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Brazilian Society of Hepatology Updated Recommendations for Systemic Treatment of Hepatocellular Carcinoma

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ABSTRACT – Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related mortality worldwide. The Brazilian Society of Hepatology (SBH) published in 2020 the updated recommendations for the diagnosis and treatment of HCC. Since then, new data have emerged in the literature, including new drugs approved for the systemic treatment of HCC that were not available at the time. The SBH board conducted an online single-topic meeting to discuss and review the recommendations on the systemic treatment of HCC. The invited experts were asked to conduct a systematic review of the literature on each topic related to systemic treatment and to present the summary data and recommendations during the meeting. All panelists gathered together for discussion of the topics and elaboration of the updated recommendations. The present document is the final version of the reviewed manuscript containing the recommendations of SBH and its aim is to assist healthcare professionals, policy-makers, and planners in Brazil and Latin America with systemic treatment decision-making of patients with HCC.

Keywords – Hepatocellular carcinoma; malignant liver tumor; systemic therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third cause of cancer-related mortality in the world. The estimated global annual incidence ranges from 500,000 to 1,000,000 cases, leading to more than 800,000 deaths per year. Hepatocellular carcinoma is an important cause of morbidity and mortality in patients with cirrhosis[1]. In Brazil, more than 70% of patients with HCC attended by the public health system are diagnosed at an advanced or terminal stage[2].

Several treatments are currently available for HCC and systemic treatment is one of the cornerstones in the management of patients with this tumor. The Brazilian Society of Hepatology (SBH) published in 2020 the Updated Recommendations for the Diagnosis and Treatment of Hepatocellular Carcinoma[3]. Since then, new scientific evidence has been published in the literature, which had a major impact on current HCC management. In the last 13 years, there have been remarkable advances in the systemic treatment of HCC, including the publication of positive phase III studies and the approval of new drugs[4]. To update the recommendations, the SBH held on September 18, 2021, a single-topic meeting to discuss and review the recommendations on the systemic treatment of HCC.

The SBH Liver Tumor Interest group chose an organizing committee that designated 25 researchers to be moderators or speakers on HCC systemic therapy issues. Some of the invited experts were asked to conduct a systematic review of the literature on each topic related to systemic treatment. The summary data and draft recommendations were presented at the meeting according to the degree of available scientific evidence. The final recommendations were defined after extensive discussion with the organizing committee members, moderators, and panelists of the meeting. The organizing committee was responsible for drafting a preliminary document, which was later submitted to SBH members via its homepage for suggestions before writing the final version of the present manuscript. The level of evidence and grade of recommendation classifications applied to this consensus are described in TABLES 1 and 2[5].

TABLE 1. Class of recommendation.

Class of Recommendation	Definition	Suggested wording
I	There was consensus. More than 90% of the panel agreed	Is recommended
IIa	There was general preference in favor. Between 70–90% of the panel agreed	Should be considered
IIb	The majority -(50–70%) of the panel agreed	May be considered
III	There was agreement that the intervention is not recommended	Is not recommended

TABLE 2. Level of evidence.

Level of evidence	Definition
A	Data derived from multiple randomized clinical trials or meta-analysis
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of experts' opinion and/or small studies, retrospective studies, or registries

The purpose of this document was to assist healthcare professionals, policy-makers, and planners in Brazil and Latin America with systemic treatment decision-making of patients with HCC. However, it is important to note that the recommendations in this manuscript, which are based on currently available evidence, were written to guide clinical practice in circumstances in which all resources and therapies are available. These recommendations should therefore be adapted according to local regulations, expertise, infrastructure, and treatment availability, with the primary aim of improving the care and quality of life of patients with HCC.

Systemic treatment indications

Patients with multifocal and advanced HCC who are not submitted to specific treatment have very poor survival rates, less than 6 months[6]. The last ten years have witnessed important advances in the systemic therapy of HCC, particularly for patients at advanced stages[7,8]. New trials are exploring combination therapies, including immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) or anti-vascular endothelial growth factor (VEGF) therapies, or even combinations of two immunotherapy regimens. The outcomes of these trials are expected to change the landscape of HCC management at all evolutionary stages[8,9].

Since the SHARP[10] study published in 2008 that first demonstrated the benefit of a drug for systemic treatment of HCC, we have so far seen a significant increase in survival from 10.7 months with sorafenib to 19.2 months with combined therapy in the IMbrave-150[11] study in a first-line setting. Objective response rates (ORR) have also increased over the years, from about 10% with TKIs to approximately 30% with combined therapy[7]. This increase in survival is the result of multiple factors, including the higher efficacy of available treatments, such as sequential therapy, improved care of patients with liver disease and cirrhosis, and earlier indication of systemic treatment and post-progression line switching.

Systemic treatment for HCC has two main objectives: to increase survival and to ensure the patient's quality of life. Patients with HCC are highly complex since in most cases we are dealing with two diseases: cirrhosis and the tumor. Thus, when assessing systemic treatment indication in these patients, besides the tumor characteristics, we must also consider liver function and the presence or absence of cirrhosis complications. It is also crucial to evaluate the general condition of the patient and the presence of tumor-related symptoms (Eastern Cooperative Oncology Group Performance Status – ECOG-PST), as well as the presence of comorbidities[3,12]. Assessing all of these aspects, the Barcelona staging system (BCLC)[13] assists in the classification of patients with HCC and in the suggestion of the appropriate treatment for each tumor stage. This system is being used worldwide, particularly in Western countries. On the other hand, treatment individualization and a multidisciplinary approach are essential for the best management of each patient. According to the studies performed[7], systemic treatment is indicated in two main situations:

BCLC C – advanced stage

This group comprises patients with vascular invasion or extrahepatic metastases and/or mild cancer-related symptoms (ECOG-PS 1–2), with relatively preserved liver function[13]. Patients classified as BCLC C are the main group with an indication for systemic therapy of HCC. In the pivotal studies that established first- and second-line systemic treatments, patients with advanced HCC accounted for 78 to 91% of all patients included in the trials. It should be noted that in these studies the vast majority of patients had preserved liver function – Child-Pugh A in 97 to 100% – and good performance status (ECOG-PS 0 or 1)[7].

Based on these data, systemic treatment with molecular therapies or immunotherapy is recommended for HCC patients with advanced disease (BCLC C) and well-preserved liver function, promoting survival gains in patients with sensitive tumors of 2 years or more[7,13].

BCLC B – intermediate stage

This group is composed of patients with multifocal tumors without vascular invasion or extrahepatic metastasis, who have preserved liver function and are asymptomatic (ECOG-PS 0)[3,12].

Systemic therapy should be considered for patients who are ineligible for or progress after transarterial chemoembolization/embolization (TACE/TAE)[3,8,12-14]. These patients may be candidates for systemic therapies if they do not respond to TACE (no response after two or more TACE sessions), if they develop intractable progression (major intrahepatic progression, macrovascular invasion, metastasis, symptomatic progression), or if they show deterioration of liver function or other features such as technical unfeasibility[3,12,13,15,16]. Patients with BCLC B accounted for 4.7 to 22% of all patients in the main trials evaluating systemic therapy for HCC. In subgroup analysis, as well as patients with advanced stage, BCLC B patients showed benefit in terms of survival and progression free survival (PFS)[7]. In the GIDEON study that analyzed real-life systemic therapy with sorafenib, 19% of patients were BCLC B[17].

Treatment migration strategy

The stage migration strategy is a therapeutic choice whereby a theoretically recommended treatment for a different stage is selected as the best first-line treatment option[12]. If the recommended option is not feasible due to an individual condition or if there is untreatable progression, the most appropriate treatment option at the same stage or for a subsequent more advanced stage should be offered[3,12,13,16]. Transferring new drugs to earlier lines of therapy or to patients with early stages of the disease holds the promise of curative treatment for a larger number of patients[9].

Systemic therapy in patients with impaired liver function

As described above, the vast majority of patients included in the pivotal trials had preserved liver function (Child-Pugh A)[7]. Thus, most of the data we have on the systemic treatment of HCC in patients with impaired liver function come from real-life studies. The GIDEON study was the largest study evaluating the use of sorafenib in patients with HCC in this setting. The results showed that median survival was longer in Child-Pugh A patients than in Child-Pugh B and C patients (13.6 vs 5.2 and 2.6 months, respectively). On the other hand, the rate of drug-related adverse events (AEs) was similar between Child-Pugh A and B patients[17]. Other studies found similar results[18,19]. A meta-analysis published in 2018 demonstrated that HCC patients with Child-Pugh B liver function had worse survival compared to Child-Pugh A patients, but with a similar response rate, safety, and tolerability of first-line sorafenib[18].

A prospective national study published by Leal et al. analyzed the overall survival (OS) and safety profile of HCC patients treated with sorafenib according to Child-Pugh subclassifications and showed that patients with Child-Pugh B7 liver function had a satisfactory mean survival of 8 months, shorter than that of Child-Pugh A patients (12 months) but significantly longer than that of patients with Child-Pugh > B7 (≤5 months). The study also observed a satisfactory safety profile of Child-Pugh B patients treated with sorafenib[19].

Recently, a retrospective analysis of the CELESTIAL trial demonstrated the safety and efficacy of cabozantinib for patients with advanced HCC and Child-Pugh B at study week 8. Fifty-one patients were allocated to receive cabozantinib and 22 to receive placebo. The median OS was 8.5 versus 3.8 months (hazard ration [HR]: 0.32, 95% confidence interval [CI] 0.18–0.58) and the median PFS was 3.7 versus 1.9 months (HR: 0.44, 95%CI 0.25–0.76), respectively. The best response was stable disease in 57% versus 23% of the patients, a finding encouraging prospective studies of patients with advanced HCC and Child-Pugh B liver function[20]. On the other hand, a multicenter, retrospective study evaluating 59 patients with Child-Pugh B who received regorafenib after sorafenib showed worse outcomes and a higher frequency of severe AEs, discouraging its use in this population[21].

Regarding ICI therapies in patients with advanced HCC and Child-Pugh B liver function status, in the phase I/II CheckMate 040 study, nivolumab showed clinical activity and an acceptable safety profile in patients with HCC who had mild to moderate impairment of liver function or liver decompensation (Child-Pugh B7–B8)[19,22]. Moreover, in a recently

published real-life study with 154 (76%) Child-Pugh A patients and 48 (24%) Child-Pugh B patients who received atezolizumab + bevacizumab, median OS was 14.9 months (95%CI 13.6–16.3) and median PFS was 6.8 months (95%CI 5.2–8.5), with lower OS for Child-Pugh B patients, but with no difference in response rates across Child-Pugh classes. Patients with Child-Pugh B reported similar tolerability compared to Child-Pugh A patients. However, prospective studies are necessary to validate the use of combined therapy in this treatment-deprived population[23].

Recommendations

- Systemic therapy is indicated for patients with advanced HCC (BCLC C) and well-preserved liver function (Child-Pugh class A). **Level of evidence A. Grade of recommendation I**
- Systemic therapy should be considered for patients with early- or intermediate-stage HCC (BCLC A or BCLC B) and well-preserved liver function (Child-Pugh class A), who are ineligible for or who progress after locoregional therapy (stage migration strategy). **Level of evidence A. Grade of recommendation I**
- Systemic therapy may be indicated in well-selected patients with HCC and cirrhosis Child-Pugh class B with a score no greater than seven. **Level of evidence C. Grade of recommendation I**

MECHANISM OF ACTION OF THE MAIN DRUGS USED FOR SYSTEMIC TREATMENT OF HEPATOCELLULAR CARCINOMA

Tyrosine kinase inhibitors

Hepatocarcinogenesis is driven by the hyperactivation of different intracellular signaling pathways involved in cell proliferation and angiogenesis, which are composed of receptors and mediators with tyrosine kinase activity. In the field of HCC, increasing evidence indicates a role of alterations in epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), hepatocyte growth factor receptor (HGF/c-Met), and fibroblast growth factor receptor (FGFR) pathways. The binding of growth factors to the extracellular domain of these receptors further activates intracellular protein kinases such as RAS/RAF/MEK[24]. Turning on these mediators can induce liver tumors in experimental models[25]. Similarly, knockdown experiments showed that inactivation of these kinases may have antitumor effects, providing proof of concept that blocking these pathways may achieve successful HCC control[26].

Hepatocellular carcinoma is a highly vascularized tumor in which VEGF/VEGFR are overexpressed. The levels of VEGF are correlated with angiogenesis, microvessel density, and a poor prognosis[27]. Consequently, the VEGFR pathway is considered a potential actionable target in HCC. The FGFR pathway is closely associated with angiogenesis, modulation of the tumor microenvironment, and resistance to anti-VEGFR therapies[28]. Finally, the Met receptor is associated with mesenchymal-epithelial transition, resistance to anti-angiogenic therapies, and a poor prognosis in patients with HCC[29].

Tyrosine kinase inhibitors used in the treatment landscape of HCC show a wide range of targets and activities, as follows[30]:

- Sorafenib: Raf, KIT, VEGFR-2 -3, and PDGFR
- Lenvatinib: VEGFR-1, -2, -3, FGFR1, -2, -3, -4, PDGFR, KIT, and RET
- Regorafenib: VEGFR-2, -3, PDGFR, Flt-3, and c-KIT
- Cabozantinib: VEGFR1-3, Met, and AXL.

Recent studies suggest that TKIs such as sorafenib and regorafenib may also exert immunomodulatory activity by mediating M1 macrophage polarization, suppressing tumor-associated macrophages, and increasing CD8+ lymphocyte infiltration within the tumor microenvironment[31]. This finding reinforces a potential synergistic effect of this class of drugs with immunotherapeutic agents.

Finally, ramucirumab is a monoclonal antibody targeting VEGFR. Its antitumor effect occurs through occupation and blockade of the growth factor binding site in the extracellular domain of the receptor, inhibiting intracellular activation of the VEGFR signaling pathway. This drug is also part of the therapeutic landscape of HCC in patients who failed sorafenib and who exhibit high levels of alpha-fetoprotein (AFP)[32].

Immunotherapy

The liver plays an important role in immunology and immune tolerance through the coordinated activity of a repertoire of immune cells. Sinusoidal endothelial cells regulate the effector immune response by inhibiting CD4+ and CD8+ T lymphocytes, thus preventing an exacerbated immune reaction against bacterial antigens coming from the enteric circulation. In addition, these cells express high levels of programmed death ligand 1 (PD-L1) receptor, an immunosuppressive transmembrane protein that inactivates the adaptive immune system by binding to the inhibitory receptor PD-1 on the lymphocyte membrane. The expression of PD-1 by CD8+ T lymphocytes is associated with a poor prognosis in patients with HCC[33].

The antitumor immune response begins with antigen-presenting cells (APC) presenting tumor antigens to T cells through interaction between the major histocompatibility complex (MHC) and T-cell receptors, representing the primary signal for T-cell activation. Another costimulatory signal involving the interaction between B7 protein on APCs and CD28 on T cells is needed to complete T-cell activation and expansion. Several co-receptors act as negative modulators of the immune response, such as CTLA-4 by binding to B7 protein, causing inactivation of T lymphocytes and blocking initiation of the antitumor immune response[34].

The PD-1/PD1-L1 pathway regulates the immune response in normal tissues infiltrated by effector T cells. Activated T cells express PD-1, while local immune activity induces the expression of PD1-L1, which negatively regulates T-cell activity and protects normal tissues from collateral cytotoxic damage caused by T-lymphocyte activity. The same mechanism is also used by tumor cells to evade the antitumor immune response. Monoclonal antibodies that block CTLA-4 or PD1/PD1-L1 increase the activity of cytotoxic T cells by allowing the effective recognition of tumor antigens and activation of cytotoxic T cells in the tumor microenvironment[35].

Within the therapeutic arsenal, several inhibitors of the PD1/PD-L1 and CTLA4-B7 checkpoints are used both in clinical studies and in clinical practice, supported by data from prospective studies:

- ipilimumab and tremelimumab: anti-CTLA-4
- nivolumab, pembrolizumab, and camrelizumab: anti-PD-1
- atezolizumab, durvalumab, and avelumab: anti-PD-L1.

Finally, the recognition of the immunosuppressive effect of VEGF led to studies that tested combinations of ICIs and anti-VEGF agents such as atezolizumab and bevacizumab[11].

First-line systemic therapy for patients with hepatocellular carcinoma

Regarding first-line systemic therapy for HCC, today three treatments are approved in Brazil. Two TKIs, sorafenib and lenvatinib, and the combination of immunotherapy with anti-VEGF (atezolizumab + bevacizumab). Below we describe in more detail the pivotal clinical trials, mechanisms of action, AEs, and other features of these treatments. These data are summarized in TABLE 3.

Sorafenib

Sorafenib was the first drug that provided a survival benefit in patients with advanced HCC. It is an oral multi-TKI that acts by blocking angiogenesis and cell proliferation. The SHARP study[10], a prospective, randomized, phase III study, showed a median survival for naïve HCC patients treated with sorafenib of 10.7 vs 7.9 months in the placebo group (P<0.001). Most patients were Child-Pugh A (97%), 38% had macroscopic vascular invasion, and 51% had extrahepatic metastases. Regarding etiology, 29% of HCC patients from Europe and the Americas were hepatitis C virus (HCV) and 19% hepatitis B virus (HBV). The same result was also found in the Asia-Pacific phase III study, in which HBV was the main cause of HCC[35].

In the real-life GIDEON study[17,36] that analyzed 3,202 HCC patients treated with sorafenib, 73% were Child-Pugh A and 25% were Child-Pugh B. The incidence of side effects was similar in both groups, although severe side effects were more frequent in Child-Pugh B patients. The median OS was longer in Child-Pugh A patients: 13.6 vs 5.2 months. In a study conducted in Brazil with 127 patients (85.6% Child-Pugh A and 12% Child-Pugh B7) from two referral centers in the South and Southeast re-

TABLE 3. Summary of positive phase III trials of first-line drugs (compared to placebo) for systemic therapy of patients with hepatocellular carcinoma and main clinical information.

Pivotal phase III study	Sharp (n=602)	Reflect (n=954)	IMbrave (n=501)
Drug	Sorafenib	Lenvatinib	Atezolizumab + Bevacizumab
Drug class	Multi-kinase inhibitor targeting VEGFR 2–3, PDGFR, and RAF kinase	Multi-kinase inhibitor targeting VEGFR 1–3, PDGFR, FGFR 1–4, KIT, and RET	Atezo: Immune checkpoint inhibitor, anti-PD-L1 Beva: anti-VEGF
Eligible patients	Patients with advanced stage HCC ineligible/after progression to surgical or locoregional therapies, Child Pugh A, ECOG PS 0–2, with no prior systemic therapy	Patients with unresectable HCC, BCLC B or C, Child Pugh A, ECOG PS 0–1 with no prior systemic therapy. Ps: excluded patients with >50% liver involvement, invasion of the bile duct, or invasion of the main portal vein	Patients with locally advanced or metastatic and/or unresectable HCC, with no prior systemic therapy. Child Pugh A, ECOG PS 0–1
Overall survival (months) (95%CI)	Drug: 10.7 (9.4–13.3) Placebo: 7.9 (6.8–9.1) HR: 0.69 (0.55–0.87), *P*<0.0001	Lenvatinib: 13.6 (12.1–14.9) Sorafenib: 12.3 (10.4–13.9) HR: 0.92 (0.79–1.06)	Atezo + Beva: 19.2 (17–23.7) Sorafenib: 13.4 (11.4–16.9) HR: 0.66 (0.52–0.85), *P*=0.0009
PFS/TTP (months)	Drug: 5.5 (4.1–6.9) Placebo: 2.8 (2.7–3.9) HR: 0.58 (0.45–0.74), *P*<0.0001	Lenvatinib: 7.4 (6.9–8.8) Sorafenib: 3.7 (3.6–4.6) HR: 0.66 (0.57–0.77), *P*<0.0001	Atezo + Beva: 6.9 (5.7–8.6) Sorafenib: 4.3 (4–5.6) HR: 0.65 (0.53–0.81), *P*=0.0001
Overall response rate – RECIST (%)	Sorafenib: ORR: 2% CR: 0% PR:2% SD:71% DCR:43%	Lenvatinib: ORR: 18.8% CR: <1% PR: 18% SD: 54% PD: 18% DCR: 72.8% Sorafenib: ORR: 6.5% CR: < 1% PR: 6% SD: 53% PD: 32% DCR: 59%	Atezo + Beva: ORR: 30% CR: 8% PR: 22% SD: 44% DCR: 74% PD: 19% Sorafenib: ORR: 11% CR: <1% PR: 11% SD: 43% DCR: 55% PD: 25%
Overall response rate – mRECIST (%)	NA	Lenvatinib: ORR: 24.1% CR: 1% PR: 23% SD: 51% PD: 15% DCR: 75.5% Sorafenib: ORR: 9.2% CR: <1% PR: 9% SD: 51% PD: 31% DCR: 60.5%	Atezo + Beva: ORR: 35% CR: 12% PR: 23% SD: 37% DCR: 73% PD: 20% Sorafenib: ORR: 14% CR: 3% PR: 11% SD: 41% DCR: 55% PD: 25%
Adverse events, any grade	Diarrhea (39%), fatigue (22%), HFSR (21%), anorexia (14%), hypertension (5%), bleeding (7%)	Hypertension (42%), diarrhea (39%), anorexia (34%), decreased weight (31%), fatigue (30%), HFSR (27%), proteinuria (25%)	Hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%), pruritus (19.5%), AST increase (19.5%), diarrhea (18.8%), anorexia (17.6%)
Adverse events grade 3 or 4	HFSR (8%), diarrhea (8%), fatigue (4%), hypertension (2%), bleeding (1%)	Hypertension (23%), decreased weight (8%), anorexia (5%), diarrhea (4%), fatigue (4%), HFSR (3%)	Hypertension (15.2%), AST increase (7%), ALT increase (3.6%), proteinuria (3%);
Dose schedule and route of administration	400 mg of sorafenib (two 200-mg tablets) taken orally twice daily	≥60 kg: 12 mg/day (three 4-mg tablets taken orally once a day) <60 kg: 8 mg/day (two 4-mg tablets taken orally once a day)	Intravenous infusion of 1200 mg atezolizumab + 15 mg/kg bevacizumab every 3 weeks
Approved for HCC	Europe, USA, Brazil	Europe, USA, Brazil	Europe, USA, Brazil

HCC: hepatocellular carcinoma; PFS: progression-free survival; TTP: time to progression; HR: hazard ratio; CI: confidence interval; ORR: overall response rate; CR: complete response; PR: partial response; SD: stable disease; DCR: disease control rate; PD: progressive disease; HFSR: hand-foot skin reaction; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

gions who underwent real-life treatment with sorafenib, the median OS was 19.9 months (64.6 % in 1 year; 26.6% in 3 years). The longer survival observed in that study when compared to the other studies mentioned above is partly due to the use of the treatment stage migration strategy (18.1% of the patients were BCLC B)[37].

A prospective, multicenter, randomized study involving a population of 4,903 patients evaluated the initial dose of sorafenib in HCC treatment. The patients were submitted to two regimens: full-dose sorafenib (800 mg/day) versus initial sorafenib dose less than 800 mg/day. After adjustment for potential confounding factors, there was no difference in OS, with lower costs and fewer gastrointestinal side effects (8.7% vs 10.8%; P=0.047) in the group that received the reduced starting dose[38]. According to these results, the dose-escalation strategy may be suitable to reduce therapy-related toxicity in HCC.

Cheng et al. investigated the incidence of AEs in 224 patients using sorafenib. The median incidence was 38.7% in the placebo-controlled group and 81.9% in the treated group. The most frequent AEs were hand-foot skin reaction (HFSR) in 45% of the patients, followed by diarrhea (25.5%), alopecia (24.8%), rash or scaling (20.1%), fatigue (20.1%), and anorexia (12.8%)[35]. Nakano et al. reported HFSR (46%), diarrhea (17%), fatigue (13%), liver dysfunction (12%), and alopecia (8%) as the most common side effects[39]. The AEs that most commonly affect quality of life and that are classified as early when they appear within the first two months of treatment are HFSR, rash, diarrhea, and fatigue.

Despite efforts to prevent and manage AEs, the occurrence of skin lesions and diarrhea are associated with longer survival and may be clinical biomarkers of the efficacy of sorafenib in patients with HCC, especially skin reactions that occur within the first 60 days of treatment[37,40].

The use of sorafenib as adjuvant therapy after resection and/or ablation did not provide a survival benefit in the STORM study[41]. However, when this drug was indicated for the treatment of HCC recurrence after liver transplantation, some authors demonstrated the safety and efficacy of its use combined or not with mTOR inhibitor, providing a survival benefit. According to a systematic review, the median OS was 12.1 months with sorafenib and 18 months with sorafenib plus mTOR inhibitor compared to 3.3 months in patients who received exclusive palliative care[42].

Finally, sorafenib should be considered a first-line systemic therapy option in HCC patients with preserved liver function and advanced (BCLC C) or intermediate HCC (BCLC B) with contraindication or tumor progression after locoregional therapy[7]. Yoo et al. showed that sorafenib can also be used as a second-line option after disease progression on atezolizumab-bevacizumab with comparable efficacy and manageable toxicities, with a median PFS of 3.4 months and a median OS of 14.7 months[43]. However, more studies are warranted to confirm the true role of sorafenib in this scenario.

Lenvatinib

Lenvatinib is an oral multi-TKI that targets kinases implicated in pathogenic angiogenesis, tumor growth, cancer progression, and normal cellular functions, including VEGFRs 1, 2 and 3; FGFRs 1, 2, 3 and 4; PDFGRα, RET, and KIT[44,45]. The drug was approved for first-line HCC systemic treatment based on an international phase III, multicenter, randomized, open-label, non-inferiority trial (REFLECT), conducted on 954 patients with previously untreated metastatic or unresectable HCC[44,45]. The patients were randomized (1:1) to receive lenvatinib or sorafenib until radiological disease progression or unacceptable toxicity. The primary endpoint was OS and REFLECT demonstrated that lenvatinib was non-inferior to sorafenib, with median OS of 13.6 months (95%CI 12.1–14.9 months) and 12.3 months (95%CI 10.4–13.9 months) in the lenvatinib and sorafenib arms, respectively (HR of 0.92)[44]. Key secondary efficacy endpoints were PFS and ORR according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). REFLECT demonstrated statistically significant improvements in the lenvatinib group, with median PFS of 7.3 vs 3.7 months (P<0.0001) and ORR of 24.1% vs 9.2% by mRECIST (P<0.0001). Serious side effects were more common among lenvatinib-treated patients (43% vs 30%). The most frequent AEs were hypertension (42%), diarrhea (39%), anorexia (34%), weight loss (31%), and fatigue (30%). Other reported adverse reactions were HFSR (27%), proteinuria (25%), dysphonia (24%),

nausea (20%), a low platelet count (18%), abdominal pain (17%), and hypothyroidism (16%)[44].

The recommended starting dose of lenvatinib is weight-adjusted: 12 mg/day if ≥60 kg or 8 mg/day if <60 kg[44]. Dose reduction may be necessary for the management of AEs[46].

It is important to note that the REFLECT trial included only patients with Child-Pugh A, ECOG-PS 0 or 1, platelet count >75,000, and adequate renal function, and excluded patients with extensive tumors (≥50% liver involvement), invasion into the bile duct, or tumor invasion of the main portal vein[46]. Recently, real-life studies that included patients beyond these criteria failed to show the same rates of efficacy or safety[47-49]; hence, lenvatinib should be preferred in patients meeting the REFLECT trial criteria[7,47].

The treatment sequence after lenvatinib still remains an issue. Standard second-line options were tested only in patients with prior exposure to sorafenib and the same performance cannot be inferred with sufficient certainty for patients who progressed to Lenvatinib[47].

Atezolizumab + bevacizumab

Atezolizumab is an ICI that acts by blocking the PD-L1 receptor (anti-PD-L1 antibody). In HCC, the drug should be administered with an anti-VEGF agent such as bevacizumab for better results in terms of both OS and PFS[50].

In the global, open-label, phase III IMbrave150 trial, a fixed dose of atezolizumab of 1200 mg and bevacizumab of 15 mg/kg every 3 weeks (n=336) was compared with sorafenib (n=165) at a 2:1 ratio in therapy-naïve patients with unresectable HCC and Child-Pugh A. Median PFS was 6.8 months in the combination group and 4.3 months in the sorafenib group (HR: 0.59, *P*<0.0001). The OS at 12 months was 67% vs 55%, respectively[11]. Median OS was not reached in the combination arm when the trial was first published, but in the updated analysis the median OS was 19.2 months in the combination group and 13.4 months in the sorafenib group (HR: 0.66; 95%CI 0.52–0.85; *P*<0.001)[51].

In subgroup analysis of IMbrave trial, a lower overall survival benefit of combined therapy was observed in patients with a non-viral etiology compared to those with viral etiology. However, future studies are required to better define the role of etiology of liver disease on prognosis, treatment response and therapeutic decision[51].

Both drugs are given intravenously at a fixed dose (1200 mg atezolizumab and 15 mg/kg bevacizumab) every 3 weeks apart until progression or the occurrence of serious side effects or death. The most common AEs are hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%), and aspartate aminotransferase (AST) elevation (19.5%)[11]. Considering the use of an anti-VEGF drug, caution must be given to potential bleeding episodes such as variceal hemorrhage[52]. In addition, one should be aware of long-term AEs of immunotherapy, named autoimmune side effects, in the thyroid, kidney, and liver itself. In patients with autoimmune diseases, immunotherapy should be carefully prescribed in order to avoid flares of these conditions[9].

Recommendations

- Atezolizumab + bevacizumab is indicated for patients with advanced HCC (BCLC C) and patients with early-stage (BCLC A) or intermediate-stage (BCLC B) HCC who are ineligible for or who progress after locoregional therapy, with well-preserved liver function (Child-Pugh class A) and ECOG-PST 0-1. **Level of evidence B. Grade of recommendation I**
- Atezolizumab + bevacizumab is the standard of care in first-line systemic therapy for HCC. **Level of evidence B. Grade of recommendation I**
- In patients with contraindications to atezolizumab + bevacizumab, sorafenib or lenvatinib should be considered the first-line systemic therapy for HCC. **Level of evidence A. Grade of recommendation I**

Second-line systemic therapy for patients with hepatocellular carcinoma

The number of treatment options for patients with advanced HCC has grown in recent years, with progressively increasing complexity of the therapeutic landscape. First-line treatment in advanced HCC frequently fails after a certain period in approximately one-quarter to one-third of patients with advanced HCC due to adaptive or intrinsic resistance, disea-

se progression, or significant toxicity[53]. These patients may therefore be eligible for the second- and later-line treatment options, based on patient characteristics, such as preserved liver function, ECOG-PST and comorbidities, first-line treatment AEs, the safety profile of second-line agents and associated health-related quality of life, and route and schedule of administration[7,53].

Regorafenib, cabozantinib and ramucirumab have been shown to prolong OS compared to placebo in phase III randomized controlled trials and are recommended for patients who progress or do not tolerate sorafenib (and eventually other systemic therapies)[7,53]. The main characteristics and indications of these tree drugs are summarized in TABLE 4.

Regorafenib

Regorafenib is an oral multi-TKI targeting VEGFR1–3, PDGFR, RAF kinase, and FGFR1–2 that can slow cancer progression. It was the first agent approved for second-line HCC treatment[9].

The pivotal study of regorafenib was the RESORCE trial (n=573), a phase III placebo-controlled trial that included patients who tolerated sorafenib but progressed at a dose ≥400 mg/day for a minimum period of 20 days, over the last 28 days of treatment[54]. Regorafenib 160 mg once daily was compared to placebo for weeks 1–3 of every 4-week cycle[54,55]. The appropriate population for regorafenib would be patients with Child-Pugh A liver function. The median OS was 10.6 months (95%CI 9.1–12.1) with regorafenib and 7.8 months (95%CI 6.3–8.8) with placebo (HR: 0.63, 95%CI 0.50–0.79; one-sided P<0.0001). The improvement in OS with regorafenib was maintained in all preplanned subgroup analyses. The median PFS by mRECIST was better for regorafenib compared to placebo (3.1 months [95%CI 2.8–4.2] with regorafenib and 1.5 months [95%CI 1.4–1.6] with placebo)[54]. The rate of grade 3-4 treatment-related AEs was 50% and the most common events were hypertension (15%), HFSR (13%), and fatigue (9%). Diarrhea was present in 3% (regorafenib arm) vs 0%

TABLE 4. Summary of positive phase III trials of second-line drugs (compared to placebo) for patients with hepatocellular carcinoma previously treated with sorafenib and main clinical information.

Pivotal phase III study	RESORCE (n=573)	CELESTIAL (n=707)	REACH-2 (n=292)
Drug	Regorafenib	Cabozantinib	Ramucirumab
Drug class	Multi-kinase inhibitor targeting VEGFR1–3, PDGFR, RAF kinase, and FGFR1–2	Multi-kinase inhibitor with potent activity against VEGFR 1–3, AXL, and MET	IgG1 recombinant monoclonal antibody, antagonist of VEGFR2, which blocks VEGF activation
Eligible patients	Patients previously treated with sorafenib who tolerated at least 400 mg/d of the drug. Child Pugh A, ECOG PS 0–1	Patients previously treated with sorafenib or up to two systemic treatments for HCC. Child Pugh A, ECOG PS 0–1	Patients with AFP ≥400 ng/mL previously treated with sorafenib, Child Pugh A, ECOG PS 0–1
Overall survival (months) (95%CI)	Drug: 10.6 (9.1–12.1) Placebo: 7.8 (6.3–8.8) HR: 0.63 (0.50–0.79), P<0.0001	Drug: 10.2 (9.1–12.0) Placebo: 8.0 (6.8–9.4) HR: 0.76 (0.63–0.92), P=0.0005	Drug: 8.5 (7.0–10.6) Placebo: 7.3 (5.4–9.1) HR: 0.71 (0.53–0.94), P=0.0199
PFS (months)	Drug: 3.1 (2.8–4.2) Placebo: 1.5 (1.4–1.6) HR: 0.46 (0.37–0.56), P<0.0001	Drug: 5.2 (4.0–5.5) Placebo: 1.9 (1–9–1.9) HR: 0.44 (0.36–0.52), P<0.0001	Drug: 2.8 (2.8–4.1) Placebo: 1.6 (1.5–2.7) HR: 0.45 (0.33–0.60), P=0.0001
Adverse events grade 3 or 4	Hypertension (15%), hand-foot syndrome (13%), fatigue (9%), and diarrhea (3%)	Hand-foot syndrome (17%), hypertension (16%), increased AST (12%), fatigue (10%), and diarrhea (10%)	Hypertension (13%), hyponatremia (6%), and increased AST (3%)
Dose schedule and route of administration	four coated tablets containing 40 mg each (160 mg regorafenib) taken orally once daily, with food, in a single dose, for 3 weeks followed by 1 week without therapy	60 mg taken orally once daily in a single dose, not with food (administer ≥2 h after and ≥1 h before eating)	Intravenous infusion of 8 mg/kg every 2 weeks
Approved for HCC	Europe, USA, Brazil	Europe, USA, Brazil	Europe, USA, Brazil

Progression-free survival; HR: hazard ratio; CI: confidence interval; AST: aspartate aminotransferase.

(placebo). AEs leading to drug withdrawal were observed in 10% of the patients and death related to the drug in 2%[54].

The recommended regorafenib dose in adults is four coated tablets containing 40 mg each (160 mg regorafenib) taken orally in a single dose, once daily for 3 weeks, followed by 1 week without therapy[54]. This is a 4-week treatment cycle. No dose adjustment is necessary if liver function is mildly or moderately compromised, while its use is not recommended if liver function is severely compromised. Although no dose adjustment is necessary if kidney function is mildly, moderately, or even severely compromised, regorafenib was not studied in patients undergoing dialysis. There are no safety data on its use in Child-Pugh B or C patients[7,9,53,54].

Cabozantinib

Cabozantinib is an oral multi-TKI with potent activity against VEGFR 1-3, AXL, and MET[56,57]. In addition to inhibiting angiogenesis and tumor growth, the drug decreases the metastatic potential and tumor invasiveness by blocking the MET receptor[58].

The CELESTIAL study was a double-blind phase III trial that randomized 707 patients at a 2:1 ratio to receive cabozantinib (60 mg daily) or placebo. Eligible patients had received prior sorafenib and showed disease progression after at least one or up to two systemic treatments for HCC[59]. The OS was significantly longer with cabozantinib than with placebo[59]. The median OS was 10.2 months with cabozantinib and 8.0 months with placebo (HR: 0.76, 95%CI 0.63–0.92; *P*=0.005). In addition, the median PFS was longer with cabozantinib (5.2 vs 1.9 months with placebo) (HR: 0.44, 95%CI 0.36–0.52; *P*<0.001) and the ORR by RECIST, version 1.1, was 4% and < 1%, respectively (*P*=0.009). Although 27% of the patients who received cabozantinib as third-line systemic therapy achieved median survival similar to the placebo group, PFS was significantly improved by cabozantinib[59].

An analysis using matching-adjusted indirect comparison (MAIC) with data from the phase III CELESTIAL and RESORCE trials was performed to compare efficacy and safety of cabozantinib versus regorafenib in patients with advanced HCC with progressive disease after sorafenib therapy. The results demonstrated that regorafenib and cabozantinib achieved similar OS and prolonged PFS[60].

The recommended dose of cabozantinib for HCC patients previously treated with sorafenib is a 60 mg tablet administered once daily separated from meals (i.e., no food should be eaten for at least 2 h before and for 1 h after taking the drug). Mild or moderate renal impairment (i.e., estimated glomerular filtration rate ≥30 mL/min/1.73 m^2) does not require dose adjustment[60]. However, the efficacy and safety of cabozantinib have not been determined in patients with severe renal or hepatic impairment and the drug should be avoided in these populations. Drugs that inhibit or induce CYP3A4 may increase or decrease plasma cabozantinib concentrations[60].

AEs caused by cabozantinib are typical of multi-targeted antiangiogenic TKIs[61]. In the CELESTIAL study, 68% of patients in the cabozantinib group had AEs grade 3 or 4. The most common events were HFSR (17%), hypertension (16%), elevated AST levels (12%), fatigue (10%), and diarrhea (10%)[61].

In summary, cabozantinib is a second-line treatment option for advanced HCC patients who previously failed sorafenib. The drug is approved in Europe and the United States[2] and was recently approved in Brazil (August 2021)[62].

Ramucirumab

Ramucirumab, the first non-TKI with proven antiangiogenic efficacy in advanced HCC, is an immunoglobulin G1 recombinant monoclonal antibody that targets VEGF receptor 2 (VEGFR2) and blocks VEGF activation, inhibiting angiogenesis and tumor growth[53].

In the first trial (REACH)[32], the benefit of ramucirumab, as compared to placebo, was demonstrated only in a subgroup of patients with AFP ≥400 ng/mL. Data from the double-blind randomized controlled REACH-2[63] trial, which included only patients with AFP ≥400 ng/mL at baseline (n=292, randomized 2:1 to ramucirumab or placebo), provided the basis for the European and American regulatory agencies to approve ramucirumab for the treatment of this subgroup of patients with advanced HCC after sorafenib[53].

The primary endpoint of the REACH-2 trial was OS. Secondary endpoints were PFS, ORR, time to tu-

mor progression (TTP), safety, time to deterioration in Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8 (FHSI-8) total score, and time to deterioration in ECOG-PST. The authors also pooled individual patient data from REACH-2 and from REACH for patients with AFP concentrations ≥400 ng/mL. At a median follow-up of 7.6 months (interquartile range 4.0–12.5), the median OS and PFS were significantly improved in the ramucirumab group compared to the placebo group. The OS was 8.5 months vs 7.3 months (HR 0.71; 95%CI 0.531–0.949; *P*=0.0199) and PFS 2.8 months vs 1.6 months (HR 0.452; 95%CI 1 0.339–0.603; *P*<0·0001). Both were significantly improved in the ramucirumab group compared to the placebo group. The proportion of patients with an objective response did not differ significantly between groups (9 [5%] of 197 vs 1 [1%] of 95; *P*=0.1697). The median time to deterioration in FHSI-8 total scores (3.7 months [95%CI 2.8–4.4] vs 2.8 months [95%CI 1.6–2.9]; HR 0.799 [95%CI 0.545–1.171]; *P*=0.238) or ECOG-PST (HR 1.082 [95%CI 0.639–1.832]; *P*=0.77) did also not differ between groups[63].

The safety profile of ramucirumab deviates substantially from TKIs. AEs leading to drug discontinuation were reported by 18% of the patients versus 11% in the placebo group. Peripheral edema, fatigue, ascites, arterial hypertension, and hyponatremia were more common in the ramucirumab group[63].

A post hoc analysis of data from REACH, REACH-2 and the pooled population found that treatment with ramucirumab increased OS compared to placebo in all radiological progression pattern subgroups[64]. The median time to deterioration in FSHI-8 total score or in the ECOG-PST did not differ between patients receiving ramucirumab and those receiving placebo in REACH-2. However, analysis of individual patient data pooled from REACH-2 and patients with AFP ≥400 ng/mL who were included in REACH demonstrated a benefit of ramucirumab in delaying symptom deterioration[64].

Overall, some points regarding the use of ramucirumab require special attention: a) the drug must only be used in HCC patients with AFP ≥400 ng/mL; b) there are no safety data on its use in Child-Pugh B or C patients; c) the drug must not be used during the postoperative period or in patients at high bleeding risk, and variceal screening is indicated in cirrhotic patients; d) data on ramucirumab use in patients who failed other TKIs like lenvatinib are still scarce[65].

Ramucirumab is administered intravenously, 8 mg/kg every 2 weeks. In case of adverse effects, the dose may be adjusted to 6 mg/kg. Dose reduction is not necessary in patients with creatinine clearance above 15 mL/min.

Recommendations

- In patients who progress to sorafenib, second-line options are regorafenib, cabozantinib and ramucirumab (in patients with AFP ≥400 ng/mL). **Level of evidence B. Grade of recommendation I**
- In sorafenib-intolerant patients, second-line options are cabozantinib and ramucirumab (in patients with AFP ≥400 ng/mL). **Level of evidence B. Grade of recommendation I**
- In patients who progress to atezolizumab + bevacizumab or lenvatinib, due to the lack of evidence, it is recommended that all currently approved first- and second-line drugs can be considered as second-line therapy. **Level of evidence C. Grade of recommendation I**
- In patients who progress after second-line therapy with prior use of Sorafenib, cabozantinib is indicated as third-line therapy. **Level of evidence B. Grade of recommendation I**
- In patients who progress after second-line therapy without prior use of sorafenib, due to the lack of evidence, it is recommended that all currently approved first- and second-line drugs can be considered as third-line therapy. **Level of evidence C. Grade of recommendation I.**

Systemic treatment algorithm for hepatocellular carcinoma

Systemic treatment is indicated for patients with advanced-stage HCC (BCLC C) and patients with early-stage (BCLC A) or intermediate-stage (BCLC B) HCC who are ineligible for or who progress after surgical and locoregional therapies (stage migration strategy and untreatable progression). Within this context, the available approved systemic options that improve

OS are the combination of atezolizumab + bevacizumab, sorafenib and lenvatinib in first-line treatment, and regorafenib, cabozantinib, and ramucirumab in second-line treatment. The combination of atezolizumab + bevacizumab is currently the standard of care in first-line systemic therapy for HCC. However, for patients with contraindications to atezolizumab + bevacizumab or in settings where this treatment is not available, sorafenib or lenvatinib should be considered the first-line systemic therapy for HCC[13]. Evaluating the contraindications to each drug is crucial to choose the best treatment. TABLE 5 lists the main contraindications to first-line systemic treatments.

Since there is no evidence for any drug in particular, all currently approved first- and second-line agents could be considered as 2nd-line options after progression or intolerance to atezolizumab + bevacizumab (cabozantinib, lenvatinib, ramucirumab - in patients with AFP >400 ng/mL, or sorafenib) or after lenvatinib (cabozantinib or ramucirumab - in patients with AFP >400 ng/mL). In addition, inclusion of the patients in clinical studies should be considered, if available.

In patients who progress after second-line therapy without prior use of sorafenib, there is no evidence for any drug in particular. All currently approved first- and second-line agents could be considered as third-line therapy, preferably one of the agents the patient has not yet received.

In patients who progress after sorafenib as first-line therapy, the second-line options are cabozantinib, ramucirumab (in patients with AFP >400 ng/mL), and regorafenib (patients tolerant to sorafenib). In patients who progress or are intolerant after se-

TABLE 5. Primary contraindications to first-line HCC systemic treatment.

Atezolizumab + Bevacizumab	Tyrosine kinase inhibitors – Lenvatinib or Sorafenib
Patients at high risk of bleeding: Thrombocytopenia with platelets <75 x 10^9/L Untreated or treated gastric or esophageal varices with high risk of bleeding Bleeding diathesis or significant coagulopathy Recent GI bleeding or hemoptysis Serious, non-healing or dehiscing wound, active ulcer or untreated bone fracture	**Patients at high risk of bleeding:** Thrombocytopenia with platelets <75 x 10^9/L Gastric or esophageal varices that require treatment Bleeding or thrombotic disorders Recent GI bleeding or hemoptysis
Severe chronic hepatitis with AST, ALT >5 xULN	**Severe chronic hepatitis with AST, ALT >5 xULN**
Autoimmune diseases and conditions requiring immunosuppression: Current or past autoimmune disease Exceptions: hypothyroidism, type 1 diabetes, skin diseases with limited involvement Any condition that requires chronic systemic immunosuppression	Absence of contraindication in patients with autoimmune diseases or conditions requiring immunosuppression.
Cardiovascular diseases: Inadequately controlled blood pressure History of hypertensive crisis or hypertensive encephalopathy Chronic heart failure (NYHA class >1), myocardial infarction or stroke in the last 3 months Unstable angina Unstable arrhythmia Significant vascular disease (including recent peripheral arterial thrombosis) in the last 6 months	**Cardiovascular diseases:** Inadequately controlled blood pressure or need of >1 antihypertensive medication Chronic heart failure (NYHA class > II) Unstable angina, myocardial infarction or stroke in the last 6 months Arrhythmia requiring medical treatment QTc >480 ms
Populations with unknown benefit: HBV-HCV coinfection HIV infection ECOG >1 Child-Pugh class B or C Current moderate to severe ascites or any history of hepatic encephalopathy Liver transplantation Brain or leptomeningeal metastasis Fibrolamellar HCC, sarcomatoid HCC or mixed cholangiocarcinoma and HCC	**Populations with unknown benefit:** HIV infection ECOG >1 Child-Pugh class B or C Liver transplantation HCC with ≥50% liver involvement, invasion into the bile duct, or invasion of the main portal branch (only for lenvatinib) Brain or leptomeningeal metastasis

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ECOG: Eastern Cooperative Oncology Group Performance Status; NYHA: New York Heart Association; HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus. Modified from Bruix et al. (J Hepatology 2021)[7].

cond-line therapy with prior use of sorafenib, cabozantinib is indicated as third-line systemic therapy for HCC. There are no randomized controlled trials evaluating atezolizumab + bevacizumab as second-line treatment after TKIs. On the other hand, this may be considered a therapeutic option for patients without contraindications to the combined treatment, but who were not previously treated with this option because it was not yet available.

FIGURE 1 illustrates the systemic treatment algorithm for HCC suggested by SBH.

MANAGEMENT OF ADVERSE EVENTS

Tyrosine kinase inhibitors

The main AEs of TKIs used in the management of HCC are HFSR, diarrhea, fatigue, and hypertension. In addition, many other AEs have been described in clinical trials and real-life studies, notably, alopecia, weight loss, abdominal pain, anorexia, pruritus, skin rash, dry skin, voice changes, increased liver enzymes, and liver dysfunction[10,35,36,44,54,59].

In the SHARP trial, the overall incidence of AEs was 80% in the subgroup of patients using sorafenib and 52% in the placebo subgroup[10]. The significantly more frequent AEs in the subgroup receiving sorafenib compared to placebo were diarrhea (39% vs 11%; $P<0.001$), HFSR (21% vs 3%; $P<0.001$), alopecia (14% vs 2%; $P<0.001$), anorexia (14% vs 3%; $P<0.001$), weight loss (9% vs 1%; $P<0.001$), abdominal pain (8% vs 3%; $P=0.007$), dry skin (8% vs 4%, $P=0.04$), voice changes (6% vs 1%; $P<0.001$), and hypertension (5% vs 2%; $P=0.05$). The most common severe AEs (grades 3 and 4) in the subgroup using sorafenib were diarrhea (8%), HFSR (8%), and weight loss (2%). Regarding severe laboratory abnormalities, the most frequent events in the sorafenib subgroup were hypophosphatemia (11% vs 2%; $P<0.001$) and thrombocytopenia (4% vs <1%; $P=0.006$). Also in the SHARP trial, 26% of patients using sorafenib required dose reduction compared to only 7% of patients in the placebo group. The main AEs associated with dose reduction were diarrhea (8%), HFSR (5%), and rash (3%). The rate of treatment discontinuation due to AEs

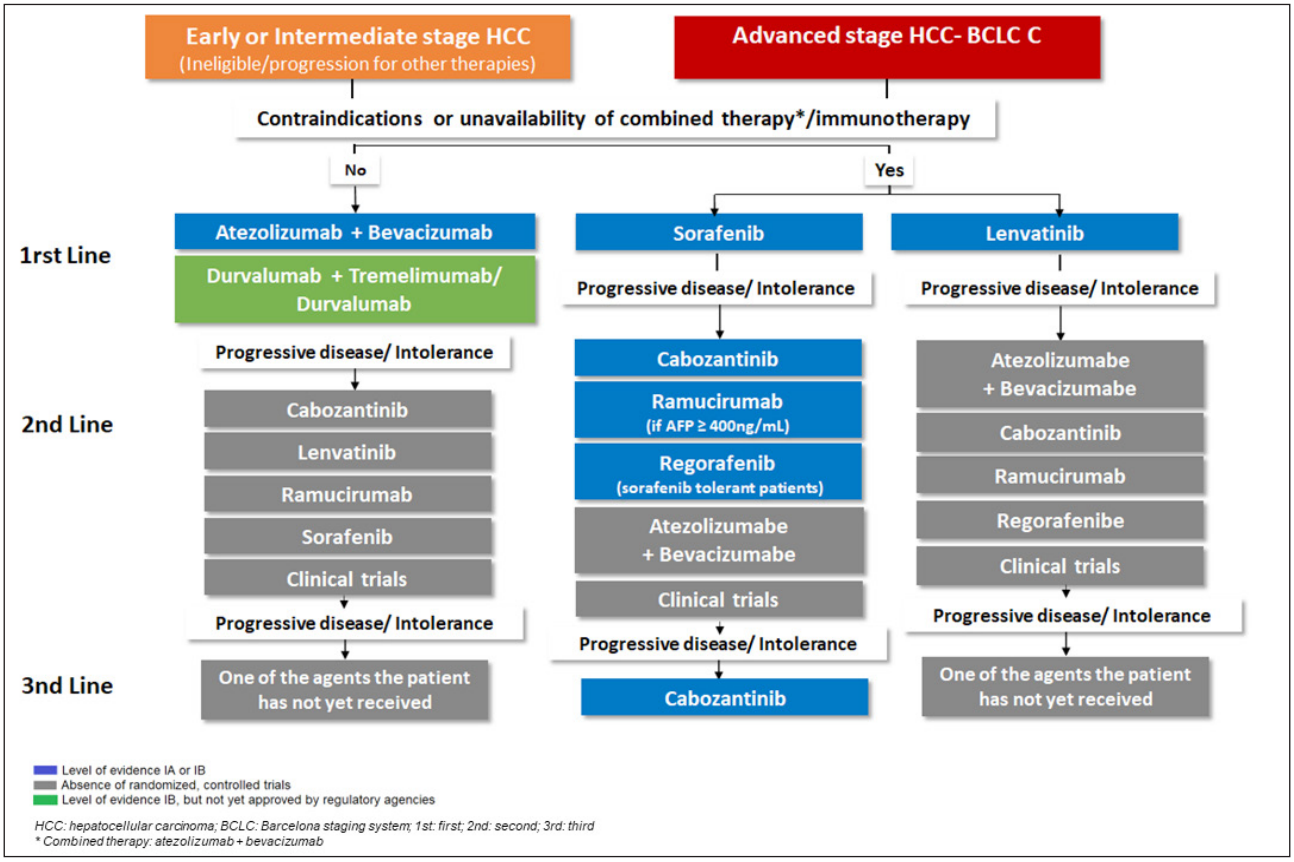

FIGURE 1. Systemic treatment algorithm for HCC suggested by SBH.

in the SHARP trial was similar between the subgroups studied: 38% sorafenib and 37% placebo. The most frequent AEs leading to treatment discontinuation in sorafenib-treated patients were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%)[10].

In the Asia-Pacific study, the most frequent severe AEs in patients receiving sorafenib were HFSR (10.7%), diarrhea (6%), and fatigue (3.4%). The main AEs associated with dose reduction were HFSR (11.4%) and diarrhea (7.4%); however, few cases led to treatment discontinuation[35].

In the real-life GIDEON study with 3,202 patients (21% Child-Pugh B and 3% Child-Pugh C), the incidence of AEs associated with sorafenib was similar regardless of the severity of liver dysfunction (17% Child-Pugh A vs 21% Child-Pugh B). The most common AEs in that cohort were diarrhea, HFSR, and fatigue. There was a higher frequency of sorafenib discontinuation in the first 8 weeks among Child-Pugh B patients (42%) compared to Child-Pugh A (26%). However, dose reduction at some point during treatment was more frequent in Child-Pugh A patients (40%) than in Child-Pugh B patients (29%)[36].

The REFLECT trial compared OS in patients treated with lenvatinib versus sorafenib. The most frequent AEs (any grade) in the lenvatinib subgroup were hypertension (42%), diarrhea (39%), anorexia (34%), and weight loss (31%). In the sorafenib subgroup, the most common AEs were HFSR (52%), diarrhea (46%), hypertension (30%), and anorexia (27%). The frequency of severe (≥ grade 3) treatment-related AEs was 57% in the lenvatinib subgroup and 49% in the sorafenib subgroup[44].

In the RESORCE trial, the main severe AEs (≥ grade 3) secondary to regorafenib compared to placebo were hypertension (15% vs 5%), HFSR (13% vs 1%), fatigue (9% vs 5 %), and diarrhea (3% vs 0%). The rate of temporary interruption or dose reductions due to drug-related AEs was 54% and the discontinuation rate was 10%[54]. Clinical practice data suggest that previous tolerance to sorafenib is a good predictor of better tolerability of regorafenib.

In the CELESTIAL study, severe AEs (≥ grade 3) occurred in 68% of patients using cabozantinib and in 36% using placebo. The significantly more frequent severe AEs in the cabozantinib subgroup compared to placebo were HFSR (17% vs 0%), hypertension (16% vs 2%), increased aminotransferases (12% vs 7%), fatigue (10 % vs 4%), and diarrhea (10% vs 2%). Dose reductions were required in 62% of patients using cabozantinib and in 13% using placebo. The discontinuation rate due to AEs was 16% in the cabozantinib subgroup and 3% in the placebo group[59].

Several studies suggest that the occurrence of AEs is positively correlated with survival. A meta-analysis evaluated the correlation between the occurrence of HFSR, TTP and OS in patients with HCC who received sorafenib[66]. The combined HR was 0.41 (95%CI 0.28–0.60; $P<0.00001$) for TTP and 0.45 (95%CI 0.36–0.55; $P<0.00001$) for OS. Another meta-analysis suggests that diarrhea (HR: 0.42, 95%CI 0.3–0.6; $P<0.00001$), hypertension (HR: 0.46, 95%CI 0.3–0.7; $P=0.0003$), and HFSR (HR: 0.47, 95%CI 0.35–0.62; $P<0.00001$) are also good predictors of survival[66]. The combination of more than one adverse event also appears to have a positive correlation with survival.

The management of patients using TKIs should be performed by multidisciplinary teams. Patient education to recognize and prevent AEs is essential. In the case of severe AEs, dose reduction or temporary discontinuation of the drug may be sufficient. However, patients who experience life-threatening or recurrent AEs should switch to a treatment with other classes of systemic therapy drugs. Recommendations for the management of AEs of TKIs in patients with HCC are mostly based on expert opinions since there is little data from clinical studies. Furthermore, most recommendations are based on experiences with sorafenib due to the longer availability of this medication in clinical practice[67-69].

Hand-foot skin reaction refers to the occurrence of lesions on the hands and/or feet that appear as hyperkeratotic patches or lesions with an erythematous base in areas of pressure or friction. Before starting treatment, patient education aimed at recognizing this adverse event is essential. The prophylactic use of 10% urea-based emollients three times per day by patients using sorafenib has been shown to be effective in reducing the incidence or delaying the onset of HFSR[68]. Some experts also recommend strategies for controlling calluses and removing areas of hyperkeratosis. Comfortable shoes and wearing socks and gloves can reduce friction and prevent lesions. Other useful precautions are

to avoid extreme temperatures of the hands and feet (hot baths and exposure to the sun or intense cold) and to completely dry after washing. The use of moisturizing lotions is highly recommended in patients who develop HFSR. In severe cases, the topical use of anesthetics and corticosteroids may be considered. Cutaneous AEs of TKIs other than HFSR have been described. Moreover, paraneoplastic cutaneous manifestations associated with HCC must also be included in the differential diagnosis of any dermatological lesion. A multidisciplinary approach involving dermatologists is important when a differential diagnosis is considered[66,68].

The blood pressure must be measured at all medical appointments. The management of hypertension should follow standard clinical practices. Calcium channel blockers may interact with TKIs[69].

Patients with diarrhea should be advised by nutritionists about a constipating diet. Loperamide is the most widely prescribed medication to manage diarrhea, which can be used on demand for symptomatic treatment or prophylactically in patients with recurrent diarrhea[69].

Fatigue is a hard-to-treat adverse event. Strategies such as daytime resting periods and regular exercises can help. It is important to consider differential diagnoses such as dehydration, hypothyroidism, anemia, sleep apnea, hypogonadism, and depression[69].

Recommendations:

- Tyrosine kinase inhibitors have a well-established safety and tolerability profile. Their main adverse events are HFSR, diarrhea, fatigue, and high blood pressure. **Level of evidence A. Grade of recommendation I**
- Grade 3 and 4 adverse events can be managed with dose reduction or temporary discontinuation of treatment. In selected cases, permanent discontinuation of treatment and migration to another systemic treatment may be necessary. **Level of evidence A. Grade of recommendation I**
- Multidisciplinary teams and patient education are essential for the prevention and for the early recognition and management of adverse events. **Level of evidence C. Grade of recommendation I**

Immune checkpoint inhibitors

The blockade of ICIs molecules often produces a wide range of immune-mediated adverse events (IMAEs) as a result of enhanced T-cell activation. IMAEs can involve almost every organ and can result in hepatitis, rash, pruritus, colitis, pneumonitis, or thyroiditis, to mention some of the most common events; however, they are usually manageable, although they can also be life-threatening[70]. Anti-CTL4 agents such as ipilimumab and tremelimumab have a toxicity profile that differs from that of anti-PD-L[70]. While the overall incidence of IMAE associated with anti-CTL4 is 24% for grade 3 or 4[71], with a shorter median time to onset, the incidence of grade 3 or 4 AEs during anti-PD-L1 use is 6%[72]. A recent meta-analysis showed ipilimumab-induced colitis was the most common cause of fatal IMAE; however, HCC patients were not included[73]. The use of ICIs in HCC patients is challenging because of underlying liver disease. Liver toxicities are more frequent and more severe in patients with HCC than in those without chronic liver disease and the diagnosis of IMAEs might be challenging because of the confounding effect of organ dysfunctions associated with this chronic condition[71]. Besides, we have few safety data on Child-Pugh B patients. The great challenge is to differentiate IMAE from cirrhosis- and/or cancer-related complications; it is therefore extremely important to know the baseline status of the patient, especially liver enzymes and liver function tests. Patient monitoring is the best tool for the early recognition of IMAEs, and early decisions may be crucial for a good outcome.

Grading AEs is an important step for guiding decisions. The Common Terminology Criteria for Adverse Events (CTCAE) are the standard classification for grading AEs in oncology and should be used in HCC patients. Obtaining a good history and laboratory evaluation prior to initiation of ICI therapy in order to establish an accurate baseline are essential. Recently, more permissive values for ALT/AST alterations in patients with enzymes levels above normal have been proposed[71].

For grade 1 AEs, only monitoring is advised. In the case of grade 2 events, the patient must be monitored weekly and withdrawal of immunotherapy must be considered, especially if the condition aggravates. In this case, corticosteroids must be started, with pred-

nisone (0.5–1 mg/kg/day) being the first choice. In the case of grade 3 events, the patient must be monitored every 2 days and treatment discontinuation is recommended, as well as higher doses of prednisone (1–2 mg/kg/day) must be started. If there is no improvement, intravenous corticosteroids and other immunosuppressive drugs, such as infliximab, should be considered. Since infliximab may induce hepatitis, in the case of liver-related IMAE, mycophenolate is the immunosuppressive drug of choice. Specialist consultation is recommended for grade 3 reactions and some grade three patients may require hospitalization, while all grade four patients must be hospitalized until improvement. It is important to rule out other conditions that may cause symptoms. Immune-mediated pneumonitis and encephalitis are very serious conditions that can rapidly deteriorate; thus, early ICI withdrawal and hospitalization are recommended and specialist consultation is necessary[71].

There is no specific rule for corticosteroids and tapering of other immunosuppressive agents, but a slow reduction over 1–2 months is used in clinical practice accompanied by close monitoring. Drug rechallenge is always a difficult decision and is not recommended for grade 3 anti-CTL4-related reactions, grade 3 pneumonitis, severe grade 3 reactions in any system, and all grade 4 reactions. In the case of less severe reactions, the drug may be restarted after the IMAE has returned to grade 1, with close monitoring[70].

Reinvigoration of antiviral immunity is associated with hepatitis flares in patients chronically infected with HBV and HCV, especially HBV patients. Some trials included patients with HBV DNA less than 500 IU/mL and no significant hepatitis reactivation was reported. HBsAg-positive patients must be under antiviral therapy. For HBsAg-negative/HBc-positive patients, the risk of reactivation seems to be very low but no conclusive data are available. The risk of hepatitis C reactivation is lower[71,74].

Recommendations:

- Baseline evaluation is important for recognizing IMAEs and all patients must be evaluated for adverse events monthly. Once an IMAE is detected, the CTCAE are the standard classification for grading adverse events and should be used for ideal management:
  - Patients with grade 1 adverse events may be monitored weekly.
  - Patients with grade 2 adverse events may be monitored every 48 h and ICIs must be withdrawn. Corticosteroids must be started if the condition worsens.
  - Patients with grade 3 and 4 adverse events must discontinue ICIs and corticosteroids must be started immediately. Other immunosuppressive therapy may be used for refractory cases. Infliximab must not be used for immune-mediated hepatitis. **Level of evidence C. Grade of recommendation I**
- Specialist consultation is recommended, especially for pneumonitis and neurological events and for all grade 3 or 4 adverse events. **Level of evidence C. Grade of recommendation I**

New and future therapies

In recent years, there have been remarkable advances in the treatment of HCC and new strategies continue to be tested in different scenarios, including adjuvant and neoadjuvant treatment. The combination of therapies in HCC aims to improve OS, but also PFS, and to increase TTP.

Systemic therapy combined with locoregional treatment

It is known that locoregional treatment, especially TACE, causes hypoxia in the tumour microenvironment, stimulating the production of local VEGF and other angiogenesis pathways. This fact suggests that the use of antiangiogenic agents may contribute to the antitumor effect of TACE. Thus, immunotherapy could be useful in combination with locoregional therapy.

Among the studies found in the literature, six were randomized trials that evaluated the benefit of the combination of TACE with systemic therapy, four using sorafenib, one brivanib, and one orantinib[75-80]. Based on these studies, no recommendation for such combination can be made at this time.

At present, there are no randomized studies that have evaluated the effect of locoregional treatment and immunotherapy. An uncontrolled study involving a series of 32 patients demonstrated a possible beneficial effect of the combination of tremelimumab

and ablation[81]. An ongoing phase I multicenter study combining DEB-TACE with nivolumab showed an ORR of 21% and stable disease in 58% of the patients, with no cases of treatment-related liver failure or grade 5 AEs[82]. The study is still in the recruitment phase and further conclusions can only be made after the inclusion of a larger number of patients.

Some ongoing trials are currently investigating systemic therapy as the treatment of choice for intermediate-stage HCC, combined with TACE - LEAP-012 (lenvatinib + pembrolizumab + TACE vs TACE) and CheckMate 74W (ipilimumab + nivolumab + TACE vs nivolumab + TACE vs TACE) - or as an alternative to TACE - ABC-HCC trial (atezolizumab + bevacizumab vs TACE) and RENOTACE trial (nivolumab + regorafenib vs TACE)[83].

Adjuvant and neoadjuvant systemic treatment

Surgical resection is the treatment of choice in cases of very early and early HCC but does not eliminate the risk of tumor recurrence, which can occur early related to the tumor, or late (after 2 years) due to the underlying disease. Thus, there is room for adjuvant treatment, which aims not only to eliminate residual microscopic disease but also to prevent the occurrence of a new primary tumor in the liver. A few years ago, a large multicenter, randomized, double-blind, placebo-controlled trial tested sorafenib after resection or ablation in order to prevent tumor recurrence. However, there were no differences in median recurrence-free survival between the two groups[41].

Currently, immunotherapy is being evaluated in some studies to establish an adjuvant strategy: nivolumab (CheckMate 9DX study, NCT03383458) and pembrolizumab (KEYNOTE 937 NCT03867084) are tested in randomized, phase III, double-blind, placebo-controlled studies of adjuvant therapy for patients with HCC after curative hepatic resection or ablation. Similar patients are being evaluated for recurrence-free survival in IMBRAVE050 (NCT04102098) after atezolizumab (anti-PD-L1 antibody) plus bevacizumab versus active surveillance, and in EMERALD-2 (NCT03847428), a multicenter study of durvalumab monotherapy or in combination with bevacizumab as adjuvant therapy[84].

Neoadjuvant therapy can be used to reduce the tumor mass and thus enable sequential curative treatment in patients who would not otherwise be candidates. TACE is the treatment of choice for intermediate tumors and has been recognized as a downstaging tool for liver transplantation[85]. Other therapeutic options have also been discussed, including radioembolization (TARE/SIRT), which seems to have some advantages over TACE[86].

Other different approaches are still being tested at different tumor stages, including pembrolizumab + resection/ablation in BCLC 0/A patients, nivolumab + irreversible electroporation in BCLC A/B patients, cabozantinib + nivolumab + resection, and pembrolizumab + lenvatinib + liver transplantation vs liver transplantation, which encompass adjuvant and neoadjuvant activity[83,87]. However, so far, systemic treatment has not been established for either adjuvant or neoadjuvant therapy[83,87].

Other systemic therapies

Recently, novel trials have been published that evaluated new drugs and combined therapies in the landscape of systemic treatment for HCC. The most important studies are summarized below.

The combination of durvalumab and tremelimumab (PD-L1 and CTLA-4 antibodies) was examined in the phase III HIMALAYA trial that mainly enrolled patients with unresectable HCC and no previous systemic treatment to receive one of three regimens: tremelimumab (300 mg, one dose) plus durvalumab (1500 mg every 4 weeks; STRIDE), durvalumab (1500 mg every 4 weeks), or sorafenib (400 mg twice daily). The primary objective was OS for STRIDE versus sorafenib and a secondary endpoint was non-inferiority on OS for durvalumab versus sorafenib. The median OS was 16.43 months (95%CI 14.16–19.58) with STRIDE, 16.56 months (95%CI 14.06–19.12) with durvalumab, and 13.77 months (95%CI 12.25–16.13) with sorafenib. The HR of OS for STRIDE versus sorafenib was 0.78 (96.02%CI 0.65–0.93; P=0.0035). The OS with durvalumab monotherapy was non-inferior to sorafenib (HR: 0.86; 95.67%CI 0.73–1.03; non-inferiority margin, 1.08). In conclusion, STRIDE significantly improved OS compared to sorafenib and durvalumab monotherapy was non-inferior to sorafenib for patients with unresectable HCC[88].

Since the HIMALAYA trial was published after the

consensus meeting and has not yet been approved by regulatory agencies in Brazil or Latin America, this treatment cannot yet be recommended as a first-line option for HCC in the present consensus and was included in the section on new treatments.

CheckMate 459 was a randomized, phase III, multicenter study that evaluated nivolumab versus sorafenib as a first-line treatment in patients with unresectable HCC. After a minimum follow-up of 22.8 months, no significant differences in OS were observed between treatments (OS of 16.4 months with nivolumab vs 14.7 months with sorafenib; *P*=0.0752)[89].

KEYNOTE-240 evaluated the efficacy and safety of pembrolizumab in a population with advanced HCC previously treated with sorafenib. Median OS was 13.9 months for pembrolizumab vs 10.6 months for placebo (HR: 0.781; 95%CI 0.611–0.998; *P*=0.0238). In that study, OS and PFS did not reach statistical significance per specified criteria of the protocol[90].

Cabozantinib and atezolizumab in a first-line setting were evaluated in a phase III trial (COSMIC-312)[91] in which patients were randomly (2:1:1) assigned to 40 mg cabozantinib orally once daily plus 1200 mg atezolizumab intravenously every 3 weeks (n=432), 400 mg sorafenib orally twice daily (n=217), or single-agent 60 mg cabozantinib orally once daily (n=188). Median OS was 15.4 months (96%CI 13.7–17.7) in the combination treatment group versus 15.5 months (12.1–not estimable) in the sorafenib group (HR: 0.90, 96%CI 0.69–1.18; *P*=0.44). Thus, the absence of an OS benefit indicates the need for additional studies to determine if cabozantinib plus atezolizumab would be an appropriate first-line treatment option in selected patient populations[91].

The phase III LEAP-002 trial[92] investigating pembrolizumab plus lenvatinib versus lenvatinib monotherapy did not meet its dual primary endpoints of OS and PFS as a first-line treatment for patients with unresectable HCC. There were trends toward improvement in OS and PFS for patients who received pembrolizumab plus lenvatinib versus lenvatinib monotherapy; however, these results did not reach statistical significance per pre-specified statistical plan[92].

In conclusion, the last four phase III studies mentioned above, unfortunately, did not confirm the benefit of this therapeutic strategy.

New systemic therapies: ongoing studies

Based on the excellent antitumor effects of ICIs in clinical trials on HCC, researchers have applied therapeutic strategies combining these ICIs with other agents to improve their efficacy, which are currently being tested in phase III trials. In addition, there are other promising agents for HCC treatment that are currently being assessed evalin phase III trials[93].

1. Combining checkpoint inhibitors with angiogenesis inhibitors

Previous studies have shown that antiangiogenic agents and immunotherapy exert a synergistic antitumor effect, inducing tumor immune stimulation and vascular remodeling[94,95]. Furthermore, the relatively different AEs that arise may facilitate their use as a combination therapy[96].

- Apatinib + camrelizumab:

The combination of apatinib (rivoceranib) and camrelizumab (SHR1210, a PD-1 antibody) was examined in a phase I study of patients with advanced HCC[97]. Among the 16 patients with HCC enrolled, the ORR was 50%. This regimen is currently being evaluated and compared with sorafenib in an ongoing phase III trial in the first-line setting of advanced HCC (NCT03764293).

2. Immune checkpoint inhibitor + immune checkpoint inhibitor

- Nivolumab + ipilimumab (PD-1 and CTLA-4 antibodies):

In 2020, the FDA accelerated the approval of nivolumab plus ipilimumab as a second-line treatment for HCC based on the results of the CheckMate 040 clinical trial. The results of that trial indicated that the ORR of the arm A dosage regimen (1 mg/kg nivolumab and 3 mg/kg ipilimumab every 3 weeks, then 240 mg nivolumab every 2 weeks) reached 32%[98]. Given the limitations of the trial, a randomized controlled trial involving a larger patient sample with stratification will be needed in the future. This combination regimen is currently being evaluated as a first-line treatment for HCC in a phase III trial (NCT04039607).

Other combination therapies are summarized in TABLE 6. With the rapid development of molecular

TABLE 6. Combination treatment of hepatocellular carcinoma in clinical trials.

Drug	Targets	Condition	Phase	Primary endpoint	Clinical trial
Atezolizumab plus Lenvatinib or Sorafenib	PD-L1 + VEGFRs, FGFRs, RAF RET, KIT	Second-line	III	OS	NCT04770896
SHR-1210 plus Apatinib	PD-1 + VEGFR-2	First-line	III	OS PFS	NCT03764293
Nivolumab plus Sorafenib	PD-1 + VEGFRs, KIT, RAF PDGFRs	First-line	II	MTD ORR	NCT03439891
Nivolumab plus Ipilimumab	PD-1 + CTLA-4	First-line	III	OS	NCT04039607
Durvalumab plus Bevacizumab	PD-L1 + VEGFA	Second-line	III	RFS	NCT03847428
Cabozantinib plus Atezolizumab	PD-L1 + VEGFR, MET, RET, KIT, AXL	First-line	III	OS PFS	NCT03755791

PD-1: programmed cell death 1; VEGFR: vascular endothelial growth factor receptor; PD-L1: programmed cell death ligand 1; FGFR: fibroblast growth factor receptor; PDGFR: platelet-derived growth factor receptor; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; OS: overall survival; PFS: progression-free survival; MTD: maximum tolerated dose; ORR objective response rate; RFS: recurrence-free survival. Modified from Luo et al.[93].

biotechnology, the increased possibility of new treatment strategies and several ongoing and promising trials, these recommendations will have to be updated regularly.

MANAGEMENT OF LIVER DISEASE IN THE CONTEXT OF SYSTEMIC TREATMENT

Management of portal hypertension and cirrhosis in patients with hepatocellular carcinoma

There is a lack of data concerning the management of cirrhosis and portal hypertension in subjects with HCC. Mortality of patients with HCC is commonly due to tumor progression; however, in one study, 43% of the deaths were attributed to common complications of cirrhosis such as infections, acute kidney injury and/or variceal hemorrhage[99], highlighting that most patients with HCC have two diseases, liver cancer and cirrhosis, which should be managed accordingly.

Most of the current guidelines on the management of portal hypertension and the aforementioned complications of cirrhosis[12,100-102] have not addressed recommendations tailored specifically to subjects with HCC. Therefore, although not evidence based, all strategies currently in use for patients with cirrhosis remain unchanged in most circumstances for subjects with cirrhosis and concurrent HCC. It is, however, important to highlight that HCC may worsen portal hypertension and may induce difficult-to-treat variceal hemorrhage[99]. Variceal bleeding in subjects with HCC is also associated with higher mortality, particularly in patients with associated portal vein thrombosis[103].

An important issue is the risk of bleeding associated with the use of TKIs[104,105] and combined therapy[99]. In one meta-analysis[106], sorafenib was associated with an increase in the rate of minor bleeding but not variceal hemorrhage. On the other hand, caution is necessary with the use of bevacizumab[11] or the combination of bevacizumab and atezolizumab[107] in subjects with HCC and esophagogastric varices (EGV) because of a higher risk of variceal hemorrhage associated with the use of those agents. The combination of bevacizumab and atezolizumab is now considered the standard of care for Child-Pugh A patients with BCLC stage C HCC and prophylaxis of variceal hemorrhage is mandatory in subjects with EGV before the use of the bevacizumab and atezolizumab combination, as well as TKIs[7]. A position paper from the European Association for the Study of the Liver (EASL) recommends either nonselective beta-blockers (NSBBs) or endoscopic band ligation (EBL) according to Baveno VI guidelines but suggests that the efficacy of NSBB may be lower in this setting. When using EBL, the EASL position paper suggests achievement of endoscopic-proven EGV eradication with no post-banding ulcers before the initiation of either TKIs or atezolizumab and bevacizumab[7].

HBV management

Antiviral therapy suppresses HBV replication in patients with HCC and may affect the prognosis by

preventing at least three potentially deleterious situations: 1) HBV reactivation, which has been described to occur at variable rates in association with different HCC therapies; 2) loss of hepatic function, which may prevent the adequate implementation of HCC therapy, and 3) HCC recurrence, which seems to occur at an increased frequency among patients with high HBV viral load compared to those with low viral load or undetectable HBV DNA[108,109]. Thus, there is compelling evidence to promptly consider HBV treatment in all patients with HBV-related HCC, ideally starting before the implementation of any type of anti-HCC therapy. Entecavir, tenofovir, and TAF are the recommended drugs since they have more potent antiviral activity and a higher barrier to resistance[108,110-115].

Regarding HBV reactivation, many studies have shown that the risk of this event is higher in the presence of practically all currently used modalities of HCC therapy and that it can effectively be prevented by antiviral therapy. Reinvigoration of antiviral immunity is associated with hepatitis flares in patients chronically infected with HBV. Some trials have included patients with HBV DNA less than 500 IU/mL and no significant hepatitis reactivation has been reported. HBsAg-positive patients must be under antiviral therapy. For HBsAg negative/anti-HBc-positive patients, the risk of reactivation seems to be very low but no conclusive data are available[108,110-115]. Close monitoring of liver enzymes, HBV viral load and HBsAg and prompt antiviral therapy upon evidence of HBV reactivation are necessary for these patients until an early prophylactic approach can be clearly defined[116].

HCV management

Although several publications have focused on the impact of direct-acting antiviral (DAA) treatment in patients with HCC, only few have described the outcomes in patients with BCLC stage B/C. When starting DAA treatment, patients with a viable tumor achieve a lower sustained virological response rate than patients with inactive or no HCC[117]. This lower sustained virological response is likely to be associated with a lower rate of improvement of cirrhosis complications in patients with HCC compared to those without HCC. There is no consensus regarding which BCLC C patients should be submitted to DAA treatment. The decision should be made on a patient-by-patient basis and each patient should be informed about all potential risks of DAA failure and HCC progression. In a recent review on this topic, Reig et al. suggested that DAA should be used in BCLC C-D patients if HCV is a plausible explanation for liver dysfunction; treating the virus may improve Child-Pugh score and HCC treatment may therefore be facilitated. This approach would exclude those patients with very massive disease in whom liver dysfunction is due to tumor burden[118].

Recommendations:

- Management of portal hypertension and complications of cirrhosis such as ascites, hepatic encephalopathy, infections, and acute kidney injury in patients with HCC should include the same strategies as those adopted for patients with cirrhosis without liver cancer. **Level of evidence C. Grade of recommendation I**
- Worsening of portal hypertension is common after the development of HCC. Screening for EGV by endoscopy is highly advised. **Level of evidence C. Grade of recommendation I**
- Adherence to current guidelines in order to prevent the first episode of variceal bleeding and recurrent bleeding is highly recommended due to the adverse impact of variceal hemorrhage on patient survival. **Level of evidence B. Grade of recommendation I**
- Variceal bleeding may be induced by the use of TKIs but is much more common with the combination of atezolizumab and bevacizumab. The use of non-selective beta-blockers or endoscopic band ligation is mandatory in HCC patients with varices before the use of these agents, particularly immunotherapy. **Level of evidence C. Grade of recommendation I**
- Therapy with potent antiviral nucleoside analogs such as entecavir, TDF or TAF is recommended in all HBsAg/HBV DNA-positive patients with HBV and HCC because they prevent clinical decompensation and can even reverse decompensation if present at baseline. **Level of evidence B. Grade of recommendation I**

- HBV treatment with nucleoside analogs is recommended in patients with HBsAg positive HBV and HCC submitted to systemic treatment in order to prevent HBV reactivation. **Level of evidence C. Grade of recommendation I**
- In HBsAg negative/anti-HBc-positive patients, the risk of reactivation seems to be very low but no conclusive data are available. Close monitoring and prompt antiviral therapy upon evidence of HBV reactivation are necessary in these patients. If HBV viral load monitoring is not available, treatment with nucleoside analogs should be initiated to prevent reactivation. **Level of evidence C. Grade of recommendation I**
- Patients with hepatitis C and intermediate/advanced-stage HCC (BCLC B/C) who are candidates for systemic therapy could be treated with DAAs to improve liver function, according to life expectancy. **Level of evidence C. Grade of recommendation IIa**

CONCLUSION

In Brazil and in Latin America, a large proportion of HCC patients are diagnosed at an advanced stage and systemic therapy is one of the cornerstones in the management of this tumor. Over the last 10 years, we have seen the emergence of new drugs for systemic treatment of HCC.

The present guidelines reviewed the mechanisms of action of the main drugs, current indications, and the most recent literature data on the landscape of systemic therapy for HCC and report the recommendations of SBH for the systemic treatment of this tumor, as well as for the management of adverse events and underlying liver disease in patients undergoing treatment. Combined therapy is currently a main focus of research on the systemic treatment for advanced HCC. With the continued development of new therapeutic strategies, it is expected that these recommendations will have to be updated regularly.

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Authors' contribution

Chagas AL Leal CRG, Mello VB, Barros FMR, Bittencourt PL, Mattos AA, Aroucha D, Fonseca LG, Silva JRL, Dottori MF, Teixeira R, Mendes LSC, Rezende REF, Filgueira NA, Coutinho AK, Araújo Neto JM, Coelho HSM, Pessoa MG, Cheinquer H, Parise ER, França A, Álvares-da Silva MR, Carrilho FJ, Coral GP, Pinto PTA, Pereira LMMB, Paraná R, Brandão-Mello CE. Chagas AL, Leal CRG, Barros FMR, Brandão--Mello CE: guideline coordinators, study concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content, study supervision. Mello VB, Bittencourt PL, Mattos AA, Aroucha D, Fonseca LG, Silva JRL, Dottori MF, Teixeira R, Mendes LSC, Rezende REF, Filgueira NA, Coutinho AK, Araújo Neto JM, Coelho HSM, Pessoa MG, Cheinquer H, Parise ER, França A, Álvares-da--Silva MR: guideline panelist, drafting of the manuscript; critical revision of the manuscript for important intellectual content. Carrilho FJ, Coral GP, Pinto PTA, Pereira LMMB, Paraná R: guideline moderators, critical revision of the manuscript for important intellectual content. Alves RCP: guideline panelist, drafting of the manuscript; critical revision of the manuscript for important intellectual content.

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RESUMO – O carcinoma hepatocelular (CHC) é uma das principais causas de mortalidade relacionada a câncer no Brasil e no mundo. A Sociedade Brasileira de Hepatologia (SBH) publicou em 2020 a atualização das recomendações da SBH para o diagnóstico e tratamento do CHC. Desde então, novas evidências científicas sobre o tratamento sistêmico do CHC foram relatadas na literatura médica, incluindo novos medicamentos aprovados que não estavam disponíveis na época do último consenso, levando a diretoria da SBH a promover uma reunião monotemática on-line para discutir e rever as recomendações sobre o tratamento sistêmico do CHC. Um grupo de experts foi convidado para realizar uma revisão sistemática da literatura e apresentar uma atualização, baseada em evidências científicas, sobre cada tópico relacionado ao tratamento sistêmico e a apresentar os dados e recomendações resumidas durante a reunião. Todos os painelistas se reuniram para discutir os tópicos e elaborar as recomendações atualizadas. O presente documento é a versão final do manuscrito revisado, contendo as recomendações da SBH, e seu objetivo é auxiliar os profissionais de saúde, formuladores de políticas e planejadores no Brasil e na América Latina na tomada de decisões sobre o tratamento sistêmico de pacientes com CHC.

Palavras-chave – Carcinoma hepatocelular; tumores malignos do fígado; tratamento sistêmico.

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