Hepatotoxicity of systemic therapies for unresectable hepatocellular carcinoma

Ciro Celsa1,2 | Paolo Giuffrida1 | Carmelo Marco Giacchetto1 | Caterina Stornello1 | Gabriele Rancatore1 | Mauro Grova1 | Maria Rita Ricciardi3 | Sergio Rizzo3 | Calogero Cammà1 | Giuseppe Cabibbo1

Received: 16 April 2021 | Revised: 30 July 2021 | Accepted: 3 August 2021
DOI: 10.1002/lci2.38

Abstract
The number of effective systemic therapies for the treatment of unresectable hepatocellular carcinoma (uHCC) is rapidly increasing and the advent of immunotherapy changed the treatment paradigm for these patients, leading to a significant improvement in survival outcomes. While sorafenib, a tyrosine-kinase inhibitor monotherapy, remained the only effective treatment for almost a decade, the combination of atezolizumab, an immune checkpoint inhibitor (ICI) targeting programmed death-ligand 1, plus bevacizumab, an antiangiogenic agent targeting vascular endothelial growth factor, now represents the new standard of care for patients with uHCC. Moreover, several further clinical trials are ongoing to evaluate novel combinations between ICIs with other drugs, belonging to the same class or to other classes. As HCC occurs in most cases in the setting of cirrhosis, the evaluation of the risk/benefit ratio of systemic treatments represents a critical point. The underlying liver disease significantly influences the safety and the effectiveness of current and future systemic treatments for uHCC. For this reason, the hepatotoxicity profile and impact on liver function of these molecules should be carefully assessed in both clinical trials and in the real-world setting. Here, we review hepatotoxicity data on systemic treatments for uHCC and offer suggestions on monitoring and managing liver-related adverse events occurring during the treatment.

KEYWORDS
HCC, hepatocellular carcinoma, hepatotoxicity, immunotherapy, systemic therapies, TKI

1 INTRODUCTION
Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and it represents the sixth most common neoplasm and the fourth most common cause of cancer-related death worldwide.1 It is expected that incidence will increase in the future and more than 1 million patients will die from HCC within 2030, according to World Health Organization annual projections.2

As HCC rarely occurs in patients who do not have advanced liver fibrosis, the development and prognosis of HCC is closely related to the presence of chronic liver disease. The natural history of HCC is highly heterogenous and it depends on clinical and biological
features that could explain the wide prognosis spectrum observed in clinical trials and in the real-world practice.\textsuperscript{5} Owing to its dismal prognosis, HCC represents the leading cause of death even in patients with compensated cirrhosis. A quite large amount of curative and palliative therapies exists, being differently applied according to the stage of the tumour and the underlying liver disease. Treatment options include curative options (liver transplant, surgical resection and thermo-ablation), treatments for intermediate stages, such as transarterial chemoembolization, and for advanced stages, such as systemic therapy. It should be highlighted that, unless liver cirrhosis is compensated, there are no available options to actively treat HCC. Moreover, the occurrence of liver decompensation represents the main driver of death in patients with early HCC and it has also a significant impact on the survival of patients with more advanced HCC stages.\textsuperscript{6,5} HCC is notoriously resistant to chemotherapy and other systemic treatment modalities; in fact, the drug-metabolizing properties of the liver, in addition to elevated levels of multidrug resistance proteins expressed by HCC cells, likely contributes to the limited efficacy of chemotherapeutics in the treatment of HCC.\textsuperscript{6}

Over the years, a huge amount of drugs have been tested, and the oral tyrosine kinase inhibitor (TKI) sorafenib has represented the first approved drug in 2007, according to the results of the SHARP trial.\textsuperscript{7} sorafenib remained the only effective first-line systemic agent for HCC until 2018, when another TKI, lenvatinib, proved its non-inferiority in phase III REFLECT trial.\textsuperscript{8} More recently, the combination of atezolizumab (an immune checkpoint inhibitor [ICI] targeting programmed death-ligand 1 [PD-L1]) plus bevacizumab (an antiangiogenic drug targeting vascular endothelium growth factor [VEGF]) showed to be more effective than sorafenib in phase III IMBrave 150 trial,\textsuperscript{9} changing the paradigm of the treatment of unresectable (uHCC) and establishing an infusional ICI-based combination therapy as the new standard of care. Similarly, also the number of available drugs for second-line treatment has recently increased. Among TKIs, Regorafenib\textsuperscript{10} showed efficacy in patients who tolerated prior therapy with sorafenib, becoming the first TKI approved after sorafenib for second-line therapy for uHCC. Thereafter, cabozantinib\textsuperscript{11} was approved in both progressor and intolerant to sorafenib, having both been compared with placebo. Ramucirumab,\textsuperscript{12,13} an anti-VEGF agent, significantly improved survival compared to placebo in patients with alpha-fetoprotein (AFP) higher than 400 ng/mL. Among ICIs, nivolumab\textsuperscript{14} and pembrolizumab\textsuperscript{15} (both agents targeting PD1) have been tested as monotherapy in the second-line setting, reaching an accelerated approval by Food and Drug Administration (FDA) in the USA according to preliminary results of phase I and II trials as well as the combination of nivolumab plus ipilimumab\textsuperscript{16} (an agent targeting Cytotoxic T-Lymphocyte Antigen-4 [CTLA-4]).

In this evolutionary scenario, the quantitative assessment of the safety of these novel agents represents a crucial point to optimize the outcomes of patients in terms of net health benefit.\textsuperscript{17} As HCC mainly occurs in the setting of cirrhosis, the potential hepatotoxicity of these drugs should be carefully evaluated, as well as their potential impact on liver decompensation, which represents an event that makes the patient no longer treatable. This issue is increasingly relevant as more sequential treatment lines are now available. Moreover, the clinical interpretation of the occurrence of liver injury in the setting of uHCC could be challenging, as it could depend on different factors including tumour progression, the decompensation of the underlying liver disease, drug-induced hepatotoxicity (including autoimmune mechanisms for ICIs) and viral (HBV or HCV) reactivation. Here, we reviewed the available data on the hepatotoxicity of systemic treatments for uHCC and we provided recommendations for monitoring and managing liver-related adverse events (AEs).

## 2 | Hepatotoxicity of TKIs in unresectable HCC

### 2.1 | First line

Drug-induced liver injury (DILI) represents one of the most common AEs in HCC patients undergoing systemic therapies. Even though TKI are generally more tolerated than other chemotherapies, they have a broad spectrum of AEs, including among others liver, skin, cardiovascular system and thyroid disorders.\textsuperscript{18} In the SHARP trial,\textsuperscript{7} 602 HCC patients with preserved liver function were included and were randomized to receive sorafenib or placebo. Most of the included patients (95%) had Child-Pugh class A (284 in the sorafenib group vs 297 in the placebo group). The primary outcome of the trial was overall survival (OS) and the trial was prematurely interrupted for efficacy: median OS was 10.7 months, as compared with 7.9 months in the placebo group (HR 0.69; 95% CI 0.55-0.87). The incidence of AEs related to treatment was 80% in the sorafenib group and 20% in the placebo group. A similar discontinuation rate as a result of treatment was found in the two groups (38% vs 37%). Liver dysfunction was one of the most frequent treatment-related AEs (trAEs) leading to discontinuation in patients treated with sorafenib (5%). Among the most common serious AEs of any cause, liver dysfunction (7% vs 5%) and ascites (5% vs 4%) were described. A similar rate of hepatobiliary events was found in the two groups (11% and 9%).

Subsequently, a trial with a similar design was conducted in the Asia-Pacific region, and similar results of efficacy and consistent safety profile were observed.\textsuperscript{19} Overall, 226 patients with HCC, of whom 97% were Child-Pugh A, were assigned to receive sorafenib or placebo. Median OS was 6.5 months in the sorafenib group, compared with 4.2 months in the placebo group, with an HR similar to that observed in the SHARP trial (HR 0.68 95% CI 0.50-0.93). Anyway, the two cohorts of patients enrolled showed significant differences in treatment duration (5 months for SHARP trial vs 3 months for Asia-Pacific), likely reflecting nuances in the severity of the background liver disease associated with liver cancer.\textsuperscript{20} It should be underlined that the underlying chronic liver disease has a significant impact on the feasibility, the efficacy and the safety of treatments for HCC, but the need for strict selection criteria in terms of liver function in registrative trials prevents a true evaluation of survival benefit in the whole cirrhotic population.\textsuperscript{21}
After sorafenib approval, a number of real-life experiences described the safety of sorafenib and validated its effectiveness in different settings. Randomized clinical trials (RCTs) obviously are the best level of evidence because of the precise design of this study and the accurate evaluation of drug efficacy and safety profile, but they could fail to detect adverse events that could be severe because of the short-term follow-up and the inclusion of selected patients. This is particularly true in the setting of cirrhosis, in which patients treated in real-life clinical practice could be different from those included in clinical trials. Indeed, more comprehensive and complementary findings often derive from properly designed observational studies giving a better assessment and a more widespread understanding of both efficacy and safety.

In this line, real-life studies can help to assess the impact of systemic therapy on the liver function of patients with cirrhosis. In 2011, Hollebecque et al assessed, for the first time, the impact of systemic therapy on the liver function of patients with cirrhosis. In a cohort of 300 consecutive patients (20% Child-Pugh B patients), Hollebecque et al showed that the median survival of the entire cohort was 11.1 months, similar to that observed in the SHARP trial, but Child-Pugh A patients had significantly better median survival (13 months, 95% CI 10.1-14.6) than Child-Pugh B patients (4.5 months, 95% CI 2.7-10.4). Among baseline prognostic factors, in multivariate analysis, Child-Pugh B, AFP and the sum of lesions were independently associated with 1-year mortality. They concluded that although Child-Pugh B patients show a sorafenib toxicity profile similar to Child-Pugh A patients, they have poorer outcomes because of liver dysfunction, making any benefit from sorafenib unlikely. Later, Pressiani et al reported clinical outcomes of OS, progression-free survival (PFS) and time to progression (TTP) in a cohort of 300 consecutive patients (20% Child-Pugh B). As expected, OS was 10 months in Child-Pugh A vs 3.8 months in Child-Pugh B patients respectively; also PFS was significantly different depending on liver function status (4.3 vs 2.1 months respectively); TTP was 4.2 vs 3.8 months.

Iavarone et al assessed the safety and effectiveness of sorafenib in a multicentre, non-interventional study (SOFIA, SOraFenib Italian Assessment). In this study, a higher rate of Child-Pugh B patients was present compared to the pivotal trial (12% vs 3-5%), but none of these patients had hepatic encephalopathy, jaundice or clinically relevant ascites at baseline. Among 133 patients having Grades 3 and 4 AEs, 16 of them suffered from gastrointestinal bleeding and worsening of liver function was observed in 25 patients with Child-Pugh class A at 12 weeks and in 17 patients at 24 weeks. Ascites developed in 71 (24%) patients, 7 (2%) patients suffered from hepatic encephalopathy and 7 (2%) of jaundice. Severe liver dysfunction also caused sorafenib dose reduction and permanent discontinuation, respectively, in 28 patients and 38 patients. Multivariate analysis proved albumin, bilirubin, age and ECOG to be significant baseline predictive factors of early discontinuation of sorafenib because of intolerance. Although this field-practice study showed sorafenib to be a safe and effective treatment for uHCC, a higher rate of drug discontinuation compared to the SHARP trial caused by liver impairment was defined, probably caused by the higher presence of Child-Pugh B patients. A subsequent real-life study from the same group showed that discontinuation of sorafenib because of worsening liver function and cirrhosis decompensation represented the worst-case scenario with a median post-sorafenib survival (mPSS) of 1.8 months compared to patients who discontinued sorafenib for progressive disease or for AEs, respectively, with an mPSS of 4.6 months and 7.3 months.

GIDEON study was a prospective, observational registry study evaluating the safety of sorafenib and treatment practices in a large cohort of 3275 patients. Enrolled patients were in Child-Pugh class A in 61%, Child-Pugh B in 21% and Child-Pugh C in 2% of cases. Although sorafenib dosing was similar irrespective of Child-Pugh score and the initial sorafenib dose and the proportion of patients with a dose reduction or increase were also comparable, the median duration of treatment was longer in Child-Pugh A. In line with previous studies, median overall survival (OS) was longer in Child-Pugh A patients (13.6 months) than in Child-Pugh B patients (5.2 months) and Child-Pugh C patients (2.6 months), but the rate of the most common adverse events (AEs) was also broadly comparable between Child-Pugh groups. Anyway, even if the global incidence of AEs was similar between different Child-Pugh classes, higher rates of serious AEs were observed in the Child-Pugh B population. The incidence of serious AEs increases with the deterioration of liver function. Moreover, a higher rate of AEs leading to definitive drug discontinuation was shown (40%) in Child-Pugh B patients, compared to Child-Pugh A (29%). Liver dysfunction secondary to sorafenib treatment was comparable among the different subgroups of Child-Pugh classes. Grades 3 and 4 liver dysfunction have been reported only in 1% of patients taking sorafenib. It is worthy to note that the higher rates of AEs in Child-Pugh B and C patients might be due not only to intrinsic drug toxicity but also to the tumour progression and on the basis of poor liver function when the TKI was started.

It should be underlined that the outcomes of sorafenib improved over time and that sorafenib arms representing the control group in most recent clinical trials displayed a higher OS compared to previous trials. The reasons for these observations could be related to better management of sorafenib dosing, better management of AEs and better accuracy of prediction of liver decompensation. Regarding the sorafenib dose, an Italian field-practice study showed that the adjustment of sorafenib dose to 400 mg/day had higher cost-effectiveness compared to the standard dose of 800 mg/day. These data were subsequently confirmed by a larger study on 4903 patients from Veterans Health Administration demonstrating that the dose adjustment was associated with a lower rate of discontinuation because of AEs and with a similar OS compared to standard dose. These findings are not surprising, considering that the standard dose was borrowed from evidence coming from patients with renal cancer and that the underlying liver dysfunction could modify sorafenib pharmacokinetics. Reduced liver function results in impaired drug metabolism and reduced albumin production that can increase the plasma concentration of TKIs, reducing their tolerability.
Congruently with the above data, it is important to precisely assess hepatic function in patients with HCC before and during treatment with TKIs. The albumin–bilirubin (ALBI) grade has been evaluated in the setting of HCC. Compared to Child-Pugh class, it could more accurately predict mortality without the need for subjective determinants of liver failure such as ascites and encephalopathy. ALBI grade resulted in good objective hepatic reserve estimation across each BCLC stage of HCC. Also in patients treated with sorafenib, ALBI grade was shown to be a better tool than Child-Pugh. Finally, in 2018, the non-inferiority of lenvatinib, compared to sorafenib was demonstrated in terms of OS (13.6 months vs 12.3 months). In this open-label, phase III RCT, almost only patients with a well-preserved liver function who had a Child-Pugh class A were included. Notably, tumour liver occupation >50%, obvious portal invasion or clear bile duct infiltration were considered absolute exclusion criteria. Patients received oral lenvatinib 12 mg/day (bodyweight >60 kg) or 8 mg/daily (bodyweight <60 kg) or sorafenib 400 mg twice/daily. Regarding the safety profile of lenvatinib, a similar rate of treatment-emergent AEs greater than Grade 3 was found in the two groups. Although hepatotoxicity was not a common AE in 2% of patients, fatal AEs occurred, and three of these patients died of acute hepatic failure. Any grade aspartate aminotransferase (AST) elevation was comparable in the lenvatinib and the sorafenib arms, respectively, 18% vs 12%. Nearly 5% of patients receiving lenvatinib had a Grade >3 of AST elevation vs 8% of patients treated with sorafenib. As soon as lenvatinib became an alternative to sorafenib, the necessity of real-life data arose. Thus, real-life practice experts for HCC (RELPEC) studies were designed in order to investigate clinical features of Japanese lenvatinib-treated patients in the real world. First, hepatic reserve function was assessed by Child-Pugh classification and ALBI grade in a cohort of 152 HCC lenvatinib-treated patients. It was observed that baseline liver function was the most relevant prognostic factor related to outcomes. Moreover, the prognosis of patients with Child-Pugh B was worse as compared to those with Child-Pugh A, and lenvatinib had lower therapeutic efficacy in patients with Child-Pugh class compared to A, concluding that treatment in Child-Pugh B patients should be performed with caution. Afterwards, the RELPEC group evaluated the changes in liver function related to lenvatinib treatment. In a single arm, observational study, of 123 patients with uHCC treated with lenvatinib, a significant decline of hepatic function was observed after 4 weeks of treatment. Twenty-six patients deteriorated liver function from Child-Pugh A to Child-Pugh beyond B within 4 weeks, and four patients died because of hepatic failure four patients as a result of gastrointestinal bleeding. A worsening of the ALBI grade was also observed during lenvatinib. Similarly, a study conducted on 156 cirrhotic patients further showed that ALBI grade was better than Child-Pugh score in predicting TTP, and only hepatic reserve function at the time of lenvatinib introduction was a significant risk factor for a decline to worse Child-Pugh class.

### 2.2 Second-line

Several drugs failed to show a significant OS benefit compared to placebo after the first-line progression. According to the RESORCE trial, Regorafenib was the first approved second-line treatment in patients who progressed to sorafenib. Included patients must have tolerated sorafenib (at least 400 mg daily for at least 20 of the 28 days before discontinuation) and received their last sorafenib dose within 10 weeks of randomization. A well-tolerated safety profile was described and the most common Grade 3 or 4 AEs included hypertension, hand-foot skin reaction, fatigue and diarrhoea. All the patients in the regorafenib group experienced at least one treatment-emerging AE. AST elevation was the most common AE leading to drug discontinuation, with no differences between the two groups. New ascites development rate of any grade was comparable in both arms; conversely, hepatobiliary disorders were more common in the placebo group (18% [34/193]) vs regorafenib group (11% [40/374]).

Few field practice data are yet available on the efficacy and safety of regorafenib in uHCC. At the first interim analysis of the REFINE study, planned after all the patients included in the global cohort had been observed for at least 4 months, treatment-emergent AEs resulted consistently with those reported in the RESORCE trial. A multicentre retrospective study of 49 Child-Pugh A patients, with regorafenib treated uHCC after progression to sorafenib, showed a comparable profile of safety and hepatotoxicity in line with the RESORCE trial.

According to the results of CELESTIAL trial, cabozantinib was approved for the treatment of advanced HCC in patients who have received at least one and up to two previous systemic treatments, regardless of the tolerance to sorafenib. Serious AEs were reported in 50% of patients who received cabozantinib and in 37% of patients who received placebo. Elevation of AST was among the most common AEs leading to dose reduction and Grades 3 and 4 AEs, respectively, 12% with cabozantinib vs 7% with placebo. Fatal liver related AEs were reported in 4 patients in the cabozantinib group (one hepatic failure, one portal vein thrombosis, one upper gastrointestinal haemorrhage and one hepatorenal syndrome) and in 1 patient in the placebo group (hepatic failure). Comparable liver toxicities profile was also documented in a subgroup analysis of phase III CELESTIAL trial, including patients who had received only sorafenib as first-line treatment. Safety was consistent with the reported global study population. First results from real-world data have been recently presented. In a small cohort of 74 German patients with uHCC who started cabozantinib as second- and third-line treatment, 26 (35%) patients needed a dose reduction as a result of side effects, and no worrying liver-related AEs were described. An Italian multicentre real-life study assessed the safety and efficacy of cabozantinib in 52 patients with uHCC and preserved liver function (Child-Pugh A). Alanine aminotransferases (ALT) elevation was among the most common trAEs (17%), reaching Grades 3 and 4 in 6% of patients, and one case of fatal liver failure has been described.
Data on hepatotoxicity associated with TKI treatments for uHCC reported in clinical trials are shown in Table 1. Ramucirumab is an anti-VEGF and a VEGF-receptor-2 monoclonal antibody and it was studied in two phase III RCTs.\textsuperscript{12,13} In the REACH trial, ramucirumab was tested as second-line therapy in patients previously treated with sorafenib, either progressed or intolerant. In this study, 565 patients were randomly assigned to receive ramucirumab or placebo. Treatment with ramucirumab did not show a significant improvement in OS. Median OS for ramucirumab was 9.2 months vs 7.6 months in the placebo group (HR 0.87 [95% CI 0.72-1.05]; P = .14). Child-Pugh B patients were initially enrolled in this study, although an increased rate of liver adverse events was noted in this subgroup, therefore protocol was amended not to include patients beyond Child-Pugh A and those patients already enrolled were not included in the intention-to-treat analysis. Ascites was among the most common Grade 1 adverse event, respectively, in 42 patients (21%) vs 13 (14%). Patients in the ramucirumab group developed ascites of any grade more frequently than in the placebo group. Any grade of liver injury or liver failure was more common in patients treated with ramucirumab compared to patients receiving placebo (140 [51%] vs 103 [37%]). No difference in any grade of liver dysfunction between treatment groups was observed after further analysis adjusted for duration of treatment exposure.\textsuperscript{12} Subsequently, a post hoc analysis demonstrated a longer OS of patients treated with ramucirumab with AFP higher than 400 ng/ml.\textsuperscript{12} This brought to the REACH II, an RCT of Ramucirumab vs placebo in patients with uHCC previously treated with sorafenib and with alpha-fetoprotein values ≥ 400 ng/ml. Median OS was 8.5 months with ramucirumab and 7.3 months with placebo (HR 0.71 [95% CI 0.53-0.95]; P = 0.0199). Only Child-Pugh A patients were enrolled. Only two patients (1%) in the ramucirumab group developed hepatic encephalopathy as treatment-related serious AEs, none in the placebo group. Grades 1 and 2 liver injury were more frequent in patients treated with ramucirumab compared to placebo, respectively, in 42 patients (21%) vs 13 (14%). Patients in the ramucirumab group developed ascites of any grade more frequently than in the placebo group.\textsuperscript{13}

These evidence underline that an accurate assessment of liver function is needed in patients with uHCC receiving systemic therapy with TKIs. This is particularly relevant now as sequential treatments are available. The prevention of liver decompensation represents a key issue because it allows to continue systemic therapy in patients without progression and without severe adverse events or to shift to a subsequent line of treatment in patients with progression or who did not tolerate the previous line. Real-life studies represent useful tools to integrate evidence coming from RCTs, as they assess treatment effectiveness in patients encountered in day-to-day clinical practice and give more robust evidence about efficacy in the real-world population. Therefore, the evaluation of such a complex prognosis in HCC, which depends on an interaction between the degree of liver impairment and tumour burden, cannot exclude a detailed assessment of hepatic function.

We recommend assessing liver function before and during TKI treatment with physical examination (to detect clinical signs of cirrhosis decompensation), liver function tests (to early capture changes in ALBI grade and Child-Pugh score), abdominal ultrasound (to detect macrovascular invasion or mild/moderate ascites) and upper endoscopy (to assess portal hypertension) (see Table 2). When possible, etiological treatments for underlying liver disease should be considered, such as nucleos(t)ide analogues (NUCs) for HBV, direct-acting antiviral agents for HCV and alcohol withdrawal. When starting sorafenib in patients with more advanced liver disease (ie Child-Pugh class B without ascites), the dose adjustment to 400 mg/d may be considered, together with a toxicity-guided approach. Transient worsening of transaminases or bilirubin may be managed with dose adjustment during TKI treatment, while significant changes in ALBI grade and Child-Pugh score or the occurrence of decompensating events should lead to treatment interruption and to the identification and treatment of any precipitant factors.

### 3 | HEPATOTOXICITY OF ICI-BASED THERAPIES IN UNRESECTABLE HCC

The introduction of ICIs has changed the landscape of systemic treatments for HCC. ICIs are monoclonal antibodies against immune checkpoint molecules. They target three main molecules: PD-1, PDL-1 and CTLA-4. PD1 is the target of nivolumab and pembrolizumab; PDL-1 is the target of durvalumab, atezolizumab and avemumab; and CTLA-4 is targeted by ipilimumab and tremelimumab. The mechanism of action of these molecules is to restore T-cell activity against tumour.\textsuperscript{64} They had an important role in maintaining immune homeostasis and the alteration of this stability can lead to a range of immune-related AEs (irAEs). The most commonly involved organs are the skin, liver, gastrointestinal tract and endocrine glands. Adverse events against the liver are defined as hepatic irAEs or immune-mediated hepatitis.\textsuperscript{45-47} While irAEs have been extensively studied in solid neoplasms other than HCC treated with ICIs, data on hepatotoxicity of these drugs in patients with HCC and cirrhosis are less conspicuous. As previously described, patients with cirrhosis and HCC treated with systemic therapies, including ICIs, can have multiple causes of liver injury and the differential diagnosis is often challenging, leading to different therapeutic approaches.\textsuperscript{48} ICI trials showed that the incidence of liver toxicity is mainly linked to the type of drug, the posology and the combination of them.\textsuperscript{47} The incidence of liver toxicity is higher in patients who received combination therapy than in those under monotherapy, but it remains lower compared to other organ toxicities.\textsuperscript{48}

#### 3.1 | ICI monotherapies

Nivolumab and pembrolizumab, based on results from single-arm phase II trials, have been approved by FDA to treat patients who progressed or are intolerant to first-line sorafenib. Safety of nivolumab was evaluated in Checkmate 040 trial\textsuperscript{14} showed that AEs were similar to those previously reported in other cancers, with the exception of
TABLE 1  Data on hepatotoxicity of tyrosine-kinase inhibitors in patients with unresectable hepatocellular carcinoma reported in clinical trials

| Trial/Year (Ref) | Treatment | Pts in each arm N | Liver dysfunction any grade, % | Liver dysfunction AE, % | Elevated AST any grade N(%) | Elevated AST grade ≥ 3 N(%) | Increased bilirubin any grade N(%) | Increased bilirubin grade ≥ 3 N(%) | Ascites any grade N(%) | Ascites grade ≥ 3 N(%) |
|-----------------|-----------|------------------|-------------------------------|------------------------|-----------------------------|-----------------------------|----------------------------------|----------------------------------|----------------------|----------------------|
| **First-line**  |           |                  |                               |                        |                             |                             |                                  |                                  |                      |                      |
| SHARP 2008 (7) | Sorafenib  | 297              | <1                            | 7                      | -                           | -                           | -                                | -                                | -                    | -                    |
|                 | Placebo   | 302              | 0                             | 5                      | 7                           | -                           | -                                | -                                | -                    | -                    |
| Cainap et al 2015 (68) | Sorafenib | 521              | -                             | -                      | -                           | 64 (12.5)                   | -                                | 21 (4)                           | -                    | 17 (3.5)             |
|                 | Linifanib | 514              | -                             | -                      | -                           | 62 (12)                     | -                                | -                                | 32 (6)               | 31 (6)               |
| Johnson et al 2013 (69) | Sorafenib | 578              | -                             | -                      | 26                          | 17                         | 18                               | 9                                | -                    | -                    |
|                 | Brivanib  | 577              | 25                            | -                      | -                           | -                           | -                                | -                                | -                    | -                    |
| SUN1170 2013 (70) | Sorafenib | 544              | -                             | -                      | 92 (17)                     | 49 (9)                      | -                                | -                                | 66 (12)              | 18 (3)               |
|                 | Sunitinib | 530              | 80 (15.2)                     | 46 (9)                 | -                           | -                           | 41 (11.5)                       | 89 (25)                          | 31 (9)               |                      |
| SEARCH 2015 (71) | Sorafenib | 355              | -                             | -                      | 75 (21)                     | 42 (12)                     | 76 (21.5)                       | 43 (12)                          | 81 (22.5)            | 35 (10)              |
|                 | Sorafenib + Erlotinib | 362 | 79 (22) | 50 (14) | 68 (19) | - | - | - | - | - |
| REFLECT 2019 (8) | Lenvatinib | 476              | -                             | -                      | 65 (14)                     | 80 (17)                     | 71 (15)                          | 63 (13)                          | -                    | -                    |
|                 | Sorafenib | 478              | 24 (5)                        | 38 (8)                 | 31 (7)                      | 23 (5)                      | -                                | -                                | -                    | -                    |
| iMbrave 150 2020 (9) | Atezo + Beva Sorafenib | 336 | 64 (19.5) | 23 (7) | 43 (13) | 8 (2.5) | - | - | - |
|                 | Sorafenib | 165              | 26 (16.7)                     | 8 (5)                  | 22 (14)                     | 10 (6.5)                    | -                                | -                                | -                    | -                    |
| **Second line** |           |                  |                               |                        |                             |                             |                                  |                                  |                      |                      |
| RESORCE 2016 (10) | Regorafenib | 379              | -                             | -                      | 48 (13)                     | 19 (5)                      | 70 (19)                          | 25 (6)                           | 8 (2)                | 3 (1)                |
|                 | Placebo   | 194              | 15 (8)                        | 10 (6)                 | 7 (4)                       | 4 (2)                       | 1 (1)                            | 1 (1)                            |                      |                      |
| CELESTIAL 2018 (11) | Cabozantinib | 470              | 105 (22)                      | 55 (12)                | 45 (10)                     | 17 (4)                      | 57 (12)                          | 18 (5)                           |                      |                      |
|                 | Placebo   | 237              | 27 (11)                       | 16 (7)                 | 7 (3)                       | 2 (1)                       | 30 (13)                          | 11 (5)                           |                      |                      |

Abbreviations: AE, adverse events; AST, aspartate aminotransferases.
TABLE 2 Recommendations for the management of systemic treatments in patients with hepatocellular carcinoma

1. Before starting treatment with TKIs or ICIs, physicians should:
   • Perform complete baseline evaluation of underlying liver disease aetiology (HBV, HCV, alcohol, metabolic, autoimmune), estimate liver function (Child-Pugh, Model for End stage of Liver Disease), stage accurately HCC (BCLC), and screen for portal hypertension with upper endoscopy.
   • Treat underlying liver disease: use antiviral agents when appropriate, encourage alcohol withdrawal, treat metabolic comorbidities.

2. During treatment with TKIs or ICIs, physicians should:
   • Educate patients on the early recognition of adverse events.
   • Regularly and closely monitor hepatic function, using clinical, laboratory and instrumental parameters, with careful assessment of coagulation profiles, particularly in patients undergoing combination treatment with Atezolizumab plus Bevacizumab.
   • Recognize early signs of hepatic decompensation and treat complications as early as possible.
   • Evaluate the effectiveness of HCC treatment; in case of progression and stable liver function think of a subsequent treatment.
   • Reassess patients quality of life and cost–benefits frequently and at first signs of hepatic decompensation;
   • Recognize and treat side effects associated with systemic therapy by adjusting dosage rather than interrupting treatment, if possible.

3.2 ICI-based combination therapies

The combination of an anti-PD-L1 (atezolizumab) and an anti-VEGF (bevacizumab) was assessed in phase III Imbrave 150 trial. As previously mentioned, atezolizumab plus bevacizumab represent the first treatment strategy that resulted significantly superior to sorafenib, both in terms of OS (HR 0.58, 95% CI 0.42-0.79; P < .001) and PFS (HR 0.59; 95% CI 0.47-0.76; P = .0022). Regarding the hepatotoxicity profile, any grade hepatitis occurred in 5 (1.8%) patients, most of them (4 patients) having Grades 3 and 4 hepatitis. Any grade and Grades 3 and 4 AST increase occurred in 63 (22.6%) and 37 (13.3%) patients, whereas any grade and Grades 3 and 4 ALT increase occurred in 49 (17.6%) and 17 (6%) patients respectively. Serum bilirubin increase of any grade occurred in 62 (18.6%) patients, while 21 (7.5%) patients experienced Grades 3 and 4 bilirubin increase.

Tremelimumab, the first CTLA-4 blockade inhibitor evaluated in HCC patients, was evaluated in a phase II study demonstrating encouraging outcomes. Although approximately 45% of patients had Grade 3 or Grade 4 elevations in transaminases after the first dose, liver function usually remained stable.

A higher incidence of elevations in transaminases and bilirubin levels. Treatment with nivolumab resulted in treatment-emergent Grade 3 or 4 AST increase in 17 (6.5%) patients, grade 3 or 4 ALT increase in 9 (3.4%) patients and Grade 3 or Grade 4 bilirubin in only 1 (0.4%) patient. Immune-mediated hepatitis requiring systemic corticosteroids occurred in 8 (5%) patients. A subanalysis of CheckMate-040 trial conducted in the subset of Asian patients demonstrated a similar safety profile in Asian and in the overall population. Increases inaminotransferases were infrequent in both populations and ascites or encephalopathy never occurred. Unfortunately, CheckMate-459 comparing nivolumab to sorafenib for first-line treatment failed to show significant superiority of sorafenib in terms of OS. In the real-world setting, a multicentre observational study confirmed the safety profile of nivolumab observed in clinical trials, showing an overall trAE rate of 26.6% and grade > trAE rate of 6.4%, without significant differences in trAE rates between patients in Child-Pugh class A and B. Finally, a recent study showed that the use of nivolumab before liver transplant for HCC was effective and safe, in contrast with previous evidence suggesting a risk of severe transplant rejection in patients treated with anti-PD1 before transplant. Further studies are needed to evaluate the effectiveness and safety of ICI treatments before liver transplants.

Phase II KEYNOTE-224 trial evaluated the effectiveness and safety of pembrolizumab in the treatment of patients with uHCC that progressed during sorafenib treatment or who did not tolerate sorafenib. AEs occurring in patients with HCC were similar to those described in other tumours; however, there were increased incidences of Grade 3 or Grade 4 ascites (8%) and immune-mediated hepatitis (2.9%). Grades 3 and 4 laboratory abnormalities that occurred at a higher incidence than in other KEYTRUDA trials were AST (7%) and ALT (4%) increases and hyperbilirubinemia (2%). Subsequently, phase III KEYNOTE-240 trial compared pembrolizumab vs placebo in the second-line setting. Despite the encouraging results of phase II trial, pembrolizumab did not show a significant OS and PFS improvement compared to placebo, not reaching the statistical significance pre-specified criteria. Median OS was 13.9 months for pembrolizumab vs 10.6 months for placebo (HR 0.78; 95% CI 0.61-0.99; P = .0238) and median PFS was 3.0 months vs 2.8 months at final analysis (HR 0.71; 95% CI 0.57-0.90; P = .0022). Regarding the hepatotoxicity profile, any grade hepatitis occurred in 5 (1.8%) patients, most of them (4 patients) having Grades 3 and 4 hepatitis. Any grade and Grades 3 and 4 AST increase occurred in 63 (22.6%) and 37 (13.3%) patients, whereas any grade and Grades 3 and 4 ALT increase occurred in 49 (17.6%) and 17 (6%) patients respectively. Serum bilirubin increase of any grade occurred in 62 (18.6%) patients, while 21 (7.5%) patients experienced Grades 3 and 4 bilirubin increase.

The combination of an anti-PD-L1 (atezolizumab) and an anti-VEGF (bevacizumab) was assessed in phase III Imbrave 150 trial. As previously mentioned, atezolizumab plus bevacizumab represent the first treatment strategy that resulted significantly superior to sorafenib, both in terms of OS (HR 0.58, 95% CI 0.42-0.79; P < .001) and PFS (HR 0.59; 95% CI 0.47-0.76; P < .001). Regarding the hepatotoxicity profile, ALT elevation of all grades and grade > 3 have occurred in 14% and 3.6% patients, respectively, in the atezolizumab plus bevacizumab arm and 9% and 1.3%, respectively, in the sorafenib arm. Grades 3 and 4 AST elevation and ascites occurred in 7.0% and 1.8% in the combination arm and in 5.1% and 1.3% in the sorafenib group. Grades 3 and 4 bleeding was reported in 6.4% of the patients treated with atezolizumab plus bevacizumab, but they did not significantly differ from the sorafenib arm (5.8%). Although upper endoscopy and primary prophylaxis were requested within 6 months prior to treatment start, and only 26% of patients had oesophageal varices at baseline, bleeding from oesophageal varices occurred in 6 patients (1.8%) who received atezolizumab plus bevacizumab and in only 1 patient (<1%) receiving sorafenib. If these results could be translated to a real-life population of patients with cirrhosis and higher prevalence of severe portal hypertension remains to be investigated and an ongoing phase IIIb single-arm multicentre study specifically designed to assess the impact of atezolizumab plus bevacizumab on bleeding events is currently ongoing (AMETHISTA, NCT04487067).

In March 2020, FDA approved the combination of nivolumab plus ipilimumab according to the results of CheckMate-040 trial;
the most common Grade 3 or Grade 4 adverse events were rash (8%), abdominal pain (6%) and ascites (6%). The most common Grade 3 or Grade 4 laboratory abnormalities were increased AST (40%), increased lipase (26%) and increased ALT (21%). Serious adverse events occurred in 59% of patients, with the most commonly increased AST, including ascites, oesophageal varices bleeding and increased bilirubin. Treatment was discontinued in 29% of patients and delayed because of AEs in 65%.

Other combination strategies have been evaluated or are currently under investigation. The results of the combination of lenvatinib plus pembrolizumab have been recently reported in a phase I trial including 100 patients, showing an acceptable safety profile, with 20% and 11% of patients experiencing any grade and Grades 3 and 4 AST increase respectively.

Data on hepatotoxicity associated with ICI-based treatments for uHCC reported in clinical trials are shown in Table 3.

### 3.3 Management of hepatotoxicity associated with ICIs

Immune-mediated hepatitis associated with ICIs is a diagnosis of exclusion. The causality between the drug exposure and the onset of liver injury can be tested through the Roussel Uclaf causality assessment method that has been validated in both retrospective and prospective studies. Hepatotoxicity related to ICIs typically presents as asymptomatic mixed hepatocellular and cholestatic liver injury found on routine biochemical tests. Clinical presentation can differ between CTLA-4 and PD-1/PD-L1 inhibitor. Anti-CTLA-4-related liver injury is often more severe compared to anti-PD-1 and anti-PDL-1. The onset of hepatotoxicity was reported to be 3 weeks after anti-CTLA-4 initiation and 14 weeks after anti-PD-1/PDL-1 initiation.

The diagnostic workup should include baseline viral hepatitis serology (HAV, HBV, HCV and HEV) depending on baseline serology and immune status to exclude viral reactivation as the cause of liver injury. Additional workup should include tests for Epstein-Barr virus and cytomegalovirus infections. The usefulness of assessing antinuclear antibodies and/or anti-smooth muscle antibodies to obtain a differential diagnosis with autoimmune hepatitis (AIH) remains to be established. Ultrasound or CT scan imaging should be performed in order to evaluate the intrahepatic progression of HCC and/or possible biliary obstruction. Although it is not recommended by the European Society for Medical Oncology (ESMO), a liver biopsy could help to identify ICI-related liver injury and to stage its severity. Cohen et al performed a study on 60 liver biopsies in patients with tumours other than HCC (most of them with melanoma) treated with ICIs who developed liver injury during treatment. In this study, a predominantly hepatitis pattern of inflammation was present in 28 cases (47%), while a predominantly cholangitic pattern, with portal-based inflammation, was observed in 16 cases (27%). In the remaining cases, a mixed hepatocytic and cholangitic pattern of injury, a pattern resembling fatty liver or mild non-specific changes were found. Another study demonstrated that histology abnormalities related to anti-CTLA-4 were characterized by granulomatous hepatitis, including fibrin ring granulomas and central vein endothelitis, whereas anti-PD-1/PD-L1-associated liver injury was characterized by lobular hepatitis. Moreover, liver biopsy allows excluding AIH, as its histological features, such as plasma cell infiltration, severe interface hepatitis, piecemeal necrosis and rosette formation, are usually absent in ICI-mediated hepatitis.

The Common Terminology Criteria for Adverse Events (CTCAE) established by the Cancer Therapy Evaluation Program of the National Cancer Institute is usually employed to grade the severity of hepatotoxicity related to ICIs. The CTCAE classifies the severity as grades 1-5, with Grade 5 referring to fatal hepatotoxicity. However, we believe that this tool is affected by some limitations. The higher grades of severity (Grades 3-4) driven by elevations of ALT or AST do not necessarily require the presence of direct evidence of loss of hepatocyte function. It should be noted that this scale does not take into account some relevant clinical data. For example, it does not take into account biochemical tests that measure liver function (ie bilirubin, albumin and INR) or the presence of clinical symptoms of liver failure (ie ascites, encephalopathy, variceal bleeding) that are commonly used to stage the severity of liver impairment in patients with cirrhosis; it does not take into account HCC burden that could be a reason for the presence of abnormal liver function tests before starting ICI-based treatment; it does not take into account the duration of liver injury and the response to steroid treatment. Therefore, the development of novel comprehensive clinical tools to stage the severity of liver injury related to ICIs in patients with HCC is needed.

The treatment of ICI-mediated hepatitis still remains a challenging issue, as no evidence-based treatments are available. In most cases, the treatment is similar to that of AIH or of transplant rejection. The main aims of the treatment should be to minimize the morbidity and mortality from ICI toxicity without reducing their antitumour activity. ESMO guidelines suggest using corticosteroids from Grade 2 to Grade 3 of liver injury and temporarily withdraw treatment with ICIs, while in the case of Grade 4 hepatitis, treatment should be permanently stopped. The use of liver biopsy is recommended only in cases refractory to corticosteroids and/or mycophenolate. A new algorithm for patients with liver disease has been recently proposed. Considering that in the setting of cirrhosis, liver function tests are usually abnormal before starting ICIs and that the decision to use corticosteroids should be based on the dynamic changes in liver function tests and according to the presence of features of liver failure. A liver biopsy could be needed from Grade 3 and may be helpful for the choice of treatment. In this line, it has been shown that patients with liver biopsy showing low histological grade activity and with normal bilirubin and INR can improve liver injury without corticosteroid therapy. However, these data were obtained in a setting of patients with melanoma treated with ICIs and data on the usefulness of liver biopsy to guide the treatment of ICI-mediated hepatitis are still lacking. Moreover, the safety of corticosteroid treatment for ICI hepatotoxicity in patients with cirrhosis and HCC remains to be explored.
### TABLE 3  Data on hepatotoxicity of immune-checkpoint inhibitors in patients with unresectable hepatocellular carcinoma reported in clinical trials

| Study, year Ref | Treatment | Patients in each arm N | Increased AST Any grade N (%) | Increased AST Grade ≥3 N (%) | Elevated ALT Any grade N (%) | Elevated ALT Grade >3 | Increased Bilirubin Any Grade N (%) | Increased Bilirubin Grade ≥3 N (%) |
|-----------------|-----------|------------------------|-------------------------------|-----------------------------|----------------------------|------------------------|----------------------------------|---------------------------------|
| CT-2007-01 2013 (55) | Tremelimumab | 21 | 14 (70) | 9 (45) | 11 (55) | 5 (25) | - | - |
| Checkmate 040 2017 (14) | Nivolumab | 262 | 37 (14.1) | 17 (6.5) | 25 (9.5) | 9 (3.4) | 7 (2.7) | 1 (0.4) |
| Keynote 224 2018 (15) | Pembrolizumab | 169 | 14 (13) | 7 (7) | 9 (9) | 4 (4) | 5 (5) | 2 (2) |
| Keynote 240 2020 (54) | Pembrolizumab Placebo | 278 | 63 (22.6) | 37 (13.3) | 49 (17.6) | 17 (6.1) | 52 (18.6) | 21 (7.5) |
| | | 135 | 22 (16.4) | 10 (7.5) | 13 (9.7) | 4 (3.0) | 17 (12.7) | 7 (5.2) |
| iMbrave 150 2020 (9) | Atezolizumab + Bevacizumab Sorafenib | 336 | 64 (19.5) | 23 (7) | 46 (14.0) | 12 (3.6) | 43 (13) | 8 (2.5) |
| | | 165 | 26 (16.7) | 8 (5) | 14 (9.0) | 2 (1.3) | 22 (14) | 10 (6.5) |
| Keynote 524 2020 (57) | Lenvatinib + Pembrolizumab | 100 | 20(20) | 11 (11) | - | - | - | - |
| Checkmate 040 2020 (16) | Nivolumab + Ipilimumab | 148 | Arm A 10 (20) | Arm A 8 (16) | Arm A 8 (16) | Arm A 4 (8) | - | - |
| | | Arm A 50 | Arm B 10 (20) | Arm B 4 (8) | Arm B 7 (14) | Arm B 3 (6) | - | - |
| | | Arm B 49 | Arm C 6 (13) | Arm C 6 (13) | Arm C 4 (8) | Arm C - | - | - |

Abbreviations: AE, adverse events. AST, aspartate aminotransferases. ALT, alanine aminotransferases.
Figure 1 depicts the suggested approach for the diagnostic management of hepatotoxicity associated with ICI-based treatments. We recommend that viral hepatitis serology, transaminase levels (ALT and AST), bilirubin, albumin and INR should be tested prior to starting therapy with checkpoint inhibitors (Table 2). Viral hepatitis serology includes HBV surface antigen (HBsAg), Hepatitis-B core antibody (HBcAb) and hepatitis C virus (HCV) antibody. A positive HBsAg or HBcAb serology should prompt checking HBV DNA and subsequent treatment with NUCs (entecavir or tenofovir) in patients with HBsAg and/or HBV-DNA positivity. A positive HCV antibody should be followed by HCV RNA levels. An ‘HBcAb positive/HBV DNA negative’ identified prior exposure to HBV and although the rate of potential HBV reactivation is low, HBV-DNA should be monitored during treatment. The decision to treat or not patients with HCV-RNA positivity should be tailored according to tumour burden, degree of liver impairment and performance status. Transaminase (ALT and AST) and bilirubin levels should be checked prior to each dose of therapy. Abnormalities in liver function tests should be considered according to the baseline values and the choice to start corticosteroid treatment should be carefully evaluated taking into account the risk/benefit ratio in the setting of cirrhosis. Accurate assessment of drugs or herbal use should be performed and hepatotoxic drugs discontinued. If liver biopsy could be a useful tool to stratify the risk of severe ICI-mediated hepatitis and to identify most severe patients requiring immunosuppressive treatments remains to be assessed. Novel clinical tools combining biochemical and histological features are needed to improve the management of hepatotoxicity associated with ICIs.

Regarding the combination atezolizumab plus bevacizumab, the risk stratification of the portal hypertensive bleeding deserves further considerations. We recommend that all patients should perform upper endoscopy within 6 months before starting any systemic treatment for HCC, especially in those eligible to treatment with atezolizumab plus bevacizumab, in order to assess the bleeding risk associated with portal hypertension. In the presence of medium/large oesophageal varices, prophylaxis of bleeding should be promptly started by using non-selective beta-blockers and/or endoscopic variceal ligation.

4 | DISCUSSION

Effective systemic treatments for uHCC increased during the last years, expanding the therapeutic options and opening to the possibility to use different drugs (belonging to different classes with different mechanisms of action) in a sequential way. Particularly, the advent of immunotherapy represented a significant innovation that changed the paradigm of treatment of uHCC, as the combination of the ICI atezolizumab with the anti-VEGF bevacizumab now represents the new standard of care for first-line treatment. Moreover, novel combination therapies of ICI plus TKI or ICIs plus another ICI showed promising preliminary data, with median OS times that are approaching to reach almost 2 year, that is a surprisingly favourable outcome compared to that obtained with the past standard of care, consisting in TKI monotherapy with sorafenib or lenvatinib. In the face of this extraordinary improvement in survival outcomes, the

---

**Figure 1** Approach to the diagnostic management of hepatotoxicity associated with immune-checkpoint inhibitors-based treatments

| Baseline Testing | Monitoring on therapy | Imaging | Liver Biopsy |
|------------------|-----------------------|---------|--------------|
| ALT, AST, Bilirubin, GammaGT, ALP | Δ ALT, Δ AST, Δ ALP, ΔGammaGT | Dynamic CT or MRI | Not evaluated in patients with HCC |

ALT, alanine aminotransferase. AST, aspartate aminotransferase. ALP, alkaline phosphatase. PLT, platelets. INR, international normalised ratio. EBV, Epstein Barr virus. CMV, Cytomegalovirus. CT, computed tomography. MRI, magnetic resonance imaging.
assessment of the safety of these treatments is a crucial point. This is particularly relevant because HCC occurs in the majority of cases in the setting of cirrhosis and in this particular clinical scenario the risk of developing hepatotoxicity from this novel systemic treatment, potentially leading to hepatic decompensation, should be carefully assessed. Hepatic decompensation represents the main driver of death in patients with early HCC and it represents a competing risk with HCC progression in more advanced HCC stages. Nevertheless, clinical trials often present an inadequate reporting of liver decompensating events, which instead, in our opinion, should be reported as a time-to-event outcome. Time-to-decompensation and decompensation free survival have indeed a great impact on survival, therefore, they should be outlined in future clinical trials as safety measures to better evaluate patients outcomes. (Figure 2). Efforts to prevent hepatic decompensation during systemic treatment for HCC should be optimized in clinical practice, as decompensating events could make patients not more eligible to subsequent lines of treatment. This is particularly important at this time, as the therapeutic armamentarium for uHCC has recently increased, allowing to use of sequential treatments to the third line and beyond. Etiological treatments for cirrhosis can be effective in preventing hepatic decompensation and improving OS, as shown with DAAs for the treatment of HCV infection in patients with early stage HCC; however, their impact on survival of patients with intermediate- or advanced-stage HCC remains to be assessed. It is possible to speculate that also in patients with uHCC the protective effect of DAAs on liver function may translate in a significant survival advantage, allowing the patients with preserved liver function to receive more subsequent lines of treatment.

As previously stated, the introduction of ICI s in the management of uHCC, especially in combination with other classes of drugs (anti-VEGF or TKIs) or with another ICI, led to an improvement in the survival outcomes observed in clinical trials. Also the safety profile, compared to that of TKIs, appeared to be improved. However, it should be noted that RCTs typically include a highly selected population of patients with well-preserved liver function and without severe portal hypertension or significant comorbidities. Therefore, the hepatotoxicity profile of ICI s in patients with more advanced liver disease should be carefully assessed in next generation real-world studies or in further RCTs assessing hepatic decompensation as a clinically meaningful endpoint. At the same time, the impact of the combination of atezolizumab plus bevacizumab on the risk of portal hypertensive bleeding is still under evaluation. As the balance between benefit and risks can often be difficult to assess in oncology, especially in the setting of HCC and cirrhosis, novel measures that combine effectiveness and safety are needed. According to ASCO statements, a net health benefit is defined as the balance between clinical benefit and toxicity and it could be used to compare different treatment strategies. More recently, an innovative measure combining effectiveness and safety has been proposed. Similar to the incremental cost-effectiveness ratio used for pharmacoeconomic purposes, the incremental safety-effectiveness ratio is defined as the ratio between the difference in serious adverse events and the difference in OS between two treatment strategies. This measure

![Figure 2](image-url)
could be useful to improve the collaborative decision-making process, involving physicians and patients, in the choice of the optimal tailored treatment for each patient.67

In conclusion, it is expected that the number of effective ICI-based combination therapies will increase in the next future, potentially leading to their use also in neoadjuvant or adjuvant ICI-based combination therapies will increase in the next future, potentially leading to their use also in neoadjuvant or adjuvant therapies. In the future, better informed clinical decision making and to optimize the outcomes of patients with HCC.

ACKNOWLEDGEMENTS
All the authors take full responsibility for the preparation of the manuscript and approved the final draft manuscript.

CONFLICT OF INTEREST
The other authors have no disclosure to declare.

REFERENCES
1. Villanueva A. Hepatocellular carcinoma. N Engl J Med. 2019;380:1450-1462.
2. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Aberra S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the global burden of disease study 2015. JAMA Oncol. 2017;3(12):1683-1691. https://doi.org/10.1001/jamaoncol.2017.3055
3. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Cammà C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. Hepatology. 2010;51(4):1274-1283. doi:https://doi.org/10.1002/hep.23485
4. Cabibbo G, Petta S, Barbara M, et al. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. J Hepatol. 2017;67(1):65-71. doi:https://doi.org/10.1016/j.jhep.2017.01.033
5. Reig M, Cabibbo G. Antiviral therapy in the palliative setting of HCC (BCLC-B and -C). J Hepatol. 2021;74(5):1225-1233. doi:https://doi.org/10.1016/j.jhep.2021.01.046
6. Song R, Ikeguchi M, Zhou G, Kuo MT. Identification and characterization of a hepatoma cell-specific enhancer in the mouse multidrug resistance mdr1b promoter. J Biol Chem. 1995;270(43):25468-25474. doi:https://doi.org/10.1074/jbc.270.43.25468
7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390. doi:https://doi.org/10.1056/NEJMoa0708857
8. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-1173. doi:https://doi.org/10.1016/S0140-6736(18)30207-1
9. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894-1905. doi:https://doi.org/10.1056/NEJMo a1915745
10. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66. doi:https://doi. org/10.1016/S0140-6736(16)32453-9
11. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379(1):54-63. doi:https://doi.org/10.1056/NEJMo a1717002
12. Zhu AX, Park JO, Ryoo B-Y, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859-870. doi:https://doi.org/10.1016/S1470-2045(15)00050-9
13. Zhu AX, Kang Y-K, Yen C-J, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased a-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019;20:282-296.
14. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492-2502. doi:https://doi.org/10.1016/S0140-6736(17)31046-2
15. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940-952. doi:https://doi.org/10.1016/S1470-2045(18)30351-6
16. Yao T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomised clinical trial. JAMA Oncol. 2020;6(11):e204564. doi:https://doi.org/10.1001/jamaoncology.2020.4564. Epub ahead of print. Erratum in: JAMA Oncol. 2021 Jan 1;7(1):140.
17. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol. 2015;33(23):2563-2577. doi:https://doi.org/10.1200/JCO.2015.61.6706. Epub 2015 Jun 22. PMID: 26101248; PMCID: PMC5015427.
18. Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf. 2013;36(7):491-503. doi:https://doi.org/10.1007/s4026 4-013-0048-4
19. Cheng A-L, Kang Y-K, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25-34. doi:https://doi.org/10.1016/S1470-2045(08)70285-7
20. Lavarone M, Cabibbo G, Biolato M, et al. Predictors of survival in patients with advanced hepatocellular carcinoma who permanently
discontinued sorafenib. Hepatology. 2015;62(3):784-791. doi:https://doi.org/10.1002/hep.27729

21. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology. 1999;29(1):62-67. doi:https://doi.org/10.1002/hep.510290145

22. lavarone M, Cabibbo G, Piscaglia F, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology. 2011;54(6):2055-2063. doi:https://doi.org/10.1002/hep.24644

23. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: the GIDEON study. J Hepatol. 2016;65(6):1140-1147. doi:https://doi.org/10.1016/j.jhep.2016.07.020

24. Silverman SL. From randomized controlled trials to observational studies. Am J Med. 2009;122(2):114-120. doi:https://doi.org/10.1016/j.amjmed.2008.09.030

25. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. Arch Intern Med. 2007;167(16):1752-1759. doi:https://doi.org/10.1001/archinte.167.16.1752

26. Hollebeque A, Cattan S, Romano O, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. Aliment Pharmacol Ther. 2011;34(10):1193-1201. doi:https://doi.org/10.1111/j.1365-2036.2011.04860.x

27. Pressiani T, Boni C, Rimassa L, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol. 2013;24(2):406-411. doi:https://doi.org/10.1093/annonc/mds343

28. Yau T, Park JW, Finn RS, et al. CheckMate 459: A randomized, multicenter phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). Abstract. Ann Oncol. 2019;459:v874-v875. doi:https://doi.org/10.1093/annonc/mdz394.029

29. Reiss KA, Yu S, Mamtani R, et al. Starting dose of sorafenib for the treatment of hepatocellular carcinoma: a retrospective, multi-institutional study. J Clin Oncol. 2017;35(31):3575-3581. doi:https://doi.org/10.1200/JCO.2017.73.8245

30. Oettl K, Birner-Gruenberger R, Spindelboeck W, et al. Oxidative albumin damage in chronic liver failure: relation to albumin binding capacity, liver dysfunction and survival. J Hepatol. 2013;59(5):978-983. doi:https://doi.org/10.1016/j.jhep.2013.06.013

31. Abou-Alfa GK, Amadori D, Santoro A, et al. Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis. Gastrointest Cancer Res. 2011;4(2):40-44.

32. Rimassa L, Danesi R, Pressiani T, Merle P. Management of adverse events associated with tyrosine kinase inhibitors: improving outcomes for patients with hepatocellular carcinoma. Cancer Treat Rev. 2019;77:20-28. doi:https://doi.org/10.1016/j.ctrv.2019.05.004

33. Johnson PJ, Berhanie S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol. 2015;33(6):550-558. doi:https://doi.org/10.1200/JCO.2014.57.9151

34. Pinato DJ, Sharma R, Allara E, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 2017;66(2):338-346. doi:https://doi.org/10.1016/j.jhep.2016.09.008

35. Hiraoka A, Kumada T, Michitaka K, Kudo M. Newly proposed ALBI grade and ALBI-T score as tools for assessment of hepatic function and prognosis in hepatocellular carcinoma patients. Liver Cancer. 2019;8(5):312-325. doi:https://doi.org/10.1159/000494844

36. Hiraoka A, Kumada T, Atsukawa M, et al. Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions—multicenter analysis. Cancer Med. 2019;8(8):3719-3728. doi:https://doi.org/10.1002/cam4.2241

37. Hiraoka A, Kumada T, Atsukawa M, et al. Early relative change in hepatic function with lenvatinib for unresectable hepatocellular carcinoma. Oncology. 2019;97(6):334-340. doi:https://doi.org/10.1159/000502095

38. Hiraoka A, Kumada T, Fukuishi S, et al. Post-progression treatment eligibility of unresectable hepatocellular carcinoma patients treated with lenvatinib. Liver Cancer. 2020;9(1):73-83. doi:https://doi.org/10.1159/000503031

39. Lim HY, Kim YJ, Huang Y-H. Regorafenib in patients (pts) with unresectable hepatocellular carcinoma (uHCC) in real-world practice in Asia: interim results from the observational REFINE study. Ann Oncol.31(4):S699. Abstract.

40. Yoo C, Park J-W, Kim YJ, et al. Multicenter retrospective analysis of the safety and efficacy of regorafenib after progression on sorafenib in Korean patients with hepatocellular carcinoma. Invest New Drugs. 2019;37(3):567-572. doi:https://doi.org/10.1007/s10637-018-0707-5

41. Kelley RK, Ryoo B-Y, Merle P, et al. Second-line cabozantinib after sorafenib treatment for advanced hepatocellular carcinoma: a subgroup analysis of the phase 3 CELESTIAL trial. ESMO Open. 2020;5(4):e000714. doi:https://doi.org/10.1136/esmoopen-pen-2020-000714

42. Finkelmeier F, Scheiner B, Lehy C, et al. Cabozantinib in advanced hepatocellular carcinoma: efficacy and safety data from an international multicenter real-world cohort. J Clin Oncol. 2020;38(15_suppl):e16668.

43. Tovoli F, Dadduzio V, De Lorenzo S. Real-life clinical data of cabozantinib for unresectable hepatocellular carcinoma. Sci Open. doi:https://doi.org/10.1016/j.jannoc.2020.08.1115

44. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-264. doi:https://doi.org/10.1038/nrc3239. Published 2012 Mar 22.

45. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016;27(4):559-574. doi:https://doi.org/10.1093/annonc/mdv623

46. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158-168. doi:https://doi.org/10.1056/NEJMr1703481

47. Peerapathdit TB, Wang J, Ondenwald MA, Hu S, Hart J, Charlton MR. Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. Hepatology. 2020;72(1):315-329. doi:https://doi.org/10.1002/hep.31227

48. De Martin E, Michot J-M, Rosnorduc O, Guettier C, Samuel D. Liver toxicity as a limiting factor to the increasing use of immune checkpoint inhibitors. JHEP Rep. 2020;2(6):100170. doi:https://doi.org/10.1016/j.jheprep.2020.100170

49. Yau T, Hsu C, Kim T-Y, et al. Nivolumab in advanced hepatocellular carcinoma: Sorafenib-experienced Asian cohort analysis. J Hepatol. 2019;71(3):543-552. doi:https://doi.org/10.1016/j.jhep.2019.05.014

50. Fessas P, Kaseb A, Wang Y, et al. Post-registration experience of nivolumab in advanced hepatocellular carcinoma: an international study. J Immunother Cancer. 2020;8(2):e001033. doi:https://doi.org/10.1136/jitc-2020-001033

51. Tabrizian P, Florman SS, Schwartz ME. PD-1 inhibitor as bridge therapy to liver transplantation? Am J Transplant. 2021;21(5):1979-1980. doi:https://doi.org/10.1111/ajt.16448

52. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. PLOS ONE. 2016;11(7):e0160221. doi:https://doi.org/10.1371/journal.pone.0160221
53. Finn RS, Ryoo B-Y, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. J Clin Oncol. 2020;38(3):193-202. doi:https://doi.org/10.1200/JCO.19.01307

54. Sangro B, Gomez-Martín C, de la Mata M, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013;59(1):81-88. doi:https://doi.org/10.1016/j.jhep.2013.02.022

55. NCT04487067. https://clinicaltrials.gov/ct2/show/NCT04487067. Accessed on April 15, 2021.

56. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020;38(26):2960-2970. doi:https://doi.org/10.1200/JCO.20.00808

57. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci. 2016;17(1):14. doi:https://doi.org/10.3390/ijms17010014

58. De Martin E, Michot J-M, Papouin B, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol. 2018;68(6):1181-1190. doi:https://doi.org/10.1016/j.jhep.2018.01.033

59. Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of immune checkpoint inhibitors: an evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int. 2018;38(6):976-987. doi:https://doi.org/10.1111/liv.13746

60. Haanen J, Carbonnel F, Robert C, Kerr K, Peters S, Larkin J, Jordan K. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv119–iv142. doi:https://doi.org/10.1093/annonc/mdx225

61. Cohen JV, Dougan M, Zubiri L, Reynolds KL, Sullivan RJ, Misdraji J. Liver biopsy findings in patients on immune checkpoint inhibitors. Mod Pathol. 2021;34(2):426-437. doi:https://doi.org/10.1038/s41379-020-00653-1

62. Zen Y, Yeh MM. Hepatotoxicity of immune checkpoint inhibitors: a histology study of seven cases with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol. 2018;31(6):965-973. doi:https://doi.org/10.1038/s41379-018-0013-y

63. Lee P-C, Chao Y, Chen M-H, et al. Risk of HBV reactivation in patients with immune checkpoint inhibitor-treated unresectable hepatocellular carcinoma. J Immunother Cancer. 2020;8(2):e001072. doi:https://doi.org/10.1136/jitc-2020-001072

64. Sangro B, Celsa C, Calvaruso V, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol. 2019;71(2):265-273. doi:https://doi.org/10.1016/j.jhep.2019.03.027

65. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci. 2016;17(1):14. doi:https://doi.org/10.3390/ijms17010014

66. Johnson PJ, Qin S, Park J-W, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable hepatocellular carcinoma: results from a randomized phase III trial. J Clin Oncol. 2015;33(2):172. doi:https://doi.org/10.1200/JCO.2013.54.3298

67. De Martin E, Michot J-M, Papouin B, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol. 2018;68(6):1181-1190. doi:https://doi.org/10.1016/j.jhep.2018.01.033

68. Haanen J, Carbonnel F, Robert C, Kerr K, Peters S, Larkin J, Jordan K. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv119–iv142. doi:https://doi.org/10.1093/annonc/mdx225

69. Johnson PJ, Qin S, Park J-W, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol. 2013;31(28):3517-3524. doi:https://doi.org/10.1200/JCO.2012.48.4410

70. Cheng A-L, Kang Y-K, Lin D-Y, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol. 2013;31(32):4067-4075. doi:https://doi.org/10.1200/JCO.2012.45.8372

71. Zhu AX, Rosmorduc O, Evans TRJ, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2015;33(6):559-566. doi:https://doi.org/10.1200/JCO.2013.53.7746

How to cite this article: Celsa C, Giuffrida P, Giacchetto CM, et al. Hepatotoxicity of systemic therapies for unresectable hepatocellular carcinoma. Liver Cancer Int. 2021;2:82–95. https://doi.org/10.1002/lci2.38