Looking Toward the Future: Emerging Therapies for Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related deaths worldwide. Despite the decreasing prevalence of hepatitis C, the burden of HCC is expected to rise owing to the increasing prevalence of metabolic syndrome and increased global alcohol consumption. Guideline-concordant screening with ultrasound every 6 months has been associated with increased rates of early-stage detection and receipt of curative treatment. However, most patients with cirrhosis do not undergo screening, with HCC often diagnosed only at an advanced stage when curative resection or ablation is not feasible. Systemic medical therapy is indicated in patients diagnosed with infiltrative or advanced HCC, or when early-stage disease progresses or recurs after resection, transplant, or other locoregional therapy. Sorafenib was approved as first-line therapy for HCC in 2007. Since 2017, there has been an exponential rate of approval of novel agents targeting HCC, including lenvatinib, regorafenib, and cabozantinib. Checkpoint inhibitors, including pembrolizumab, nivolumab, ipilimumab, and combination therapy with atezolizumab plus bevacizumab and durvalumab plus tremelimumab, have expanded treatment options. This article describes treatment for all HCC stages, with a brief discussion of locoregional therapy for context, as some emerging treatment regimens combine locoregional and systemic therapies. The article highlights approved systemic therapies that are guideline-endorsed and emerging therapies for advanced HCC.

Keywords
Hepatocellular carcinoma, liver cancer, systemic therapy, immunotherapy, chemotherapy

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer-related deaths worldwide.[1] The highest rates of HCC are seen in Eastern Asia, Micronesia, and Northern Africa, correlating with a continued high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) in these regions.[1,2] In the United States, HCC incidence and mortality

rates are higher in rural areas, especially in the Southern and Western United States.[3] Disease burden is higher among racial and ethnic minorities when compared with non-Hispanic White patients.[3] In the United States and worldwide, the incidence of HCC is 2- to 3-fold higher in men than women,[1,4,5] partially attributed to higher prevalence of risk factors among males, such as alcohol, HCV infection, diabetes, and injection drug use.[5]

Although chronic HBV and HCV infections are still leading causes of HCC globally,[6] HBV vaccination[7] and treatment for HBV and HCV have altered HCC epidemiology. Global increases in obesity and metabolic syndrome have led to increased prevalence of nonalcoholic fatty liver disease,[8] now known as metabolic dysfunction-associated steatotic liver disease (MASLD). Global MASLD prevalence is 25%,[9] and MASLD is the fastest-rising cause of HCC among US patients listed for liver transplant (LT).[8] Over the past decade, global per-capita consumption of alcohol has risen and is projected to increase by 2030, with a corresponding rise in alcohol-associated HCC.[10]

Regardless of etiology, chronic hepatic necrosis and inflammation lead to fibrosis and cirrhosis. Regenerating nodules may eventually develop into dysplastic and then malignant neoplastic lesions. As recommended by international liver societies,[11,12] individuals at risk should undergo biannual ultrasound with or without alpha-fetoprotein (AFP) measurement. Surveillance has been associated with improved rates of early-stage detection (relative risk [RR], 1.86; 95% CI, 1.73-1.98) and receipt of curative treatment (RR, 1.83; 95% CI, 1.69-1.97), with 33% reduced rate of death (hazard ratio [HR], 0.67; 95% CI, 0.61-0.72).[13]

However, most patients with cirrhosis do not undergo HCC screening.[14] In the United States, more than two-thirds of HCC patients are diagnosed with multinodular disease[15] and only 50.8% have disease localized to the liver.[16] An international study found that Barcelona Clinic Liver Cancer (BCLC) stage C (advanced) was the most common stage at diagnosis from 2005 to 2013.[17] This article describes treatment for all stages of HCC, briefly covering locoregional therapies for context. Most patients with HCC will receive systemic therapy as either first-line therapy or subsequently if disease progresses. Thus, this article focuses primarily on current and emerging systemic therapies for advanced HCC.

Treatment of Very Early– and Early-Stage Hepatocellular Carcinoma

The most commonly used HCC staging systems include the American Joint Committee on Cancer tumor/node/metastasis (TNM) system,[18] which is used mainly with surgical resection or transplant, and the more widely used BCLC staging system.[19] The TNM model, which is also used for other solid tumors, does not capture complications of cirrhosis or functional status, which impact treatment eligibility, tolerability, and response. Both the European Association for the Study of the Liver[20] and the American Association for the Study of Liver Diseases[12] utilize BCLC staging, which incorporates tumor characteristics, the presence/absence of clinically significant portal hypertension (CSPH), and functional status. The BCLC system encompasses 5 stages: very early (0), early (A), intermediate (B), advanced (C), and terminal (D), with specific substages tied to treatment options (Figure).

Very early–stage HCC (BCLC 0) is defined as a solitary nodule 2 cm or smaller without evidence of vascular invasion or metastases in a patient with preserved liver function. Although LT offers the lowest risk of recurrence,[21] BCLC 0 HCC does not qualify for Model for End-Stage Liver Disease exception points.[22] Surgical resection is appropriate treatment for patients without CSPH,[23] which is defined as hepatic venous pressure gradient greater than 10 mm Hg. Patients with CSPH have higher risk of postoperative complications and shortened long-term survival.[24] In patients with contraindications to resection or LT, ablative therapies such as radiofrequency ablation or microwave ablation offer similar survival benefit[25] with reduced costs.[26]

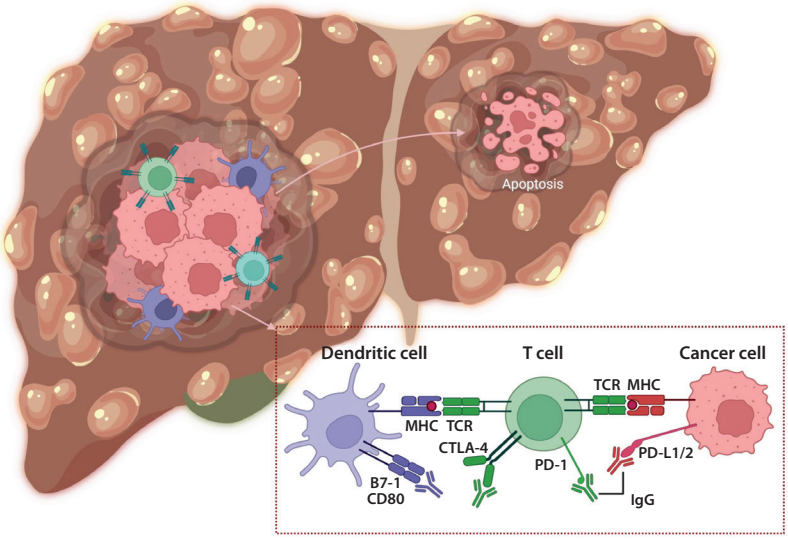
Early-stage HCC (BCLC A) refers to patients without cancer-related symptoms who have either a solitary nodule not greater than 5 cm in size or up to 3 nodules, each 3 cm or smaller. The original and revised BCLC staging systems consider solitary nodules as BCLC A, regardless of size. However, in clinical practice, individuals with solitary tumors larger than 5 cm are treated as BCLC B, as they exceed the Milan criteria.[27,28] Treatment depends on the size, number, and anatomic distribution of multiple tumors plus the degree of liver dysfunction. As with BCLC 0, patients with solitary BCLC A tumors without CSPH are eligible for resection. The SURF trial, a multi-institutional randomized controlled trial involving 301 patients in Japan, found no significant differences in recurrence-free survival between surgery (3.5 years) and radiofrequency ablation (3 years) for patients with multifocal HCC meeting the Milan criteria.[27,29]

In patients with CSPH, LT is the preferred treatment. Locoregional therapies, including ablation, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE), are frequently recommended to prevent tumor progression.[20] TACE delivers chemotherapy emulsified in ethiodized oil (Lipiodol, Guerbet) or drug-eluting microspheres[30,31] directly to tumors through branches of the hepatic artery,[32] whereas TARE delivers yttrium-90–coated microspheres. Although patients with multifocal disease are best managed with LT to decrease

	Very early BCLC 0	Early BCLC A	Intermediate BCLC B	Advanced BCLC C	Terminal BCLC D
ECOG performance status	0	0	0	1-2	3-4
Liver function	Preserved	Preserved	Preserved	Preserved	End-stage
Tumor characteristics	Solitary tumor ≤2 cm	Solitary tumor or multinodular ≤3 nodules each ≤3 cm	Multinodular exceeding BCLC A (Milan) criteria	Portal invasion and/or extrahepatic spread	Any

Downstaging | Progression

Eligible for liver transplant via extended criteria	Well-defined tumors with vascular access	Infiltrative, diffuse, and/or bilobar disease



ECOG performance status	
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair

Figure. Hepatocellular carcinoma (HCC) is typically staged according to the Barcelona Clinic Liver Cancer (BCLC) stages. The BCLC schema incorporates Eastern Cooperative Oncology Group (ECOG) performance status and tumor characteristics. Intermediate stage (BCLC B) has 3 subgroups based on transplant eligibility and tumor characteristics. Approved therapies for HCC target tyrosine kinase receptors; programmed death 1 (PD-1); its ligands, programmed death ligand 1 and 2 (PD-L1/PD-L2); cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4); or B7-1 indirectly through PD-L1. Effective targeting of checkpoint inhibitors augments the immune response.

Ig, immunoglobulin; MHC, major histocompatibility complex; TCR, T-cell receptor.

recurrence, the LEGACY study demonstrated that TARE offered an 88.3% objective response rate (ORR), and 62.2% of patients had a duration of response exceeding 6 months.[33] TARE is useful for downstaging and bridging to LT in patients with good liver function, but can also be utilized in cases where surgical resection or LT is contraindicated.

Locoregional Treatments for Intermediate-Stage Hepatocellular Carcinoma

Intermediate-stage HCC (BCLC B) represents a heterogeneous group of patients with large solitary tumors (eg, >5 cm) or multifocal tumors exceeding BCLC A criteria. In the updated BCLC classification,[20] BCLC B is

stratified into 3 subgroups according to tumor burden, liver function, and treatment eligibility. The first subgroup includes patients with well-defined HCC nodules who are LT candidates if they meet institutional or national extended criteria for LT.[34] As the tumor burden in BCLC B exceeds the Milan criteria,[27] most centers and regulatory bodies (eg, the United Network for Organ Sharing) will not award HCC exception points unless patients have undergone downstaging. Patients with multifocal disease with preserved liver function may undergo downstaging to decrease tumor burden and become eligible for transplant.[35] Downstaging is achieved through either locoregional therapy, systemic therapy, or a combination of both. Current investigations are underway for combination immunotherapy and tyrosine kinase inhibitors as a downstaging strategy for HCC.[36] Additionally, LT may be possible for patients with BCLC B tumors in centers performing living donor LT or those governed by regulatory bodies other than the United Network for Organ Sharing. The second BCLC B subgroup includes patients with well-defined nodules who are not extended-criteria LT candidates but have preserved portal flow and arterial access, enabling intra-arterial treatment. The third subgroup includes patients with diffuse, infiltrative HCC.[37] TACE improves survival in patients with unresectable HCC compared with conservative management.[38] However, optimal candidates have preserved liver function, for example, bilirubin not greater than 2 mg/dL and controlled ascites, which can limit its application. In practice, TACE is often performed in patients not meeting these criteria, after a thoughtful assessment of risks and benefits.[39] Ideally, arterial therapies reduce tumor burden so that patients can receive LT (eg, downstaging). Local recurrence or progression typically requires additional TACE, ablation, or TARE.[33,40] Ongoing clinical trials (eg, NCT04803994) are investigating the efficacy and safety of immune checkpoint inhibitors (ICIs) combined with TACE vs TACE alone in patients with intermediate HCC.

Systemic Therapies for Intermediate- and Advanced-Stage Hepatocellular Carcinoma

Advanced-stage HCC (BCLC C) includes patients with cancer-related symptoms, vascular invasion, or extrahepatic spread. Systemic therapy is the mainstay of treatment for patients with BCLC C disease and BCLC B patients with diffuse, infiltrative, or bilobar involvement. Since sorafenib was approved in 2007, other targeted therapeutic options have been introduced, including lenvatinib (Lenvima, Eisai), regorafenib, ramucirumab (Cyramza, Lilly), and cabozantinib (Cabometyx, Exelixis). Also, ICIs are now used alone or in combination for treatment of advanced HCC. These include pembrolizumab (Keytruda, Merck), nivolumab (Opdivo, Bristol Myers Squibb), ipilimumab (Yervoy, Bristol Myers Squibb), atezolizumab (Tecentriq, Genentech), bevacizumab, durvalumab (Imfinzi, AstraZeneca), and tremelimumab.

Targeted Therapy

HCC requires tyrosine kinase receptors for growth and metastasis. Sorafenib, which inhibits several tyrosine kinase receptor pathways, has been used to treat advanced, unresectable HCC since approval by the US Food and Drug Administration in 2007. The SHARP trial, a multicenter, double-blind, randomized phase 3 trial, demonstrated significantly higher median overall survival (OS) in patients treated with sorafenib compared with placebo (10.7 months vs 7.9 months, respectively; $P<.001$).[41,42] Additionally, there was longer time to radiologic progression of disease with sorafenib compared with placebo (5.5 months vs 2.8 months, respectively; $P<.001$). Patients in the SHARP trial had Child-Pugh (CP) class A liver function and Eastern Cooperative Oncology Group performance status of no more than 2. Because HCC typically develops in patients with cirrhosis, many have synthetic dysfunction. The GIDEON study, a nonrandomized prospective registry of HCC patients treated with sorafenib, included 367 CP-B patients and 35 CP-C patients.[43] In an interim analysis of 1571 patients, increasing CP score was associated with shorter median duration of sorafenib use, for example, 6.7 weeks in CP-B9 patients vs 13.7 weeks in CP-A patients. The final GIDEON safety population included 3202 patients, of whom 666 had CP-B status and 74 had CP-C status at study entry. There was substantial regional variation with regard to sorafenib dose at initiation and dose reduction.[44] Subsequent analysis revealed similar rates of drug-related adverse events at 17% in CP-A patients and 21% in CP-B patients, but lower median OS in CP-B patients, 5.2 months, compared with 13.6 months in CP-A patients.[45]

Regorafenib, an oral multikinase inhibitor, emerged as a promising second-line treatment in patients with tumor progression on sorafenib in 2017. In the RESORCE trial,[46] patients who received regorafenib after sorafenib failure achieved significantly increased OS compared with those who received placebo (10.6 months vs 7.8 months, respectively; $P<.0001$). Also, survival was longer in patients who switched to regorafenib after TACE failure vs those who underwent repeated TACE.[47] Multiple small studies have examined regorafenib combined with locoregional therapies or after immunotherapy. In 59 patients with progression after first-line therapy, combined regorafenib/TACE was associated with an ORR of 42.3% compared with 11% with regorafenib monotherapy.[48] A recent case series of 5 patients suggested that regorafenib could effectively delay disease

progression with a disease control rate of 80% after failing atezolizumab plus bevacizumab therapy.[49]

Lenvatinib, an oral antiangiogenic agent, was determined to be noninferior to sorafenib in an open-label, multicenter phase 3 study.[50] Median OS in the lenvatinib arm was 13.6 months, compared with 12.3 months in the sorafenib arm (HR, 0.92; 95% CI, 0.79-1.06). Lenvatinib-treated patients had longer time to progression compared with patients treated with sorafenib (7.4 months vs 3.7 months, respectively; *P*<.0001). A meta-analysis of 15 studies reaffirmed that lenvatinib did not increase OS and was associated with longer progression-free survival (PFS) (HR, 0.63; 95% CI, 0.53-0.74; *P*<.00001) and improved disease control rate (odds ratio, 2.42; 95% CI, 1.79-3.28; *P*<.00001), compared with sorafenib in patients with advanced HCC.[51]

Cabozantinib, an oral multikinase inhibitor of vascular endothelial growth factor (VEGF) 1 to 3, mesenchymal epithelial transition factor, and anexelekto, was approved in 2018. The CELESTIAL trial,[52] a double-blind, randomized phase 3 trial of 707 patients, reported median OS of 10.2 months in the cabozantinib arm compared with 8 months with placebo (*P*=.005). The patients had been previously treated with sorafenib or other systemic therapies, and more than 90% had BCLC C disease. Treatment with cabozantinib was associated with longer median PFS compared with placebo (5.2 months vs 1.9 months, respectively; *P*<.0001). Since its approval as second-line monotherapy, research has been conducted to examine the efficacy of cabozantinib combined with or after immunotherapy.[53]

Ramucirumab, a human recombinant immunoglobulin G1 monoclonal antibody, binds to vascular endothelial growth factor receptor 2 (VEGFR-2) and prevents binding of VEGF-A, VEGF-C, and VEGF-D, thereby inhibiting downstream signaling implicated in angiogenesis. In the REACH-2 trial, a randomized, double-blind, multicenter phase 3 trial of 292 patients, those treated with ramucirumab had longer median OS than those who received placebo (8.5 months vs 7.3 months, respectively; *P*=.0199), and those with AFP levels greater than 400 ng/mL had better response.[54] Subsequent research has confirmed ramucirumab's effectiveness with a favorable safety profile and mild deterioration of liver function compared with sorafenib and lenvatinib.[55]

Immunotherapies

The introduction of monoclonal antibodies that block key immune signaling molecules in T-cell activation and thereby inhibit malignant growth has expanded treatment options. Programmed death 1 (PD-1), a receptor found on T cells and B cells, plays a critical role in T-cell exhaustion and host response to tumors.[56] When PD-1 binds to its ligands, programmed death ligand 1 and 2 (PD-L1 and PD-L2), which are expressed on cancer cells and antigen-presenting cells, the immune response is downregulated.[57-59] PD-L1 also binds to the B7-1 receptor (CD80) on antigen-presenting cells. ICIs have improved clinical outcomes in patients with advanced HCC. Nivolumab monotherapy was approved in 2017 and pembrolizumab in 2018. Subsequently, combination ICI therapies were approved for treatment of HCC. First, nivolumab combined with ipilimumab was approved for HCC in 2020, followed by atezolizumab plus bevacizumab in 2020, and durvalumab plus tremelimumab in 2022. Ipilimumab and tremelimumab are ICIs that block the interaction of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) with CD80 and CD86, leading to activation of regulatory T cells.[60]

Nivolumab, an anti–PD-1 monoclonal antibody, showed promising results in a phase 1/2 dose-escalation and expansion trial conducted in 262 patients. The ORR ranged from 15% to 20%, and median OS was 15 months in the dose-escalation phase.[61] A larger multicenter phase 3 trial that randomized patients to receive nivolumab (n=371) or sorafenib (n=372) did not find statistically significant survival differences.[62] Median OS was 16.4 months with nivolumab, compared with 14.7 months with sorafenib. Following these results, nivolumab as monotherapy was voluntarily withdrawn from the US market by the manufacturer in 2021. Subsequent studies have demonstrated efficacy and safety of low-dose nivolumab monotherapy in cases of advanced HCC with impaired liver function.[63,64] Thus, nivolumab is still used off-label in select patients and settings.

The PD-1 inhibitor pembrolizumab demonstrated antitumor activity in the KEYNOTE-224 trial, which examined 104 patients with advanced HCC who previously received sorafenib.[65] A subsequent randomized, double-blind phase 3 trial, KEYNOTE-240 reported median OS of 13.9 months in patients treated with pembrolizumab compared with 10.6 months with placebo (*P*=.0238). Although clinically significant, these findings did not meet the prespecified endpoints for statistically significant improvement in OS or PFS.[66] KEYNOTE-394, a double-blind phase 3 trial conducted in 453 patients in Asia, revealed that second-line pembrolizumab was associated with median OS of 14.6 months vs 13 months with placebo (*P*=.018), with ORRs of 12.7% in the pembrolizumab arm and 1.3% in the placebo arm (*P*<.0001).[67] Ongoing studies are examining combination therapy with pembrolizumab, other ICIs, or nonimmunomodulating systemic drugs.

Combination Immune Checkpoint Inhibitors

The first dual ICI therapy for HCC, ipilimumab and

nivolumab, was investigated as second-line therapy via an open-label, multicohort phase 1/2 study of 148 patients in CheckMate 040.[60] The ORR ranged from 27% to 32%, depending on study arm. Median duration of response ranged from 15.2 months to not reached. Treatment-related adverse events ranged from 71% to 94%. Increased toxicity was observed with combination therapy compared with nivolumab monotherapy. More recently, results were published from CheckMate-9DW, an open-label, randomized phase 3 trial that compared ipilimumab and nivolumab vs lenvatinib or sorafenib as first-line therapy for patients with unresectable HCC.[68] This study demonstrated an ORR of 36% in patients treated with immunotherapy vs 13% in patients treated with lenvatinib or sorafenib. Of note, median OS with combination therapy was 23.7 months vs 20.6 months in the lenvatinib or sorafenib group. Treatment-related adverse events were similar in each group. Currently, ipilimumab and nivolumab are used as salvage therapy in patients previously treated with ICIs[69]; however, the aforementioned results and ongoing research (NCT05199285) may lead to ipilimumab and nivolumab being used in the first-line setting.

Combination therapy with atezolizumab and bevacizumab was the first immunotherapy regimen approved for first-line treatment for advanced HCC.[70] Atezolizumab binds to PD-L1, and bevacizumab is an anti-VEGF monoclonal antibody that suppresses angiogenesis and hinders tumor expansion. The IMbrave150 trial, a global, open-label phase 3 trial of 501 patients comparing atezolizumab plus bevacizumab vs sorafenib, reported a HR for death of 0.58 (95% CI, 0.42-0.79; $P<.001$). Median PFS was 2.5 months longer in patients treated with atezolizumab plus bevacizumab. An updated analysis revealed that median OS was 19.2 months in patients treated with atezolizumab plus bevacizumab vs 13.4 months with sorafenib ($P=.0009$).[71] Bevacizumab increases bleeding risk; therefore, endoscopy to screen for varices is strongly recommended.[72] Emerging data suggest that clinical features may risk-stratify which patients require endoscopy[73]; patients with prior variceal bleed are at greatest risk for acute variceal bleeding.[74]

The Single Tremelimumab Regular Interval Durvalumab (STRIDE) regimen was compared with sorafenib or durvalumab monotherapy in the phase 3 HIMALAYA trial, a large multicenter study of 1171 patients. Tremelimumab binds CTLA-4, like ipilimumab, and durvalumab binds to PD-L1. Median OS was 16.43 months with the STRIDE regimen, 16.56 months with durvalumab monotherapy, and 13.77 months with sorafenib.[75] An updated analysis revealed that the 48-month OS rate was 25.2% with the STRIDE regimen vs 15.1% with sorafenib.[76] Durvalumab monotherapy was noninferior to sorafenib; however, sorafenib was associated with more high-grade adverse effects (52.4% vs 37.1% with durvalumab).[75] The American Society of Clinical Oncology strongly recommends either atezolizumab plus bevacizumab or durvalumab plus tremelimumab as first-line treatment for patients with CP-A advanced HCC.[77]

Emerging Therapies

Until recently, effective options for patients with advanced-stage HCC were lacking.[78-80] After sorafenib's approval in 2007, it was the only approved systemic therapy for 10 years.[79] As knowledge of the mechanisms of tumorigenesis and HCC progression expands, so does the development of novel targeted agents. Despite encouraging results of phase 1/2 trials with ICI monotherapy, approximately two-thirds of patients do not achieve adequate response owing to resistance created by the tumor microenvironment.[57,58] In HCC, the tumor microenvironment is hypoxic, which elicits the release of VEGF leading to the cascade of myeloid-derived suppressor cells, activated T cells, regulatory T cells, natural killer cells, dendritic cells, and monocytes that express PD-1. The tumor microenvironment influences tumor development and progression along with immune escape and evasion.[58,81] The interaction between tyrosine kinase–dependent oncogenic pathways and ICIs has informed several ongoing clinical trials to expand therapeutic options geared toward inhibiting protumor pathways and enhancing antitumoral immune cytotoxicity.[57,58]

A search of ClinicalTrials.gov found 179 clinical trials for HCC from January 1, 2022 until September 1, 2024, of which 97 are ongoing. Owing to the limited scope of this review, the following section highlights select phase 3 trials investigating novel agents that have not yet received approval. Several phase 3 trials encompass combination therapy and monotherapy for advanced HCC. These options include several PD-1 inhibitors, including tislelizumab, camrelizumab, budigalimab, toripalimab, finotonlimab, nofazinlimab, penpulimab, and sintilimab. The Table lists select emerging therapies, their mechanism of action, and trial status. Tislelizumab was noninferior to sorafenib in an open-label multiregional study of 674 patients (RATIONALE-301).[82] Median OS was 15.9 months in patients treated with tislelizumab compared with 14.1 months in patients who received sorafenib. The ORR was 14.3% for tislelizumab vs 5.1% for sorafenib.

The remaining trials in the Table involve combination therapies. A small phase 2 study found that toripalimab plus bevacizumab was associated with 63.5% survival at 24 months.[83] This combination is being compared with sorafenib in patients with advanced HCC in a phase 3 multicenter study (NCT04723004). Combination

Table. Emerging Therapies for Hepatocellular Carcinoma

Drug name	Study identifier	Mechanism of action	Country of study	Trial and status
Tislelizumab		Anti–PD-1 antibody		
	NCT03412773		Multinational	RATIONALE-301 Phase 2 Completed
Camrelizumab (SHR-1210)		Anti–PD-1 antibody		
+ Apatinib	NCT03764293	VEGFR-2 inhibitor	Multinational	Phase 3 Completed
+ Lenvatinib	NCT05738616	VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor	China	LEN-TAC Phase 3 Recruiting
+ TACE				
+ Apatinib	NCT06172205	VEGFR-2 inhibitor	China	Phase 3 Recruiting
+ FOLFOX				
Budigalimab		Anti–PD-1 antibody		
+ Livmoniplimab (ABBV-151)	NCT06109272	Anti–GARP-TGF-β1 antibody	Multinational	LIVIGNO-2 Phase 2/3 Active, not recruiting
Toripalimab (JS001)		Anti–PD-1 antibody		
+ Bevacizumab	NCT04723004	Anti-VEGF antibody	China	Phase 3 Active, not recruiting
+ Lenvatinib	NCT04523493	VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor	Multinational	Phase 3 Active, not recruiting
+ Radiotherapy	NCT04709380		China	Phase 3 Terminated
+ Lenvatinib	NCT06201065	VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor	China	Phase 3 Recruiting
+ FOLFOX-HAIC				
Finotonlimab (SCT-I10A)		Anti–PD-1 antibody		
+ SCT510	NCT04560894	Anti-VEGF antibody	China	Phase 2/3 Active, not recruiting
Nofazinlimab (CS1003)		Anti–PD-1 antibody		
+ Lenvatinib	NCT04194775	VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor	Multinational	Phase 3 Active, not recruiting
Penpulimab (AK105)		Anti–PD-1 antibody		
+ Anlotinib	NCT04344158	VEGFR-1 to -3, c-kit, FGFR 1-3, and PDGFR-α inhibitor	China	Phase 3 Active, not recruiting
+ Anlotinib	NCT05344924	VEGFR-1 to -3, c-kit, FGFR 1-3, and PDGFR-α inhibitor	China	Phase 2/3 Unknown status
+ TACE				
Sintilimab		Anti–PD-1 antibody		
+ IBI310	NCT04720716	Anti–CTLA-4 antibody	China	Phase 3 Unknown status
Rulonilimab		Anti–PD-1 antibody		
+ Lenvatinib	NCT05408221	VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor	China	Phase 2/3 Recruiting

(Table continues on following page)

Table. (*Continued)* Emerging Therapies for Hepatocellular Carcinoma

Drug name	Study identifier	Mechanism of action	Country of study	Trial and status
Tiragolumab (MTIG7192A)		TIGIT inhibitor		
+ Atezolizumab	NCT05904886	Anti–PD-L1 antibody	Multinational	SKYSCRAPER-14 Phase 3 Active, not recruiting
+ Bevacizumab		Anti-VEGF antibody		
Namodenoson (CF102)		A3 adenosine receptor agonist		
	NCT05201404		Multinational	Phase 3 Recruiting
+ ADI-PEG 20	NCT05317819	Arginine degradation	Taiwan, Vietnam	Phase 3 Recruiting
AlloStim		Immunotherapy Allogeneic Th1-like cell therapy		
	NCT05033522		Malaysia, Thailand	Phase 2/3 Recruiting
QL1706 (PSB205)		Anti–PD-1/CTLA-4 antibody		
+ Bevacizumab	NCT05976568	Anti-VEGF antibody	China	Phase 2/3 Not yet recruiting
+ Chemotherapy				
Lenvatinib		VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor		
+ TACE	NCT05718232		China	Phase 3 Not yet recruiting
+ SBRT				

CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOX-HAIC, folinic acid, fluorouracil, and oxaliplatin via hepatic arterial infusion chemotherapy; GARP–TGF-β1, glycoprotein A repetitions predominant–transforming growth factor-beta 1; PD-1, programmed death 1; PDGFR-α, platelet-derived growth factor receptor-alpha; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; Th1, T-helper cell 1; TIGIT, T-cell immune receptor with immunoglobulin and ITIM domains; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

therapy with camrelizumab (SHR-1210) and rivoceranib (apatinib), a small-molecule VEGFR-2 inhibitor, offered median OS of 23.8 months compared with 15.2 months in patients treated with sorafenib (P<.0001) in the phase 3 CARES-310 trial of 543 patients.[84] This combination has also been trialed via hepatic artery infusion.[85]

As first-line therapy for HCC, finotonlimab (SCT-I10A) in combination with SCT510 (a bevacizumab biosimilar candidate)[86] was associated with longer median OS compared with sorafenib (22.1 months vs 14.2 months, respectively; P=.0008) in a multicenter phase 3 trial conducted in China (NCT04560894).[87] An open-label phase 1b study of sintilimab plus the CTLA-4 inhibitor IBI310 is underway in advanced HCC[88] after a similar phase 1b study in advanced non-small cell lung cancer found promising survival benefit in patients with progression after anti–PD-1/-L1 therapy.[89] Resistance to immunotherapy is a growing concern, and this combination had favorable results in the ORIENT-32 trial,[90] with improved median PFS and OS compared with sorafenib.

There are multiple studies investigating combination therapy with immunotherapy and kinase inhibitors. Rulonilimab is being investigated in a phase 2 study to evaluate its safety when combined with lenvatinib and in a phase 3 study to evaluate its efficacy compared with lenvatinib and placebo for advanced HCC (NCT05408221). In a double-blind, multicenter phase 3 study, toripalimab plus lenvatinib (NCT04523493) is being compared with lenvatinib monotherapy and placebo. A similar study combining nofazinlimab and lenvatinib is underway (NCT04194775). An open-label phase 1b/2 trial (NCT04172571) found that combination penpulimab and anlotinib, a multikinase inhibitor targeting VEGFR-1 to -3, c-kit, fibroblast growth factor receptor 1 to 3, and platelet-derived growth factor receptor–α, achieved an ORR of 31% with acceptable toxicity.[91]

Novel Targets and Strategies

Livmoniplimab (ABBV-151) is a monoclonal antibody that binds to the glycoprotein A repetitions predominant, which is expressed on regulatory T cells and activates the transforming growth factor β1 complex. In the ongoing phase 3 LIVIGNO-2 trial (NCT06109272), livmoniplimab combined with the PD-1 inhibitor budigalimab is under evaluation in patients with advanced HCC naive to anti–PD-1 therapy. Although a phase 1

study (NCT03821935)[92] reported an ORR of 33% in patients with HCC naive to anti–PD-1 therapy, enrollment in the HCC cohort was first paused and eventually discontinued as 58.3% of the cohort developed grade 3 or 4 treatment-related adverse events.

The SKYSCRAPER-14 phase 3 trial will evaluate the efficacy of adding tiragolumab to atezolizumab plus bevacizumab. Tiragolumab, a T-cell immune receptor with immunoglobulin and ITIM domains inhibitor, could reduce the risk of ICI resistance, similar to what happens with CTLA-4 inhibition.[57,58,93] In the phase 1b/2 MORPHEUS-Liver study (NCT04524871), this triplet therapy was associated with greater ORR compared with only atezolizumab plus bevacizumab (42.4% vs 11.1%, respectively) as well as longer PFS.[94]

Although most phase 3 trials involve ICI-based systemic therapy, many more co-stimulatory and co-inhibitory receptors may potentially play a role in HCC treatment.[93] Novel agents involved in current and pending phase 3 trials include namodenoson, an A3 adenosine receptor agonist, which was previously shown to have a favorable response in HCC patients with CP-B7 cirrhosis.[95] Despite not providing an OS benefit vs placebo in patients with previously treated advanced HCC and CP-B7 cirrhosis, the cloned arginine-degrading enzyme ADI-PEG 20 is being studied in patients with advanced HCC and high arginine levels after showing survival benefit associated with prolonged arginine depletion[96,97] (NCT05317819). The ALIVE trial (NCT05033522) will investigate AlloStim immunotherapy, an allogeneic T-helper cell 1–like cell therapy, and its ability to downregulate checkpoint molecules in the tumor microenvironment. QL1706, a single bifunctional MabPair product that consists of 2 monoclonal antibodies targeting PD-1 and CTLA-4, will be paired with bevacizumab with or without chemotherapy and compared with sintilimab (NCT05976568).

Future Directions and Clinical Needs

According to preclinical and clinical studies, radiofrequency ablation, microwave ablation, stereotactic body radiation therapy, TACE, and TARE can be combined with immunotherapy to improve HCC outcomes.[58,98] Theoretically, tumor antigens released by locoregional therapy may stimulate antitumor immunity and could act synergistically with immunotherapy. In clinical practice, systemic therapies are often delivered just before or after locoregional therapies, especially in BCLC B patients with infiltrative disease or for local control in BCLC C patients with large intrahepatic tumor burden. However, additional studies are needed to define the ideal sequencing and timing between treatment modalities.

Currently, several phase 3 trials are evaluating combined locoregional and systemic therapies for advanced HCC. A multicenter, randomized phase 3 trial of 338 patients noted superior OS in patients treated with TACE and lenvatinib compared with those treated with lenvatinib monotherapy (17.8 months vs 11.5 months, respectively; $P<.001$).[99] Other trials will examine TACE combined with penpulimab and anlotinib (NCT05344924), TACE and lenvatinib plus stereotactic body radiation therapy in the SEARCH trial (NCT05718232), and TACE combined with lenvatinib and camrelizumab for treatment of unresectable HCC in the LEN-TAC study (NCT05738616). Of note, camrelizumab, apatinib, and FOLFOX (which consists of leucovorin calcium [folinic acid], fluorouracil, and oxaliplatin) will be evaluated for efficacy in advanced HCC (NCT06172205). A phase 1/2 trial that combined yttrium-90 and durvalumab in 24 BCLC B/C patients demonstrated a complete response rate of 29.2% and ORR of 83.3%.[100] Ongoing studies will look to replicate outcomes from other studies showing that patients who underwent curative treatments (surgery, radiofrequency ablation, or percutaneous ethanol injection) and adjuvant immunotherapy experienced longer OS compared with patients who did not receive immunotherapy.[101,102]

Posttransplant Treatment

LT is the ideal curative therapy for HCC, as transplantation not only removes the cancer but also removes the most important risk factor for HCC (ie, cirrhosis). Although originally reserved for patients who fulfilled the Milan criteria, as discussed previously, transplantation is still possible for patients with tumors outside of these criteria, after downstaging using various treatments including surgery, locoregional therapies, or systemic therapies. Although ICIs can also be used for downstaging or bridging therapies, prior immunotherapy could contribute to increased risk of rejection or graft loss and is currently under investigation.[36,103]

Effective downstaging has increased the number of transplants for HCC and thus the number of patients at risk for HCC recurrence.[104,105] Although immunosuppression with calcineurin inhibitors reduces graft rejection, these agents promote cancer cell survival and HCC recurrence.[104,105] The current recommendation is to taper calcineurin inhibitors to the lowest effective dose and to consider leveraging the antitumoral effects of mammalian targets of rapamycin inhibitors such as sirolimus and everolimus.[105]

Recurrence of HCC after transplant represents a leading cause of death. Thus, post-LT surveillance is vital.[104,106] Data are lacking on the best frequency, duration, and imaging modality to maximize patient outcomes;

however, close surveillance is associated with early detection and better prognosis. Recurrence is most common within the first 2 to 3 years posttransplant. Surveillance with AFP measurement and cross-sectional imaging is performed every 3 to 6 months up until 5 years.[106] Patients with high-risk features such as micro- or macrovascular invasion or tumor burden significantly exceeding the Milan criteria should receive more intensive surveillance.

If HCC does recur, treatment options are similar to the options for de novo HCC. Historically, surgical treatments have achieved the best survival outcomes in patients with limited tumor burden.[104,105] In patients ineligible for surgery or locoregional treatments, systemic therapies (eg, tyrosine kinase inhibitors) have shown some promise. Despite this, these systemic therapies are difficult to tolerate owing to significant drug interactions with immunosuppressants. There is potential for ICI therapy in post-LT HCC recurrence.[104,105] However, the same mechanisms enhancing the antitumoral immune response may lead to rejection and subsequent graft loss.[105,107-109] Unlike most patients with de novo HCC, post-LT patients typically have normal liver function and do not have cirrhosis. Those who have undergone recent LT have increased risk of rejection compared with those with a remote history of LT.[110] Thus, ICI therapy should be considered only if all other treatment options have been exhausted, and the patient understands the increased risk and implications of rejection. There is a pressing need to develop therapies that meet the specific needs of this unique population.[103]

Conclusion

The management of HCC has evolved since the approval of sorafenib, with even more treatments on the horizon, offering hope to patients. This comprehensive article covered a fraction of the targets, trials, and therapies. Treatment of HCC is incredibly complex; individuals with multifocal disease may have multiple affected pathways, which may complicate application of novel targeted therapies. Additionally, HCC mainly affects patients with cirrhosis, which impacts eligibility for and tolerance of treatments. As treatment evolves, it will be critical to determine the best treatment option, sequence, and/or combination for each patient and/or population.

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