Review

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Rie Sugimoto *, Motoyuki Kohjima, Masatake Tanaka

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Review

Advances in Systemic Therapy for Hepatocellular Carcinoma and Future Prospects

Rie Sugimoto [1,*], Motoyuki Kohjima [2] and Masatake Tanaka [3]

[1] Department of Hepato-Biliary-Pancreatology NHO Kyushu Cancer Center
[2] Department of Gastroenterology, National Hospital Organization Kyushu Medical Center
[3] Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University
* Correspondence: sugirie5@rr.iij4u.or.jp; Tel.: +81925413231

Simple Summary: Systemic therapy for hepatocellular carcinoma is evolving rapidly. The introduction of multi-tyrosine kinase inhibitors and immunotherapy has led to improvements in response rates and survival rates. Additionally, the application of these therapies is expanding beyond advanced-stage cancer to include their combination with local therapies at the intermediate stage. Further efforts are needed to optimise treatment selection and develop new drugs to improve the prognosis of patients.

Abstract: The treatment of hepatocellular carcinoma has shifted significantly from the era of local therapy to the era of drug therapy, partly because of changes in background factors. Drug therapy for hepatocellular carcinoma has made rapid progress in recent years. We have moved from an era where sorafenib monotherapy was used to prolong survival, to an era of sequential therapy with multiple tyrosine kinase inhibitors, and further improvements in patient prognosis have been achieved with the introduction of immunotherapy combining atezolizumab and bevacizumab. The availability of highly effective drugs has expanded the range of diseases treatable by drug therapy. Additionally, instead of initiating drug therapy at advanced stages, combining it with local therapies such as transarterial chemoembolization at an earlier stage with the aim of achieving a cure has become possible, improving treatment outcomes further. Currently, the number of regimens requiring consideration, involving combinations of multiple drugs and local therapies, has increased, leading to various trials being conducted. Additionally, cases of hepatocellular carcinoma that were previously unresectable have become resectable after drug therapy, necessitating the establishment of a resectability classification system. This review summarises the current evidence for drug therapy of hepatocellular carcinoma and discusses future treatment strategies, treatment combinations, and prospects.

Keywords: hepatocellular carcinoma; systemic chemotherapy; combination immunotherapy; molecular targeted agent; combination of locoregional therapy and systemic chemotherapy

1. Introduction

Until around the year 2000, the treatment strategy for hepatocellular carcinoma focused on the surveillance of high-risk cases for early detection, with local therapy being the primary treatment modality. Advances in systemic therapy progressed little after the introduction of the multiple tyrosine kinase inhibitor (mTKI) sorafenib in 2009 [1]. However, with the advent of nucleoside analogues that could cure hepatitis C, altered the underlying risk factors for hepatocellular carcinoma, shifting the primary cause of carcinogenesis from viral hepatitis to metabolic dysfunction-associated steatohepatitis [2]. This made it difficult to identify high-risk cases, leading to an increase in cases diagnosed at an advanced stage and heightening the need for new systemic therapies. Regorafenib [3] emerged as a second-line treatment following disease progression in patients on

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sorafenib. Additionally, lenvatinib demonstrated non-inferiority in overall survival (OS) compared with sorafenib and had favourable progression-free survival (PFS) and objective response rates (ORR) as a first-line therapy [4]. Regarding second-line therapies, ramucirumab [5] and cabozantinib [6] were subsequently introduced as effective treatment options. Furthermore, combination immunotherapy has been added to these options. Atezolizumab plus bevacizumab is the first combination immunotherapy for hepatocellular carcinoma and the first regimen to demonstrate superior OS and PFS compared with sorafenib [7]. Durvalumab plus tremelimumab, the first regimen to combine two immune checkpoint inhibitors (ICI), had superior OS compared with sorafenib [8]. Furthermore, nivolumab plus ipilimumab demonstrated superior OS compared with lenvatinib or sorafenib [9]. Drug therapy was initially indicated for advanced cancer where local therapies such as resection or transarterial chemoembolization (TACE) were not feasible, and was primarily targeted at Barcelona clinic liver cancer (BCLC) C. However, the concepts of TACE-refractory [10]and TACE-ineligible [11] patients emerged, significantly expanding the treatment population. Although local therapy was initially thought to have a narrower indication, its application has expanded through the combination of various systemic drug therapies [12,13]. The era has arrived where local therapy and drug therapy are not mutually exclusive but are combined to improve patient prognosis. This review discusses the advances in various drug therapies for hepatocellular carcinoma, future prospects for the development of new therapeutic agents, and strategies for combining and optimising treatment modalities.

2. Advances and Prospects in Systemic Therapy for Advanced Stage Hepatocellular Carcinoma

A. Advances and Prospects in First-Line Therapies

In 2017, the SHARP trial demonstrated that sorafenib significantly outperformed placebo in terms of OS and PFS for the treatment of advanced hepatocellular carcinoma, making it the first oral mTKI approved as a systemic drug therapy for hepatocellular carcinoma [1]. The median OS of sorafenib was 10.7 months compared with 7.9 months for placebo. Subsequent trials failed to demonstrate superior efficacy over sorafenib, but in 2018, the REFLECT trial finally demonstrated that lenvatinib was non-inferior to sorafenib [4]. Lenvatinib is an oral mTKI with selective inhibitory activity against receptor tyrosine kinases including VEGFR, FGFR, PDGFR, KIT, and RET. The median OS of patients treated with lenvatinib was 13.6 months, compared with 12.3 months for sorafenib. The overall response rate (ORR) in the REFLECT trial was 40.6% (sorafenib 12.4%, odds ratio 5.01). Because of this high response rate, lenvatinib became a key drug in subsequent combination trials. A key feature of lenvatinib is its high tumour blood flow inhibitory effect, characterised by early tumour blood flow reduction and tumour vascular normalisation [14]. Various administration methods have been developed to mitigate the fatigue side effect of lenvatinib while maintaining treatment intensity, including a weekend-off regimen where treatment was suspended only on weekends [15].

In 2020, groundbreaking trial results were reported. In the IMbrave150 trial, atezolizumab (anti-PD-L1 antibody) plus bevacizumab (anti-VEGF antibody) significantly extended OS compared with sorafenib (19.2 months versus 13.4 months) [16]. PFS was also significantly improved, at 6.9 months versus 4.3 months [7]. The hazard ratio (HR) was 0.66 (95% confidence interval [CI] 0.53–0.85) for OS and 0.65 (95% CI 0.53–0.81) for PFS, both of which were statistically significant. This made atezolizumab plus bevacizumab the first immunoconjugate therapy to show efficacy for the treatment of hepatocellular carcinomas, and it was positioned as the first-line therapy. It has been reported that only about 30% of hepatocellular carcinomas have lymphocyte infiltration in the tumour (immune hot), and about 30% have WNF/β-catenin mutations without CD8-positive cell infiltration (immune excluded). In some cases, T-cell activity is suppressed by the immunosuppressive microenvironment (immune cold) [17]. Atezolizumab plus bevacizumab therapy was thought to exert its antitumour effect through the combined effects of an ICI plus an

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anti-VEGF inhibitor, by suppressing immunosuppressive Tregs, restoring the immune activity of CD8-positive cells [18], normalizing the tumour vasculature, promoting CD8-positive cell infiltration into the tumour [19], and inducing cell death and subsequent cancer antigen release through direct antitumour and necrotic effects [20,21]. The anti-tumour effect is thought to be exerted by multiple mechanisms, such as promoting cell death and the release of cancer antigens through direct anti-tumour effects and necrotic effects. The most frequent adverse reactions reported as G3 or higher were hypertension (12.2%), increased aspartate aminotransferase (5.1%), increased alanine aminotransferase (1.3%), thrombocytopenia (1.3%), and proteinuria (0.6%). The study also included patients with portal vein tumour plug (Vp)4, demonstrating efficacy in patients with or without a tumour plug [7]. In addition, a Phase II study was conducted to evaluate the efficacy and safety of this regimen in Child-Pugh B patients, which showed a certain level of efficacy and safety [22], but the number of patients was low (n=31), which is insufficient to provide definitive evidence.

Durvalumab (anti-PDL-1 antibody) + tremelimumab (anti-CTLA-4 antibody) is the first combination regimen of two ICIs. Durvalumab plus tremelimumab significantly improved OS compared with sorafenib in the HIMALAYA trial (16.4 months versus 13.8 months [HR 0.78, 95% CI 0.65–0.92]) [23]. In addition, a hazard ratio of 0.76 for OS at 5 years was reported. This regimen is the first VEGF inhibitor-free regimen for hepatocellular carcinoma and can be used in patients with bleeding risk, urinary protein, refractory hypertension, and thromboembolism risk. Given the increasing age of patients diagnosed with hepatocellular carcinoma, and the fact that viral cirrhosis is decreasing and MASH is increasing as a cause of liver cancer, the indications for VEGF-free regimens may increase. The frequency of immune-mediated adverse events is relatively high, and the use of high-volume systemic steroids at a rate of 20.1% should be noted. Another regimen was presented in the HIMALAYA trial. Durvalumab alone was non-inferior to sorafenib for OS [23]. This regimen had a low rate of grade 3 or higher adverse events (12.9%) and no VEGF inhibition, making it a relatively safe drug to use without the risk of urinary protein in an ageing population of liver cancer patients.

In May 2025, the results of a study of nivolumab (anti-PD-1 antibody) + ipilimumab (anti-CTLA-4 antibody) therapy were published (CheckMate9DW study) [24]. Nivolumab plus ipilimumab significantly improved OS compared with lenvatinib or sorafenib (23.7 months versus 20.6 months [HR 0.79 95% CI 0.65–0.96]). The Kaplan-Meier curves for this regimen crossed early, with a survival advantage for lenvatinib or sorafenib in the first 6 months, but a consistently better OS for nivolumab plus ipilimumab thereafter (HR 1.65 95% CI 1.12–2.43 for nivolumab plus ipilimumab at 6 months). This was the first study to demonstrate efficacy against a control arm that included lenvatinib, whereas all previous studies that showed efficacy had used sorafenib as the control arm. The study excluded Vp4, so caution should be exercised when interpreting the results. The ORR for nivolumab plus ipilimumab was 36%, which was significantly better than the control arm (13%) ($p<0.0001$). Immunological adverse events with nivolumab plus ipilimumab occurred in 58% of patients, with grade 3 and 4 events occurring in 28% of patients. High-volume steroids were required in 29% of patients and treatment-related deaths occurred in 12 patients (3%), most of which were related to liver injury. Therefore, in the future, the liver function of patients should be closely monitored.

In 2025, the results of the HEPATORCH trial were published [25], showing that tripalimumab (anti-PD-1 antibody) + bevacizumab was a significant improvement over sorafenib with a PFS of 5.8 months versus 4.0 months (HR 0.69, p=0.0086, OS: 20.0 months versus 14.6 months HR;0.76,p=0.039). This has led to its approval by China's State Administration of Medicines.

In the CheckMate 459 trial, a single-agent nivolumab study, nivolumab was not superior to sorafenib with OS of 16.4 months versus 14.7 months [26]. However, a phase I/II study in CHILD B patients (CheckMate 040 cohort 5) showed efficacy of 12% for the ORR and 55% for disease control rate（DCR), with a good safety profile, indicating the potential of nivolumab for the unmet needs of Child B patients [27].

Penbroliumab was shown to be effective in the Phase II KYENOTE-244 trial as a single agent, with an ORR of 16% and a median OS of 17 months [28]. However, in the LEAP-002 trial of

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combination immunotherapy, pembrolizumab plus lenvatinib had a median OS of 21.2 months, but failed to meet the pre-specified p-value for lenvatinib and did not demonstrate efficacy [29]. This may have been influenced by the fact that the median OS of the control group receiving lenvatinib monotherapy was 19 months, which was longer than the 13.6 months observed in the REFLECT trial. As seen for existing treatments, improvements in patient prognosis related to the development of various treatment sequences have been observed with other agents. In the SHARP trial, the median OS of the sorafenib group was 10.7 months, whereas in the REFLECT trial, the median survival duration was 13.6 months for lenvatinib and 12.3 months for sorafenib. However, in the IMbrave150 trial, the median OS was 13.4 months for sorafenib, and 20.6 months for both sorafenib and lenvatinib in the CheckMate 9DW trial, indicating that the OS is improving with sorafenib. Overall, the prognosis for hepatocellular carcinoma is steadily improving.

Numerous trials aimed at developing first-line drugs for future use are currently underway. Among the trials with published results, in addition to the previously mentioned LEAP-002 trial, the COSMIC 312 trial compared cabozantinib plus atezolizumab with sorafenib. However, the interim analysis failed to demonstrate an improvement in OS (cabozantinib plus atezolizumab: 15.4 months; sorafenib: 15.5 months), and the trial did not show efficacy [30].

The anti-PD-1 antibody, tislelizumab, demonstrated non-inferior OS prolongation compared with sorafenib in the RATIONALE-301 trial, with a median OS of 15.9 months versus 14.1 months (HR 0.85), and an objective response rate of 14.3% versus 5.4% [31]. Additionally, grade 3 or higher adverse events were less frequent compared with sorafenib (22.2% versus 53.4%).

There are also several ongoing Phase III clinical trials. The IMbrave152 trial is comparing combination therapy consisting of atezolizumab and bevacizumab plus tislotuzumab with the combination therapy of atezolizumab and bevacizumab alone (NCT05904886) [32]. A similar additional therapy trial, TRIPLET-HCC (PRODIGE81-FFCD2101) [33] (NCT05665348), is assessing the addition of ipilimumab to atezolizumab and bevacizumab and is ongoing worldwide. In terms of the development of drugs with mechanisms of action other than immune checkpoint inhibition, a Phase II/III trial is currently underway comparing atezolizumab plus bevacizumab or tremelimumab plus durvalumab with the TGF-β inhibitor livmoniplimab and the PD-1 antibody budigalimab (NCT06109272) [34]. The SIERRA trial is targeting the unmet needs of Child B patients, and a trial administering tremelimumab plus durvalumab to patients with hepatocellular carcinoma scoring 7 or 8 on the Child B scale is also ongoing (NCT05883644) [35].

Table 1. Phase III trials aimed at developing a first-line drug for hepatocellular carcinoma.

Trial name (registration no.)	Regimen	CONTROL Arm	Phase
IMbrave152	Atezolizumab + bevacizumab + tiragolumab	Atezolizumab + bevacizumab	III
TRIPLET-HCC	Atezolizumab + bevacizumab + ipilimumab	Atezolizumab + bevacizumab	III
NCT06109272	Livmoniplimab + budigalimab	Atezolizumab + bevacizumab/tremelimumab + durvalumab	II/III
SIERRA	Tremelimumab + durvalumab	None	IIIb

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NCT04194775	Nofazinelimab + Lenvatinib	Lenvatinb	III
NCT04401800	Tislelizumab + Lenvatinib	None	III
NCT04720716	IBI310 + sintilimab	Sorfenib	III
NCT04344158	AK105 + anlotinib	Sorfenib	III

B. Advances and Prospects in Second-Line and Beyond Therapies

To date, following the failure of sorafenib, the only agents with randomized prospective trial evidence as second-line or later therapies are regorafenib (RESORCE trial) [3], cabozantinib (CELESTIAL trial) [6], and the monoclonal antibody ramucirumab (REACH-2 trial, in cases with α-fetoprotein (AFP) ≥400 ng/mL) [5]. Regorafenib demonstrated a significant improvement in OS and PFS of patients who were resistant to sorafenib and who tolerated the treatment in the RESORCE trial [3]. Ramucirumab, an antibody targeting VEGFR2, demonstrated efficacy in the REACH-2 trial targeting patients with AFP ≥400 ng/mL [5]. Furthermore, subgroup analysis showed that the same intensity of treatment was possible and similar outcomes were achieved in older patients in analyses divided into those younger than 65 years, between 65 and 75 years, and older than 75 years. [36] Cabozantinib is a drug with an inhibitory mechanism distinct from other molecular targeted agents, including VEGFR2, MET, and AXL. The CELESTIAL trial demonstrated improvements in OS and PFS [6]

Pembrolizumab demonstrated a statistically non-significant improvement in OS of 13.9 months versus 10.6 months (HR: 0.781, 95% CI: 0.611–0.998, p=0.0238) compared with placebo in patients with hepatocellular carcinoma who had previously received sorafenib therapy (KEYNOTE-240 trial) [37]. However, this regimen may represent a useful option for patients who have failed mTKI therapy.

There are currently no treatment regimens with evidence supporting their use as second-line therapy following ICI. However, in the IMbrave150 trial, the rate of progression to second-line therapy was 35% [16], indicating that the efficacy of second-line therapy should also be carefully considered.

Currently, the IMbrave251 trial (NCT04770896 https://clinicaltrials.gov/show/NCT04770896) is assessing secondary treatment regimens in patients who failed to demonstrate efficacy after treatment with ICI. This trial is comparing the combination of atezolizumab and lenvatinib or sorafenib with lenvatinib or sorafenib alone in patients who have failed treatment with atezolizumab and bevacizumab. Additionally, the ongoing LIVERATION trial (NCT05201404) is evaluating the efficacy and safety of namodenoson (an A3 adenosine receptor agonist) in patients with Child-Pugh B7 hepatocellular carcinoma who experienced disease progression after first-line therapy. Additionally, results of the efficacy and safety of the combination therapy of regorafenib and pembrolizumab following ICI treatment have been published in a Phase II study, with a median PFS of 2.8 months after atezolizumab + bevacizumab and 4.2 months after other ICI treatments (NCT04696055) [38].

C. Treatment Algorithms for Advanced Hepatocellular Carcinoma in the Guidelines of Various Countries (as of May 2025)

Although various guidelines have been published by countries worldwide, this article will discuss the drug therapy algorithms for advanced hepatocellular carcinoma as outlined in the representative guidelines of the European Society for Medical Oncology (ESMO), the American Association for the Study of Liver Diseases (AASLD), and the Japanese Society of Hepatology(JSH). The most recent revision is the ESMO guidelines, which were published in 2025 [39]. If

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immunotherapy is indicated as the first-line treatment for BCLC B-C, the following combinations are recommended: atezolizumab plus bevacizumab, durvalumab plus tremelimumab, camrelizumab plus rivoceranib, nivolumab plus ipilimumab, durvalumab, or tislelizumab. If immunotherapy is not indicated, lenvatinib or sorafenib is indicated. For second-line therapy following the failure of ICI therapy, lenvatinib, regorafenib, cabozantinib, sorafenib, or ramucirumab (AFP ≥ 400 ng/ml) are recommended for grade IV. In cases where ICI is not appropriate and lenvatinib has failed, sorafenib, regorafenib, cabozantinib, and ramucirumab (AFP ≥ 400 ng/ml) are listed as recommendation grade VI. If sorafenib has failed, regorafenib, cabozantinib, and ramucirumab (AFP ≥ 400 ng/ml) are listed as recommendation grade I.

According to the AASLD recommendations [40], the first step for patients with BCLC C or BCLC B with multifocal disease, contraindications for local therapy or progression after local therapy, Child-Pugh A, or ECOG 0 or 1, is to determine whether immunotherapy is appropriate. If so, the risk of gastrointestinal bleeding should be assessed. If the risk is low, atezolizumab plus bevacizumab should be considered. If there is a risk for bleeding, durvalumab plus tremelimumab or sorafenib or lenvatinib is recommended. If immunotherapy is not appropriate, sorafenib or lenvatinib is recommended. For second-line therapy, if progression occurs after atezolizumab plus bevacizumab, sorafenib or lenvatinib is primarily recommended, with regorafenib, cabozantinib, ramucirumab, and durvalumab plus tremelimumab weakly recommended. Following sorafenib or lenvatinib, the administration of regorafenib, cabozantinib, and ramucirumab is strongly recommended, with nivolumab plus ipilimumab or pembrolizumab recommended with caution.

According to the guidelines of the JSH [41], the applicability of combination immunotherapy for hepatocellular carcinoma with good performance status and Child-Pugh class A that is not eligible for surgical resection, liver transplantation, or local therapy such as TACE, is determined based on the presence or absence of the condition. If applicable, atezolizumab plus bevacizumab or durvalumab plus tremelimumab is recommended. If not, sorafenib, lenvatinib, or durvalumab are listed as alternatives. A notable feature is that two immunotherapy regimens can be used sequentially as second-line therapy. Additionally, a comparison table of results from the IMbrave150 trial and the HIMALAYA trial is provided as an explanation of this algorithm, noting that the HR for OS relative to sorafenib were 0.65 and 0.78, respectively, and differences in steroid usage rates were also clearly stated [42]. However, with the advancement of systemic drug therapy, the concept of TACE resistance has emerged [10].

As such, treatment sequences and drug therapy usage differentiation for hepatocellular carcinoma vary slightly between the guidelines of different countries, and there is currently no clear evidence for any particular sequences.

3. Advances and Prospects for the Use and Combination of Drug Therapy and Locoregional Therapy for Intermediate- and Advanced-Stage Hepatocellular Carcinoma

A. Differentiation Between Drug Therapy and Local Therapy

Unlike other cancers, liver cell cancer has several local treatment options, such as ablation therapy and TACE. Therefore, local therapy has traditionally been considered the primary treatment for middle-stage cancer. In particular, TACE has historically been considered appropriate if the cancer is confined to the liver. TACE provides long OS when complete response (CR) is achieved with initial treatment, but the prognosis is poor when CR is not achieved [43]. TACE non-response is defined as the absence of efficacy after two consecutive TACE procedures or the occurrence of vascular invasion or extrahepatic metastasis. In such patients, it has been suggested that switching to systemic drug therapy rather than continuing TACE may improve their prognosis. However, it was reported that 20%–30% of patients who continue treatment until TACE non-response occurs, progress to Child-Pugh B [44]. As a result, a deterioration in liver reserve function may prevent subsequent

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systemic drug therapy. In response to this, the concept of TACE unsuitability was proposed. What is TACE unsuitability? It can be defined as follows.

(i) Unlikely to respond to TACE: confluent multinodular type, massive or infiltrative type, simple nodular type with extranodular growth, poorly differentiated type, intrahepatic multiple disseminated nodules, or sarcomatous changes after TACE

(ii) Likely to develop TACE failure/refractoriness: Up-to-7 criteria out nodules

(iii) Likely to become Child-Pugh B or C after TACE: Up-to-7 criteria out nodules (especially bilobar multifocal hepatocellular carcinoma) modified albumin-bilirubin (mALBI) grade 2b

The Up-to-7 criteria is a classification standard based on whether the sum of the tumour size and number exceeds 7, reflecting the tumour volume. A retrospective analysis by Kudo et al. compared groups that received lenvatinib therapy and those that underwent TACE in a tendency score-matched analysis of a group where TACE was expected to be ineffective, and reported that lenvatinib was more effective in terms of OS and PFS [45]. Although it was a retrospective study and bias was unavoidable, requiring careful interpretation, it contains very important implications. In addition to this definition, other criteria such as Up-to-11 also exist as factors to determine the efficacy of TACE [46].

Regarding the future prospects for TACE and systemic drug therapy, the ABC-HCC trial (NCT04803994) [47] is currently underway. This is a global Phase IIIb randomized, multicentre, open-label trial comparing atezolizumab plus bevacizumab with TACE for intermediate-stage hepatocellular carcinoma, and the results are eagerly awaited. Additionally, the RENOTACE trial (NCT04777851) comparing regorafenib plus nivolumab with TACE, and the REPLACE trial (NCT04777851) [48] comparing regorafenib plus pembrolizumab with TACE are also underway.

B. Combination of Drug Therapy and Local Therapy

In 2019, Kudo et al. reported that sorafenib plus TACE significantly improved PFS compared with TACE alone [49] in contrast to previous combination trials of sorafenib and TACE that did not demonstrate efficacy [50]. One reason for this was the use of TACE-specific treatment efficacy assessment (RECICL) to highlight the efficacy of TACE as a local therapy. Although this trial did not show a statistically significant difference in OS, it was considered clinically useful, and subsequent reports continued to describe combinations of drug therapy and local therapy. The TACTICS-L trial reported that a combination of lenvatinib plus TACE achieved a PFS of 28 months and an ORR of 88.7% in patients with BCLC B hepatocellular carcinoma [12]. Peng et al. reported the results of a randomized trial comparing lenvatinib monotherapy with lenvatinib plus TACE for advanced hepatocellular carcinoma, where lenvatinib plus TACE demonstrated significantly better overall OS [13]. In 2023, an ABC conversion therapy combining atezolizumab plus bevacizumab therapy with TACE, radiofrequency ablation, and resection was reported, achieving a CR rate of 30% and a complete remission (cancer-free, drug-free) rate of 19% [51]. Additionally, in 2024, it was reported that durvalumab plus bevacizumab plus TACE significantly improved PFS compared with TACE alone (10.5 months versus 8.2 months, HR: 0.77) (Phase III, EMERALD-1 trial) (NCT03778957) [52]. However, in that trial, no additive effect of durvalumab alone over TACE was observed, and the efficacy of combination therapy with TACE using ICI alone without VEGF inhibition was not established. A large-scale randomized controlled clinical trial is currently underway to evaluate the combination of atezolizumab plus bevacizumab therapy with TACE for unresectable hepatocellular carcinoma (IMPACT trial jRCTs051230037), and the results are awaited (NCT03778957 https://clinicaltrials.gov/show/NCT03778957). Other trials include the LEAP-012 global trial comparing lenvatinib plus pembrolizumab plus TACE versus TACE alone [53] and the CheckMate 74W trial (TACE plus nivolumab plus ipilimumab versus TACE plus nivolumab versus TACE alone).

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Table 2. Phase III trial based on the combination of mTKI and/or ICI with TACE.

Trial name (registration no.)	Regimen	CONTROL Arm	Phase
ABC-HCC (NCT04803994)	TACE + additional on demand TACE	Atezolizumab + bevacizumab	III
TALENT-ACE (NCT04712643)	Atezolizumab + bevacizumab + on-demand TACE	TACE alone	III
EMERALD-3 (NCT05301842)	Tremelimumab + durvalumab + lenvatinib + TACE	Tremelimumab + durvalumab + TACE/TACE alone	III
LEAP-012 (NCT04246177)	Lenvatinib + pembrolizumab + TACE	TACE alone	III
REPLACE (NCT04777851)	Regorafenib + pembrolizumab	TACE alone	III
CheckMate74W (NCT04340193)	Nivolumab + ipilimumab + TACE	Nivolumab + TACE/TACE alone	III
RENOTACE (NCT04777851)	Regorafenib + nivolumab	TACE alone	III

4. Systemic Therapy and Radical Treatment

Conventionally, drug therapy has been indicated only for hepatocellular carcinoma when resection is not feasible. However, reports have increasingly suggested that conversion resection may be possible after drug therapy [54], leading to the need for a definition of “borderline resectable” in relation to resection. In 2023, the Japanese Society of Hepatology and the Japanese Society of Hepato-Biliary-Pancreatic Surgery published an Expert Consensus Statement [55] where the resection feasibility classification does not include an “unresectable” category, instead dividing cases into three categories: resectable, borderline 1, and borderline 2. This classification was adopted because the emergence of potent chemotherapy has made resection possible in cases where upfront resection was previously considered impossible because of portal vein tumour thrombus or distant metastasis. Regarding preoperative chemotherapy, the LENS-HCC study [56] demonstrated the efficacy of lenvatinib as preoperative adjuvant chemotherapy, and the RACB trial [57] is currently underway to evaluate the feasibility of conversion resection using atezolizumab plus bevacizumab.

5. Advances and Prospects of Drug Therapy as Adjuvant Chemotherapy After Surgery

Regarding postoperative chemotherapy for hepatocellular carcinoma, an interim analysis of the IMbrave050 trial reported that the combination of atezolizumab plus bevacizumab significantly improved PFS in patients with high-risk hepatocellular carcinoma following surgery [58]; however, the final analysis did not demonstrate efficacy (NCT04102098). Currently, there are no proven treatment effects for postoperative adjuvant chemotherapy, but multiple trials are ongoing. The

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CheckMate 9DX trial (NCT03383458) is evaluating the efficacy of nivolumab for PFS in patients with hepatocellular carcinoma at high risk for recurrence after resection or ablation [59]. The EMERALD-2 trial (NCT03847428) [60] is evaluating the efficacy and safety of durvalumab monotherapy and durvalumab plus bevacizumab combination therapy as adjuvant therapy for patients with high risk for recurrence following curative resection or ablation. The KYENOTE-937 (NCT03867084) trial is evaluating the safety and efficacy of pembrolizumab as adjuvant therapy for patients with hepatocellular carcinoma who achieved a radiological CR following surgical resection or local ablation, compared with placebo [61]. The results of these trials are awaited.

6. Future Directions of Hepatocellular Carcinoma Chemotherapy

Currently, various drug development efforts are underway for hepatocellular carcinoma at different stages, including multiple combination immunotherapies and novel molecular targeted agents for advanced hepatocellular carcinoma, combinations of TACE with molecular targeted agents for hepatocellular carcinoma classified as BCLC B, combinations of TACE with combination immunotherapy, combinations with radiation therapy, and chemotherapy aimed at preventing tumour recurrence. Future drug therapy for hepatocellular carcinoma is expected to shift from a treatment approach focused on extending survival by sequentially administering single agents to a treatment approach aimed at achieving a cure by combining various drugs and local therapies. Additionally, the emergence of diverse drugs raises challenges such as drug selection, sequencing, and the development of appropriate biomarkers for optimal drug use.

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Abbreviations

The following abbreviations are used in this manuscript:

OS	overall survival
PFS	progression-free survival
ORR	overall response rate
DCR	disease control rate
BCLC	Barcelona clinic liver cancer
TACE	transarterial chemoembolization
mTKI	multiple tyrosine kinase inhibitor
AFP	α-fetoprotein
ICI	immune checkpoint inhibitor
CR	complete response
mALBI	modified albumin-bilirubin
RFA	radiofrequency ablation
Vp	portal vein tumour plug

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