

# New concepts in the treatment of hepatocellular carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death and occurs mainly in the context of chronic liver disease at cirrhosis stage. The Barcelona Clinic Liver Cancer classification, first established in 1999, is the most commonly used staging system for HCC in Western countries that link tumor burden, liver function and performance status with prognosis and therapeutic management. Since the first publication of this classification, it has been implemented in several clinical guidelines and recent major therapeutic advances in the management of HCC have modified the therapeutic landscape of HCC. Accordingly, an updated version was recently published in 2022, incorporating an expert clinical decision-making component and the concept of treatment stage migration. This update also introduces the positive results of recent randomized clinical trials, and introduces atezolizumab/bevacizumab (A/B) as a first-line combination regimen for patients with advanced HCC. Finally, the complexity of the management of patients with HCC highlights the need for a multidisciplinary approach including input from hepatology, surgery, radiology, medical oncology, and radiation oncology.

## KEYWORDS

ablation, BCLC, down staging, hepatocellular carcinoma, immunotherapy, liver transplantation, surgery, systemic treatment, TACE

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## BRIEF CLINICAL CASE

A 41-year-old male, with performance status (PS) 1, was diagnosed with hepatocellular carcinoma and tumor portal vein thrombosis developed on Child-Pugh A hepatitis B-related cirrhosis, and upper endoscopy identified large esophageal varices without past history of bleeding. First-line systemic treatment with atezolizumab and bevacizumab was discussed. Considering the increased bleeding risk associated with bevacizumab, should atezolizumab be administered in monotherapy? Are other vascular endothelial growth factor (VEGF) inhibitors such as tyrosine kinase inhibitors (TKI) indicated, in monotherapy or in combination with immunotherapy?

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide with an increasing incidence.<sup>1,2</sup> Tumor staging is key for treatment and prognosis, as well as the assessment of liver cirrhosis in term of liver function and presence of portal hypertension. The Barcelona Clinic Liver Cancer

(BCLC) staging system links tumor features, underlying liver disease, and progression free survival (PS) with prognosis and treatment guidelines for HCC(3). In 2022, the BCLC group updated their treatment algorithm, incorporating an expert clinical decision-making component and the concept of treatment stage migration (TSM), a situation wherein the treatment modality normally recommended for a more advanced stage is chosen (Figure 1). Non-liver related patient characteristics (age, comorbidities, availability) as well as tumor features such as localization may prompt TSM. This update highlights the different parameters that physicians and multidisciplinary tumor boards should integrate into a personalized HCC treatment approach.

## EARLY-STAGE HEPATOCELLULAR CARCINOMA (BARCELONA CLINIC LIVER CANCER 0/A)

Very early stage (0) HCC is defined as a solitary HCC  $\leq 2$  cm without vascular invasion or extrahepatic spread and early stage (A) as a solitary HCC irrespective of size or as a multifocal HCC up to 3 nodules (none of them  $>3$  cm) without macrovascular invasion or extrahepatic spread, in patients with preserved liver function and

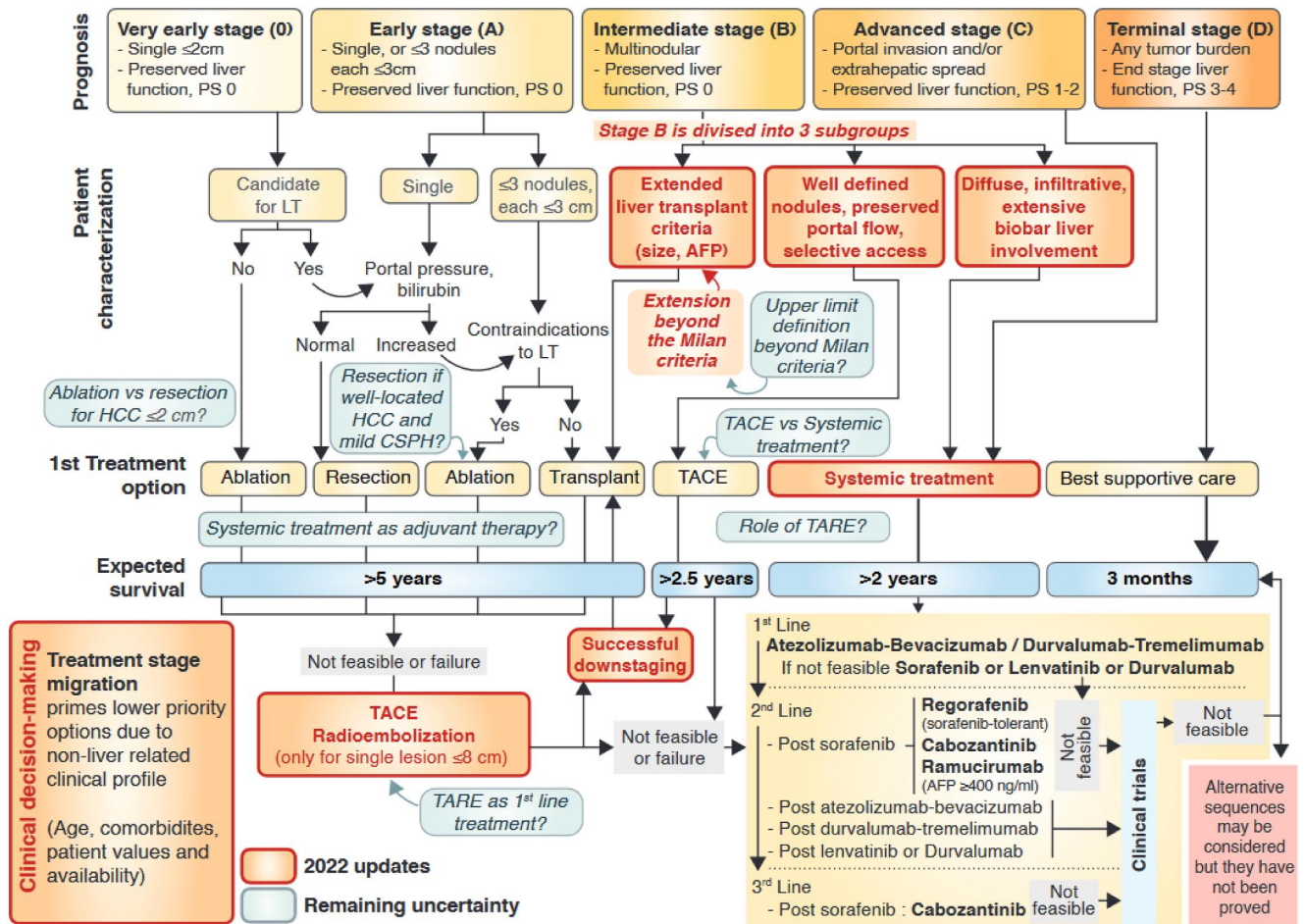


FIGURE 1 Barcelona Clinic Liver Cancer (BCLC) 2022 update: Innovations and remaining uncertainty

eastern cooperative oncology group PS 0–1. Recently, the ALBI (albumin-bilirubin) score has been developed as an HCC-specific improvement of the Child-Pugh score to reflect the severity and hence the prognosis of cirrhosis.<sup>3,4</sup> Indeed, the limitations of the Child-Pugh scoring system include the subjectivity of assessment of ascites and encephalopathy, the interdependence of the five parameters, the absence of some important prognostic parameters such as renal function, and the lack of specificity for different disease etiologies.

### Barcelona Clinic Liver Cancer 2022 update recommendation

Treatment of patients with BCLC stages 0 and A HCC incorporates 3 strategies: tumor resection (in the absence of clinically significant portal hypertension (CSPH)), local percutaneous ablation such as radiofrequency ablation (RFA), and liver transplantation (LT).<sup>5,6</sup>

In BCLC-0, ablation is the preferred option, with RFA remaining the most widely used technique, based on clinical trials showing its superiority compared to percutaneous ethanol injection.<sup>7</sup> However, studies suggested that microwave ablation could achieve the same outcomes than RFA.<sup>8</sup> Nevertheless, if ablation is not feasible for any reason, resection should be considered first, and then trans arterial chemoembolization (TACE) when surgical resection is not feasible, in line with the concept of TSM.

In BCLC-A, resection and RFA gives the same survival benefit for two or 3 tumors less than 2 cm. Resection is favored for single tumors >2 cm because of higher recurrence rate after monopolar RFA although several studies suggested that multibipolar RFA could achieve a better local control in the context of HCC between 2 and 5 cm.<sup>9,10</sup> In non-LT candidates' patients, presenting multifocal HCC, the 2022 BCLC update does not recommend resection but rather ablation for tumors ≤3 cm, and TACE for those >3 cm. Transarterial radioembolisation (TARE) can be considered for patients who meets LEGACY study inclusion criteria (solitary HCC ≤8 cm, child-Pugh A cirrhosis, >PS 0–1).<sup>11</sup> Of note most of tumors included in the LEGACY study had a size of less than 3 cm with a median tumor size of 2.7 cm and almost all tumors were <5 cm. For LT candidates with >6 months waiting time, percutaneous ablation, selective TACE or TARE can be used as bridging therapy. Moreover, TACE is used in some centers to treat patients with HCC and a limited tumor portal vein thrombosis. However, this practice remains outside clinical guidelines and the role of TACE in these patients should be compared to TARE and systemic treatments in term of efficacy and cost.

Additional prospective studies are warranted to define when surgical resection or ablation should be given priority over TACE for patients with up to 3 nodules. These data may provide very competitive survival figures in early-stage patients with preserved liver function and PS 0–1.

Patients with BCLC 0/A HCC who present with severe liver failure may be considered for LT if they are eligible.<sup>12,13</sup> If they are

ineligible due to extrahepatic contra-indication to LT, patients should be classified as BCLC stage D because of their poor prognosis and should receive best supportive care (BSC).

### Ablation versus resection versus Liver transplantation?

The treatment approach for BCLC-A patients varies according to tumor size, tumor number, assessment of liver function and presence of portal hypertension. Ablation or resection are the main treatment options; and the choice depends on age; tumor location; comorbidities; and absence of CSPH, defined as hepatic venous pressure gradient <10 mmHg. Liver transplantation had the advantage of treating both cancer and liver disease and remains the option of choice when tumor burden is limited (Milan criteria) and microvascular invasion unlikely (e.g. using the alpha-fetoprotein [AFP] score).<sup>12,13</sup> However, the organ shortage limits the access to transplantation and consequently a strategy of resection or ablation first followed by salvage transplantation at tumor recurrence have been proposed.<sup>14,15</sup> For small cancers (multiple tumors <2 cm), resection and thermal ablation showed similar results in terms of survival, while resection was associated with a lower rate of local progression, at the cost of greater morbidity.<sup>9,16,17</sup> For very early HCC and in the presence of two or three nodules ≤3 cm, Cuchetti et al. showed that RFA is more cost-effective than resection; for single larger early stage HCCs, surgical resection remains the best strategy compared to monopolar RFA because of better survival rates at an acceptable increase in cost.<sup>16</sup> Response rates to ablation are excellent, with 5-year overall survival (OS) of up to 68%.<sup>18</sup> Moreover, novel methods such as percutaneous irreversible electroporation or multibipolar percutaneous no-touch RFA have shown promising results, yet they remain to be assessed in prospective trials.<sup>19–21</sup> Overall, there is no clear data-driven approach, with no well-designed RCTs in early HCC comparing resection to ablation in candidates for either therapy. A multicenter randomized controlled trial (RCT) evaluated the efficacy of surgery versus RFA for small hepatocellular carcinoma and showed that surgery and RFA were both safe therapeutic approaches and provided equally 3-year recurrence free-survival for early-stage HCC <3 cm (49.8% vs. 47.7% respectively,  $p = 0.793$ ).

### Laparoscopic surgery

Improvement of surgical technique, patient selection and perioperative care have significantly reduced surgical mortality to 1%–3% in expert centers. Patients with CSPH are at high-risk of developing serious complications if undergoing surgical resection, and thus should be considered for LT which showed improved medium- and long-term survival.<sup>22,23</sup>

Laparoscopic liver resection has gained widespread popularity and is now an accepted treatment of HCC, associated with better short-term outcomes and similar oncological survival compared to

the standard open approach.<sup>24-27</sup> In a retrospective study, Yoon et al., showed no significant difference between pure laparoscopy right hepatectomy and open right hepatectomy regarding complications, 2-year disease-free survival rate and 2-year OS rate.<sup>25</sup> The mean comprehensive complication index, which accounts for the severity of complications, was significantly lower in the pure laparoscopy right hepatectomy group. More recently, Troisi et al., performed a multicenter propensity score-matched study in order to compare advantages of laparoscopic over open liver resection in the treatment of HCC with Child–Pugh grade B cirrhosis.<sup>28</sup> Laparoscopic liver resection for HCC in selected patients with Child–Pugh B cirrhosis was associated with reduced blood loss and overall morbidity, and a lesser likelihood of postoperative liver decompensation, leading to shorter hospital stay, maintaining safe oncological outcomes. Patients without preoperative portal hypertension and with an early Child–Pugh B7 cirrhosis were the best candidates to exploit the benefits of minimally invasive surgery in this study. However, percutaneous RFA remains a challenger in this population of patients with mild liver failure. As minimally invasive approaches have shown promising results in terms of reduced surgical stress and postoperative decompensation, laparoscopy appears to be reasonable option for patients with more comorbidities and higher operative risk. On the other hand, laparoscopic cases were technically easier, with fewer and smaller lesions, distant from major vessels, and more frequently requiring partial resection in antero-lateral segments. Technical issues are part of the selection algorithm and should be considered in the setting of liver cirrhosis. Patient characteristics and surgical factors represent the mainstay in appropriate selection. Therefore, laparoscopic resection could be considered if HCC is in the appropriate location and in the case of mild CSPH although no cut-off can be currently recommended.<sup>24,26</sup> A minimally invasive approach is of uttermost importance in this setting as it minimizes surgical stress and enhances patient recovery.

### Role of trans-arterial radioembolization

In clinical practice, TARE has been proposed in the different stages of the BCLC classification although randomized trials were all negative in advanced stages, and only non-randomized studies were conducted for early stages. Nevertheless, TARE has been used as a bridge to resection, treating the tumor while simultaneously inducing contralateral hypertrophy, thereby increasing the future remnant liver by 26%–47% over 44 days–9 months.<sup>29,30</sup>

Many retrospective, multicenter studies have demonstrated the feasibility and safety of radioembolization in HCC.<sup>31-34</sup> These findings were confirmed in prospective, non-randomized studies, which found TARE-Y90 to be feasible and safe in patients, even with macrovascular invasion. Although radioembolization was initially reserved for advanced stages, recent data suggest that it could compare favorably with chemoembolization in intermediate stages, especially since its tolerance is better.<sup>34</sup> Illustratively, Salem et al. and

Kulik et al. found no difference in OS between radio- and chemoembolization in BCLC A/B patients.<sup>31,35</sup> In the future, improving the outcomes of TARE could rely on recent technological advances such as personalized dosimetry. A recent randomized phase two trial showed that personalized, compared to standard dosimetry, significantly improved the objective response rate in patients with locally advanced HCC.<sup>36</sup>

Nevertheless, the level of evidence remains insufficient to validate TARE as a first-line treatment at this stage. In the 2022 BCLC update, TARE could be considered for early-stage HCC (i.e., BCLC 0/A), but only for patients with a solitary tumor measuring less than 8 cm who could not be treated with usual curative treatments. Consequently, TARE has a limited role in current guidelines, contrasting with its more widespread use in clinical practice.

## INTERMEDIATE STAGE HEPATOCELLULAR CARCINOMA (BARCELONA CLINIC LIVER CANCER B)

The BCLC B stage comprises a heterogeneous group of patients with preserved liver function Child–Pugh class A or class B liver function and large and/or multifocal HCC (defined as more than three tumors regardless of size, two to three tumors >3 cm in maximal diameter, or one single unresectable tumor >5 cm), and without cancer-related symptoms, macrovascular invasion, or extrahepatic spread.<sup>37,38</sup>

### A highly heterogeneous group

Barcelona Clinic Liver Cancer B stage poses challenges for therapeutic management, different according to the tumor burden within this stage as there is considerable variation in the clinical benefit patients from TACE. In 2012, a panel of experts proposed a classification with 4 subgroups B1 to B4 according to the following criteria: Child-Pugh score, beyond Milan and within up-to-7, PS, presence of portal venous thrombosis.<sup>39</sup> Patients classified as B1 (Child-Pugh 5-7, normal PS and up-to-7 tumor burden) had a median OS of 41 months. Meeting the up-to-7 criterion indicates that these patients are also to be considered for transplantation, either according to extended criteria or downstaging strategies. In this context, the 2022 BCLC version considered this heterogeneity and stratifies the BCLC-B into three groups of patients according to tumor burden and liver function.

The first subgroup corresponds to potential candidates for LT if they meet the ‘Extended Liver Transplant criteria’ (usually based on size and/or AFP) endorsed by each institution/country.<sup>12,13,40</sup> The second subgroup is composed by patient ineligible for LT but with well-defined nodules, preserved portal flow and allowing selective access to feeding tumor arteries. Those patients are candidates for TACE. Finally, the third subgroup includes patients with diffuse, infiltrative, extensive bilobar liver disease. As those patients do not benefit from TACE, systemic treatment is usually recommended.

## Trans arterial chemoembolization

The place of TACE has been further strengthened by several RCTs, which demonstrated improved OS compared to BSC for patients in intermediate-stage HCC (BCLC B).<sup>41,42</sup> The 2003 meta-analysis by Llovet et al. provided the groundwork to establish TACE as the standard of care for unresectable HCC.<sup>43</sup> TACE type (conventional or using drug-eluting beads) is left to local practice because no RCT has shown an advantage in meaningful clinical endpoints.<sup>44</sup> A recent monocentric phase II RCT comparing TARE with TACE in patients with unresectable HCC showed median time to overall tumor progression was 17.1 versus 9.5 months ([Hazard ratio (HR)], 0.36; 95% CI: 0.18, 0.70;  $p = 0.002$ ) in the TARE and TACE arm respectively.<sup>45</sup> Median OS was 30.2 months after TARE versus 15.6 months after TACE ([HR], 0.48; 95% CI: 0.28, 0.82;  $p = 0.006$ ).<sup>45</sup>

## Extended Liver Transplant criteria and downstaging

The Milan criteria are still largely implemented worldwide to select patients with HCC for LT. Hence, for a subgroup of patients at BCLC stage B, downstaging is attempted to bring tumors within Milan criteria by using liver directed therapy.

The benefits of downstaging include decreasing tumor burden and allowing time to identify those with less aggressive biology. Parikh et al. reported in a meta-analysis of downstaging HCC a success rate of downstaging HCC to within Milan criteria of over 40%, and a post-LT recurrence rate of 16%.<sup>46</sup> A prospective non-randomized downstaging study in LT candidates reported non-significant difference in 5-years post-LT OS between those down staged and T2 patients (AFP level  $\leq 1000$  ng/ml and either of the following: one lesion  $\geq 2$  cm and  $\leq 5$  cm in size, 2 or 3 lesions each  $\geq 1$  cm and  $\leq 3$  cm in size) at listing: 90.8% versus 88%, respectively, with acceptable HCC recurrence of 7.5% among the down staged cohort.<sup>47</sup> Mehta et al. confirmed these results in an observational study with excellent outcomes of LT following downstaging and found that patients with Child-Pugh class B or C and AFP  $> 1000$  ng/ml are unlikely to benefit from downstaging.<sup>48</sup> Moreover, Mazzafero et al. showed in a RCT that after effective and sustained downstaging of eligible HCCs beyond the Milan criteria, LT improved tumor event-free survival and OS compared with non-transplantation therapies.<sup>40</sup> To extend LT criteria, a recent push was made to incorporate markers of tumor biology such as serum AFP and response to neoadjuvant treatments into selection criteria, rather than simply focusing on tumor size and number for defining LT feasibility.<sup>13,49</sup> The cut-off of AFP is discussed, but it appears consensual that an AFP  $> 1000$  ng/ml contraindicates LT. Finally, post downstaging tumor response could contribute to the expansion of HCC transplantation criteria.<sup>40</sup>

Compared to the 2018 version, LT can be recommended in a subgroup of BCLC B patients, in case of successful downstaging by locoregional treatments.

The most reported common downstaging modality is TACE. Yet, external-beam radiation as a bridge to LT in a single-center study

showed no significant difference in drop-out rate, OS from listing, or LT compared to RFA or TACE.<sup>50</sup> More studies are needed to determine the best approach and protocol of down staging.

## A place for systemic treatment?

Systemic treatment is the recommended option for those BCLC B patients who are not candidates for TACE for any reason, for BCLC B patients with diffuse, infiltrative, extensive bilobar liver disease and for BCLC B patients who progressed after TACE. The increased effectiveness of current systemic treatments leads us to consider their use earlier, for some HCCs at stage B of the BCLC classification which traditionally fall under a locoregional treatment such as TACE. Some studies suggest that the effectiveness of systemic HCC treatments is significantly increased if there are given at an earlier stage of the disease.<sup>51</sup> The preservation of liver function is key in the management of HCC; thus, it is necessary to consider the liver toxicity of the atezolizumab/bevacizumab (A/B) combination or of TKI. However, this potential toxicity is less important than repeated TACE.<sup>51</sup> Compared to the 2018 version, the 2022 BCLC version identified a subgroup of BCLC B patients (diffuse, extensive bilobar liver disease) who do not benefit from TACE, for whom a systemic treatment is recommended as the first therapy. However, categorization of patients in this third subgroup remains subjective since no clear definition of this subgroup in term of tumor burden is provided. The results of an ongoing RCT comparing TACE versus systemic therapy for BCLC B patients will help defining the future standard of care in these patients (NCT04803994).

## ADVANCED STAGE HEPATOCELLULAR CARCINOMA (BARCELONA CLINIC LIVER CANCER C)

With recent advances in systemic therapies, redefining the management of unresectable disease may further improve HCC patient outcomes. The existence of portal or supra-hepatic macroscopic vascular invasion and/or extra-hepatic metastatic disease (BCLC C) constitute consensus indications for systemic treatment. Moreover, patients who progressed after TACE are also candidate for systemic treatments. Positive phase III randomized controlled trials in first and second line in advanced HCC are reported in Table 1.

## A new gold standard in first line for advanced Hepatocellular carcinoma

For almost a decade, the treatment of advanced HCC was limited to sorafenib,<sup>52,53</sup> an anti-angiogenic TKI, with a median OS at 10.7 months.<sup>52</sup> Published in 2018, the REFLECT trial showed that lenvatinib, another anti-angiogenic TKI, was non inferior to sorafenib in first line.<sup>54</sup> The results of the randomized phase III Imbrave study comparing the atezolizumab (programmed death 1

**TABLE 1** Positive phase III randomized controlled trials of systemic treatment in first- and second-line settings in advanced Hepatocellular carcinoma (HCC)

Trial/First author (year)	Characteristics of the trial	Arms	Number of patients per arms	Primary endpoint	Secondary endpoints	Results on primary endpoints Median OS months (95% CI)
<b>First-line</b>						
SHARP (2008) <sup>52</sup>	Western population	Sorafenib Placebo	299 303	OS, TTSP	TTP, DCR, safety	10.7 versus 7.9 months HR 0.69 (95% CI 0.55–0.87); <i>p</i> < 0.001
Asia-Pacific (2009) <sup>53</sup>	Eastern population	Sorafenib Placebo	150 76	None predefined		6.5 versus 4.2 months HR 0.68 (95% CI 0.50–0.93); <i>p</i> = 0.014
REFLECT (2018) <sup>54</sup>	Non-inferiority, exclusion of main tumor portal vein thrombosis	Lenvatinib Placebo	478 476	OS	PFS, TTP, ORR	13.6 versus 12.3 months HR 0.92 (95% CI 0.79–1.06); meeting criteria for non-inferiority
IMBRAVE-150 (2020) <sup>55,56</sup>	No	Atezolizumab/Bevacizumab Sorafenib	336 165	OS/PFS	ORR, QoL, response duration	19.2 versus 13.4 months HR 0.66 (95% CI 0.52–0.85); <i>p</i> < 0.001
HIMALAYA (2022) <sup>59</sup>	No	Durvalumab/Tremelimumab Sorafenib	393 293	OS	Non-inferiority OS for durvalumab versus sorafenib	16.4 versus 13.8 months HR 0.78 (CI 95% 0.65–0.92); <i>p</i> = 0.0035
<b>Second-line</b>						
RESORCE (2017) <sup>60</sup>	Patients tolerant to sorafenib	Regorafenib Placebo	379 194	OS	PFS, TTP, ORR, DCR	10.6 versus 7.8 months HR 0.63 (95% CI 0.50–0.79); <i>p</i> < 0.001
Celestial (2018) <sup>61</sup>	No	Cabozantinib Placebo	470 237	OS	PFS, ORR	10.2 versus 8.0 months HR 0.76 (95% CI 0.63–0.92); <i>p</i> = 0.005
REACH-2 (2019) <sup>64</sup>	Patients with serum AFP >400 ng/ml	Ramucirumab Placebo	197 95	OS	PFS, TTP, ORR, safety	8.5 versus 7.3 months HR 0.71 (95% CI 0.53–0.94); <i>p</i> = 0.0199
ALHEP (2021) <sup>63</sup>	RCT in China	Apatinib Placebo	267 133	OS	Safety	8.7 versus 6.8 months HR 0.785 (95% CI 0.617–0.998); <i>p</i> = 0.048
KEYNOTE-394 (2022) <sup>65</sup>	No	Pembrolizumab placebo	300 150	OS	PFS, ORR, DOR, DCR, TTP	14.6 versus 13.0 months HR 0.79 (95% CI 0.63–0.99); <i>p</i> = 0.0180

Note: All clinical trials were superiority trials except the REFLECT trial that was a non-inferiority trial.

Abbreviations: CI, Confidence interval; DCR, Disease control rate; DOR, Duration of response; HR, Hazard ratio; ORR, Objective response rate; PFS, Progression-free survival; QoL, Quality of life; TTP, Time to tumor progression; TTSD, Time to symptom deterioration; TTSP, Time to symptomatic progression.

inhibitor) + bevacizumab (anti-VEGF) combination (A/B) to sorafenib led to the modification of first-line standard for all patients with HCC eligible for systemic treatment.<sup>55,56</sup> This new combination is superior to sorafenib, indeed at the time of the primary analysis (29 August 2019), the HR for death with A/B as compared with sorafenib was 0.66 (95% confidence interval (CI), 0.52–0.85;  $p < 0.001$ ).<sup>56</sup> The median OS was 19.2 months (95% CI 17.0–23.7) with A/B and 13.4 months (95% CI 11.4–16.9) with sorafenib ( $p < 0.001$ ). Upper gastrointestinal bleeding occurred more frequently with the combination than with Sorafenib (7% vs. 4.5%).<sup>55</sup> Thus, this treatment may expose patients to bleeding complications related to portal hypertension, or related to anticoagulant therapy.<sup>57</sup> This poses new challenges with respect to the choice of first-line therapy, especially since the best method for bleeding prevention and risk stratification (e.g. according to the grade of varices or the presence of red signs) remain unknown.

The systemic therapeutic strategies of HCC are currently focusing on combinations of different types of check-points inhibitors (CPI) (anti-PD-1/PD-L1 + anti-CTLA-4) or CPI + antiangiogenics (bevacizumab or validated anti-angiogenic TKIs as monotherapy in first or second line). The main phase III trials whose results should be presented in the next years tested in first line: LEAP-002 (pembrolizumab/lenvatinib),<sup>58</sup> COSMIC-312 (atezolizumab/cabozantinib), and CHECK MATE 9DW (nivolumab/ipilimumab). Recently, the results of phase III HIMALAYA trial (durvalumab/tremelimumab) showed that a combination of CPI including durvalumab (Imfinzi) and the experimental drug tremelimumab, significantly improved OS compared to sorafenib in patients with advanced, unresectable HCC compared (16.4 vs. 13.8 months respectively,  $p = 0.0035$ ).<sup>59</sup> Moreover, these CPI alone or in combination are tested currently as an adjuvant to curative treatments such as surgical resection or thermal ablation in order to decrease tumor relapse. A major finding of the Imbrave and Himalaya trials is that sorafenib in the control arm is doing much better than in the original RCT (>13 versus 10.7 months respectively) that could be explained by a better selection of the patients in clinical trial, the better management of side effects of TKI and the effect of the subsequent lines of systemic treatments after progression under sorafenib.

Remarkably, the efficacy of these CPI combinations has allowed a paradigm shift towards the management of advanced HCC as some of these patients might be reconsidered for curative treatments such as surgical resection, thermal ablation, or even LT. These novel approaches will need to be evaluated in future clinical trials.

### Uncertainty in second line: Inclusion in randomized controlled trials

In patients treated in second line after sorafenib (progression or intolerance), four other antiangiogenic treatments significantly prolonged OS, as compared with placebo in phase III trials including regorafenib (multi-target TKI), cabozantinib (VEGF receptor 1–3, c-met and AXL inhibitor), ramucirumab for patients with an AFP >400 ng/dl (IgG1 monoclonal antibody directed against VEGF

receptor 2) and apatinib (VEGF receptor inhibitor).<sup>60–64</sup> Recently, an Asian trial comparing pembrolizumab plus BSC versus placebo plus BSC as second-line therapy after sorafenib in patients with advanced HCC has shown that pembrolizumab plus BSC significantly improved OS and PFS.<sup>65</sup> Conversely, the most relevant second-line treatment after A/B is currently unknown. Currently, clinical trials should be proposed in patients progressing after A/B, whereas TKI could be used in patients who are not eligible or refuse to participate.

## CONCLUSION

For more than 20 years, the BCLC classification has been the standard for tumor classification and the therapeutic management of patients with HCC. Barcelona Clinic Liver Cancer aims to categorize patients into five stages with different prognoses and to allocate treatment according to these stages based on the best possible contemporary evidence. New features have been added compared to the previous version with the introduction of radioembolization in the algorithm, the extension of transplantation criteria outside the Milan criteria, the downstaging strategy, the use of laparoscopy for HCC resection, the division of BCLC stage B into 3 subgroups and the introduction of A/B as first-line treatment in advanced HCC. Compared to the 2018 version, LT can be recommended in a subgroup of BCLC B patients, in case of successful downstaging by TACE or TARE. Moreover, the 2022 BCLC update incorporates an expert clinical decision-making component allowing personalized treatment based on the characteristics of the patient and the tumor, but also on local expertise and technical availability.

It is notable that the 2022 updated guidelines do not include external beam radiotherapy (EBRT) as a treatment option in the treatment algorithms for HCC. One non-inferiority RCT reported similar outcomes between proton beam therapy and RFA to treat recurrent small HCC whereas two RCT suggested a potential benefit of combination of TACE with EBRT and of surgery with EBRT for HCC with macrovascular invasion.<sup>66</sup> Moreover, in contrast to real-life practice, TARE is not recommended for BCLC C patients following three negative phase III trials.<sup>67</sup> In the absence of significant data, no evidence-based recommendation has been made regarding combination therapy options, in particular the combination of TARE with systemic therapies. In addition, the TSM only goes from left-to-right in this BCLC update, while in clinical practice some patients can benefit from a right-to-left shift but this still remains controversial.

Finally, except for serum AFP for ramucirumab, no tumor biomarkers have been linked with response to systemic treatments underlying the need to have more translational research in this field. Molecular driver targeted therapies are still an unmet need as main genetic alterations observed in HCC are currently undruggable. Additional efforts are warranted to obtain histological material in RCT in order to perform robustly designed translational research to identify new biomarkers of response and identify new therapeutic targets after progression under systemic treatments.

## CONFLICT OF INTEREST

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Sabrina Sidali has no COI.

## DATA AVAILABILITY STATEMENT

No data availability.

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