Systemic Therapy for Hepatocellular Carcinoma: Current Updates and Outlook

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Abstract: Hepatocellular carcinoma (HCC) has emerged as the culprit of cancer-related mortality worldwide with its dismal prognosis. In recent years, ground-breaking progress has been made in systemic therapy for HCC. Targeted therapy based on specific signaling molecules, including sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab, has been widely used for advanced HCC (aHCC). Immunotherapies such as pembrolizumab and nivolumab greatly improve the survival of aHCC patients. More recently, synergistic combination therapy has boosted first-line (atezolizumab in combination with bevacizumab) and second-line (ipilimumab in combination with nivolumab) therapeutic modalities for aHCC. This review aims to summarize recent updates of systemic therapy relying on the biological mechanisms of HCC, particularly highlighting the approved agents for aHCC. Adjuvant and neoadjuvant therapy, as well as a combination with locoregional therapies (LRTs), are also discussed. Additionally, we describe the promising effect of traditional Chinese medicine (TCM) as systemic therapy on HCC. In this setting, the challenges and future directions of systemic therapy for HCC are also explored.

Keywords: hepatocellular carcinoma, targeted therapy, immunotherapy, traditional Chinese medicine, locoregional therapies, adjuvant therapy, neoadjuvant therapy

Introduction

Hepatocellular carcinoma (HCC), as the most common type of liver cancer, remains a major public-health challenge worldwide.1,2 Because of risk factors for HCC, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), excessive alcohol consumption, cigarette smoking, diabetes, obesity, and dietary habits that are modifiable, its incidence is growing annually.3,4 And it is predicted that by 2025, the number of newly diagnosed HCC cases will be over 1 million annually.5

The management of HCC is mainly based on a staging system for liver cancer with regard to tumor size and number, tumor location, liver function reserves (Child–Pugh Classifications), and performance status (PS).5,6 Recently, the Barcelona Clinic Liver Cancer (BCLC) system has been commonly adopted in clinical studies and practice, which provides the most effective means for assessing patient prognosis and guiding treatment.7,8 For patients with early- or intermediate-stage HCC, hepatectomy, liver transplantation (LT), locoregional therapies (LRTs) such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radiation therapy are curative treatments that improve survival.9,10 However, up to 70% of HCC cases who received curative surgery or ablation therapy experienced recurrence within 5 years.11 In comparison, systemic therapies are the only treatments available to improve survival for patients with advanced HCC (aHCC).12 Nevertheless, the development and efficacy of systemic therapy has been challenging.13 Coupled with the dismal fact that more than half of HCC cases are diagnosed at an advanced or incurable stage, this disease has been the second most common cause of cancer mortality, with a 5-year survival rate of only 3%.1,3

Gratifyingly, substantial progress has been made in understanding the mechanisms underlying hepatocarcinogenesis and progression, as well as in the development of novel drugs to regulate specific steps of these mechanisms, over several decades.14 Since first-line sorafenib, an oral multi-tyrosine kinase inhibitor (TKI), was first demonstrated to prolong the...
survival of patients with aHCC in 2007, molecular-targeted agents have made tremendous strides in the enrichment of systemic therapy.\textsuperscript{15} Tyrosine kinase inhibitors (lenvatinib, regorafenib and cabozantinib) and a vascular endothelial growth factor (VEGF) receptor inhibitor (ramucirumab) have been established as first- or second-line therapies for patients with aHCC.\textsuperscript{16–19} Recently, immune checkpoint inhibition, which mainly modulates programmed cell death-1 (PD-1), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and their ligands (programmed cell death ligand 1/2 [PD-L1/2] and B7-1/2, respectively) has developed into a potent anti-cancer strategy.\textsuperscript{20} Anti-PD-1 antibodies (nivolumab and pembrolizumab), as well as the combination of immune checkpoint inhibitors (ICIs) and VEGF inhibitors (atezolizumab and bevacizumab, nivolumab and ipilimumab), have been approved for the treatment of aHCC.\textsuperscript{21–23}

Importantly, a growing body of preclinical studies and clinical trials based on systemic therapies are ongoing globally. Despite recent advancements, there remain some critical questions and challenges regarding the management of HCC. In this article, we summarized the systemic therapy relying on mechanisms of hepatocarcinogenesis and progression, and then elaborate the practice treatment protocols for HCC applied to clinical practice. In light of this, we finally discuss the challenges and directions in the development of systemic therapy for HCC.

### Treatment Advances in Systemic Therapy

#### Molecular Targeted Therapy

##### Targeting Molecular Pathways in HCC

The pathophysiology of HCC is known to be a complex multistep process associated with aberrant molecular events and diverse signaling pathways.\textsuperscript{2} Currently, the most concerning molecular signaling pathway is tyrosine kinase–related signaling mainly related to cell survival, proliferation, differentiation, migration, and angiogenesis. Depending on where they function, tyrosine kinases can be divided into receptor tyrosine kinases (RTKs) and non-RTKs.\textsuperscript{24} Receptor tyrosine kinases transduce extracellular signals into cells, while non-RTKs regulate intracellular signal transduction and molecular communication.\textsuperscript{24,25} Furthermore, a large number of receptors exist in the receptor tyrosine kinase group, such as VEGF receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor, hepatocyte growth factor receptor (HGFR), TIE2, FLT3, and RET.\textsuperscript{26,27} Once the above-mentioned receptor binds its cognate ligand, the latter is phosphorylated and subsequently recruits intracellular signaling molecules.\textsuperscript{24} These recruited molecules subsequently activate multiple downstream signaling pathways, such as the Ras/Raf/MEK/ERK and phosphoinositide-3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), inducing carcinogenesis, invasion, and metastasis in an oncogenic setting.\textsuperscript{25} Therefore, besides extracellular growth or angiogenic factors and their receptors, intracellular signaling molecules represent potential molecular targets.

##### First-Line Therapy

**Sorafenib**

Sorafenib is an oral multi-TKI, and holds dual anti-proliferative and anti-angiogenic effects by blocking Raf/MEK/ERK and JAK/STAT, and inhibiting VEGFRs, PDGFR-β, c-Kit, FLT3, and RET.\textsuperscript{28} The sorafenib HCC Assessment Randomized Protocol (SHARP) trial revealed the benefit of sorafenib for patients with aHCC in 2007 and made it as a first-line treatment of aHCC firstly approved by the Food and Drug Administration (FDA).\textsuperscript{15} In the SHARP trial, 602 aHCC patients without previous systemic treatments were randomly allocated to receive sorafenib or placebo, presenting a significant improvement in overall survival (OS) (10.7 vs 7.9 months; hazards ratio [HR] = 0.69; P < 0.001) and time to radiologic progression (5.5 vs 2.8 months; HR = 0.58; P < 0.001). Similar findings were also found in an Asia-Pacific (AP) trial with 226 patients, showing an improved OS (6.5 vs 4.2 months; HR = 0.68; P = 0.014) and time-to-progression (TTP; 2.8 vs 1.4 months; HR = 0.57; P = 0.0005).\textsuperscript{29}

However, some patients underwent dose reductions or even treatment interruptions due to sorafenib-related adverse events (AEs) during the trial.\textsuperscript{15} The most frequent AEs were hand-foot skin reaction (HFSR), desquamation, rash, fatigue, weight loss, hypertension as well as gastrointestinal symptoms such as anorexia, nausea, abdominal pain, and diarrhea.\textsuperscript{15,29} Therefore, coping with AEs is pivotal to improve the efficacy of sorafenib. A randomized controlled trial conducted by Ren and colleagues showed that urea-based creams improved HFSR-associated quality of life and medication compliance during sorafenib treatment.\textsuperscript{30} Paradoxically, there exists a significant correlation between AEs...
and the survival of patients with aHCC treated with sorafenib, and skin-related AEs such as HFSR may act as potential biomarkers of sorafenib efficacy.\textsuperscript{31,32} Thus, caution should be exercised while managing AEs.

Interestingly, a greater OS was apparent in the SHARP trial compared with the AP trial (10.7 vs 6.5 months). Based upon varied etiologies of HCC, the different subgroups of patients in both trials were further studied. We found that the percentages of patients with HBV in the SHARP and AP trial were 19% and 71%, respectively; while the percentages of patients with HCV were 29% and 11%, respectively. Subgroup analyses showed a better survival benefit from sorafenib in patients with HCV compared to those with HBV.\textsuperscript{33,34} A consistent result was also reported that the TTP of patients with HCV was significantly longer than that of patients with HBV (6.5 vs 4.0 months, respectively, P = 0.05).\textsuperscript{35} Together with this result, a meta-analysis of Phase III trial results confirmed that there was an improved OS for patients with HCV rather than HCV and the hepatitis status may be a dependent risk factor for the effect of sorafenib.\textsuperscript{36} Furthermore, improved OS from sorafenib treatment was achieved mainly by inhibiting the rate of tumor growth and deterioration of liver function among patients with HCV.\textsuperscript{37} Mechanistically, sorafenib suppresses the high activity of Raf-1 sustained by HCV-1 core protein, preventing the mitosis and oncogenesis of HCV-infected liver cells.\textsuperscript{38} Besides HCV infection, a low neutrophil-to-lymphocyte ratio (NLR), and the liver-confined disease without extrahepatic spread are predictive factors of a superior sorafenib response.\textsuperscript{39} Recently, the eligibility criteria of patients for treatment with sorafenib require that patients must have a good liver function reserve, commonly Child–Pugh A. The study revealed that patients with Child–Pugh B had a shorter OS and a higher incidence of AEs than those with Child–Pugh A.\textsuperscript{40} Although no clear limitation exists regarding sorafenib for patients with Child–Pugh B, special attention should be paid to AEs when treating individuals with poor liver functional reserve.\textsuperscript{41,42}

Lenvatinib

Lenvatinib is also an oral multi-TKI that exerts an anti-tumor effect by targeting VEGFR1-3, FGFR1-4, PDGFR-α, RET and c-Kit, and has been approved as first-line treatment by the REFLECT trial in 2018.\textsuperscript{43} In the REFLECT trial, 954 eligible patients, mainly from Asia, were randomly assigned to lenvatinib (n=478) or sorafenib (n=476) treatment groups.\textsuperscript{44} The lenvatinib treatment group was found to show no noticeable improvement compared with the sorafenib group regarding the primary endpoint (OS, 13.6 vs 12.3 months). However, lenvatinib treatment caused a higher objective response rate (ORR) by modified Response Evaluation Criteria in Solid Tumors (24.1% vs 9.2%), and a longer progression-free survival (PFS) (7.4 vs 3.7 months) and TTP (8.9 vs 3.7 months). Further, the tumor shrinkage and necrotizing effect in lenvatinib treatment group was noted.\textsuperscript{16} Thus, the higher ORR of lenvatinib may increase the tolerability and adherence to therapy of aHCC patients. On the other hand, lenvatinib resulted in HCC downstaging to achieve surgical resection. A post hoc analysis of data from the REFLECT trial indicated a greater efficacy of lenvatinib than sorafenib as assessed by OS, ORR and PFS regardless of liver function, in line with the above-mentioned results.\textsuperscript{45} In terms of AEs, patients who received lenvatinib experienced more serious AEs than those who received sorafenib, such as proteinuria, anemia, dyspnoea, hypertension, thrombocytopenia and hypothyroidism.\textsuperscript{16} Therefore, lenvatinib is also more prone to treatment discontinuation (40% vs 32%) due to AEs. This might partially account for the shorter treatment duration (5.7 months) than TTP in lenvatinib treatment group.\textsuperscript{16} The inclusion criteria of the REFLECT trial required a Child-Pugh A hepatic function, and patients with ≥50% liver tumor occupation as well as obvious invasion of the bile duct and/or the main portal vein were excluded.\textsuperscript{16} Vogel et al argued that the baseline liver function was a significant prognostic factor, and a better liver function may be predictive of a higher efficacy of lenvatinib or sorafenib.\textsuperscript{45} Further subgroup analyses showed that patients with HBV infection and a high alpha-fetoprotein (AFP) level in serum (>200 ng/mL) may benefit more from lenvatinib, which was quite different from sorafenib treatment.\textsuperscript{16,43,44} In addition, the evaluation of health-related quality of life (HRQOL) during treatment demonstrated that to some extent, lenvatinib delayed functional deterioration, such as fatigue, pain and diarrhea, supporting the use of lenvatinib in clinical domains.\textsuperscript{46,47} With respect to the cost-effectiveness of treatment, lenvatinib may also achieve a better efficacy at a lower cost than sorafenib.\textsuperscript{48}

Second-Line Therapy

Regorafenib

In 2017, regorafenib was approved by the FDA as second-line therapy for patients with HCC progression during
Hence, regorafenib, as a fluorinated analog of sorafenib, shares a broader spectrum of molecular targets (such as VEGFR 1–3, PDGFR, FGFR, TIE2, c-Kit, RET, Raf-1, and BRAF) and performs more robust anti-proliferative and anti-angiogenic effects than sorafenib. The double-blind RESORCE phase III trial randomized 573 patients with sorafenib-refractory aHCC to regorafenib (n=379) and placebo (n=194) groups. Regorafenib significantly prolonged OS compared with the placebo (10.6 vs 7.8 months; HR = 0.63; P < 0.0001). Moreover, PFS (3.1 vs 1.5 months; HR = 0.46; P < 0.001) and TTP (3.2 vs 1.5 months; HR = 0.44; P < 0.001) were also significantly extended in regorafenib treatment, compared with placebo. In addition, this trial further demonstrated that regorafenib showed a better ORR (10.6% vs 4.1%, P = 0.005) as well as disease control rate (DCR) (65.2% vs 36.1%, P = 0.001) than placebo. Subsequently, the efficacy of regorafenib also arose in all relevant subgroups such as region, portal vein thrombosis, and serum AFP levels. Also, an exploratory analysis derived from the RESORCE trial described that regorafenib clinically benefited aHCC patients, independent of their last sorafenib dose and the stage of their disease progression with prior sorafenib treatment. However, the inclusion criteria of the RESORCE trial were highly strict, and only patients who not only had documented radiological progression of HCC after tolerating at least 400 mg of sorafenib per day for 20 of the last 28 days, but also preserved good liver function (Child–Pugh A) were enrolled. This determines regorafenib is not suitable for all post-sorafenib patients with aHCC in clinical practice. Kim et al also concluded that patients with Child–Pugh B had a poorer clinical prognosis and higher incidences of severe AEs during regorafenib treatment compared to those with Child-Pugh A. Hence, cautious patient selection is crucial, especially with respect to liver function.

There were AEs similar to sorafenib during regorafenib treatment, including HFSR, fatigue, hypertension, diarrhoea as well as increased serum aspartate aminotransferase (AST) level and bilirubin. Moreover, the rates of AEs were largely similar regardless of the last sorafenib dose (800 mg/day). Nevertheless, some serious AEs, such as HFSR and increased AST level, may result in treatment discontinuation in regorafenib and placebo groups (10% vs 4%). Interestingly, HFSR related to regorafenib treatment correlated with an improved OS, as previously shown for sorafenib. Remarkably, a further analysis pointed out that the sorafenib–regorafenib sequential therapy significantly outperformed the sorafenib–placebo therapy to improve OS (26.0 vs 19.2 months). Additionally, Bruix et al found that the patients with an AFP response could experience an improved OS from regorafenib than those without an AFP response. Thereby, patient selection based on single or multiple good biomarkers may maximize the efficacy of regorafenib. Another exploratory study identified that plasma proteins (angiopoietin 1, cystatin B, the latency-associated peptide of transforming growth factor-β [TGF-β] 1, oxidized low-density lipoprotein receptor 1, and C-C motif chemokine ligand 3) were negatively correlated with increased OS after regorafenib treatment, while the converse was true for plasma miRNAs (miR-30A, −122, −125B, −200A, −374B, −15B, −107, −320, and −645). These results may guide the individualized prescription of regorafenib for aHCC in the clinic, although the mechanisms involved have yet to be established.

**Cabozantinib**

Cabozantinib is another oral multi-TKI targeting VEGFR 1–3, MET, RET, KIT, TIE2, FLT3, c-MET, and AXL, due to which cabozantinib has also been shown to abrogate sorafenib-resistance by suppressing tumor cell proliferation and angiogenesis. Based on the CELESTIAL trial, cabozantinib was recommended as second-line treatment for aHCC patients in January 2019. Patients with aHCC who suffered from disease progression when receiving at least one systemic regimen including sorafenib were randomly assigned into cabozantinib and placebo treatment group. The trial showed a significantly longer OS (10.2 vs 8.0 months; HR = 0.76, P < 0.001) and PFS (5.2 vs 1.9 months; HR = 0.44; P < 0.001) in cabozantinib than placebo groups. Moreover, cabozantinib resulted in a significant improvement in ORR (4% vs 0.4%, P = 0.009) and DCR (64% vs 48%, P < 0.001). These clinical outcomes were evaluated based on albumin–bilirubin (ALBI) in the CELESTIAL trial. The patients in the cabozantinib cohort had longer OS as well as PFS than those in placebo cohort, regardless of ALBI grades. However, subgroup analysis of cabozantinib cohort revealed that outcomes were significantly better in the subgroup of ALBI grade 1 than grade 2. In addition, subgroup analysis indicated that cabozantinib was more favorable for the patients with extrahepatic spread, a high serum concentration of AFP (>400 ng/mL), or good PS (0–1). In terms of etiologic factors, cabozantinib tended to achieve better therapeutic
effects in cases with HBV than those with HCV, which was consistent with lenvatinib rather than sorafenib. Hypertension, palmar–plantar erythrodysesthesia (PPE), HFSR, diarrhea, fatigue, and elevated AST were most frequently observed during cabozantinib treatment. Similar to sorafenib and regorafenib, a negative relationship existed between AEs and survival outcomes. Patients with severe hypertension or PPE from cabozantinib therapy had better OS and PFS than those without these two AEs. Despite a relatively high incidence of serious AEs (68%), the discontinuation of treatment due to AEs occurred in only 16% of cases treated with cabozantinib. As previously described, cabozantinib has been shown to play a major part in addressing the c-MET-induced sorafenib resistance. Together, these results suggest that cabozantinib may be a well-tolerated oral drug for the aHCC patients with intolerance to sorafenib or other therapies.

Of patients enrolled in the CELESTIAL trial, 72% who had previously received only sorafenib and 28% received two systemic therapies, suggesting that cabozantinib may act as second- or third-line treatment. For patients with prior sorafenib, cabozantinib still prolonged OS from 7.2 to 11.3 months, irrespective of the duration of previous sorafenib treatment. More interestingly, sorafenib–cabozantinib sequential therapy appeared to improve PFS more than sorafenib–regorafenib sequential therapy, albeit of a similar OS between both sequential therapies. Nevertheless, cost-effectiveness analysis showed that cabozantinib was a poorly cost-effective drug as a second-line treatment for aHCC. Thus, modestly controlling costs seems to favor the clinical use of cabozantinib. Additionally, the CELESTIAL trial revealed that low levels of MET, GAS6, HGF, ANG2, VEGF-A, as well as Interleukin (IL)-8, and high levels of insulin-like growth factor 1 in serum were associated with a good prognosis of aHCC patients treated with cabozantinib. However, the translation of these serum biomarkers into the clinic has yet to be achieved.

Ramucirumab

Unlike TKI, ramucirumab is an intravenous recombinant monoclonal antibody against VEGFR-2 that blocks the ligand–receptor interaction and its downstream signaling to exert an antitumor effect. Ramucirumab did not achieve a significant improvement of OS for the patients with prior sorafenib regimen compared to placebo in the Ramucirumab After Sorafenib in Patients With Advanced Hepatocellular Carcinoma (REACH) trial (9.2 vs 7.6 months, HR = 0.87, P = 0.14). However, a subgroup analysis substantiated that the patients with an elevated AFP (≥400 ng/mL) obtained a better survival benefit from ramucirumab treatment than those with AFP<400 ng/mL (OS, 7.8 vs 4.2 months; HR = 0.67; P = 0.006). The REACH-2 trial was subsequently conducted in aHCC patients with AFP ≥400 ng/mL, and showed that ramucirumab produced a longer OS (8.5 vs 7.3 months; HR = 0.71; P = 0.0199) and PFS (2.8 vs 1.6 months; HR = 0.45; P < 0.0001) than placebo with no difference in ORR (5% vs 1%, P = 0.1697). Furthermore, ramucirumab also potently improved DCR (59.9% vs 38.9%; P = 0.0006) compared to placebo. On the basis of REACH and REACH-2 trials, a pooled efficacy analysis also favored the above results that aHCC patients with AFP ≥400 ng/mL enjoyed a better outcome than those with placebo (OS 8.1 vs 5.0 months; HR = 0.69; P = 0.0002).

Ramucirumab was shown to be well tolerated and have a manageable safety profile in aHCC patients with AFP ≥ 400 ng/mL as well as a prior sorafenib treatment. The grade 3 or worse AEs related to ramucirumab, including hypertension, hyponatremia and increased AST, were not common. In addition, treatment discontinuation from emergent AEs was observed in only 9.5% of patients receiving ramucirumab. It is well known that the Child–Pugh classification plays a pivotal role in evaluating severity of liver disease and prognosis of a patient with liver disease. Thus, several subgroup analyses based on REACH and REACH-2 trials were carried out to assess the relationship between several variables of the Child–Pugh classification (ALBI grade and ascites) and outcomes of aHCC patients during ramucirumab treatment. Patients with ABLI grade 1 or better had a longer OS than those with grade 2 in ramucirumab arm, while a great survival benefit from ramucirumab was obtained in all of patients irrespective of ascites. More importantly, ramucirumab is the first FDA approved drug for aHCC patient depending on the biomarker-selected group (AFP≥400ng/mL). However, the molecular mechanism underlying the ramucirumab selective trend is still unknown.

Other Targeted Agents

As is well known, hepatocarcinogenesis and its subsequent progression is a complex multistep process, accompanied with the sophisticated crosstalk of numerous signaling pathways. And a large number of agents targeting signaling
molecules have been emerging over recent decades. In light of this, these targeted agents, apart from drugs approved by FDA, will be briefly elucidated based on where they function directly.

**Agents Targeting the Extracellular Space or Membrane**

As already mentioned above, RTKs transduce extracellular signals into the cell and subsequently regulate a variety of pathophysiological process, particularly in hepatocarcinogenesis. These RTKs include VEGF, FGFR, PDGFR, EGFR, HGFR, TIE2, FLT3, and RET, among others. To date, targeting these receptors has been shown to be a powerful treatment modality. In a randomized multi-center Phase II–III trial clinical trial, donafenib, as a deuterated sorafenib derivative, brought a significant therapeutic advantage over sorafenib (OS, 12.1 vs 10.3 months; HR = 0.831; P = 0.0245) with a lower incidence of serious AEs (grade ≥3) than sorafenib (38% vs 50%; P = 0.0018) in aHCC patients from China.\(^{75,76}\) This exciting result thereby renders it as the first monotherapy agent due to OS superior to sorafenib for aHCC, with a favorable safety and tolerability. Yet, it remains to be buttressed by an international multi-center clinical trial. Similarly, another oral multi-TKI, nintedanib (BIBF 1120), was documented to have a similar OS to sorafenib in aHCC cases (10.2 vs 10.7 months; HR = 0.94), while it may lead to different but generally manageable AEs.\(^{77}\)

Unfortunately, the development of some novel targeted agents have been halted before entering into clinical application. The clinical trial might not be further conducted due to the low efficacy of several agents, including dovitinib,\(^{78}\) brivanib,\(^{79}\) vandetanib,\(^{80}\) and erlotinib.\(^{81}\) In addition, the terrible safety frequently erodes the feasibility of some agents in clinical practice, such as linifanib (ABT-869)\(^{82}\) and sunitinib.\(^{83}\) Nevertheless, the combination of these agents significantly improved the outcomes of aHCC patients. The combination of sunitinib and TACE prolonged OS of aHCC patients in comparison to TACE plus placebo (20.5 vs 25 months).\(^{84}\)

In addition to RTKs, a variety of non-RTKs also exist in cellular membrane, like the receptors binding to TGF-β which are serine/threonine kinases.\(^{85}\) TGF-β signaling pathway was documented to promote cancer progression in the late phase.\(^{86}\) Thus, targeting TGF-β pathway is still a potential strategy for the management of HCC. Galunisertib (LY2157299), a small molecule inhibitor of TGF-β1 receptor I, was identified to provide a longer OS for aHCC patients with AFP or TGF-β responders.\(^{87}\) Moreover, several glycoproteins that bind to the cellular membrane may be promising targets in treatment regimens for HCC. For instance, endoglin (CD105), as a co-receptor for TGF-β, is strongly associated with angiogenesis, inflammation, and fibrogenesis in hepatocarcinogenesis.\(^{88}\) Studies revealed that TRC105 alone, as an anti-CD105 monoclonal antibody, inhibited tumor angiogenesis and exhibited a significant effect on ORR (25%) of HCC combining with sorafenib.\(^{89}\) Recently, a multi-center Phase II study is undergoing to evaluate this effect.

**Agents Targeting the Intracellular Space**

Several important downstream signaling pathways located inside of cell play crucial roles in tumor development. The PI3K/AKT/mTOR pathway may be involved in vascular invasion, intrahepatic metastasis, and sorafenib resistance.\(^{90,91}\) SF1126 is a novel dual target inhibitor against PI3K/BRD4 and Ras/Raf/MAPK pathways,\(^ {92}\) and had a significant antitumor effect as either a single agent or in combination with sorafenib.\(^ {93}\) In terms of mTOR inhibitors, everolimus alone or combined with sorafenib rarely showed better survival benefits, despite the strongly reversing effects of everolimus on sorafenib resistance in aHCC.\(^ {94,95}\) In HCC, and associated with a poor prognosis,\(^ {96,97}\) MEK inhibitors (selumetinib and refametinib) and sorafenib appear to have a synergistic effect on HCC.\(^ {98,99}\) Likewise, sorafenib also exerted a synergistic effect with several small molecule inhibitors targeting nuclear signaling molecules, including resminostat (a histone deacetylases inhibitor),\(^ {100}\) palbociclib (PD-0332991),\(^ {101}\) and ribociclib (cyclin-dependent kinase 4/6 inhibitors).\(^ {102}\) Nevertheless, OPB-111077 (STAT3 inhibitor)\(^ {103}\) and CT-707 (YAP signaling inhibitor)\(^ {104}\) demonstrated limited efficacy only in vivo or in vitro HCC models. Further clinical trials remain to be required to validate the efficacy of the agents.

**Cytotoxic Chemotherapy**

Cytotoxic chemotherapy for aHCC has been challenging since several decades. Few clinical trials demonstrate that cytotoxic agents provide significant survival benefits for aHCC patients, particularly in those with cirrhosis and poor
hepatic function that may increase the toxicity of cytotoxic drugs and the difficulty of delivery to HCC lesions.\textsuperscript{105,106} Moreover, HCC cells frequently express intrinsic drug resistance via drug-resistant genes such as \textit{MDR1} gene, resulting in a RR below 25% of cytotoxic agents in aHCC patients.\textsuperscript{107,108} Considering the cost and availability of treatment regimens for aHCC, cytotoxic chemotherapy is still an alternative in less-developed countries and regions.\textsuperscript{109} More recently, emerging novel chemotherapeutic agents and combination regimens were shown to greatly improve the survival of aHCC patients.

**Single-Agent Chemotherapy**

Doxorubicin rarely increases survival benefits in aHCC patients with a low ORR (< 20%), although numerous studies and clinical trials have been conducted to assess its efficacy.\textsuperscript{110,111} A randomized controlled trial demonstrated that aHCC patients did obtain a longer OS after doxorubicin treatment compared to those without (10.6 vs 7.5 weeks; \( \text{P} = 0.036 \)). However, doxorubicin led to serious AEs, such as neutropenia and cardiotoxicity. And the mortality related to AEs was up to 25%.\textsuperscript{112} Capecitabine, as a prodrug of 5-fluorouracil (5-FU), has been shown to be a standard therapy for HCC with its good antitumor activities and low toxicity.\textsuperscript{113} For aHCC patients with who discontinued treatment owing to disease progression or AEs, metronomic capecitabine may be a potent second-line systemic therapy, extending OS to 9.5 months from 5.0 months of the control.\textsuperscript{114,115} Remarkably, capecitabine also reduced the risk of HCC recurrence and even improved the survival of such patients after surgery as one of several adjuvant therapies.\textsuperscript{116,117} Nonetheless, other single agents, such as gemcitabine,\textsuperscript{118} oxaliplatin,\textsuperscript{119} and irinotecan,\textsuperscript{120} were only used in aHCC patients with a good PS and liver function, for which these agents may exist intolerant toxicity or their antitumor effect were just dependent on a small sample study.

**Combination Chemotherapy**

Currently, combination chemotherapy has been well recognized to improve the survival of aHCC patients in comparison to single-agent treatment. A multicenter, open-label, randomized, phase III study (the EACH study) from China demonstrated that aHCC patients with the FOLFOX4 regimen (fluorouracil, leucovorin, and oxaliplatin) showed a better PFS and ORR than those with doxorubicin alone, whereas the median OS of this study was not significantly changed (6.4 vs 4.97 months; \( \text{HR} = 0.80; \text{P} = 0.07 \)).\textsuperscript{121} However, OS in FOLFOX4 arm tended to increase and presented a significant advantage over that in the single-agent treatment arm as the follow-up continued (5.9 vs 4.3 months; \( \text{HR} = 0.74; \text{P} = 0.03 \)).\textsuperscript{122} The FOLFOX4 regimen had also a relatively well tolerance in treatment of Chinese aHCC patients. Although a higher occurrence of hematological toxicity (neutropenia, leukopenia, and thrombocytopenia) was observed in the FOLFOX4 treatment group, the difference was not significant.\textsuperscript{123} Therefore, the FOLFOX4 regimen was approved as an alternative strategy for aHCC in China. As aforementioned, sorafenib was not recommended for aHCC patients with Child–Pugh B or more severe, particularly in cirrhosis patients. However, oxaliplatin-based chemotherapy appears to exert strong anti-tumor role for these patients. An exploratory study observed that aHCC patients with Child–Pugh B cirrhosis did not show a compromising OS (5.5 vs 4.0 months; \( \text{P} = 0.19 \)) and PFS (3.0 vs 2.4 months; \( \text{P} = 0.42 \)) compared to those with Child–Pugh A in the gemcitabine plus oxaliplatin (GEMOX) regimen, without more AEs like thrombocytopenia and peripheral neuropathy.\textsuperscript{123} Thus, GEMOX was feasible and tolerated for aHCC patients who were ineligible for sorafenib due to Child–Pugh B cirrhosis. More than that, GEMOX regimen was also confirmed to act as a second-line therapy in aHCC patients after failure of sorafenib, with 8.3 months of OS and 3.1 months of PFS, despite the lack of control group.\textsuperscript{124} A prospective study remains to be required to validate this conclusion. Of note, GEMOX regimen was detected to induce tumor sharp shrinking and downsizing, providing a secondary local therapy for 8.5% of the patients without local therapy option initially in the multicenter AGEO study.\textsuperscript{125}

Several other platinum-based regimens, such as XELOX (oxaliplatin plus capecitabine),\textsuperscript{126} PIAF (cisplatin, interferon, doxorubicin, and 5-FU),\textsuperscript{127} GP (gemcitabine plus cisplatin),\textsuperscript{128} and cisplatin plus capecitabine\textsuperscript{129} were mostly explored in phase II trials for aHCC treatments. It is noteworthy that oxaliplatin-based regimens seem to show a superiority over cisplatin-based regimens with a less toxicity profile (toxicity-related mortality rate: less than 3% vs 9%). In light of this, a systematic review and pooled analysis indicated that GEMOX combination may exert better antitumor activities than other oxaliplatin-based regimens, with FOLFOX4 regimen not included.\textsuperscript{130} Given that all of
these results are based on small scale or single arm studies, such chemotherapy regimens are just alternative options in aHCC cases with good PS as well as the infeasibility of sorafenib owing to liver function or economic status.

**Immunotherapy**

HCC is confirmed to be a strongly immunogenic tumor showing potential anticancer immunity.\(^{131}\) Disappointingly, the impaired antigen recognition and presentation process, as well as the immunosuppressive tumor microenvironment (TME) orchestrated by tumor and stromal cells, assist HCC cells to escape from this anticancer immunity.\(^{132}\) Tumor-associated antigens (TAAs) are recognized and then eliminated by cytotoxic T-lymphocytes (CTLs) only after they are processed and presented by major histocompatibility complex class I (MHC-1).\(^{133}\) Clinical findings revealed that cytokines (IL-1, −4, and −5) were upregulated in aHCC, and closely associated with vascular invasion and distant metastasis.\(^{134}\) Alterations in these cytokines may lead to a higher ratio of CD4+ to CD8+ T cells and a lower expression of MHC-1, preventing TAs from being recognized by CTLs and inducing immune escape.\(^{135}\) Moreover, myeloid-derived suppressor cells (MDSCs) incur immune tolerance by impeding T-cell activation and upregulate regulatory T cells (Tregs) via the release of immunosuppressive factors (IL-10 and TGF-β).\(^{136}\) In turn, Tregs can also prevent immune surveillance against HCC with negative regulatory immune activity.\(^{137}\) In addition, as immune suppressor cells, M2-polarized tumor-associated macrophages facilitate an immunosuppressive TME.\(^{138}\) The upregulation of co-inhibitory lymphocyte signals also acts as a crucial role in the immunosuppressive TME. And these signals include immune checkpoint ligands, such as PD-1, CTLA-4, lymphocyte-activation gene 3 (LAG3), T-cell immunoglobulin, mucin domain containing-3 (TIM-3), and their receptors.\(^{139}\) Furthermore, other machinery of immune evasion also exists, including up-regulated levels of tolerogenic enzymes, the presence of a metabolically unfriendly milieu for immune cells, and the attenuated Ig-mediated opsonization.\(^{139}\) Any attempt to address these barriers in order to eliminate tumor cells through the host immune system conceives a promising immunotherapy.

**Second-Line Therapy**

**Nivolumab**

Nivolumab is the first fully-humanized Ig G4 monoclonal antibody against PD-1, restoring host immune activity against tumor cells by the competitive blockade of PD-1 immune checkpoint signaling.\(^{140}\) In the phase I/II Checkmate 040 trial, nivolumab was demonstrated to provide a substantial ORR of 15–20% and DCR of 58–64% for aHCC patients regardless of prior therapies like sorafenib, with a manageable safety profile. Importantly, the aHCC patients with prior sorafenib treatment still have an encouraging ORR (19%) and OS (13.2 months) in nivolumab treatment.\(^{140}\) Based on these results, nivolumab was approved by the FDA as a second-line drug for aHCC patients. Thereafter, a randomized multicenter phase III study (Checkmate 459) was conducted to compare nivolumab with sorafenib as first-line therapy in aHCC patients without systemic therapy.\(^{141}\) Nivolumab was not inferior to sorafenib regarding mean OS (16.4 vs 14.7 months; HR = 0.85; P = 0.0752), although OS did not reach the predefined standard of statistical significance (HR = 0.84, P = 0.0419). Furthermore, there was a better ORR in nivolumab group than sorafenib group (15% vs 7%). Additionally, nivolumab also showed a less toxic profile than sorafenib, with a lower incidence of grade 3/4 treatment-related AEs (22% vs 49%) such as rash, diarrhea, pruritus, and other immune-related diseases.\(^{141,142}\) More recently, some studies also compared the efficacy and safety of nivolumab with regorafenib in aHCC patients after sorafenib failure and demonstrated a better ORR and lower treatment-associated AEs in nivolumab group than those in regorafenib group.\(^{143,144}\) Therefore, nivolumab may serve as a first-line or second-line drug for such patients. Further analysis of CheckMate 040 Cohort 5 suggested that nivolumab might be suitable for aHCC patients with Child-Pugh B.\(^{145}\) However, such patients showed poor clinical survival compared to those with Child–Pugh A, with a short OS and low ORR.\(^{146,147}\) Surprisingly, the sub-analyses of CheckMate-040 revealed that aHCC patients treated with nivolumab underwent the disease progression, but had a nonconventional benefit.\(^{148}\) It indicates that the reliable response biomarkers for nivolumab is of importance for evaluating clinical outcome. A handful of biomarkers are currently identified to be associated with an improved survival and response in nivolumab treatment, such as PD-1 and PD-L1 expression,\(^{141,149}\) a good AFP response,\(^{150}\) inflammatory cytokines (CD3 and CD8)\(^{149}\) and peripheral blood mononuclear cells (effector T cells and nonclassical monocytes).\(^{151}\) This algorithm remains yet to be confirmed in some large prospective studies.
Pembrolizumab
Similarly, another monoclonal PD-1 antibody (pembrolizumab) was approved for second-line treatment of aHCC on the basis of the efficacy and safety profile in the single-arm Keynote-224 trial.\cite{152} In the global, randomized, double-blind, phase III trial Keynote-240, however, pembrolizumab did not satisfy the preplanned statistical threshold (\(P=0.0174\)), although it achieved a statistically improved OS (13.9 vs 10.6 months, \(P=0.0238\)) and PFS (3.0 vs 2.8 months, \(P=0.0022\)) in aHCC patients after sorafenib failure compared to placebo.\cite{153} Gratifyingly, the latest clinical data from the phase III Keynote-394 study conducted in Asia demonstrated that the significantly improved OS (13.6 vs 13.0 months, \(P = 0.0180\)) and PFS (2.6 vs 2.3 months, \(P = 0.0032\)) for patients with previously treated aHCC compared to placebo, which met its prespecified statistical criteria of 0.019307 and 0.013447, respectively. The incidence of treatment-related AEs was relatively higher in pembrolizumab arm than that in placebo arm (66.9\% vs 49.7\%), which was consistent with that in the trial Keynote-224 and Keynote-240.\cite{154} In addition, the post hoc analysis of Keynote-240 revealed that pembrolizumab did not significantly affect liver function in comparison to placebo in aHCC, and exhibited an improved survival regardless of ALBI grade.\cite{155} The HRQOL assessment documented that pembrolizumab could provide a good HRQOL to aHCC patients.\cite{156} Together with these results they potently establish the second-line treatment of pembrolizumab for aHCC patients receiving sorafenib previously. However, pembrolizumab was shown not to be a cost-effective therapy for HCC.\cite{157} Moreover, the clinical study (NCT04442581) comparing cabozantinib with pembrolizumab in the first-line setting is ongoing.

Other Immunotherapies
With the encouraging clinical survival benefit of aHCC patients from nivolumab and pembrolizumab, interest in other immunotherapies, such as other ICIs (PD-1/PD-L1 and CTLA-4 inhibitors), cytokines, adoptive T-cell transfer therapy, and HCC vaccines, has dramatically increased.\cite{139,158}

In addition to nivolumab and pembrolizumab, several other anti–PD-1 antibodies were also shown to exhibit a certain antitumor effect in aHCC. An example is camrelizumab, which yielded an OS at 6 months of 74.4\% and OR of 14.7\% for pretreated Chinese patients with aHCC, with a manageable toxicity like increased AST and decreased neutrophils.\cite{159} Based on a Phase I trial of tislelizumab showing an antitumor activity for HCC, a phase II trial (NCT03419897) assessing its efficacy and safety profile in pretreated aHCC patients and a global randomized phase III RATIONALE-301 trial (NCT03412773) comparing tislelizumab to sorafenib as a first-line agent in aHCC patients are currently in progress.\cite{160} The positive results of such studies deserve attention as tislelizumab can attenuate a potentially negative impact on other immune cells like macrophages with its high binding affinity and specificity for PD-1, which may address the anti-PD-1 therapy resistance.\cite{160} In addition, durvalumab, a fully-humanized IgG1 against PD-L1, was evaluated in aHCC patients with prior sorafenib treatment in a phase I/II clinical trial. Interestingly, the patients with HCV appear to enjoy a better survival than the overall cases (OS 19.3 vs 13.2 months; ORR 25\% vs 10.3\%) in durvalumab treatment.\cite{161} The underlying mechanisms of its etiological trend remain to be identified.

CTLA-4 is an immune system checkpoint molecule that maintains immune response in check by limiting the over-activation of effector T cells and mediating the impact of Tregs on immune response, rendering it a promising target for immunotherapy.\cite{162} An anti–CTLA-4 antibody, tremelimumab, was observed to have a partial response rate of 17.6\% and TTP of 6.48 months with a manageable toxicity like rash in a phase II trial.\cite{163} Thereafter, the development of tremelimumab focuses on the combination with locoregional therapy such as RFA or TACE.\cite{164} Another anti–CTLA-4 antibody, ipilimumab, exhibited a great antitumor activity as combination therapy rather than single-agent regimens.\cite{165} To date, interferon-\(\alpha\) (IFN-\(\alpha\)), IL-12, and other cytokines appear not to provide a clear survival advantage for HCC.\cite{166} Apart from anti–PD-L1/PD-1 and anti–CTLA-4 antibodies, nevertheless, other novel targets, such as LAG3, TIM-3, and immune-receptor tyrosine-based inhibitory motif domain, and immune checkpoint bi-specific antibodies against CTLA-4 and PD-1, like MEDI5752, may be promising immunotherapies for aHCC patients.\cite{133,167}

Adoptive Cell Transfer
In contrast to restore or augment the preexisting immune responses with checkpoint inhibition therapy, adoptive cell transfer (ACT) therapy induces novel or different immune responses by re-transferring autologous or allogeneic immune
cells back to patients following their expansion and modification in vitro.\textsuperscript{168} This also determines the highly specificity and individualization of ACT. Of ACT therapies, chimeric antigen receptor T cells (CAR-T cells), T cell receptor (TCR) engineered T cells, cytokine-induced killer cells (CIKs), and tumor-infiltrating lymphocytes (TILs) currently show promising antitumor activities for HCC.\textsuperscript{168,169}

ACT therapy largely depends on the modification of various and specific TAAs in vitro. The identification of TAAs that trigger an efficient immune response to eliminate tumor cells appears particularly important.\textsuperscript{170} Modified TCR-engineered T cells present the ability of recognizing and binding to the MHC of antigen-presenting cells and TAAs of tumor cells. Unlike conventional T cells, antigens recognized by these T cells are not confined to membrane-bound antigens.\textsuperscript{171,172} TCR engineered T cells specific to HBV antigens were successfully established and revealed to provide antitumor activities in recurrent HBV-related HCC after LT with a good safety profile.\textsuperscript{173,174} In addition, TCR-engineered T cells targeting AFP or glypican-3 (GPC-3) were shown to inhibit the progression of HCC in vitro and in vivo.\textsuperscript{175,176} There are currently several ongoing trials involving in TCR-engineered cells recognizing various TAAs in HCC, such as AFP (NCT03971747, 04368182, and 03132792), HBV antigen (NCT03899415), and melanoma antigen gene protein (NCT03441100). CAR-T cells recognize and kill hepatoma cells expressing specific TAAs without MHC restriction, which may prevent the tumor immune escape induced by MHC down-regulation.\textsuperscript{177} In prospective phase I clinical studies, autologous GPC-3–CAR-T cell therapy showed favorable survival (OS rates at 3 years, 1 years, and 6 months: 10.5%, 42.0% and 50.1%, respectively) in patients with GPC-3 positive aHCC. Its concomitant toxic effects were tolerable and reversible, while one patient suffered from grade 5 cytokine release syndrome.\textsuperscript{178} Over half of patients with CD133-positive unresectable HCC obtained a median OS of 12 months and overall PFS of 6.8 months after CD133-CAR-T cells reinfusion.\textsuperscript{179} Besides CAR-T cells and TCR engineered T cell therapies, CIKs, and TILs are also undergoing clinical trials with excellent Experimental results.\textsuperscript{171,180} ACT therapy will provide a potential alternative for the treatment of HCC.

Vaccines
Therapeutic vaccines mainly involve dendritic cell (DC), peptides, and oncolytic viruses. DC vaccines, as a cellular vaccine, can incur strong antitumor immune response via the recruitment of effector T cells and subsequent release of TAAs derived from tumor lysis.\textsuperscript{181} Phase I and II clinical trials confirmed that DCs pulsed with tumor lysis exhibited antitumor efficacy and a safety profile in aHCC patients, with a mean survival of 5.5 months.\textsuperscript{182,183} Moreover, the feasibility and tolerability of peptide vaccines, such as AFP,\textsuperscript{184} GPC-3,\textsuperscript{185} and multidrug resistance-associated protein 3,\textsuperscript{186} were proved in clinical studies. Nevertheless, these clinical studies on DC and peptide vaccines revealed marginal antitumor activity probably owing to a lack of large-scale studies and a control group. In contrast, oncolytic virus therapy is a promising option in the development of tumor vaccines. Oncolytic viruses are gene-modified viruses that replicate and lyse specific tumor cells with its specific cellular tropism obtained, releasing TAAs for the activation of antitumor immune response.\textsuperscript{187,188} The modified poxvirus, JX-594, inserted into the human granulocyte-macrophage colony stimulating factor gene was demonstrated to confer aHCC patients with a longer OS in high than low doses (OS, 14.1 vs 6.7 months) in a randomized phase II trial (TRAVERSE).\textsuperscript{189} However, the subsequent phase III trial (PHOCUS) comparing JX-594 plus sorafenib with sorafenib alone indicated that JX-594 did not provide improved antitumor efficacy.\textsuperscript{190} The result may be associated with the immunosuppressive TME of HCC. Therefore, the clinical trials comparing JX-594 with nivolumab (NCT03071094) and other ICIs in aHCC are ongoing.\textsuperscript{191}

Combination Therapy
As abovementioned, the development and progression of HCC is a sophisticated process mediated by multiple pathways. Additionally, single-agent therapies frequently result in dose- or time-dependent severe AEs, thereby leading to treatment interruption due to intolerance. Thus, the efficacy of single-agent, such as tyrosine kinase inhibitors (TKIs), ICIs or cytotoxic chemotherapy, may have reached a plateau at an OS of 14–16 months. Various combination regimes of ICIs and anti-VEGF monoclonal antibodies have altered this picture and greatly improved survival of aHCC patients. Since various combination regimes of ICIs and anti-VEGF monoclonal antibodies emerged in 2020, however, the therapeutic efficacies in aHCC have achieved an unprecedented improvement.\textsuperscript{22,23}
ICI–Anti-Angiogenic Therapy Combination

Antiangiogenic therapy enhances the functions of effector T-cells and immune cells infiltration into TME by normalizing aberrant vasculature, and blunts the functions of suppressive immune cells (Treg cells and MDSCs), finally to augment tumor responsiveness to immunotherapy.192

First-Line Therapy

Atezolizumab Plus Bevacizumab

The combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) was firstly proved to greatly improve OS (19.2 vs 13.4 months; HR = 0.66; P = 0.0009), ORR (29.8% vs 11.3% per Response Evaluation Criteria in Solid Tumors version 1.1) and complete response rate (CRR) (7.7% vs 0.6%) of aHCC patients over sorafenib in the IMbrave150 trial.22,193 Importantly, the HRQOL in atezolizumab plus bevacizumab group was not inferior to the sorafenib group, with a longer median time to the deterioration of quality of life (11.2 vs 3.6 months). Moreover, there was not significantly different in the risk of grade 3 or 4 AEs between both groups, such as proteinuria, diarrhea and autoimmunne events.22 Notably, bevacizumab may induce bleeding, and the assessment of varices via upper-gastrointestinal endoscopies and treatment when necessary was required at least 6 months before enrollment. In addition, this improved survival benefit was also confirmed in aHCC patients in China.194 To date, the combination regime of atezolizumab and bevacizumab has been approved as first-line therapy for aHCC by American Society of Clinical Oncology, European Society for Medical Oncology, Chinese Society of Clinical Oncology (CSCO), and National Comprehensive Cancer Network guidelines.195–197 In a single-center study, aHCC patients with a low NLR had a prolonged PFS in comparison to those with a high NLR (cumulative PFS at 150 days: 64% vs 20%), favoring the pretreatment NLR value as a potent predictor of the response to atezolizumab-bevacizumab therapy for aHCC.198 Furthermore, atezolizumab-bevacizumab therapy was demonstrated to enabled aHCC patients to receive a long-term disease-free status (19 months) after hepatectomy.199 As later-line therapy, the doublet did not provide great clinical efficacy for the aHCC patients with prior TKIs treatment, which may be associated with resistance to anti-VEGF TKIs.200 Certainly, further clinical studies are still needed. Regarding of cost-effectiveness in clinical practice, atezolizumab-bevacizumab treatment was no cost-effective alternative compared to sorafenib for aHCC.201 Therefore, the economic status of HCC patients has to be considered for a better clinical benefit from this regimen.

Other ICI–Antiangiogenic Therapies

The great success of the combination of atezolizumab and bevacizumab has changed the therapeutic regimens for HCC. The phase II/III ORIENT-32 trial conferred the combination of sintilimab (anti-PD-L1) and bevacizumab as the first-line treatment for unresectable HCC because this combination exhibited a better survival benefit than sorafenib.23 In addition to the synergistic antitumor effect of anti-angiogenic therapy and immunotherapy, adding anti-PD-1 antibody to lenvatinib treatment enhanced the antitumor efficacy by increasing the proportion of CD8+ T cells in a HCC model.202 This was supported by the phase Ib study where lenvatinib plus pembrolizumab had improved ORR (46%), PFS (9.3 months), and a prolonged median OS of 22 months in patients with unresectable HCC, with manageable toxicities.203 On the basis of promising results from this study, the double-blind randomized controlled phase III LEAP-002 trial comparing this combination with lenvatinib plus placebo is currently in progress. And the promising result of this phase III trial might establish a new therapeutic benchmark in the treatment of aHCC in the near future.204 Another combination of lenvatinib plus nivolumab also achieved similar antitumor activities in aHCC patients in a preliminary study.205 In addition, the VEGF Liver 100 trial evaluating the efficacy and safety of avelumab (anti-PD-L1 antibody) plus axitinib (TKI) as a first-line regimen for aHCC patients indicated that such patients without prior treatment in this combination received a favorable ORR (31.8%) and PFS (5.5 months) with a manageable safety profile, while OS data were unavailable at cut-off date.206 As for HBV-positive aHCC patients, a multicenter, open-label phase II trial was carried out to assess the efficacy and safety of the anti-PD-1 antibody, camrelizumab (SHR-1210), plus apatinib (anti-VEGFR2) as first- or second-line therapy for aHCC patients in China on the basis of their previous study.207,208 In this phase II trial, the combination of camrelizumab and apatinib showed an exciting survival benefit in either the first- or second-line setting in aHCC patients. The ORR, 12-month survival rate, and PFS were 34.3% vs 22.5%, 74.7% vs
68.2% and 5.7 vs 5.5 months, in first- vs second-line therapy, respectively. Along with this, the ongoing randomized, open-label, multicenter, phase III trial (NCT03764293) comparing this combination with sorafenib in aHCC is key. Interestingly, synergic effects may exist in the combination of the immune checkpoint bispecific antibodies AK104 (anti-PD-1/CTLA-4 bispecific antibody) and lenvatinib owing to its promising antitumor effects and an acceptable safety in aHCC.

Currently, various combinations of ICIs and anti-angiogenic drugs dramatically improve clinical survival for aHCC patients. The triplet combination of TKI agents and two ICIs, for example, may achieve a surprising OS of over 25 months. However, the concomitant toxicity should be taken into considerations. Therefore, a number of trials weighing the efficacy and safety of combinations of ICIs and anti-angiogenic drugs or TKIs are under way (Table 1).

ICI–ICI Combinations
Non-redundant and complementary checkpoint signals may provide evidence for the combination of two ICIs. Furthermore, blocking the B7-CTLA-4 pathway mediated by anti-CTLA-4 antibody exerts antitumor effects by increasing the activated CD8+ T cell level in lymph nodes and subsequently increasing activated CD8+ T cells infiltrating into tumor tissues. In turn, only when the required CD8+ T cells exist in tumor tissues, the inhibition of the PD-1/PD-L1 pathway activates tumor immunity. Moreover, anti-CTLA-4 antibody may potently attenuate Treg cells in the immunosuppressive TME (Figure 1).

Second-Line Therapy
Nivolumab Plus Ipilimumab
An important exploration involving the combination therapy of two ICIs comes from the CheckMate 040 study evaluating the efficacy and safety of nivolumab plus ipilimumab (anti-CTLA-4 antibody) in aHCC patients previously receiving sorafenib. In this phase I/II study, the best survival benefits, with the OS of 22.8 months and ORR of 32%, presented at the highest ipilimumab dose arm (ipilimumab 3 mg/kg plus nivolumab 1 mg/kg, 4 doses administered every 3 weeks, and then nivolumab 240 mg every 2 weeks). And the duration of response (DOR) even reached 4 years in some patients. Of the three different doses of ipilimumab arms, a higher dose of ipilimumab combined with nivolumab appeared to exhibit a better survival outcome. However, a higher ipilimumab dose conceived the more immune-mediated toxicities, rendering almost everyone in the highest ipilimumab dose arm experience AEs (94%). Fortunately, these immune-related AEs were manageable by systemically administering corticoid. In light of the efficiency and safety profile of the combination regimen, nivolumab in combination with ipilimumab was approved by the FDA as second-line treatment in aHCC. A further meta-analysis validated that the combination of nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) seemed to provide a superior OS and PFS over regorafenib (160 mg), nivolumab (3 mg/kg), and cabozantinib (60 mg) monotherapy for aHCC patients as second-line therapy. Of note, this combination regimen may act as a rescue strategy for the aHCC patients with anti-PD-1/L1 therapy failure, achieving encouraging survival benefits (mean OS = 10.9 months, ORR = 16%) with tolerable toxicity. As aforementioned, the synergistic effect between nivolumab and ipilimumab may explain this situation. To explore clinical efficacy with this combination, a phase III trial CheckMate 9DW (NCT04039607) comparing nivolumab plus ipilimumab with sorafenib or lenvatinib monotherapy in the first-line setting for aHCC is under way.

Other ICI–ICI Combination Therapies
The efficacy of anti-CTLA4 dose dependence also appeared in another combination of tremelimumab plus durvalumab for aHCC. A phase II/II trial testing the efficacy and safety of the combination showed that the higher tremelimumab dose group (tremelimumab 300 mg+durvalumab 1500 mg followed by durvalumab every 4 weeks) obtained a better OS (18.7 months) and ORR (24%) with positive tolerability than other arms as a second-line treatment. In a subsequent clinical study, this novel treatment regimen also displayed the better clinical benefit-risk profile than the lower tremelimumab dose regimen, single agent tremelimumab or durvalumab, suggesting that a higher dose of tremelimumab may trigger a stronger immune response and thus strengthen the anti-tumor activity of durvalumab. The latest findings of the multicenter, phase III HIMALAYA study based on this revealed the superiority of the higher tremelimumab dose regimen over sorafenib on survival benefits (OS, 16.4 vs 13.8 months, P = 0.0035), thus strongly supporting the use of
| ClinicalTrials.Gov Identifier | Interventions (Mechanism) | Phase, Setting | Primary Outcome | Measures | Study Completion |
|------------------------------|---------------------------|----------------|----------------|----------|-----------------|
| **ICI-antiangiogenic therapy** |                           |                |                |          |                 |
| NCT04770896 (554)            | Atezolizumab+lenvatinib/sorafenib vs lenvatinib/sorafenib | III, HCC previously treated with atezolizumab and bevacizumab | OS | Oct. 2024 |
| NCT04560894 (621)            | SCT-I10A+SCT510 vs sorafenib | III, aHCC | OS, PFS | Sep. 2024 |
| NCT04523493 (519)            | Toripalimab+lenvatinib vs lenvatinib | III, aHCC | OS, PFS | Jan. 2025 |
| NCT04465734 (477)            | HLX10+HLX04 vs sorafenib | III, aHCC | OS, PFS | Mar. 2024 |
| NCT04344158 (648)            | AK105+anlotinib vs sorafenib | III, aHCC | OS | Dec. 2024 |
| NCT04194775 (525)            | CS1003+lenvatinib vs lenvatinib | III, aHCC | PFS, OS | Jun. 2023 |
| NCT03764293 (510)            | Toripalimab+lenvatinib vs lenvatinib | III, aHCC | PFS, OS | Dec. 2021 |
| NCT03794440 (595)            | Sintilimab+IBI305 vs sorafenib | III, aHCC | PFS, OS | Jun. 2022 |
| NCT03755791 (740)            | Atezolizumab+cabozantinib vs sorafenib | III, aHCC | OS | Dec. 2022 |
| NCT03605706 (396)            | FOLFOX4+SHR-1210(PD-L1 mAb) vs SHR-1210 | III, aHCC | OS | Apr. 2022 |
| NCT04712643 (490)            | Sintilimab+IBI310 vs sorafenib | III, aHCC | OS | Dec. 2023 |
| NCT0439607 (634)             | Nivolumab+ipilimumab vs sorafenib | III, aHCC | OS | Jan. 2025 |
| NCT03298451 (1504)           | Durvalumab+tremelimumab vs sorafenib | III, aHCC | OS | Apr. 2022 |
| **ICI-ICI**                  |                           |                |                |          |                 |
| NCT04720716 (490)            | Sintilimab+IBI310 vs sorafenib | III, aHCC | OS, ORR | Dec. 2023 |
| NCT04039607 (634)            | Nivolumab+ipilimumab vs sorafenib | III, aHCC | OS | Jan. 2025 |
| NCT03298451 (1504)           | Durvalumab+tremelimumab vs sorafenib | III, aHCC | OS | Apr. 2022 |
| **Other combinations**       |                           |                |                |          |                 |
| NCT03605706 (396)            | FOLFOX4+SHR-1210(PD-L1 mAb) vs SHR-1210 | III, aHCC | OS | Dec. 2021 |
| NCT03680508 (42)             | TSR-042(PD-1 mAb)+TSR-022(TIM-3 mAb) vs TSR-042 | II, aHCC | ORR | Oct. 2023 |
| NCT03647163 (40)             | Pembrolizumab(PD-1 mAb)+VSV-IFN-β-NIS(Oncolytic virus) vs pembrolizumab | III, aHCC | ORR, safety | Jun. 2023 |
| NCT02794249 (89)             | PDR001(PD-1 mAb)+HNC280(c-Met inhibitor) vs placebo | III, aHCC | DLTs, MTD, ORR | Jun. 2021 |
| **LRT-systemic therapy**     |                           |                |                |          |                 |
| NCT04712643 (342)            | TACE+atezolizumab + bevacizumab vs TACE | III, untreated HCC | PFS, OS | Feb. 2027 |
| NCT04268888 (522)            | TACE/TAE + nivolumab vs TACE/TAE | III, intermediated HCC | OS, TTP | Jun. 2026 |
| NCT04246177 (950)            | TACE+lenvatinib+pembrolizumab vs TACE+placebo | III, incurable/non-metastatic HCC | OS, PFS | Dec. 2029 |
| NCT04246177 (950)            | TACE+lenvatinib+pembrolizumab vs TACE+placebo | III, incurable/non-metastatic HCC | OS, PFS | Dec. 2029 |
| NCT04167293 (116)            | SBRT+sintilimab vs sintilimab | III, HCC with PVI after arterially directed therapy | PFS | Oct. 2022 |
| NCT04568598 (206)            | TAI+lenvatinib vs lenvatinib | III, aHCC | OS | Dec. 2022 |
| NCT04395967 (336)            | TACE+lenvatinib vs lenvatinib | III, aHCC | OS | Jun. 2023 |
| NCT04177495 (710)            | TACE+durvalumab+bevacizumab vs TACE+placebo | III, locoregional HCC not amenable to curative therapy | PFS | Aug. 2024 |
| NCT03775395 (250)            | HAIC+sintilimab vs HAIC+sorafenib | III, aHCC | OS | Dec. 2021 |

**Notes:** Trials include the combination of locoregional therapies with systemic therapies.

**Abbreviations:** OS, overall survival; PFS, progression-free survival; ORR, overall response rate; DLTs, dose limiting toxicities; MTD, maximum tolerated dose; TTP, time to TACE progression; ICI, immune checkpoint inhibitor; LRT, locoregional therapy; mAb, monoclonal antibody; PD-L1, programmed cell death protein 1; PD-L1, programmed death 1 ligand 1; PVI, portal vein invasion; TACE, transarterial chemoembolization; TAI, transarterial infusion chemotherapy; HAIC, hepatic arterial infusion chemotherapy; TIM-3, T cell immunoglobulin and mucin domain containing 3; SBRT, stereotactic body radiotherapy; TAI, transarterial infusion chemotherapy; FOLFOX4, fluorouracil, leucovorin, and oxaliplatin; HCC, hepatocellular carcinoma; aHCC, advanced HCC.
the Single Tremelimumab Regular Interval Durvalumab regimen (tremelimumab 300 mg + durvalumab 1500 mg followed by durvalumab every 4 weeks) as first-line therapy for aHCC. Moreover, numerous ICI combination regimes (Table 1), like IBI310 (anti-CTLA-4 antibody) plus sintilimab, are undergoing to explore a highly efficacious systemic therapy with a favorable safety profile.

Chemotherapy-Based Combinations

We have previously described the superiority of oxaliplatin-based chemotherapies over other combination chemotherapies in terms of antitumor effects and toxicity profiles. Accordingly, the combinations with oxaliplatin-based regimens are of considerable interest as promising alternatives for aHCC patients, particularly in less developed regions. In a single-arm phase II study, the combination of sorafenib and modified FOLFOX achieved encouraging clinical efficacy with an ORR of 18% and TTP of 7.7 months in aHCC patients without prior systemic therapies. Considering its concomitant AEs, especially in hepatotoxicity, this regimen may be limited to those patients with a good liver function reserve.

Furthermore, the regimens of sorafenib plus XELOX (SECOX) or GEMOX were observed to have a relatively satisfying TTP of 5.92 months and 6.2 months, respectively. Both regimes showed a tolerable safety profile. As a consequence of these results, the combinations of oxaliplatin-based regimens plus sorafenib have become the front-line therapy for aHCC patients with good PS and liver function in China. Nevertheless, subsequent studies argued that adding GEMOX or XELOX to sorafenib did not seem to improve survival benefits, resulting in an inferior OS than sorafenib alone (13.5 vs 14.8 months and 7.1 vs 12.5 months, respectively). Although there seems to be a better clinical outcome for aHCC regarding TTP (6.4 vs 2.8 months) and OS (13.7 vs 6.5 months) in the combination of sorafenib and doxorubicin than doxorubicin alone (13.5 vs 14.8 months and 7.1 vs 12.5 months, respectively). Although there seems to be a better clinical outcome for aHCC regarding TTP (6.4 vs 2.8 months) and OS (13.7 vs 6.5 months) in the combination of sorafenib and doxorubicin than doxorubicin plus placebo in a phase II clinical trial, this combination failed to significantly improve survival for aHCC patients in comparison to sorafenib alone (OS, 9.3 vs 9.4 months) in a phase III CALGB 80802 clinical trial. Taken together, the combinations of chemotherapy with TKIs are not recommended as a standard treatment for aHCC, in the setting of the availability of first-line (lenvatinib) or second-line (cabozantinib and ramucirumab).

Similar to the synergistic effects of anti-CTLA-4 antibody when combined with anti-PD-1/L1 antibody, selected immunogenic chemotherapeutics sensitized tumors to host antitumor T cell immunity, instigating CD8+ T cells to

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**Figure 1** Brief mechanisms of action mediating synergistic effects of combined immunotherapies. (a) Blocking the PD-1/L1 pathway alone does not induce an antitumor immune response, but inhibition of the CTLA-4 pathway via anti-CTLA-4 antibody promotes activated CD8+ T cells accumulating in lymph nodes and then infiltrating into TME, enhancing the antitumor effects of anti-PD1/L1 antibody. (b and c) LRTs or metronomic CTs trigger the release or exposure of immunostimulatory molecules like TAAs by damaging cancer cells, followed by the blockade of the PD-1/L1 and CTLA-4 pathway by anti-PD1/L1 and anti-CTLA-4 antibody, resulting in robust antitumor immune response.

**Abbreviations**: HCC, hepatocellular carcinoma; LRTs, locoregional therapies; TACE, transarterial chemoembolization; TA, thermal ablation; CTs, chemotherapies; TAAs, tumor-associated antigens; APCs, antigen-presenting cells; MHC-1, major histocompatibility complex class 1; TCR, T cell receptor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; TME, tumor microenvironment.
infiltrate into tumor to facilitate ICIs against various cancers.\textsuperscript{228} Furthermore, metronomic chemotherapy also triggers the secretion or exposure of immunostimulatory molecules, like TAAs, by damaging cancer cells to elevate responsiveness to ICIs (Figure 1).\textsuperscript{229} Based on this rationale, a single-arm phase II study was conducted to evaluate the efficacy and safety of camrelizumab plus FOLFOX4 or GEMOX chemotherapy as first-line therapy for aHCC. An encouraging ORR of 26.5% and PFS of 5.5 months were obtained and severe immune-related AEs were found in only 5.9% of aHCC patients.\textsuperscript{230} Currently, a multicentered randomized Phase III trial (NCT03605706) is underway to compare camrelizumab combined with FOLFOX4 regimen to placebo combined with FOLFOX4 as first-line therapy in aHCC patients. Further investigations are warranted to identify the administration strategy of chemotherapy that facilitates rather than attenuates the immune system in these combination treatments.\textsuperscript{231}

### Combination of Systemic and LRTs

LRTs (thermal ablation [TA], stereotactic body radiotherapy [SBRT], and TACE) are already widely used for HCC since they directly impair tumors and reduce the tumor burden. Yet, quite a few HCC patients suffered from disease progression following LRTs, largely TACE. Accordingly, whether the addition of systemic therapies to LRTs could address this issue is to be explored.

Clinical trials of the combination of sorafenib to TACE showed mixed results. The phase II TACTICS trial showed a significantly improved PFS in sorafenib plus TACE group than TACE alone group (25.2 vs 13.5 months; \(P = 0.006\)), with a better OS at 2 years (77.2% vs 64.6%).\textsuperscript{232} Another observational study demonstrated that the combination of TACE plus sorafenib significantly improved OS compared to sorafenib or TACE alone arm regardless of HCC patients with BCLC stage B or C.\textsuperscript{233} Sorafenib seems to synergize TACE to improve survival benefit in HCC. Theoretically, VEGF and other angiogenic pathways, which are activated by the hypoxic environment created by TACE, may promote angiogenesis and revascularization to induce the residual viable tumor to grow. It is the anti-angiogenic agent, sorafenib, that disables angiogenic pathways to achieve a synergistic effect.\textsuperscript{234} In the phase III STAH and TACE 2 trials, sorafenib combined with TACE failed to improve OS (12.8 vs 10.8 months, \(P = 0.29\)) and PFS (238 vs 235 days, \(P = 0.94\)).\textsuperscript{235,236} In addition, meta-analyses concluded that sorafenib combined with TACE did not improve clinically relevant outcomes for HCC patients,\textsuperscript{237,238} with more AEs\textsuperscript{237} and less cost-effectiveness.\textsuperscript{239} Thus, this regimen is not recommended for HCC patients to date. Combinations of sorafenib and hepatic arterial infusion chemotherapy (HAIC) appear to exhibit diametrically opposed clinical outcomes depending on the chemotherapeutic drugs infused. HAIC of FOLFOX added to sorafenib was observed to improve survival benefit\textsuperscript{240} and HAIC of cisplatin with fluorouracil or not was not.\textsuperscript{241,242} Moreover, sorafenib in combination with radiotherapy, SBRT, and Yttrium-90 radioembolization showed an improved survival compared to sorafenib alone to some extent.\textsuperscript{243–245} These results should be confirmed by more ongoing studies to identify the duration, sequencing, dose, and timing of administration. A slew of clinical trials, such as the efficacy of lenvatinib plus TACE (NCT03838796), are ongoing (Table 1).

There also exists a synergistic effect in the combination of immunotherapy and LRTs. LRTs like TACE and TA, not only release plenty of TAAs triggering potent antitumor immune responses, but also produce some danger signals that awake host innate immune system and develop effector T cell immunity.\textsuperscript{234,246} In this setting, LRTs enable itself to couple with immunotherapy. Duffy et al combined LRTs (TACE or ablation) with tremelimumab to assess their safety and efficacy in HCC.\textsuperscript{164} There were a remarkably increase of CD8+ T cells and immune cells infiltrating into tumor after ablation (Figure 1). The combination of ablation and tremelimumab resulted in a partial response of 26.3%, as well as an OS of 12.3 months and median time to progression of 7.4 months.\textsuperscript{164} Clinical trials comparing this regimen with ablation or tremelimumab alone are warranted. More recently, the phase III EMERALD-1 clinical trial to evaluate TACE coupled with durvalumab and bevacizumab is underway. Similarly, numerous clinical trials are ongoing to explore the efficacy and safety of the combination of ICIs and LRTs (Table 1).

### Adjuvant and Neoadjuvant Therapy

Although surgical tumor removal, including resection and LT, is a potentially curative therapy for HCC, recurrence after surgery is extremely common, presenting in over 70% of HCC cases within 5 years.\textsuperscript{5,247} By and large, the recurrence within 2 years may arise from the remnants and aggressiveness of the primary tumor, while the recurrence beyond 2
years largely results from de novo hepatocarcinogenesis related to underlying liver diseases like hepatitis or liver cirrhosis.248 Furthermore, the frequent diagnosis at advanced stages and a terrible liver function reserve always deprive patients of surgical resection, with only 20% of HCC patients eligible for curative resection.249 Therefore, in the setting of recent inspiring achievements of systemic therapies, preoperative and postoperative strategies based on the aforementioned risk factors deserve exploration to improve surgical resectability and decrease postoperative recurrence with the ultimate aim of improving clinical outcomes for HCC patients.

Adjuvant Therapy
As noted above, adjuvant therapy reduces the early recurrence of HCC through eradicating remnant tumor cells or inhibiting hepatocarcinogenesis.250 Some relevant studies indeed improve recurrence-free survival (RFS) and OS of HCC patients after surgery despite the lack of guidelines recommending adjuvant treatment.11,251,252 Immunotherapy was shown to effectively prevent metastases or de novo tumorigenesis via boosting or modifying the host immune function.253 Several randomized controlled trials demonstrated that the adjuvant immunotherapy with CIKs might improve clinical benefits to HCC patients in terms of RFS and OS after curative resection. The phase III multi-center study explored the adjuvant effects of activated CIKs on HCC patients after curative resection with a follow-up of up to 68.5 months. The mean RFS was significantly higher in the immunotherapy group than in no adjuvant therapy group (44 vs 30 months, \( P = 0.01 \)). It was the same for RFS rate at 5 years (44.8% vs 33.1%).254,255 Nonetheless, another similar trial suggested that CIK therapy failed to extend the DFS and OS of HCC patients although its primary outcome, time to recurrence, was prolonged to 13.6 months from 7.8 months of no CIK treatment group.256 Meta-analysis of the above studies concluded that adoptive immunotherapies like CIKs could eradicate the small intrahepatic metastases from the primary tumor but not multicentric relapse, resulting in the improvement of the early (less than 3 years) rather than late recurrence.257 Additionally, the GPC3-derived peptide vaccine,185 autologous DCs,258 and DC vaccine plus activated T-cell transfer259 were revealed to reduce HCC recurrence and improve clinical outcomes for HCC patients after curative operation. Clinical trials assessing the efficacy and safety of ICIs as adjuvant therapy for HCC have been lacking until now. However, the results of multiple ongoing trials, such as nivolumab (NCT03383458) and pembrolizumab (NCT03867084), are worthy of awaiting (Table 2). Of these, the phase III CheckMate 9DX trial evaluating nivolumab as an adjuvant therapy for HCC is extremely exciting, since one half of the sales of nivolumab is forecasted to be attributed to its sales in the adjuvant setting in 2027260.

Molecular targeted drugs as an adjuvant therapy look dismal owing to the failure of the phase III STORM trial. This trial indicated that sorafenib failed to significantly prolong RFS for HCC following resection or ablation in comparison to the placebo arm, with a more frequent incidence of AEs (28% vs less than 1%).261 Yet, the pity of the STORM trial does not seem equivalent to the ineffectiveness of molecular targeted agents as an adjuvant therapy for HCC. And the development of molecular targeted agents in postoperative adjuvant therapy needs further investigations. An example is sorafenib treatment following curative hepatectomy that improved RFS and OS in HCC patients with microvascular invasion.262 Two phase III trials, IMbrave 050 and EMERALD-2, exploring the molecular targeted agents plus ICIs as adjuvant therapy are underway. The feasibility of chemotherapy in the adjuvant treatment for HCC has been assessed in several studies. The HCC patients receiving capecitabine after curative resection had a lower risk of tumor recurrence, but no extended OS.116 However, chemotherapy is not supported in the adjuvant treatment for HCC because of its toxicity and uncertain efficacy based on meta-analyses and clinical trials to date.263 Notably, traditional Chinese medicine (TCM) has achieved outstanding breakthroughs in reducing HCC recurrence and metastasis currently. Erzhu Qinggan Jiedu Recipe,264 Huater granule265 and traditional herbal medicine266 were confirmed to significantly improve RFS and OS in the adjuvant setting for HCC.

Neoadjuvant Therapy
Neoadjuvant therapy facilitates the tumor downstage to increase surgical resectability as a bridging treatment, and decreases the recurrence following operation. Like adjuvant therapy for HCC, neoadjuvant therapy for HCC is not also endorsed in current clinical guidelines given the potentially invasive and metastatic properties and thereby lack of adequate clinical studies. Despite several clinical trials, including BIOSHARE trial proved that preoperative sorafenib
| Clinical Trials.Gov Identifier | Interventions (Mechanism) | Phase, Setting | Primary Outcome |
|-------------------------------|---------------------------|----------------|-----------------|
|                              |                           |                | Measures        | Study Completion |
| Neoadjuvant therapy           |                           | II, resectable recurrent HCC | DFS            | Jun. 2022        |
| NCT04615143 (43)             | Tislelizumab(PD-1 mAb)    | II, potential resectable HCC | ORR            | Dec. 2022        |
| NCT03510871 (40)             | Nivolumab(PD-1 mAb)+ipilimumab(CTLA-4 mAb) | II, resectable HCC | PRR            | Oct. 2022        |
| NCT03867370 (40)             | Toripalimab(PD-1 mAb)+lenvatinib(TKI) vs toripalimab | II, early and intermediate HCC | PFS            | May. 2022        |
| NCT04174781 (61)             | Sintilimab(PD-L1 mAb)+DEB-TACE | III, HCC at high risk of recurrence after liver transplantation | TFSR           | Sep. 2022        |
| Adjuvant therapy             |                           | III, HCC with solitary tumor more than 5cm and MVI after radical hepatectomy | OS             | Dec. 2021        |
| NCT04168944 (108)           | Lenvatinib(TKI) vs placebo | III, HCC after curative hepatectomy | RFS            | Sep. 2023        |
| NCT02738697 (290)            | FOLFOX                    | III, HCC at complete radiological response after surgical resection or local ablation | RFS            | Jun. 2023        |
| NCT04143191 (158)           | Sorafenib(TKI)+TACE vs sorafenib | III, HCC at high risk of recurrence after curative treatment | RFS            | May. 2024        |
| NCT03867084 (950)           | Pembrolizumab(PD-1 mAb) vs placebo | III, HCC at high risk of recurrence after curative resection or ablation | RFS            | Jul. 2027        |
| NCT03847428 (888)           | Durvalумab(PD-L1 mAb)+bevacizumab(VEGF mAb) vs durvalумab | III, HCC at high risk of recurrence after curative treatment | RFS            | Jul. 2024        |
| NCT04102098 (662)           | Atezolizumab(PD-L1 mAb)+bevacizumab(VEGF mAb) vs active surveillance | III, HCC at high risk of recurrence after surgical resection or ablation | RFS            | Jul. 2024        |
| NCT04639180 (674)           | Camrelizumab(PD-1 mAb)+apatinib(TKI) vs active surveillance | III, HCC at high risk of recurrence after curative resection or ablation | RFS            | Jul. 2024        |

**Abbreviations:** OS, overall survival; DFS, disease-free survival; ORR, overall response rate; RFS, recurrence-free Survival; PFS, progression-free survival; PRR, pathological response rate; TFSR, tumor free survival rate; mAb, monoclonal antibody; VEGF, vascular endothelial growth factor; PD-1, programmed cell death protein 1; PD-L1, programmed death 1 ligand 1; MVI, microvessels invasion; CTLA-4, cytotoxic T lymphocyte-associated protein 4; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; TKI, tyrosine kinase inhibitor; mAb, monoclonal antibody; DEB-TACE, drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; aHCC, advanced HCC.
yielded significantly downstage for patients with resectable HCC with a good safety, more studies substantiating this result remain to be warranted for the limited scale and patient population of these trials.\textsuperscript{267,268} The outstanding overall response achieved by immunotherapy in aHCC has renewed the interest in neoadjuvant treatment of resectable HCC. The interim report from a small, randomized phase II trial validated that perioperative immunotherapy (nivolumab with or without ipilimumab) produced a notable pathological CRR (29%), without delay of surgical resection.\textsuperscript{269} And the final result may improve the dismal situation of neoadjuvant therapy for HCC. Furthermore, the combination of molecular targeted agents and ICIs also showed surprising clinical benefits in the neoadjuvant setting for the patients with resectable HCC.\textsuperscript{270,271} Yarchoan et al indicated that cabozantinib combined with nivolumab induced a marked pathologic response and conferred surgical resection to patients initially beyond traditional resection criteria.\textsuperscript{270} Meanwhile, other combination therapies (NCT03222076 and NCT04425226) as tumor downstage treatments are being evaluated to provide more radical surgical opportunities to HCC patients (Table 2).

**TCM**

TCM is based on thousands of years of clinical experience against HCC with the unique philosophic regimen of theories, diagnosis and treatments. In theoretical systems of TCM, “a concept of holism” and “the treatment according to syndrome differentiation” are highly valued. The former supports the human systems as a holism to maintain a dynamic equilibrium of external environments and internal organism system. And the loss of relative equilibrium will incur the occurrence of diseases. It is via the latter that TCM restores this equilibrium to cure diseases. In the setting of TCM theory and accumulating clinical experience, HCC fits into the category of “Zheng Jia” and “Ji Ju”, with basic pathogenic mechanisms including spleen deficiency, qi stagnation, blood stasis, excessive heat, yin deficiency, and dampness.\textsuperscript{272,273} In view of this, there are numerous traditional Chinese medicines (TCMs) usually subdivided into formulas and single herbs fighting against HCC through clearing heat, detoxifying the body, eliminating dampness, calming the liver wind, or strengthening qi. The antitumor effects against HCC of TCMs, particularly formulas, possess multi-component, multi-target, and various biological pathways features on the basis of the integrity of organism, which coincides with the complex mechanisms of hepatocarcinogenesis and progression.\textsuperscript{274}

TCMs were shown to potently alleviate AEs from conventional treatments, such as chemotherapy and molecular targeted therapy, but also enhance the therapeutic effect of other treatments for HCC.\textsuperscript{275} YIV-906 (PHY906), derived from a Chinese herbal formula named Huang-Qin Decoction, consists of four herbal ingredients (Glycyrrhiza uralensis Fisch, Paeonia lactiflora Pall, Scutellaria baicalensis Georgi, and Ziziphus jujuba Mill).\textsuperscript{276} In phase I/II clinical trials, capecitabine combined with YIV-906 potentiated its anti-hepatoma activity, resulting in a mean OS of 9.2 months. Of note, the incidence of severe gastrointestinal toxicity associated with capecitabine was significantly reduced compared with capecitabine treatment alone.\textsuperscript{276,277} In addition, YIV-906 was confirmed to enhance the antitumor activity of sorafenib mediated by stimulating tumor autophagy and apoptosis as well as immune response from TME.\textsuperscript{278} A phase II clinical trial (NCT04000737) is undergoing to compare YIV-906 plus sorafenib versus sorafenib alone regarding of efficacy and safety as a first-line treatment for aHCC patients with HBV. Moreover, Yang and his team reported that the anti-tumor activity of anti-PD1 was markedly enhanced in combination of YIV-906 via promoting the adaptive and innate immune responses.\textsuperscript{279} In terms of single herbs, Kanglaiyaite as an extract from Coix seeds also enhanced the suppressive effects of cisplatin on HCC cells, exhibiting synergistic effects in the combination with conventional treatments.\textsuperscript{280} Of significant mention is icaritin, a prenyllflavonoid derivative from epimedium. A single-arm phase I study preliminarily confirmed that icaritin at an optimized dose conferred the safety profile and durable survival benefits to aHCC patients through modulating host immune activities, accompanied by an OS of 192 days, but did not induce immune-related AEs (like interstitial lung disease and thyroid dysfunction).\textsuperscript{281} Subsequently, the underlying mechanisms were established that the immunomodulating activities induced by icaritin involving the crosstalk of various cytokines, immune cells, and immune checkpoints via IL-6/JAK/STAT3 pathways rather than a single target, which is superior over conventional targeted therapies and ICIs for aHCC treatment.\textsuperscript{282} Based on these premises, at 2021 CSCO, Qin shared the results of a multicenter, randomized, double-blind phase III clinical trial (NCT03236636) comparing the safety profile and efficacy of icaritin with cinobufotalin in first-line Treatment of aHCC subjects. Patients receiving icaritin treatment showed a significantly prolonged mean OS compared with the control arm (13.45 vs 6.87 months, HR = 0.43, P = 0.0092), with a lower incidence of AEs (12.6% vs 26.2%). The final results of this trial will bring outstanding breakthroughs in...
immunotherapies for aHCC. Moreover, numerous TCMs, such as Huaier Granule and Jinlong Capsule, are widely used for HCC treatment, while other clinical trials (NCT03851471, NCT02399033) assessing the efficacy of TCMs for HCC are underway. Several limitations of TCMs still remain, including their poor absorption, low bioavailability, and unknown molecular mechanisms, despite the dramatic emergence of novel drug delivery systems, TCM analogs, and high-throughput and omics technologies. Of course, this may be associated with the concept of “holism” during HCC treatment. There is still a long way to go to make full use of TCMs for HCC in not only the East but also the West.

Conclusion and Outlook

Recent decades have witnessed remarkable progress in systemic therapy for aHCC, with the approvals of first-line drugs, including lenvatinib beyond sorafenib, and second-line drugs, including molecular targeted inhibitors (MTIs) (regorafenib, cabozantinib and ramucirumab) and ICIs (pembrolizumab and nivolumab). Subsequently, the advent of combination modalities of ICIs and MTIs enable the clinical efficacy of systemic therapy to reach a record high for aHCC. Atezolizumab-bevacizumab combination achieved a high OS of 19.2 months in the first-line setting for aHCC with tolerable toxicity and nivolumab-ipilimumab combination has been also established the one of top options for aHCC patients with the prior treatment of a first-line TKI (sorafenib or lenvatinib) (Table 3). Additionally, systemic therapy, especially ICIs, has been confirmed to potently reduce tumor burden to facilitate TACE and surgical resection, which may improve clinical outcomes and reduce the recurrence after operation.

Despite this, some challenges deserve cautious consideration in the development of systemic therapy for aHCC. The triplet combination of nivolumab + ipilimumab + cabozantinib failed to report satisfactory survival benefits compared to the nivolumab + cabozantinib arm (PFS, 6.8 vs 5.5 months; ORR, 26% vs 17%), but with a terribly higher incidence of AEs (71% vs 42%). Thus, greater advances in HCC will rely on the elucidation of its complex biological mechanisms from multiple perspectives, such as the interactions of molecules and cells, and the role of TME. The current boom in multi-omics analysis and high-throughput sequencing may help identify novel therapeutic targets for HCC treatment. Moreover, synergistic rather than additive combinations, particularly in immune-based regimens, should be extensively explored beyond atezolizumab-bevacizumab combination on the basis of the immunomodulatory mechanisms. Immune-based combination therapy will usher in a new first-line treatment landscape in the next few years. Regarding treatment efficacy for HCC, delayed responses or pseudo-progressions in HCC are worthy of note that patients initially receive the progressive disease assessed after treatment, but later obtain a decrease in tumor burden or a treatment benefit. An instance is the nivolumab treatment with which aHCC patients show delay clinical benefits. The mechanism behind the pseudo-progressions remains uncertain, which makes discriminating it from hyperprogression tricky. Moreover, a portion of aHCC patients fail to obtain clinical benefit or just develop resistance to systemic therapy. Therefore, some predictive biomarkers seem to be pivotal to assess treatment efficacy and select HCC patients likely to benefit more from treatment. AFP is an only valuable biomarker to guide treatment and predict prognosis for HCC, while considerable effort has been made to pursuit potential biomarkers for HCC. Of note, several emerging biomarkers, such as prothrombin induced by vitamin K absence-II (PIVKA-II), featuring a higher sensitivity and specificity than AFP have not yet been widely deployed in preclinical and clinical settings. The limitation of geographic populations and underlying liver disease, and the uncertain biomechanisms to some extent contribute to the existing disappointing situation. Further well-designed, large-scale, and international multicenter prospective clinical studies as well as in-depth mechanistic studies are warranted to validate the clinical power of these biomarkers. In addition, the shortage of effective biomarkers for HCC may result from the limited cancerous tissue available for molecular testing and the molecular heterogeneity of HCC. Stringent collection and analysis of blood samples from HCC patients should be implemented to overcome this barrier. New serum biomarkers and the DNA sequencing of circulating tumor cells may be promising biomarkers useful to decision-making for HCC. Interestingly, multiple biomarkers in concert may also exhibit superiority over biomarkers used alone. This is exemplified by the multi-marker panels consisting of AFP, PIVKA-II, and other biomarkers. AEs or toxicities during HCC treatment also need to be considered with caution owing to their undesirable impact on the efficacy of systemic therapy and quality of life. An optimal dosing schedule, therapy duration, and rational combination regimens are warranted in future clinical trials to ameliorate AEs or toxicities.
Table 3 Summary of Efficacy and Safety of the Approved Systemic Therapies for aHCC

| Source | Targets | Treatment (No. of Patients) | Main Efficacy and Safety Results |
|--------|---------|----------------------------|---------------------------------|
|        |         |                            | OS Med. (Months) | PFS Med. (Months) | ORR | Grade ≥3 TRAEs |
|        |         |                            | HR (95% CI) | P value | HR (95% CI) | P value |        |
| First-line |       |                            |                |          |                |          |        |
| SHARP (2007), Llovet et al | VEGFRs, PDGFR-β | Sorafenib (297) 400 mg bid. vs Placebo (302) | 10.7 vs 7.9 | 0.69 (0.55–0.87) <0.001 | 5.5 vs 2.8 | 0.58(0.45–0.74) <0.001 | 2% vs 1% (RECIST v1.1) | 80% vs 52% † |
| REFLECT (2018), Kudo et al | VEGFR1-3, FGFR1-4, PDGFRα, c-Kit, FLT3, RET | Lenvatinib (478) 12 mg (>60 kg), 8 mg (<60 kg) qd. vs Sorafenib (476) 400 mg bid. | 13.6 vs 12.3 | 0.92 (0.79–1.06) NA | 7.4 vs 3.7 | 0.66(0.57–0.77) <0.0001 | 40.6% vs 12.4% (mRECIST) | 75% vs 67% |
| CheckMate 459 (2019), Yau et al | PD-1 | Nivolumab (371) 240 mg q2w. vs Sorafenib (372) 400 mg bid. | 16.4 vs 14.7 | 0.85 (0.72–1.02) 0.08* | 3.7 vs 3.8 | 0.93 (0.79–1.10) NA | 15% vs 7% (RECIST v1.1) | 22% vs 49% |
| IMbrave 150 (2020), Finn et al | PD-L1+VEGF | Atezolizumab 1200 mg+bevacizumab 15mg/kg, q3w (336) vs Sorafenib (165) 400 mg bid. | 19.2 vs 13.4 | 0.66 (0.52–0.85) <0.001b | 6.8 vs 4.3 | 0.59 (0.47–0.76) <0.001b | 27.3% vs 11.9% (RECIST v1.1) | 36% vs 46% |
| Second-line |       |                            |                |          |                |          |        |
| RESORCE (2017), Bruix et al | VEGFR, PDGFR, BRAF, RET, RAF-1, FGFR, Tie-2 | Regorafenib (379) 160 mg qd. vs Placebo (194) | 10.7 vs 7.8 | 0.63 (0.50–0.79) <0.0001 | 3.1 vs 1.5 | 0.46(0.37–0.56) <0.0001 | 11% vs 4% (mRECIST) | 67% vs 39% |
| CELESTIAL (2019), Abou-Alfa et al | VEGFR, MET, AXL, RET | Cabozantinib (470) 60 mg qd. vs Placebo (237) | 10.2 vs 8.0 | 0.76 (0.63–0.92) 0.005 | 5.2 vs 1.9 | 0.44(0.36–0.52) <0.001 | 4% vs 0.4% (RECIST v1.1) | 67.7% vs 36.3% |
| REACH-2 (2019), Zhu et al | VEGFR 2 | Ramucirumab (197) 8 mg/kg, q2w. vs Placebo (95) | 8.5 vs 7.3 | 0.71 (0.53–0.95) 0.019* | 2.8 vs 1.6 | 0.45(0.34–0.60) <0.0001 | 5% vs 1% (RECIST v1.1) † | 11% vs 5% ‡ |
| KEYNOTE-240 (2020), Finn et al | PD-1 | Pembrolizumab (278) 200mg q2w. vs Placebo (135) | 13.9 vs 10.6 | 0.78(0.61–0.998) 0.02* | 3.0 vs 2.8 | 0.78 (0.61–0.99) 0.02* | 18.3% vs 4.4% (RECIST v1.1) | 18.6% vs 7.5% |
| CheckMate-040 (2020), Yau et al | PD-1+CTLA-4 | Nivolumab 1mg/kg+ipilimumab 3mg/kg, q2w. (50)* vs Nivolumab 3mg/kg+ipilimumab 1mg/kg, q2w. (49)* vs Nivolumab 3mg/kg+ipilimumab 1mg/kg, q4w. (49) | 22.8 vs 12.5 vs 12.7 | NA | NA | NA | NA | 32%vs31%vs31% (RECIST v1.1) | 53% vs29% vs31% |

Notes: a primary end points not met; b primary end points met; * four doses followed by nivolumab 240mg q2w; † not significant; ‡ Any grade.

Abbreviations: aHCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; HR, hazard ratio; TRAEs, treatment-related adverse events; NA, not available; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; qd, once daily; bid, twice daily; q2w, once every 2 weeks; q3w, once every 3 weeks; q6w, once every 6 weeks.
Furthermore, a better understanding of underlying mechanisms is crucial for improving the management of AEs as well as choosing the next treatment. However, toxicities or AEs may represent clinical benefits in such cases as TKI-induced AEs and immune-mediated AEs associated with ICIs. Last but not least, the integration of multidisciplinary treatments, including the combination of systemic and LRTs as well as adjuvant and neoadjuvant therapy, should be implemented to establish an optimal treatment strategy in terms of OS of aHCC patients and their quality of life.

Overall, the optimal combined combination regimens based on a better understanding of biological mechanisms of HCC, personalized treatments depending on accurate, user-friendly biomarkers, and rational multiple disciplinary intervention are the direction of effort in the near future, which will achieve an excellent prognosis and a better quality of life for aHCC patients.

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**Disclosure**
The authors declare that they have no conflicts of interest in this work.

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