT = A Study to Evaluate the Efficacy and Safety of Sintilimab in Combination With IBI305 (Anti-VEGF Monoclonal Antibody) Compared to Sorafenib as the First-Line Treatment for Advanced Hepatocellular Carcinoma; STRIDE = single tremelimumab regular interval durvalumab.

for the combination treatment group versus 15.5 months (12.1–not estimable) for sorafenib group, and had lower-than-expected response rates.[30]

2. IMmunoNIB trial (A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects With Hepatocellular Carcinoma; ClinicalTrials.gov identifier: NCT03418922): this single-arm phase II trial assessed the combination of nivolumab and lenvatinib in advanced-stage HCC. The study failed to reach its prespecified ORR of at least 40%, with an ORR of 28% and a median OS of 27.1 months.[31]
3. Mount Sinai Health System Study: this retrospective study (does not have NCT number) evaluated the addition of TKIs (lenvatinib or sorafenib) to immunotherapy (nivolumab) in patients with unresectable HCC who progressed on first-line immunotherapy. The study concluded that adding a TKI after progression on single-agent immunotherapy did not show a significant clinical benefit compared with second-line TKIs alone, with an ORR of 15% and a median OS of 9.5 months.[32]
4. LEAP-002 trial (A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib [E7080/MK-7902] in Combination With Pembrolizumab [MK-3475] Versus Lenvatinib in First-line Therapy of Participants With Advanced Hepatocellular Carcinoma [LEAP-002]; ClinicalTrials.gov identifier: NCT03713593): this phase III study investigated the combination of lenvatinib (a multi-kinase inhibitor) and pembrolizumab (anti-PD-1) in the first-line treatment of advanced HCC.[33] The combination did not meet statistical significance for OS and PFS. The median OS was 21.2 months for the combination group versus 19.0 months for lenvatinib alone (HR: 0.84; 95% CI: 0.70–1.02; p=0.0227), and the median PFS was 8.2 months for the combination versus 8.0 months for lenvatinib (HR: 0.867; 95% CI: 0.72–1.04; p=0.0466).[33]
5. Anti-PD-L1 antibody TQB2450 combined with TKI AL2846: this phase 1b study evaluated the combination in immunotherapy-refractory advanced HCC. The study reported an ORR of 0% for patients with HCC, with a median PFS of 5.55 months and a median OS of 16.72 months, failing to demonstrate significant clinical benefits.[34]

These trials highlight the ongoing challenges in finding effective combination therapies for advanced HCC. The ASCO guidelines reflect these findings, indicating that these combinations did not support a change in clinical practice.

Predictive biomarkers and subgroup heterogeneity

Emerging evidence suggests that specific subgroups of patients with advanced HCC may derive greater benefit from immunotherapy or targeted therapies based on aetiology, tumour biology and biomarkers.[5]

1. Viral versus non-viral aetiology:
   a. HBV- or HCV-related HCC: the IMbrave150 trial (A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma; ClinicalTrials.gov identifier: NCT03434379) showed that the combination of atezolizumab and bevacizumab improved OS in patients with viral hepatitis (HR: 0.62; 95% CI: 0.44–0.87) more than in non-viral HCC (HR: 0.83; 95% CI: 0.59–1.17).[35] Similarly, the HIMALAYA trial reported consistent OS benefits with STRIDE across HBV (HR: 0.67) and HCV (HR: 0.73) subgroups, but HBV-associated HCC showed the strongest survival advantage.[25,26] In the ORIENT-32 trial, the sintilimab + IBI305 combination demonstrated OS benefits in HBV-infected Chinese population (HR: 0.57).[27]
   b. Non-viral HCC: with non-viral HCC, particularly those with metabolic dysfunction-associated steatosis liver disease, may respond less robustly to immunotherapy regimens. In CheckMate 040, for example, the nivolumab + ipilimumab achieved a lower ORR in non-viral HCC (25%) compared with viral HCC.[28]
2. Tumour burden and aggressiveness:
   a. Macrovascular invasion (MVI) or EHS: in IMbrave150, patients without EHS had a median OS of 24.8 months with atezolizumab and bevacizumab versus 12.3 months in those with EHS.[35] The HIMALAYA trial showed that STRIDE improved OS in patients without MVI (HR: 0.69) but had limited benefit in those with MVI (HR: 0.94).[26] In CheckMate 040, the nivolumab + ipilimumab group had better responses in patients with EHS (median OS: 19.9 months).[28]
3. Biomarker-driven subgroups:
   a. PD-L1 expression: in KEYNOTE-224 (A Phase 2 Study of Pembrolizumab [MK-3475] as Monotherapy in Subjects With Advanced Hepatocellular Carcinoma [KEYNOTE-224]; ClinicalTrials.gov: NCT02702414), pembrolizumab achieved a higher ORR in PD-L1-positive tumours (25%) versus PD-L1-negative tumours (12%). However, IMbrave150 showed that atezolizumab and bevacizumab provided benefits regardless of PD-L1 status.[36]

b. AFP levels: elevated AFP (>400 ng/mL) is associated with worse prognosis, but HIMALAYA demonstrated that STRIDE improved OS even in high-AFP subgroups (HR: 0.70).[25,26]

In addition to the scores already mentioned, the albumin–bilirubin measures liver function that eliminates subjective variables such as ascites and encephalopathy, providing superior prognostic stratification within both Child–Pugh A and B classes.[37]

Cirrhosis is a critical determinant of prognosis and treatment selection in HCC, as the majority of the patients with HCC present with cirrhosis. Most clinical trials restrict first-line systemic therapy to patients with preserved liver function (Child–Pugh A), as these patients have a lower risk of mortality and are more likely to respond to the treatment. In addition, the evidence is limited to small prospective and retrospective cohorts.[5,38,39] The CheckMate 040 showed that, in a specific population (patients with Child–Pugh B7–B8), nivolumab is tolerable, but survival continues to be inferior to Child–Pugh A.[28]

Combining therapies in Barcelona Clinic Liver Cancer stages II and III hepatocellular carcinoma

TACE is established as the standard treatment for intermediate-stage HCC within the BCLC staging system.[40] However, the heterogeneity among patients in BCLC stages II and III has prompted investigations into combining TACE and other local therapies with systemic treatments to enhance outcomes. This section explores these combinations, focusing on BCLC stages II and III, where such strategies are increasingly relevant.

Barcelona Clinic Liver Cancer stage II hepatocellular carcinoma

For intermediate-stage HCC (BCLC stage II), TACE remains the cornerstone of therapy.[40] The 2025 ESMO guidelines recommend TACE as the primary treatment for patients with BCLC stage II with preserved liver function (Child–Pugh A/B7) and no vascular invasion, citing its ability to achieve ORRs of 40–60%. Advantages include localized tumour control and suitability for patients with multifocal disease, but limitations involve potential liver decompensation in patients with borderline liver function and variable response due to tumour heterogeneity.[12]

The TACTICS trial (Phase II Study: Transcatheter Arterial Chemoembolization Therapy In Combination With Sorafenib [TACTICS]; ClinicalTrials.gov: NCT01217034), a randomized multicentre study, compared TACE combined with sorafenib to TACE alone in patients with unresectable HCC.[41] This trial demonstrated that sorafenib, administered before and after TACE, significantly extended PFS from 13.5 months to 25.2 months and time to untreatable progression from 20.6 months to 26.7 months.[42] These findings suggest that combining TACE with sorafenib enhances tumour control in patients with BCLC stage II. Additionally, preliminary investigations into TACE paired with immunotherapy are underway, though data remain limited.[42] Recent advancements have further supported this approach. The phase III LEAP-012 trial (A Phase 3 Multicenter, Randomized, Double-blinded, Active-controlled, Clinical Study to Evaluate the Safety and Efficacy of Lenvatinib [E7080/MK-7902] With Pembrolizumab [MK-3475] in Combination With Transarterial Chemoembolization [TACE] Versus TACE in Participants With Incurable/Non-metastatic Hepatocellular Carcinoma [LEAP-012]; ClinicalTrials.gov: NCT04246177), published in *The Lancet*, evaluated the combination of lenvatinib (a TKI), pembrolizumab (an ICI) and TACE in patients with intermediate-stage HCC.[43] The trial reported a median PFS of 14.6 months for the combination therapy compared with 10 months for TACE alone, representing a 34% reduction in the risk of disease progression or death (HR: 0.66; 95% CI: 0.51–0.85; p=0.001). The combination showed a higher ORR (46% versus 28%), but increased grade 3–4 adverse events (e.g. hypertension, transaminase elevation) highlight the need for careful patient selection. These results align with ESMO recommendations to consider TACE-systemic therapy combinations in selected patients with BCLC stage II, though long-term OS data are still needed.[12] Additionally, preliminary investigations of TACE paired with immunotherapy are underway, though data remain limited.[42] These combined approaches offer potential for optimizing outcomes in intermediate-stage HCC.

Barcelona Clinic Liver Cancer stage III hepatocellular carcinoma

In advanced HCC (BCLC stage III), systemic therapies such as atezolizumab plus bevacizumab and durvalumab plus tremelimumab have emerged as the standard of care.[24] The 2025 ESMO guidelines endorse atezolizumab plus bevacizumab as the preferred first-line therapy for patients with BCLC stage III with Child–Pugh A liver function, based on the IMbrave150 trial's median OS of 19.2 months (HR: 0.58; 95% CI: 0.42–0.79) and ORR of 27.3%. Advantages include superior efficacy over sorafenib and suitability for patients with MVI, but limitations include a 7% risk of bleeding events and the need for pre-treatment variceal screening. The guidelines also support durvalumab plus tremelimumab (STRIDE regimen) from the HIMALAYA trial, with a median OS of 16.4 months (HR: 0.78; 95% CI: 0.65–0.93) and a 5-year OS rate of 15.2%, offering durable responses and utility in patients ineligible for anti-VEGF therapies. Its limitations include a lower ORR (20.1%) and immune-related adverse events (e.g. hepatitis, 8%). Lenvatinib and sorafenib are alternative first-line options, with lenvatinib providing a higher ORR (24%) but requiring frequent dose adjustments due to toxicity, and sorafenib limited by modest OS (10.7 months).[12] However, for patients with localized liver tumour burden, adding local therapies to systemic regimens may provide additional benefits.

EMERALD-1

The EMERALD-1 trial (A Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter Study of Transarterial Chemoembolization [TACE] in Combination With Either Durvalumab Monotherapy or Durvalumab Plus Bevacizumab Therapy in Patients With Locoregional Hepatocellular Carcinoma [EMERALD-1]; ClinicalTrials.gov: NCT03778957), a phase III study published in *The Lancet*, has provided compelling evidence for this strategy.[44] It evaluated the addition of durvalumab (an ICI) with or without bevacizumab (an anti-VEGF agent) to TACE in patients with unresectable HCC eligible for embolization, typically associated with BCLC stage III. The trial demonstrated a significant improvement in PFS, with median PFS increasing from 8.2 months with placebo plus TACE to 15.0 months with durvalumab and bevacizumab plus TACE. This suggests that combining TACE with immunotherapy and targeted agents could enhance outcomes in advanced HCC.[44]

Additionally, transarterial radioembolization (TARE) is emerging as a promising locoregional therapy for HCC. The ongoing EMERALD-Y90 trial (Phase II Single-Arm Study of Durvalumab and Bevacizumab Following Transarterial Radioembolization Using Yttrium-90 Glass Microspheres [TheraSphere™] in Unresectable Hepatocellular Carcinoma Amenable to Locoregional Therapy; ClinicalTrials.gov identifier: NCT06040099) is investigating the combination of durvalumab and bevacizumab following TARE, indicating a need for further research to evaluate its efficacy and safety in patients with BCLC stage III.[45]

Future perspectives

The management of HCC is undergoing transformative advancements, driven by molecular profiling, biomarker discovery and innovative

therapeutic combinations. Molecular studies have identified targets such as FGFR4, mesenchymal-epithelial transition (MET) factor and wingless related integration site/β-catenin pathway alterations, which are now being explored in clinical trials. For instance, FGFR4 inhibitors like fisogatinib are under investigation for tumours with FGFR4 overexpression, while MET inhibitors such as tepotinib show promise in the 5% of HCC cases harbouring MET amplification.[3,5] Concurrently, strategies targeting the Wnt/β-catenin pathway aim to reverse immune exclusion in 'cold' tumours, with early-phase trials combining inhibitors like Foscenvivint (PRI-724) and ICIs to enhance T-cell infiltration.[4] Glypican-3, overexpressed in 70% of HCCs, is another emerging target, with chimeric antigen receptor T-cell therapies and antibody-drug conjugates like codrituzumab demonstrating preclinical efficacy.[46]

Biomarker-driven approaches are critical to optimizing therapy. Tumour mutational burden and immune gene signatures, such as CD8+ T-cell infiltration, are being validated as predictors of ICI response, while liquid biopsies tracking circulating tumour DNA or PD-L1 offer non-invasive tools for monitoring resistance.[4,11] Spatial proteomics has further uncovered stromal subpopulations, like cancer-associated fibroblasts expressing fibroblast activation protein (CAF-FAP), which correlate with ICI resistance and are being targeted in combination trials.[3] These efforts align with the 2024 ASCO guidelines emphasizing biomarker integration to personalize frontline therapy.[5]

Combination strategies remain a cornerstone of innovation. Building on the success of atezolizumab plus bevacizumab in IMbrave150, newer regimens such as durvalumab with lenvatinib aim to enhance vascular normalization and immune synergy.[24] Dual checkpoint blockade, exemplified by the STRIDE regimen (tremelimumab + durvalumab) in HIMALAYA, is being refined to reduce toxicity while maintaining efficacy, particularly in HBV-associated HCC.[25,26] Stromal-targeted therapies, including CAF-FAP inhibitors paired with anti-PD-1, are showing preclinical promise by remodelling the tumour microenvironment.[25,26] Additionally, combining locoregional therapies like TACE or yttrium-90 radioembolization with ICIs is under investigation, with early trials reporting prolonged PFS.[47]

Addressing subgroup heterogeneity remains pivotal. HBV-driven HCC, characterized by higher neoantigen loads, shows robust responses to ICIs, whereas NAFLD-/NASH-associated tumours may require metabolic modulators like FGF21 analogues to overcome immunosuppressive microenvironments.[46]

Beyond immunotherapy, recent advances in metabolic treatments may change HCC prevention in NASH. GLP-1 receptor agonists, such as semaglutide, have demonstrated improvements in hepatic inflammation and resolution of steatohepatitis without worsening fibrosis in a phase II trial.[48] The percentage of patients in whom NASH resolution was achieved with no worsening of fibrosis in 36–59% of the patients using semaglutide (dose dependent) compared to 17% in the placebo group, suggesting a potential role in reducing the time to cirrhosis and HCC.[48] Similarly, resmetirom, a selective thyroid hormone receptor-beta agonist, has shown promising results in reducing hepatic fat and improving fibrosis in a phase II trial, representing another disease-modifying strategy that may decrease long-term HCC risk.[49]

In patients with cirrhosis, dose-adjusted ICIs (e.g. reduced-dose pembrolizumab) are being tested to balance efficacy and safety, while post-transplant protocols explore mammalian target of rapamycin inhibitors like everolimus combined with ICIs to prevent recurrence without compromising graft survival.[11]

Novel approaches such as faecal microbiota transplantation to modulate the gut–liver axis and enhance ICI responses in antibiotic-exposed patients highlight the intersection of microbiome science and oncology.[3]

Additionally, research is ongoing to improve TKI efficacy in HCC treatment. Some promising approaches include studying specific TKIs such as mesenchymal-epithelial transition factor receptor tyrosine kinase (c-MET) or transforming growth factor β receptor (TGFβR) inhibitors in sub-populations with HCC .[20] Additionally, future research will focus on understanding how combination therapies can address resistance mechanisms.[18] Despite their limitations, TKIs remain a crucial option in the treatment of advanced HCC, particularly when other treatments are no longer effective or feasible, offering hope for improved outcomes in this challenging disease[20].

Global accessibility and equity are equally urgent priorities. Scalable comprehensive genomic profiling (CGP) platforms in Asia and Europe have reduced testing costs to under US$1,000, democratizing precision medicine, while initiatives like the Asia-Pacific Hepatocellular Carcinoma Trials Group are addressing the underrepresentation of non-Western populations in clinical research.[4]

Looking ahead, new combination therapies aim to redefine standards of care. With these advancements, the OS in advanced HCC could increase considerably in the next decade, marking a paradigm shift in outcomes for this historically intractable disease. ❑

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