Review

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An overview: Management of patients with advanced hepatocellular carcinoma

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SUMMARY Hepatocellular carcinoma (HCC) has constituted a significant health burden worldwide, and patients with advanced HCC, which is stage C as defined by the Barcelona Clinic Liver Cancer staging system, have a poor overall survival of 6-8 months. Studies have indicated the significant survival benefit of treatment based on sorafenib, lenvatinib, or atezolizumab-bevacizumab with reliable safety. In addition, the combination of two or more molecularly targeted therapies (first- plus second-line) has become a hot topic recently and is now being extensively investigated in patients with advanced HCC. In addition, a few biomarkers have been investigated and found to predict drug susceptibility and prognosis, which provides an opportunity to evaluate the clinical benefits of current therapies. In addition, many therapies other than tyrosine kinase inhibitors that might have additional survival benefits when combined with other therapeutic modalities, including immunotherapy, transarterial chemoembolization, radiofrequency ablation, hepatectomy, and chemotherapy, have also been examined. This review provides an overview on the current understanding of disease management and summarizes current challenges with and future perspectives on advanced HCC.

Keywords Hepatocellular carcinoma, Advanced, Management, Molecularly targeted therapies, Portal vein tumor thrombosis

1. Introduction

Primary liver cancer is the sixth most common carcinoma and the third leading cause of cancer-related death (*1*), with 905,667 new cases and 830,180 deaths worldwide in 2020 (*2*). Hepatocellular carcinoma (HCC), accounting for about 90% of primary liver cancer, has constituted a significant health burden all around the world (*3*). The well-established risk factors for HCC include hepatitis virus infection (hepatitis B and C virus), alcohol consumption, obesity, diabetes, and aflatoxin exposure (*1*). The 5-year survival rate is less than 20% for patients with HCC and is determined by disease stage (*4*). From 2000 to 2015, the overall HCC death rate increased by 48.6% in males (95% CI: 43.9-53.4%; from 7.52 to 11.18 per 100,000 persons) and 34.7% in females (95% CI: 28.1-41.7%; from 2.82 to 3.80 per 100,000 persons) (*5*).

Advanced HCC, also referred to as Barcelona Clinic Liver Cancer (BCLC) stage C (BCLC-C) (*6,7*), is defined as patients with segmental or portal macrovascular invasion or extrahepatic spread who exhibit cancer-related symptoms (Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1-2) (*8*). Due to the tumor extent or cirrhosis, advanced HCC tends to be surgically unresectable, with a poor median survival of 6-8 months (*9,10*). Importantly, portal vein tumor thrombosis (PVTT) commonly occurs in patients with advanced HCC, which results in aggressive disease progression, impaired liver function reserve, an increased recurrence rate, and a reduced median survival time (2-4 months) (*11*). This review summarizes the current management of patients with advanced HCC (BCLC-C) (Figure 1) and it discusses recent developments as well as current challenges in this field.

2. Management of advanced HCC: Systemic therapies

Advanced HCC was historically incurable until the appearance of sorafenib (*12*), a tyrosine kinase inhibitor (TKI) (*13-15*). Currently, systemic therapy is the primary option for advanced HCC (*16*), and several updated molecularly targeted agents (*17-19*), together with combination therapy (immune checkpoint inhibitors

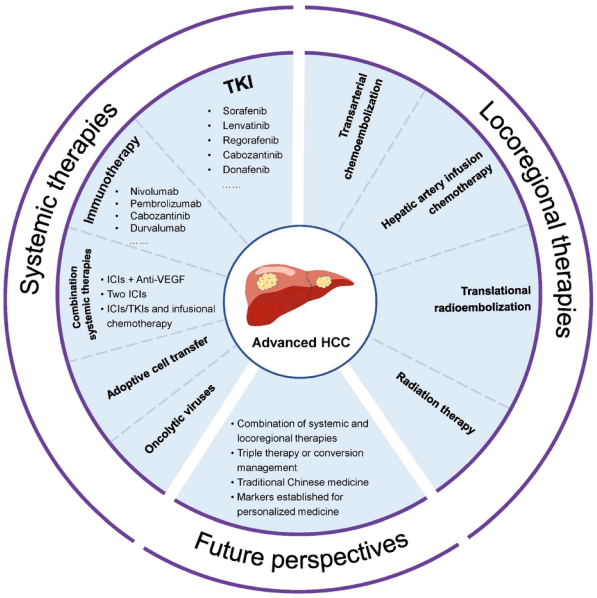

Figure 1. Current management of patients with advanced hepatocellular carcinoma. Systemic therapies include TKI, immunotherapy, combination systemic therapies, adoptive cell transfer, and oncolytic viruses. Locoregional therapies include transarterial chemoembolization, hepatic artery infusion chemotherapy, translational radioembolization, and radiation therapy. Potential management strategies are also listed, such as a combination of systemic and locoregional therapies, triple therapy or conversion management, traditional Chinese medicine, and markers for personalized medicine. HCC, hepatocellular carcinoma; TKI, tyrosine kinase inhibitor.

(ICIs) or other antibodies), have displayed remarkable efficacy (*20*).

2.1. Monotherapy with TKI

2.1.1. Sorafenib

Sorafenib is a TKI that inhibits the activity of kinases and pathways (platelet-derived growth factor receptor (*PDGFR*), *c-KIT*, vascular endothelial growth factor receptor (*VEGFR*), *RET*, *RAS*/*RAF*/mitogen-activated protein kinase (*MAPK*), *FLT-3* and Janus kinase (*JAK*)/signal transducer and activator of transcription protein (*STAT*)) to result in antiangiogenic, antiproliferative, and proapoptotic action (*21*). The survival benefit of sorafenib was first revealed in a phase 2 study involving 137 patients with advanced HCC (median overall survival (OS): 9.2 months) in 2006 (*22*). A multicenter randomized trial subsequently indicated that sorafenib (400 mg twice a day) resulted in a longer OS compared to a placebo (10.7 *vs.* 7.9 months; hazard ratio (HR): 0.69, 95% confidence interval (CI): 0.55-0.87) (*12*). Further subgroup analysis suggested that sorafenib could improve survival and disease control, regardless of etiology, baseline tumor burden, disease stage, or prior therapy (*23,24*).

Several studies reported the use of sorafenib in patients with advanced HCC and PVTT (Table 1) (*25-31*). In a study by Jeong *et al.* (*32*), 30 patients with advanced HCC and PVTT received sorafenib monotherapy. Among these individuals, 10% were reported to have a partial response to revascularization and 30% had stable disease (*32*). The median OS was 3.1 months (95% CI: 2.70-3.50), with a median progression-free survival (PFS) of 2.0 months (95% CI: 1.96-2.05). In addition, Ahn *et al.* (*28*) compared sorafenib to hepatic arterial infusion chemotherapy in patients with advanced HCC and PVTT. The group receiving sorafenib had a significantly shorter time to progression (TTP, 2.1 *vs.* 6.2 months) and a reduced disease control rate (37% *vs.* 76%) than the group receiving arterial infusion chemotherapy. Still, more solid evidence and further validation are required to support the administration of sorafenib in patients with advanced HCC and PVTT.

The combination of sorafenib with other drugs or treatments is another hot topic, and a growing number of studies have suggested the potential survival benefit of combination therapy to treat advanced HCC. Goyal *et al.* (*33*) combined sorafenib with FOLFOX (5-fluorouracil 1,200 mg/m^2/day continuous infusion for 46 hours, leucovorin 200 mg/m^2 and oxaliplatin 85 mg/m^2 twice a week) in patients with advanced HCC, who received sorafenib (400 mg twice daily) for 2 weeks followed by FOLFOX. The median TTP was 7.7 months (95% CI: 4.4-8.9), the overall response rate (ORR) was 18%, and the median OS was 15.1 months (95% CI: 7.9-16.9) (*33*). In a phase 2 trial comparing sorafenib (400 mg twice daily; n = 46) with sorafenib-GEMO (400 mg twice daily; 1000 mg/m^2 gemcitabine; 100 mg/m^2 oxaliplatin; n = 48), There were no significant differences in the median OS between the group receiving sorafenib alone and the group receiving sorafenib-GEMOX (14.8 months (90% CI, 12.2-22.2) *vs.* 13.5 months (90% CI: 7.5-16.2)). However, the median TTP improved in the group receiving sorafenib-GEMOX compared to the group receiving sorafenib alone (6.2 months (95% CI: 3.7-7.2) *vs.* 4.6 months (95% CI: 3.8-6.2)) (*34*). In addition, phase I trials have revealed the potential effect of the combination of sorafenib and trametinib (median PFS: 3.7 months; median OS: 7.8 months) (*35*) or enzalutamide (median PFS: 2.9 months; median OS: 6.7 months) (*36*) in patients with advanced HCC. In addition, a multicenter study compared sorafenib alone (n = 169) with the combination of sorafenib and transarterial chemoembolization (TACE) (n = 170) (*37*). There were no significant differences in the median OS (12.8 *vs.* 10.8 months, HR: 0.91, P = 0.290), while the median TTP (5.3 *vs.* 3.5 months, HR: 0.67, P = 0.003) and median PFS (5.2 *vs.* 3.6 months, HR: 0.73, P = 0.010) were significantly higher in the group receiving sorafenib and TACE. Similarly, in a retrospective study by Wu *et al. (38)*, the combination of sorafenib and TACE resulted in a significantly prolonged median OS (17.9 *vs.* 7.1 months) and median TTP (9.3 *vs.* 3.4 months) compared to the group receiving TACE alone.

Table 1. Recent studies on sorafenib-based therapy to treat advanced HCC with PVTT

Author	Year	Type	OS	PFS	TTP	ORR	Adverse events
Jeong *et al.*[32]	2013	Retrospective (n = 30)	3.1	2.0	NA	NA	Fatigue (43.3%) and hand-foot skin reaction (30.0%)
Nakazawa *et al.*[31]	2014	Retrospective (n = 97)	4.3	NA	NA	NA	Elevated AST/ALT (6%), anorexia/nausea (4%)
Song *et al.*[29]	2015	Prospective (n = 60)	5.5	NA	2.1	NA	NA
Kim *et al.*[30]	2015	Retrospective (n = 66)	3.2	NA	1.6	NA	NA
Choi *et al.*[25]	2018	Prospective (n = 29)	7.2	NA	2.7	3.40%	Hyperbilirubinemia (34.5%), hand-foot syndrome (31.0%), and elevated AST (27.6%)
Kodama *et al.*[27]	2018	Retrospective (n = 36)	5.3	2.1	NA	NA	Elevated AST/ALT (8.3%), elevated bilirubin (5.5%), diarrhea and general fatigue (13.9%)
Kaneko *et al.*[26]	2020	Retrospective (n = 291)	14.4	NA	NA	NA	NA
Ahn *et al.*[28]	2021	Retrospective (n = 35)	6.4	NA	2.1	NA	Anemia (20%), hand-foot skin reaction (28.6%), dyspepsia/anorexia (25.7%), and elevated AST (22.9%)

OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, overall response rate; AST, aspartate transaminase; ALT, alanine transaminase; NA, not available.

The combination of selective internal radiation therapy and sorafenib was also studied in patients with advanced HCC, and the median OS was 12.1 months (sorafenib alone: 11.4 months, HR: 1.01, P = 0.953) (*39*). Although the efficacy of combination therapies seems encouraging, these therapies require adequate liver reserve given drug-related hepatotoxicity (such as elevated AST or ALT, diarrhea, or hyperbilirubinemia) (*34,35*).

Since sorafenib was the most widely used targeted drug in patients with advanced HCC, drug resistance posed a serious issue and significantly limited its efficacy (*40,41*). A poor prognosis (median TTP: 2.9 months) and liver function (Child-Pugh score, ≥ 7) were observed in patients with advanced HCC resistant to sorafenib (*42*). However, the specific rate of sorafenib resistance has not been reported, and few studies investigated the mechanisms underlying that drug resistance. Xu *et al.* (*43*) revealed that *circRNA-SORE* was significantly up-regulated in sorafenib-resistant HCC cells. When *circRNA-SORE* is silenced, the apoptosis of HCC cells induced by sorafenib increases, suggesting the pivotal role of circRNA-SORE in maintaining the resistance of HCC cells to sorafenib. In addition, circRNA-SORE was reported to induce sorafenib resistance by regulating β-catenin signaling and stabilizing Y-box binding protein 1 (*13*). Phosphoglycerate dehydrogenase is a critical molecule for sorafenib resistance in HCC (*44*). In addition, liver X receptor activation might also enhance sorafenib sensitivity in HCC (*45*).

Predicting the prognosis for patients with advanced HCC receiving sorafenib has recently been investigated. The acyl-CoA synthetase long-chain family member 4 protein was proposed as a biomarker of sorafenib sensitivity in HCC, given its negative association with IC_{50} values for sorafenib in HCC cell lines (R = -0.952, P < 0.001) (*46*). Colagrande *et al.* (*47*) performed contrast-enhanced CT on patients with advanced HCC receiving sorafenib before (T0) and 60-70 days (T1) after initiation of treatment, and the VED_{T0} and VED_{T1} values were calculated accordingly. Results revealed that patients with VED_{T0} > 70% had a higher median OS rate than those with lower VED_{T0} (451.5 *vs.* 209.5 days, P = 0.032), and the area under the curve was 0.716. In addition, magnetic resonance imaging can also be used to predict the prognosis for patients at BCLC-C receiving sorafenib (*48,49*).

In addition, the interaction between sorafenib and other drugs, which might influence efficacy, remains a major problem. A secondary analysis of phase 3 clinical trials (n = 542) revealed that administration of proton pump inhibitors did not induce adverse survival outcomes during sorafenib treatment (*50*). Combining pravastatin (*51*) (10.7 *vs.* 10.5 months, P = 0.975) with sorafenib had no significant influence on OS in patients with advanced HCC. Interestingly, patients receiving sorafenib and aspirin were reported to have a better prognosis than those receiving sorafenib alone (OS, 18.3 *vs.* 8.8 months, HR: 0.57, P < 0.001; PFS, 7.3 *vs.* 3.0 months, HR: 0.61, P < 0.001) (*52*).

2.1.2. Lenvatinib

Lenvatinib is an oral TKI recommended as a first-line therapy along with sorafenib (*53*). It inhibits *VEGFR*, *PDGFR*, *KIT*, *RET* and fibroblast growth factor receptor activity (*54*). To the extent known, the efficacy of lenvatinib was first indicated in a phase 2 study of lenvatinib in 46 patients with advanced HCC, who had a median OS of 18.7 months (95% CI: 12.7-25.1) and median TTP of 7.4 months (95% CI: 5.5-9.4) (*55*). A subsequent non-inferiority trial involved 954 patients and randomly assigned those patients to receive lenvatinib (n = 478) or sorafenib (n = 476). Results revealed that median OS was 13.6 months (95% CI: 12.1-14.9) in the group receiving lenvatinib, which was non-inferior to that in the group receiving sorafenib (12.3 months, 95% CI: 10.4-13.9; HR: 0.92, 95% CI: 0.79-1.06) (*15*). In addition, studies indicated that lenvatinib might be superior to sorafenib in maintaining liver function and improving the prognosis for patients with advanced HCC. A study by Terashima *et al.* (*56*) retrospectively examined 180 patients with advanced HCC and a Child-

Pugh score of 5-7, and a better Child-Pugh score was noted in patients receiving lenvatinib (n = 45) than those receiving sorafenib (n = 135) after 4 weeks (P = 0.048) and 12 weeks (P = 0.036). Similarly, Kim *et al.* (*57*) reported that lenvatinib treatment is significantly associated with a longer PFS, with an HR of 0.461, compared to sorafenib. When lenvatinib was combined with PD-1 blockades, patients with advanced HCC had a median PFS of 6.6 and OS of 11.4 months (*57*).

Despite the survival benefits, lenvatinib-related adverse events are frequent, and liver function and PVTT play an important role in the efficacy of lenvatinib. In a phase 2 study of lenvatinib administration (*55*), frequent adverse events including hypertension (76.1%), hand-foot syndrome (65.2%), decreased appetite (60.9%), and proteinuria (60.9%) were observed, which led to a dose reduction (34 patients, 74%) or discontinuation (10 patients, 22%) (*55*). Recently, two retrospective, real-world studies of lenvatinib in advanced HCC were conducted in South Korea and China. In South Korea, Cheon *et al.* (*58*) analyzed the survival outcomes of 67 patients with advanced HCC receiving lenvatinib as first-line therapy. In patients with Child-Pugh class A cirrhosis (n = 74), PFS was 4.6 months (95% CI: 3.1-6.1) and OS was10.7 months (95% CI: 4.8-16.5) while PFS was 2.6 months (95% CI: 0.6-4.6) and OS was 5.3 months (95% CI: 2.0-8.5) in patients with Child-Pugh class B cirrhosis (n = 18). Wang *et al.* (*59*) performed a real-world study involving 54 patients with HCC receiving lenvatinib in China, and an ORR of 22% was observed with a PFS of 168 days and an adverse event rate of 92.8%. That study noted that PVTT was significantly associated with a poor PFS as an independent risk factor (HR: 0.38, P = 0.037).

Interestingly, lenvatinib was studied in patients with advanced HCC and PVTT. Chuma *et al.* (*60*) indicated that patients with advanced HCC and tumor thrombus in the main portal vein trunk had a median PFS of 101 days and OS of 201 days after lenvatinib treatment. Similarly, in a retrospective study by Maruta *et al. (26)*, 54 patients with advanced HCC and PVTT who received lenvatinib treatment had an OS of 14.7 months. Patients with PVTT still had a significantly poorer survival than those without PVTT (6.5 *vs.* 14.2 months) (*61*). A point worth noting is that patients with advanced HCC and PVTT still had a poor prognosis despite systemic treatment.

Although lenvatinib may provide additional survival benefits over sorafenib in patients with advanced HCC, a lenvatinib-susceptible subgroup of patients with HCC needs to be selected. Myojin *et al.* (*62*) proposed a *ST6GAL1*-based stratification strategy for lenvatinib or sorafenib. They conducted genetic screening on a mouse model of HCC (C57BL/6J male mice) and evaluated the biomarker candidate (*ST6GAL1*) in human HCC cell lines (serum samples from 76 patients with advanced HCC receiving curative hepatectomy and 96 patients receiving TKI therapy). Results suggested that a high level of *ST6GAL1* expression was significantly associated with a better treatment response to lenvatinib than sorafenib. However, for patients with a low level of *ST6GAL1* expression, there were no significant differences in OS between lenvatinib and sorafenib treatment. The predictive factors for clinical outcomes of lenvatinib therapy have also been examined. A study by Shomura *et al.* (*63*) prospectively enrolled 46 patients with advanced HCC who received lenvatinib therapy and it followed them for about 2 years. Results revealed that grade 2/3 hypothyroidism occurred in patients with a shorter treatment duration than in those with grade 0/1 (HR: 4.28, P = 0.011). Patients with grade 2/3 hypothyroidism had a significantly longer OS than those with grade 0/1 (age-adjusted HR: 0.21, 95% CI: 0.05-0.94).

2.1.3. Regorafenib

Like sorafenib, regorafenib is an oral multi-kinase inhibitor that suppresses angiogenesis, oncogenesis, and the tumor microenvironment (*64*), and it has been recommended as a second-line therapy for advanced HCC by the European Association for the Study of the Liver (EASL) (*6*). The RESORCE trial involved 573 patients with HCC who tolerated sorafenib (≥ 400 mg/day for 28 days) and who had relatively good liver function (Child-Pugh class A) (*19*). When given regorafenib 160 mg, survival improved significantly compared to a placebo (median OS, 10.6 *vs.* 7.8 months, HR: 0.63, P < 0.001). However, several complications were reported, of which the most common grade 3 or 4 adverse events were hypertension (15% *vs.* 5%), a hand-foot skin reaction (13% *vs.* 1%), fatigue (9% *vs.* 5%), and diarrhea (3% *vs.* 0%). A subsequent real-world study indicated that regorafenib after sorafenib led to a prolonged OS in patients with advanced HCC compared to a placebo (9.7 *vs.* 6.0 months, P < 0.001) (*65*). In another real-world study, sequential therapy (regorafenib after sorafenib) was administered to 133 patients with HCC, who had a median OS of 10.0 months, a PFS of 2.7 months, and a TTP of 2.6 months (*66*). The survival outcomes were comparable to those in the RESORCE trial (n = 573, OS: 10.6 months) and a phase III study in Japan (n = 44, OS: 17.3 months) (*67*).

The safety and efficacy of regorafenib as a second-line agent to treat patients with advanced HCC and Child-Pugh class B cirrhosis have been indicated. Kim *et al.* (*68*) retrospectively examined 59 patients with advanced HCC and Child-Pugh class B cirrhosis who received regorafenib after sorafenib (37 receiving 2nd line systemic therapy and 22 receiving 3rd-4th line systemic therapy). The median OS was 4.6 months and PFS was 1.8 months, which were significantly worse than those in patients with Child-Pugh class A cirrhosis (P < 0.001 and P = 0.008, respectively). In addition, compared to patients with Child-Pugh class A cirrhosis, grade 3 or 4 adverse effects were more common in

patients with Child-Pugh class B cirrhosis (27.1% *vs.* 14.1%, $P = 0.017$), including increased blood bilirubin, a hand-foot skin reaction, and skin rash.

Recently, the combination of regorafenib and immunotherapy (*e.g.*, anti-PD-1 agents) was also examined in animal models. For example, Shigeta *et al.* (*69*) intraperitoneally injected regorafenib (at 10 mg/kg daily) or/and PD-1 antibodies (at 10 mg/kg thrice a week) in orthotopic HCC mice. Compared to regorafenib or anti-PD-1 alone, mice receiving regorafenib plus an anti-PD-1 antibody had a significant survival benefit (HR: 0.17, $P < 0.001$), which might be attributed to the promotion of cytotoxic T lymphocyte infiltration *via* the *CXCL10/CXCR3* axis.

In addition, several biomarkers with which to predict the OS of patients receiving regorafenib were examined. Teufel *et al.* (*70*) collected tumor tissues and baseline plasma samples from patients with advanced HCC in the RESORCE trial and reported that the decreased expression of 5 proteins in plasma was significantly associated with better OS after regorafenib treatment, including angiopoietin 1 (HR: 1.12, 95% CI: 1.05-1.19), the latency-associated peptide of transforming growth factor beta 1 (HR: 1.36, 95% CI: 1.12-1.65), cystatin B (HR: 1.46, 95% CI: 1.15-1.85), oxidized low-density lipoprotein receptor 1 (HR: 1.35, 95% CI: 1.16-1.57), and C-C motif chemokine ligand 3 (HR: 1.02, 95% CI: 1.01-1.04). In addition, Tong *et al.* (*71*) indicated that annexin A3 (*ANXA3*) is a potential biomarker with which to predict the effect of sorafenib and regorafenib treatment in a mouse model of HCC. A high level of *ANXA3* expression could increase the resistance of HCC cells to sorafenib and regorafenib. Interestingly, when *ANXA3* was inhibited in the immune-competent mouse model, a significantly decreased liver/body weight ratio was observed after both sorafenib and regorafenib treatment.

2.1.4. Cabozantinib

Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (including *VEGFR*, *MET*, *RET*, *AXL* and *KIT*) that are associated with oncogenesis, angiogenesis, tumor growth, and metastasis (*72*). The CELESTIAL trial (a randomized, double-blind, phase 3 trial) (*17*) involved 707 patients with advanced HCC who had received sorafenib treatment, and it evaluated the effect of cabozantinib. Results revealed a significantly improved OS and PFS in the group receiving cabozantinib compared to the group receiving a placebo (OS: 10.2 *vs.* 8.0 months, $P = 0.005$; PFS: 5.2 *vs.* 1.9 months, $P < 0.001$). In addition, adverse events of grade 3 or 4 were 68% in patients receiving cabozantinib and 36% in patients receiving a placebo.

In a secondary analysis of the CELESTIAL trial, Shlomai *et al.* (*73*) evaluated the cost-effectiveness of cabozantinib according to the Markov model. Results revealed that the mean incremental cost of cabozantinib for patients with HCC was USD 76,406 and the incremental cost-effectiveness ratio compared to supportive care was USD 469,374/quality-adjusted life-year (QALY) (based on 60 mg cabozantinib daily), which is not cost-effective at conventional willingness-to-pay thresholds (USD 50,000-150,000 per QALY). Based on adjusted second-line populations in the RESORCE and CELESTIAL trials, Kelley *et al.* (*74*) compared patients receiving regorafenib ($n = 573$) with those receiving cabozantinib ($n = 266$). Results revealed no significant differences in median OS (10.6 *vs.* 11.4 months, $P = 0.347$), while the median PFS was longer in the cabozantinib group (5.6 *vs.* 3.1 months, $P < 0.001$). In a recent multicenter, real-life cohort study involving 88 patients with advanced HCC, a median OS of 7 months was reported after the start of cabozantinib treatment (*75*).

2.1.5. Donafenib

Donafenib is a novel small-molecule TKI developed by creatively substituting a trideuteriomethyl group for a methyl on sorafenib to inhibit *VEGFR*, *PDGFR*, and various *Raf* kinases (*76*). In a phase 2-3 trial (ZGDH3), donafenib was given 200 mg orally, twice daily. The PFS and ORR were similar, but donafenib displayed superiority over sorafenib in improving OS (12.1 *vs.* 10.3 months) (*77*). Moreover, improved safety and tolerability indicate a potential option for the first-line treatment of advanced HCC (*78*).

2.2. Immunotherapy

Antigen-presenting cells mediate T cell activation after recognizing a cancer cell antigen. However, immune tolerance by HCC can be induced by the increased differentiation of Treg cells, upregulated immunosuppressive cytokines, and elevated expression of co-inhibitory molecules (*e.g.*, PD-1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4)). The immunosuppressive microenvironment facilitates the growth and progression of HCC, which provides a therapeutic target for advanced HCC (*79*).

A meta-analysis of 2,402 patients with advanced HCC who received ICIs revealed that the mean OS was 15.8 months (*80*). Moreover, the overall ORR was 22.7% and the disease control rate was 60.7%. In the subgroup, the OS was 18.7 months for patients receiving nivolumab ($n = 846$) and 13.3 months for those receiving pembrolizumab ($n = 435$). The overall rate of treatment discontinuation due to adverse events was 14.9%.

A growing number of studies on ICIs have indicated that PD-1/PD-L1 blockade immunotherapy is a novel optional therapy with which to treat advanced HCC (*81-83*). In a real-world study based on 55 patients with advanced HCC receiving an anti-PD-1 agent, Cui *et al.* (*84*) noted a median OS of 15 months, a median PFS

of 10 months, and a disease control rate of 89%. In addition, a meta-analysis of 1,232 patients with advanced HCC receiving PD-1 or PD-L1 inhibitors revealed that the median PFS was 3.58 months (95% CI: 2.65-4.50), the median OS was 12.24 months (95% CI: 10.48-14.00), the overall ORR was 20% (95% CI: 0.16-0.24), the disease control rate was 60% (95% CI: 0.54-0.67), the rate of adverse events was 63% (95% CI: 0.45-0.78), and the rate of serious adverse events was 11% (95% CI: 0.06-0.22) (*85*).

2.2.1. Nivolumab (anti-PD1 antibody)

Nivolumab is a PD-1 ICI with a durable response and manageable safety, and it has been recommended for patients with advanced HCC by the American Society of Clinical Oncology (ASCO) owing to its additional survival benefits (*53*). A dose-escalation and expansion trial of nivolumab (CheckMate 040) was performed in 262 patients with advanced HCC (48 in the dose-escalation phase and 214 in the dose-expansion phase) (*18*). The ORR was 20% (95% CI: 15-26%) in patients receiving nivolumab 3 mg/kg in the dose-expansion phase and 15% (95% CI: 6-28%) in the dose-escalation phase. In dose escalation, 3 patients (6%) had serious treatment-related adverse events (including pemphigoid, adrenal insufficiency, and a liver disorder), and the incidence of adverse events was not significantly associated with the drug dose (*18*). Given the difference in incidence and pathogenesis in Asian and non-Asian populations (*86,87*), the safety and efficacy of nivolumab in Asians were further indicated in CheckMate 040 (*86*). ORR was 14% in the overall population and 15% in the Asian cohort. The median duration of response was longer in the overall population (19.4 months, 95% CI: 9.7-not evaluable) than in Asian patients (9.7 months, 95% CI: 5.6-not evaluable), while the median OS was similar between the overall population (15.1 months, 95% CI: 13.2-18.2) and Asian patients (14.9 months, 95% CI: 11.6-18.9).

Nivolumab was also studied in patients with advanced HCC and Child-Pugh class B cirrhosis. Kambhampati *et al.* (*88*) retrospectively studied the effect of nivolumab in 18 patients with advanced HCC and Child-Pugh class B cirrhosis from the Hepatobiliary Tissue Bank and Registry and CheckMate 040 trial, which reported an ORR value of 17% (3 of 18 patients, including 2 partial responses and 1 complete response). The median OS was 5.9 months (95% CI: 3.0 months-not evaluable), and the median PFS was 1.6 months (95% CI: 1.4-3.5 months). In addition, most patients (94%, 17 of 18 patients) experienced grade ≥ 3 adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)), and treatment-related grade ≥ 3 adverse events were reported in 28% of patients (5 of 18 patients).

In addition, the safety and efficacy of nivolumab were recently studied in the real world. Fessas *et al.* (*89*) conducted an international, multicenter observational study (eight centers in North America, Europe, and Asia) involving 233 patients with advanced HCC receiving nivolumab alone. They reported that the ORR was 22.4% and the disease control rate was 52.1%, with a median OS of 12.2 months (95% CI: 8.4-16.0) and PFS of 10.1 months (95% CI: 6.1-14.2). Still, the OS was shorter in patients with Child-Pugh class B cirrhosis (n = 75) than in those with Child-Pugh class A cirrhosis (n = 158) (7.3 *vs.* 16.3 months, $P < 0.001$). Based on 203 patients with advanced HCC receiving nivolumab, Choi *et al.* (*90*) indicated that the median OS was significantly shorter in patients with Child-Pugh class B cirrhosis (n = 71) than Child-Pugh class A cirrhosis (n = 132) (11.3 *vs.* 42.9 weeks, HR: 2.10). In patients with Child-Pugh class B cirrhosis, those with a score of 8-9 had a worse OS than those with a score of 7 (7.4 *vs.* 15.3 weeks, HR: 1.93, $P < 0.020$). In another real-world study involving 34 patients with advanced HCC, Scheiner *et al.* (*91*) reported similar results with a PFS of 4.3 months (95% CI: 2.0-6.7) and an OS of 9.0 months (95% CI: 5.5-12.5). These studies indicated that the OS remained poor in patients with Child-Pugh class B cirrhosis despite nivolumab treatment, and more management therapies should be explored for patients with advanced HCC and Child-Pugh class B cirrhosis.

2.2.2. Pembrolizumab (anti-PD1 antibody)

Pembrolizumab (anti-PD1 antibody) is another ICI that was approved as second-line systemic therapy for the treatment of advanced HCC based on the results of a phase 2 trial (KEYNOTE-224) (*92*). In KEYNOTE-224, pembrolizumab performed well, resulting in a median PFS of 4.9 months (95% CI: 3.4-7.2), an OS of 12.9 months (95% CI: 9.7-15.5), and an ORR of 17% (95% CI: 11-26).

A subsequent phase III trial (KEYNOTE-240) compared pembrolizumab and a placebo, but results did not reach the prespecified boundaries of statistical significance in terms of OS and PFS (*93*). A presentation at the ASCO gastroenterology (GI) 2022 meeting indicated that pembrolizumab resulted in a better OS (14.6 *vs.* 13 months) and PFS (2.6 *vs.* 2.3 months) compared to a placebo.

2.2.3. Camrelizumab (anti-PD1 antibody)

Camrelizumab is a humanized monoclonal anti-PD1 antibody that has a different binding epitope than nivolumab and pembrolizumab (*94*). It was well tolerated in patients with an advanced solid tumor (*95,96*). A multicenter, phase 2 single-arm study (NCT02989922) indicated that the ORR to camrelizumab was 14.7% (95% CI: 10.3-20.2) and the OS probability at 6 months was 74.4% (95% CI: 68.0-79.7). Grade 3/4 treatment-related

adverse events (TRAEs) occurred in 22% patients and the rate of treatment-related death was 0.9% (*97*).

2.2.4. Durvalumab (anti-PD-L1)

Intravenous durvalumab is a human monoclonal antibody that has anti-tumor action by binding to the PD-L1 receptor on the surface of cancer cells (*98*). A phase 1/2 study (NCT01693562) evaluated the safety and efficacy of durvalumab in patients with HCC, and it noted an ORR of 10.3%, a median OS of 13.2 months (95% CI: 6.3-21.1), and a rate of Grade 3/4 TRAEs of 20%, as was reported at the ASCO GI 2017 meeting. However, most studies tend to favor anti-PD-1 over anti-PD-L1 therapy because of the poor pharmacokinetic properties of anti-PD-L1 antibodies and the additional blockade of PD-L2 interactions (*99-101*).

2.2.5. Tremelimumab (anti-CTLA-4)

Tremelimumab is a lgG2 monoclonal antibody specific for CTLA-4 that can promote T cell activation and proliferation by blocking the binding of CTLA-4 (*102*). A clinical trial (NCT01008358) of tremelimumab in patients with HCC indicated that the disease control rate was 76.4%, the median TTP was 6.48 months (95% CI: 3.95-9.14), and the median OS was 8.2 months (95% CI: 4.64-21.34) (*103*).

2.3. Combination systemic therapies

2.3.1. Combinations of ICIs and an anti-*VEGF* antibody

VEGF overexpression is a critical mechanism of tumor angiogenesis and is related to immunosuppressive action in HCC (*104*). Combinations of ICIs and an anti-*VEGF* antibody can lead to synergistic anti-tumor action against advanced HCC. Therefore, atezolizumab plus bevacizumab was recommended as first-line therapy according to guidelines (*53,105,106*). Atezolizumab is a PD-L1 blocker and bevacizumab is a *VEGF* inhibitor. Atezolizumab plus bevacizumab has superseded sorafenib as first-line treatment for unresectable HCC, and the former is now approved by the US FDA because of its superior performance (PFS: 6.8 *vs.* 4.3 months, OS: 19.2 *vs.* 13.4 months, ORR: 30 *vs.* 11%) (*16*).

Both lenvatinib and cabozantinib can inhibit *VEGF* receptors. Lenvatinib plus pembrolizumab displayed encouraging results with an ORR of 46.0% (95% CI: 36.0-56.3) and median PFS of 9.3 months (95% CI: 5.6-9.7) in a phase 1b trial (*107*). Atezolizumab plus cabozantinib was evaluated by the COSMIC-312 phase III trial, and results revealed that atezolizumab-cabozantinib was superior to sorafenib in terms of PFS (6.8 *vs.* 4.2 months).

2.3.2. Combinations of 2 ICIs

A combination of PD-1 and CTLA-4 antibodies has been used to treat numerous cancers including HCC. A previous trial (phase I/II) investigated the efficacy and safety of durvalumab-tremelimumab and found that T300 + D1500 (tremelimumab 300 mg plus durvalumab 1,500 mg (one dose each during the first cycle) followed by durvalumab 1,500 mg once every 4 weeks) displayed the most encouraging benefit-risk profile (*108*). T300 + D1500 (STRIDE) was further evaluated in a phase III trial (HIMALAYA), the results of which were reported at the ASCO GI 2022 meeting. T300 + D1500 led to a significantly better OS of 16.4 months compared to sorafenib alone at 13.8 months (HR: 0.78; 95% CI: 0.65-0.92; $P = 0.0035$). The ORR to STRIDE was 20.1%, which was higher than that for sorafenib alone (5.1%). T300 + D1500 is a promising treatment strategy for patients with HCC who are not eligible for atezolizumab plus bevacizumab (*109*).

Moreover, the US FDA recently approved the combined use of atezolizumab and bevacizumab in patients with advanced HCC who had not previously received systemic treatment (*110*). Atezolizumab is a monoclonal antibody that inhibits the interaction of PD-L1 with programmed cell death protein 1 (PD-1) and *CD80* receptors, whereas bevacizumab blocks vascular endothelial growth factor A. In a global open-label trial (IMbrave 150 trial), patients with advanced HCC without previous systemic treatment were randomly assigned to receive either atezolizumab plus bevacizumab ($n = 336$) or sorafenib ($n = 165$) in a 2:1 ratio (*16*). OS at 12 months was significantly longer in the patients receiving atezolizumab-bevacizumab (67.2% *vs.* 54.6%) than in those receiving sorafenib. The HR for all-cause death was 0.58 (95% CI: 0.42-0.79) in patients receiving atezolizumab-bevacizumab compared to patients receiving sorafenib ($P < 0.001$) (*16*). The survival rate at 12 months was 67.2% for patients receiving atezolizumab-bevacizumab and 54.6% for patients receiving sorafenib, and a longer PFS was observed in patients receiving atezolizumab-bevacizumab (6.8 *vs.* 4.3 months, HR: 0.59, $P < 0.001$). There were no significant differences in adverse events between patients receiving atezolizumab-bevacizumab (56.5%) and patients receiving sorafenib (55.1%), except for grade 3 or 4 hypertension (*16*). A network meta-analysis of 14 trials with 6,290 patients with advanced HCC further indicated a significantly prolonged OS in patients receiving atezolizumab-bevacizumab compared to patients receiving lenvatinib (HR: 0.63), sorafenib (HR: 0.58), or nivolumab (HR: 0.68, 95% CI) alone (*111*). Moreover, atezolizumab-bevacizumab ($n = 60$) resulted in better survival benefits than atezolizumab alone in patients with advanced HCC (PFS: 5.6 *vs.* 3.4 months, $P = 0.011$) (*16*). In a subsequent study, Chiang *et al.* (*112*) performed a cost-effectiveness analysis based on the IMbrave 150 trial. Atezolizumab-bevacizumab resulted in a gain of 0.44 QALYs with a cost of USD 79,074. The incremental

cost-effectiveness ratio of atezolizumab-bevacizumab was USD 179,729 per QALY compared to sorafenib. The decreased price of atezolizumab-bevacizumab by 20% was expected to lead to a cost-effectiveness ratio of USD 150,000/QALY and a decreased price by 29% was expected to lead to a cost-effectiveness ratio of USD 100,000/QALY. This would satisfy the willingness-to-pay threshold according to that study. Compared to sorafenib alone, atezolizumab-bevacizumab provided an additional 0.53 QALYs, thus resulting in an incremental cost-effectiveness ratio of USD 145,546.21 per QALY in China (the willing-to-pay threshold was USD 28,527.00/QALY) and USD 168,030.21 per QALY in the US (the willing-to-pay threshold was USD 150,000.00 / QALY) (*113*). Therefore, despite its marked efficacy, atezolizumab-bevacizumab might not be a cost-effective strategy for the first-line systemic treatment of patients with advanced HCC in China and the US.

On March 10, 2020, FDA approved nivolumab plus ipilimumab for the treatment of patients with HCC who had previously received sorafenib (*114*). The recommended regimen is nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every three weeks for 4 cycles followed by nivolumab 240 mg biweekly. The FDA's approval was based on data from the CheckMate040 randomized clinical trial (*115*). This combination strategy is currently being studied as a first-line therapy in the phase III CHECKMATE-9DW trial.

2.3.3. Combinations of ICIs/TKIs and infusion chemotherapy

Previous studies revealed that chemotherapy can disrupt immune tolerance, facilitate an immune response, and induce immunogenic cell death (*116*). A phase 2 study investigated the combination of camrelizumab and oxaliplatin-based chemotherapy to treat advanced HCC (*117*). Results indicated that the ORR was 26.5%. A subsequent phase 3 study (NCT03605706) comparing the combination therapy to a placebo with chemotherapy is ongoing. Sorafenib plus chemotherapy was evaluated by the phase II randomized PRODIGE 10 trial (*34*). The additional clinical benefit from sorafenib plus chemotherapy seems limited, and no subsequent trial is planned.

To the extent known, there are few studies on intravenous chemotherapy treatment alone for advanced HCC since it is an alternative therapy with modest anti-tumoral responses and limited survival benefits. Abou-Alfa *et al.* (*118*) evaluated the efficacy of doxorubicin plus sorafenib compared to doxorubicin alone (n = 96). Patients receiving combination therapy had a significantly higher median OS (13.7 *vs.* 6.5 months, P = 0.006) and PFS (6.0 *vs.* 2.7 months, P=0.006).

2.3.4. Mechanisms of synergy between ICIs and other molecular therapies

All combinations of TKIs and ICIs that are efficacious against HCC are considered to be related to the inhibition of *VEGF* signaling. Although two treatments might lead to an additive effect, several experimental studies and clinical trials have provided evidence of a synergistic effect (*69,119-123*).

This synergy includes the effect of *VEGF* pathway inhibition on tumor vasculature and immune cells. Inhibition of *VEGF* causes vessel pruning (leading to hypoxia) and normalization (leading to improved drug delivery and enhancement of immune cell attachment and extravasation) (*124*). In addition, *VEGF* can affect the tumor microenvironment as a potent immunomodulatory molecule (*122*). Moreover, the effects of TKIs on HCC are not limited to *VEGF* signaling. TKIs can also block pathways that lead to immune cell exclusion, such as *MAPK*, *WNT-β-catenin*, *CDK4/6*, and *PI3K-PTEN* signaling (*125*).

2.4. Adoptive cell transfer

The mechanism of adoptive cell transfer (ACT) is the transfer of immune cells back to the body after they have been induced to possess more effective antitumor features (*126*). ACT therapies that displayed promising antitumor activity against HCC include 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) (*127*).

Autologous *GPC-3*-CAR-T cell therapy resulted in good clinical outcomes (an OS rate of 50.1% at 6 months, 42.0% at 1 year, and 10.5% at 3 years) in patients with *GPC-3*-positive advanced HCC in phase I studies (*128*). More than half of the patients with *CD133*-positive advanced HCC had a clinical benefit, with a median PFS of 6.8 months and OS of 12 months after reinfusion of *CD133*-CAR-T cells (*129*). In addition, several meta-analyses concluded that adjuvant CIK cell-based immunotherapy is a promising therapeutic approach for patients with BCLC stage B or lower HCC since it can improve OS and reduce recurrence (*130,131*). Further studies and clinical trials need to be conducted.

2.5. Oncolytic viruses

Oncolytic viruses (OVs) can preferentially infect tumor cells and cause lysis while sparing normal tissue, so they are promising treatment strategies that might be considered in multimodal therapy (*132*). In recent years, the oncolytic activity of LDO-GFP (a herpes simplex virus type 1-based oncolytic vector), Golgi protein 73-sphingosine kinase 1-short RNA-adenovirus serotype 5, and VV-IL-37 was noted *in vitro* and *in vivo* (*133-135*). OV dosing must be determined for clinical use, and thus more trials need to be conducted.

3. Management of advanced HCC: Locoregional therapies

3.1. TACE

Although TACE is not recommended for patients with advanced HCC according to the EASL (*6*) and the US Association for the Study of Liver Diseases (AASLD) (*136*), several studies suggested the survival benefits of TACE in patients with advanced HCC with or without PVTT (*137-139*). The BRIDGE study indicated that TACE was commonly used in many countries for patients with all stages of HCC (including North America, Europe, China, and South Korea) and TACE was used in about 50% of patients with BCLC-C HCC (*140*). To the extent known, Lo *et al.* (*141*) were the first to indicate that TACE could result in additional survival in patients with advanced HCC (relative risk of death: 0.49, 95% CI: 0.29-0.81, $P = 0.006$) compared to the best supportive care. Niu *et al.* (*137*) indicated the expanded OS in patients receiving TACE compared to patients receiving conservative treatment (8.67 *vs.* 1.4 months, $P < 0.001$). Recently, a randomized, multicenter prospective trial (TACTICS trial) (*142*) has revealed that TACE plus sorafenib significantly improved PFS compared to TACE alone in patients with advanced HCC, with a median PFS of 25.2 months and 13.5 months, respectively ($P = 0.006$). The 1-year survival rate was 96.2% and the 2-year survival rate was 82.7% in patients receiving combination therapy compared to rates of 77.2% and 64.6% in the TACE group.

TACE might be a treatment option for patients with advanced HCC and PVTT involving collateral vessels around the portal vein and relatively good liver function (*143*). In a large cohort of 164 patients with advanced HCC and PVTT, TACE significantly improved survival in patients with PVTT involving the segmental branches of the portal vein or above (*144*) compared to patients receiving conservative treatment. In a recent meta-analysis (*139*) of 1,933 patients with HCC and PVTT, TACE resulted in a median OS of 8 months (95% CI: 5-15) and a 1-year survival rate of 29% (95% CI: 20-40%), a 3-year survival rate of 4% (95% CI: 1-11%), and a 5-year survival rate of 1% (95% CI: 0-5%).

3.2. Hepatic artery infusion chemotherapy

As mentioned in the practice guidelines in Asian countries (*10,145*), hepatic artery infusion chemotherapy (HAIC) is widely used to treat unresectable HCC. HAIC injects a highly concentrated chemotherapeutic agent into the targeted lesion *via* the hepatic artery. A multicenter retrospective study conducted in South Korea indicated that HAIC led to favorable responses in patients with HCC and PVTT compared to sorafenib, with a longer median OS (7.1 *vs.* 5.5 months, $P = 0.011$) and TTP (3.3 *vs.* 2.1 months, $P = 0.034$) (*29*). A phase 3 trial (SILIUS, NCT01214343) conducted at 31 sites in Japan involved patients with unresectable advanced HCC to compare HAIC plus sorafenib and sorafenib monotherapy (*146*). There were no significant differences in the median OS of patients receiving HAIC-sorafenib and patients receiving sorafenib (11.8 months (95% CI: 9.1-14.5) *vs.* 11.5 months (95% CI: 8.2-14.8), $P = 0.955$). Grade 3-4 adverse events were more frequent in patients receiving HAIC-sorafenib. Nevertheless, HAIC resulted in a better response in patients with HCC and macroscopic vascular invasion. Therefore, HAIC cannot significantly provide an additional benefit for patients with advanced HCC who received sorafenib monotherapy, but it could be an additional treatment for patients with macroscopic vascular invasion (*147*).

3.3. Transarterial radioembolization

The 2018 AASLD guidelines (*148*) recommended transarterial radioembolization (TARE) as an alternative therapy to molecularly targeted agents for patients with BCLC stage C cirrhosis. In contrast to TACE, the therapeutic action of TARE is predominately radiation with yttrium 90, which is injected intra-arterially in the vessels feeding the HCC (*149*). A retrospective study conducted by Gramenzi *et al.* (*150*) noted the potential efficacy of TARE in patients with advanced HCC. Two clinical trials compared TARE and sorafenib in advanced HCC (*151,152*). The first, the SARAH (SorAfenib Versus Radioembolization in Advanced Hepatocellular Carcinoma) trial, found no significant differences in survival between patients receiving TARE or sorafenib (8.0 *vs.* 9.9 months, $P = 0.18$). The second randomized trial, the SIRveNIB (selective internal radiation therapy *vs.* sorafenib) trial, also reported no significant differences in OS between TARE and sorafenib (8.8 *vs.* 10.0 months, $P = 0.36$). Both trials rated TARE highly because of its tumor response rate and tolerability.

3.4. Percutaneous ablation

Ethanol injection (EI), microwave ablation (MWA), radiofrequency ablation (RFA), and cryoablation (CRA) are predominant forms of image-guided percutaneous ablation therapies with minimally invasive characteristics. They are frequently suggested for patients with small HCC (≤ 3 cm) and Child-Pugh class A or B hepatic functional reserve.

There was a time when EI was regarded as the standard in ablation. The survival rate in patients with HCC treated with EI has been reported to be 38-60% at 5 years (*153-156*). Nowadays, EI is seldom recommended unless RFA cannot be safely performed. A SEER database analysis indicated that EI resulted in similar clinical outcomes compared to RFA in patients with a single HCC of no more than 5 cm (*157*). Many centers considered EI as an adjuvant therapy for combination

strategies (*158*). Studies have indicated that EI can enhance the efficacy of RFA in the treatment of HCC (*159,160*), the underlying mechanism of which is that EI can induce microthrombi formation to occlude blood vessels and then reduce heat dissipation to increase the efficacy of RFA. EI combined with TACE was found to be safe for the treatment of advanced HCC and PVTT, and it resulted in a significant survival advantage over TACE alone (*161*).

MWA, in which tumor tissue is ablated by dielectric heat caused by microwave energy, has progressed beyond its initial use for early-stage HCC thanks to the development of equipment and techniques in recent years (*3*). Two clinical trials revealed that MWA is more efficacious than RFA in terms of eradicating larger tumors (size 3-5 cm) and requires less time (*162,163*). Nowadays, whether improved MWA can be suggested for intermediate-stage patients remains unknown. A recent multicenter retrospective study indicated that MWA can result in better survival for patients with HCC (BCLC stages 0-B) over a 12-year follow-up period (*164*). Only 1 randomized study of advanced HCC compared the safety and efficacy of TACE plus MWA and TACE alone, and it found that combined treatment was more efficacious (*165*). Further studies of MWA to treat advanced HCC need to be conducted.

RFA releases an electrical current within the radiofrequency range through a needle electrode and thus leads to heat-based thermal cytotoxicity (*166*). Studies revealed that RFA alone or combined with other therapies could provide additional survival benefits for patients with advanced HCC (*166-171*). For example, Duffy *et al.* (*169*) combined tremelimumab (3.5 mg/kg or 10 mg/kg for 6 doses every 4weeks) and RFA (on day 36) to treat advanced HCC, and the median OS was 12.3 months (95% CI: 9.3-15.4 months) with no dose-limiting toxicities. The 6-month probability of tumor PFS was 57.1% and the 12-month probability was 33.1% (*169*). Peng *et al.* (*168*) reported that the median OS improved significantly in patients receiving combination therapy (RFA plus TACE and sorafenib) than in patients receiving sorafenib alone (14.0 *vs.* 9.0 months, $P < 0.001$). In a study by Lyu *et al.* (*172*), patients with advanced HCC who received a PD-1 inhibitor (nivolumab or pembrolizumab) but who did not respond for at least 12 months underwent subtotal thermal ablation. Interestingly, an increased response rate from 10% (5/50) to 24% (12/50) was observed after RFA. Moreover, the efficacy and safety of RFA were evaluated in that proof-of-concept study, with a median TTP of 6.1 months (95% CI: 2.6-11.2), PFS of 5 months (95% CI: 2.9-7.1), and OS of 6.9 months (95% CI: 7.7-26.1).

CRA has an advantage of causing less damage when treating HCC compared to MWA and RFA because of its specific mechanism: tumor tissue injury is based on the formation of an ice ball at the tip of a cryoprobe (*173*). CRA is equally effective for locoregional treatment of early-stage HCC compared to RFA and MWA (*174,175*). CRA and RFA had similar rates of local tumor progression and safety even in elderly patients with small HCC (*176*). Currently, CRA is regarded as a safe alternative to RFA or MWA (*177*). Reported experience in using CRA to treat unresectable HCC is limited. Several retrospective studies compared the efficacy and safety of TACE combined with ablation (MWA, RFA, or CRA) for intermediate or advanced HCC (*178-180*). Although the efficacy of these combination strategies was comparable, TACE-MWA had the lowest complication rate (especially with regard to thrombocytopenia).

3.5. Hepatectomy

Hepatectomy might also be an optional therapy for patients with advanced HCC. It was not recommended by the EASL or JIS guidelines (*6,10*), but its survival benefits have been examined in many studies. A study by Komatsu *et al.* (*181*) involved 314 patients (BCLC-B, $n = 149$; BCLC-C, $n = 165$) who underwent complete hepatectomy or reductive hepatectomy. The median OS was 19.5 months for patients with BCLC-C undergoing complete hepatectomy and 17.6 months for those undergoing reductive hepatectomy ($P = 0.014$) but 48.9 months and 20.1 months in those with BCLC-B ($P = 0.008$). The 3-year OS rate was 18.6% for BCLC-C patients undergoing complete hepatectomy and 0% for those undergoing reductive hepatectomy. The 3-year OS rate was 47.5% in patients with BCLC-B undergoing complete hepatectomy and 0% in those undergoing reductive hepatectomy. A study by Yamamoto *et al.* (*182*), retrospectively examined 372 patients with advanced HCC and PVTT who underwent hepatectomy. Results indicated that the cumulative 5-year OS was 58.3% and the 5-year disease-free survival rate was 31.3%. A meta-analysis (*183*) compared hepatectomy to TACE or sorafenib alone for patients with advanced HCC and PVTT. There were no significant differences in survival between hepatectomy and TACE (odds ratio (OR): 0.96, 95% CI: 0.44-2.11), but hepatectomy resulted in an improved OS compared to sorafenib (OR=0.12, 95% CI: 0.06-0.24). Importantly, hepatectomy was superior in patients without PVTT in the main trunk compared to those with main portal vein invasion (OR = 2.18, 95% CI: 1.76-2.70). Still, this conclusion should be interpreted cautiously given the limited sample, publication bias, type of retrospective study, and different follow-up times.

3.6. Radiation therapy

HCC is considered to be a radiosensitive tumor, and its location in a radiosensitive organ limited the use of radiotherapy in the past. Nevertheless, recent advances in three-dimensional conformal radiation therapy (3D-CRT) have allowed safer use of radiotherapy without severe toxicity in patients with unresectable HCC. Technological

developments (intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT)) can target HCC precisely, thus providing a clinical benefit. 3D-CRT is suggested for symptomatic bony metastases caused by advanced HCC by the Asian-Pacific clinical practice guidelines (*184*) but is not recommended in the AASLD and EASL guidelines for treating HCC. A multicenter controlled study conducted by Wei *et al.* (*185*) indicated that neoadjuvant 3D-CRT provided significantly better survival outcomes than resection alone in HCC and PVTT. Even through the evidence is insufficient, 3D-CRT may be one of the promising treatment options for advanced HCC.

4. Future perspectives

4.1. Combinations of systemic and locoregional therapies

In addition to systemic treatments, local therapies such as radiotherapy, RFA, and TACE were found to induce an immune response by promoting the death of immunogenic tumor cells or destroying the tumor microenvironment thus augmenting immune simulation and antitumor action (*186-189*).

Several clinical trials are evaluating the safety and efficacy of the combination of systemic therapies (TKIs or ICIs) with locoregional treatments. As reported at the ASCO GI 2022 meeting, the LAUNCH phase III clinical trial was conducted to compare levatinib plus TACE to levatinib alone in terms of safety and efficacy. Levatinib plus TACE performed better than levatinib monotherapy with a longer OS (17.8 *vs.* 11.5 months, $P < 0.001$) and PFS (10.6 *vs.* 6.4 months, $P < 0.001$) and higher ORR (54.1% *vs.* 25.0%, $P < 0.001$), indicating that levatinib plus TACE is likely to become a novel first-line therapy. Tremelimumab plus ablation was assessed by a phase II trial, and ablation was found to be related to an increased response rate in patients with HCC who had an atypical response to an ICI after resistance to sorafenib (*169*). TARE or TACE in combination with ICIs is also being investigated in phase II trials (*190,191*).

The combination of local and systemic therapy may result in higher efficacy and fewer adverse reactions to HCC treatment. However, many details such as the optimal dose, timing, and sequence of the combination treatment strategies need to be determined, and these require a deeper understanding of their underlying mechanisms.

4.2. Triple therapy or conversion management

Successful combinations of systemic therapies and combinations of systemic and locoregional therapies allow for triple therapy. A triple therapy is a general combination of 2 systemic therapies (1 TKI and 1 ICI or 2 antibodies) and 1 locoregional therapy.

A number of retrospective studies have investigated treatment with TACE plus a PD-1 inhibitor combined with lenvatinib (*192-197*), and they have noted encouraging efficiency and manageable safety in patients with unresectable HCC. A phase II single center study revealed the safe and encouraging antitumor activity of HAIC plus levatinib-toripalimab in high-risk advanced HCC (*198*). In that trial involving 36 subjects, the primary end-point was met with a PFS rate of 80.6% (95% CI: 64.0-91.8%) at six months. Median PFS was 10.4 months (95% CI: 5.8-15.0) and OS was 17.9 months (95% CI: 14.5-21.3).

Several articles have reported on the use of triple therapy and they have also described the potential conversion of resection (*199,200*). Successful conversion criteria were: (*i*) at least partial remission; (*ii*) a future liver remnant (FLR) > 40% or non-cirrhosis > 30%; (*iii*) reversion to a branch thrombus; (*iv*) Child-Pugh < 7; and (*v*) no new resectable liver lesions during treatment. Two studies focusing on levatinib plus PD-1 inhibitors plus TACE/HAIC for advanced unresectable HCC were presented at the ASCO GI 2022 meeting. A prospective multicenter trial (NCT04997850) noted a conversion rate of 50%. Successful conversion therapy plus surgery is a type of quadruple therapy.

4.3. Traditional Chinese medicine

As mentioned in the Chinese guidelines, traditional Chinese medicine (TCM) may improve the clinical outcomes and reduce the adverse effects of other therapies (*145*). Several types of TCM (such as Huai'er granules and cinobufacini) have been used for the treatment of liver cancer in China.

Two multicenter randomized clinical trials indicated the efficacy of TCM on recurrence after curative resection of HCC (*201,202*). A trial conducted by Chen *et al.* (NCT01770431) involved 39 centers and 1,044 patients. The mean RFS in patients taking Huaier (patients who took Huaier orally) was longer than that in the control group (75.5 *vs.* 68.5 weeks; HR 0.67; 95% CI: 0.55-0.81). Another trial compared the efficacy and safety of TACE and TCM (a cinobufacini injection and Jiedu granules) for patients with HCC who underwent surgery. A TCM regimen was related to a diminished risk of HCC recurrence compared to TACE. Currently, there is insufficient evidence for TCM in patients with advanced HCC. Results of two retrospective studies indicated that TCM as adjuvant therapy can also prolong median survival time for patients with advanced HCC (*203*). In the future, TCM can be tried as a supplementary treatment for patients with HCC who have received comprehensive treatment.

4.4. Treatment-related toxicity

Combination therapies with TKIs, ICIs, and conventional therapies have actually revolutionized the management of

advanced HCC because of their marked curative effect. However, combination therapies (and especially those including more than 1 systemic therapy) are accompanied by increased toxicities and each combination strategy may cause different adverse events (*109*).

The optimal sequence of treatments and the selection of patients should be fully considered. In clinical practice, patients who do not have comorbidities and who have sufficient liver reserve will be considered for combination treatments. Most adverse events are moderate and controllable with conservative treatment, but the occurrence of rare and life-threatening toxicities should not be ignored (*204*). Patients require a detailed physical examination depending on the treatment strategy and need to be informed of precursory symptoms of adverse events for better self-monitoring during stages of treatment. For instance, patients with advanced HCC should undergo esophagogastroduodenoscopy prior to atezolizumab-bevacizumab therapy because the combination treatment is accompanied by a higher risk of bleeding (*205,206*). In addition, an evaluation for the presence of varices is recommended within 6 months of initiation of atezolizumab-bevacizumab (*110*).

4.5. Consideration of the etiology of HCC

Current international practice guidelines do not consider the influence of the etiology of HCC in their treatment algorithms (*6,148,184*). While locoregional treatments seem equally effective regardless of the etiology of HCC, little is known about the impact of non-alcoholic fatty liver disease (NAFLD) as an etiology on the efficacy of systemic therapy (*207*). An international cohort study of 5,201 patients (Europe and North America) concluded that NAFLD-driven HCC received a similar clinical benefit from sorafenib compared to other etiologies (*208*). TKIs are probably equally effective, but several studies have found that ICIs may be less effective in NAFLD-driven HCC than in viral HCC.

A meta-analysis of three randomized phase III trials involving 1,656 patients with advanced HCC found that immunotherapy did not improve survival in patients with non-viral HCC (*209*). Moreover, *in vivo* studies found that anti-PD-1 treatment did not result in regression of NAFLD-driven HCC. A recent meta-analysis of 8 trials including 3,739 patients revealed that ICIs are less efficacious in patients with non-viral HCC, while there were no differences associated with etiology in patients with HCC receiving a TKI or anti-VEGF antibody (*210*). For patients with NAFLD-driven HCC, the combination strategies may require a change, such as elimination of immunotherapy. Further clinical trials should be designed with prespecified stratification.

4.6. Molecular biomarkers

There is a clear need for reliable molecular biomarkers in HCC risk stratification, prognosis, and treatment response. Biomarkers were extensively studied in terms of microsatellite instability, PD-L1 expression, and the tumor mutational burden (*211*). Alpha fetoprotein (AFP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been found to be related to HCC treatment outcomes (*212-214*). A recent study indicated that preoperative prothrombin induced by vitamin K absence-II (PIVKA-II) has a higher positive rate than AFP in detecting resectable HCC and predicting early postoperative recurrence (*215*). The level of PIVKA-II can serve as an indicator of the presence of PVTT and an advanced tumor stage (*216*). Although the EASL guidelines state that PIVKA-II is suboptimal in terms of cost-effectiveness, it has recently been a routinely measured tumor marker similar to AFP (*6*). In addition to circulating markers, gene expression assays were also used to identify biomarkers with which to predict the response to immunotherapy. Haber *et al*. constructed a novel 11-gene signature that can predict response and survival in patients with advanced HCC who were initially treated with an anti-PD1 antibody (*217*). However, gene expression assays require invasive biopsies before treatment.

4.7. Noninvasive imaging biomarkers and artificial intelligence (AI)

HCC staging systems (*e.g.*, Barcelona Clinic Liver Cancer, Hong Kong Liver Cancer, Cancer of the Liver Italian Program, and TNM systems) occupy the central role in HCC prognosis and management (*218*). However, these systems are inadequate at accurately predicting risk and none of them provide quantitative measures. A few biomarkers have been examined and validated in their prediction of drug susceptibility and prognosis, offering an opportunity to evaluate the clinical benefits of current therapies (*33,219-221*). Besides novel serum biomarkers, various imaging modalities can also offer precious information. Image findings and data mining algorithms can be used to capitalize on imaging data. Xu *et al.* (*222*) studied radiomics, image findings, and serum indices to predict microvascular invasion using nomograms. Radiomics models established by Ji *et al.* (*223*) can accurately provide quantifiable risk measures of recurrence for early-stage HCC. In addition to tumor characteristics, stages of liver fibrosis might also affect the treatment plan and can be also predicted with radiomics and machine learning techniques (*224,225*). A multicenter study conducted in France is developing an AL algorithm based on clinical, biological, and ultrasound data to stratify the risk of HCC emergence in high- and low-risk patients (*226*). In instances where a biomarker has yet to be identified (such as therapeutic response and treatment toxicity), AI-based prediction could significantly contribute to improving clinical outcomes

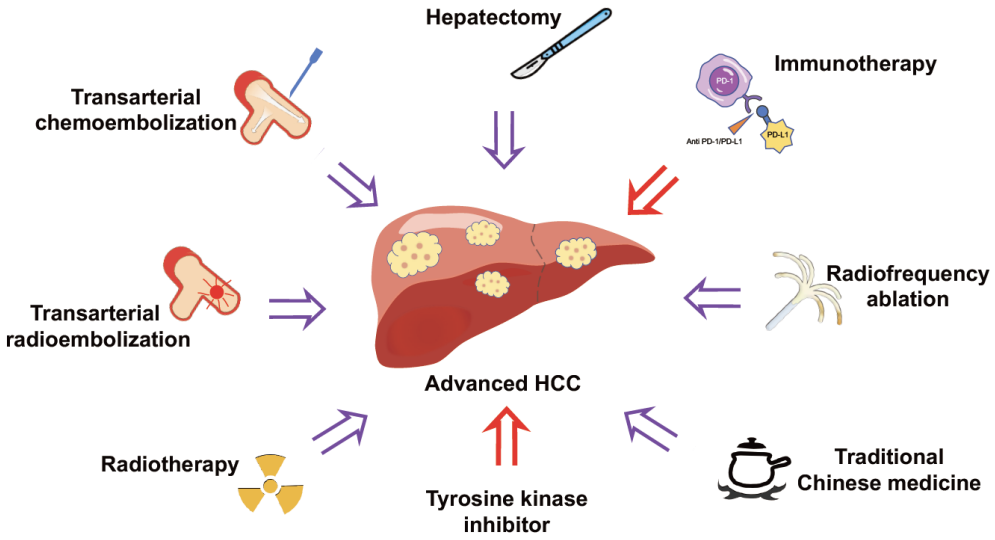

Figure 2. Management of patients with advanced hepatocellular carcinoma apart from molecularly targeted therapy. The red arrows indicate the first-line therapy to treat hepatocellular carcinoma. HCC, hepatocellular carcinoma.

and reducing healthcare expenditures. The potential of AI should be fully explored in prospective studies to improve the clinical management of patients with HCC. If tumor characteristics (such as high/low risk and resistance to chemotherapy or immunotherapy) can be determined noninvasively, more suitable treatment strategies can be formulated.

4.8. Challenges

Despite the promising developments, the optimal therapeutic strategy for advanced HCC remains vague. Several challenges regarding disease prognosis remain, and few therapies have provided additional survival benefits. Moreover, patients with advanced HCC might be further classified based on biomarkers or imaging parameters, which would help to devise proper therapies in various clinical settings. Furthermore, which targeted agents should be used once the first targeted agent (sorafenib or lenvatinib) fails remains unclear. Treatments for early or intermediate HCC (such as TACE, TARE, immunotherapy, ablation, hepatectomy, and intravenous chemotherapy) should be further examined for their potential therapeutic value in treating advanced HCC (Figure 2). Lastly, the resistance to both targeted agents and immunotherapy is another hot topic, and the underlying mechanisms should be examined to develop novel strategies to overcome drug resistance.

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