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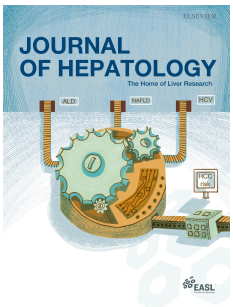

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Systemic treatment of hepatocellular carcinoma. An EASL position paper.

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Abstract

The last five years have witnessed relevant advances in the systemic therapy of hepatocellular carcinoma. New data have emerged since the development of the EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma in 2018. Drugs licensed in some countries now include four oral multi-tyrosine kinase inhibitors (sorafenib, lenvatinib, regorafenib and cabozantinib), one antiangiogenic antibody (ramucirumab) and four immune checkpoint inhibitors, alone or in combination (atezolizumab in combination with bevacizumab, ipilimumab in combination with nivolumab, nivolumab and pembrolizumab in monotherapy). Prolonged survival in excess of two years can be expected in most patients with sensitive tumours and a well-preserved liver function that render them fit for sequential therapies. With different choices available in any given setting, the robustness of the evidence of efficacy and a correct matching of the safety profile of a given agent with patient characteristics and preferences are key in making sound therapeutic decisions. The recommendations in this document amend the previous EASL Clinical Practice Guidelines and aim to help providing the best possible care for patients today. In view of several ongoing and promising trials further advances in systemic therapy of HCC are foreseen in the near future and these recommendations will have to be updated regularly.

Key Points

- The decision to start a systemic therapy should be based on tumour stage and suitability for local liver-directed therapies. Patients with extrahepatic disease, vascular invasion or bulky liver involvement are the main candidates. Patients at earlier evolutionary cancer stages could be considered for systemic therapy if treatments of higher priority have failed or are unfeasible.
- The combination of atezolizumab and bevacizumab is the preferred option for naïve patients if they meet the criteria established in the pivotal clinical trial. Sorafenib or Lenvatinib are the alternative first-line options if Atezolizumab-Bevacizumab combination is not indicated.
- Cabozantinib, Regorafenib (in sorafenib-tolerant patients) and Ramucirumab (in patients with serum alpha-fetoprotein above 400 ng/ml) all have strong scientific support as second-line therapies after Sorafenib.
- There is no scientific evidence in favour of any agent after Atezolizumab-Bevacizumab or after Lenvatinib. Therefore, the choice of a second-line agent in this setting should be based on sound clinical judgement, toxicity profile, drug availability and local regulations.
- RECIST 1.1 are the preferred criteria for the assessment of tumour response to systemic therapies. The benefit of alternative criteria like immune RECIST, modified RECIST and others should be confirmed prospectively before they can be recommended for clinical practice.
- The clinical decision to switch from first to second line therapy should not only consider progression at imaging but also liver function, general condition and pattern of progression.

Introduction

Systemic therapy for hepatocellular carcinoma (HCC) has undergone remarkable advancements over the past 13 years. Prior to 2007, there was no standard drug treatment for HCC. Cytotoxic chemotherapy was used frequently by clinicians, but its role was controversial due to a lack of high-level evidence and concern of toxicity in patients with cirrhosis. In 2007, sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI), became the first systemic agent demonstrating survival benefit in a randomized clinical trial [1]. Afterwards, sorafenib has been internationally considered a standard treatment for advanced HCC. After a decade of efforts, three other multi-TKIs (lenvatinib [2], regorafenib [3] and cabozantinib [4]), and the VEGFR2 inhibitor ramucirumab [5], were found to be effective for treating HCC from 2017 to 2019. At the same time, promising data of immune checkpoint inhibitors (ICIs) emerged and gradually shifted the direction of research to immunotherapy. The combination of atezolizumab and bevacizumab (atezo-bev) [6] and the combination of sintilimab and a bevacizumab biosimilar [7] have recently outperformed sorafenib as the first-line treatment, although the full report on the sintilimab combination is still pending. Overall, the cumulative advances in systemic therapy on HCC have not only led to improved overall survival of patients but also opened novel perspectives on the treatment strategy of intermediate- and advanced stage HCC [8]. Changes in the treatment paradigm occurring after the publication of the EASL Clinical Practice Guidelines on the Management of HCC [9] deserve analysis and guidance. The European Association for the Study of the Liver (EASL) appointed us authors of this position paper and the content has been approved by EASL Governing Board.

General considerations concerning systemic therapy of HCC

In general, overall survival (OS) of patients treated with systemic agents has gradually improved through time (table 1). In the first-line setting, the median OS of sorafenib-treated patients has improved from 10.7 months in the SHARP study (2005-2006)[1], to 12.3 months in the REFLECT study (2015)[2], and over 13 months in the IMbrave-150 study (2018-2019)[6]. A similar trend was observed in the control/placebo arms in second line studies. The median OS in the control arms of RESORCE (2013-2015)[3] and CELESTIAL (2013-2017)[4] was approximately 8 months and over 10 months in the recent KEYNOTE-240 study (2016-2017)[10]. The exact reason for above improvements in OS remains unclear but is likely contributed by multiple factors including the use of sequential therapy, improved care of patients with chronic hepatitis and cirrhosis, earlier commencement of systemic treatment, increased recruitment of patients with indolent tumours, and the shift to second line trials of patients with marginal progression or with a pattern of progression with minor impact in prognosis [11]. Regarding objective tumour remission, TKIs have an overall response rate (ORR) by RECIST criteria lower than 10%, with the only exception of lenvatinib (ORR of 18.8% [2]). Hence, they are generally considered cytostatic agents. ICI monotherapy is associated with higher ORR in the range of 15 to 20%, and combinational treatment could further increase ORR to approximately 30%, including 8% complete responses [6].

In HCC patients with preserved hepatic function in Child-Pugh class A, currently approved systemic agents are overall safe (table 1). Considering only intense toxicities (grade 3 or higher), three patterns of events exist dependent on the mechanism of action of the agent. For TKIs, the most common events are hand-foot-skin reaction, diarrhoea and hypertension. For anti-angiogenic monoclonal antibodies, hypertension, proteinuria and haemorrhage. For ICIs, immune-mediated adverse events (AE) especially hepatitis, which appears as elevation of transaminases [12].

The prognosis of patients with HCC is influenced by tumour burden, patients' performance status and background hepatic function. Table 2 summarizes the characteristics of the study populations of randomized clinical trials for currently approved systemic agents. For disease burden, despite variable proportion of macrovascular invasion or extrahepatic disease amongst different studies, BCLC stage C consistently constitutes the predominant population, in a range of 78 to 91%. As a measure to test novel agents in fit populations, all clinical trials have recruited mostly patients with ECOG performance status of 0 or 1 and Child-Pugh class A function, with additional exclusion criteria based on albumin and bilirubin levels or the presence of ascites. Finally, all phase III clinical trials have applied 3 to 5 stratification factors during the randomization procedures to minimize imbalances of study population between the experimental and control arm. Pattern of progression and limited time span between progression and trial entry to exclude very indolent tumours have only been considered in the RESORCE trial [3]. Evidence of efficacy and safety provided for the population described above should not be extrapolated loosely to patients in earlier stages of the disease or having worse liver function.

Overall survival is the sole robust endpoint to assess the benefit from any intervention in advanced HCC. All proposed surrogates lack adequate validation [13,14], and their validity may only be raised as a suggestion [15,16]. Its use in early development trials to assess activity ends in an educated guess. Absence of response does not rule out survival benefit. Increased ORR does not secure increased survival of the whole cohort on an intention to treat basis while it may predict survival benefit for the individual patient. Expanded time to progression (TTP) also fails to predict improved OS. The value of PFS as a surrogate for OS is controversial since it has been suggested that a benefit in PFS may predict a benefit in OS when the hazard ratio for PFS is lower than 0.6 [17]. Nevertheless, the statistical analysis supporting this concept has some limitations and a formal, strong validation is still pending [16,18].

Scientific evidence of clinical efficacy of licensed agents.

First line setting

The efficacies of currently approved systemic agents are summarized in table 1. For patients naïve to systemic therapy, sorafenib prolongs OS compared to placebo [1], atezo-bev prolongs OS compared to sorafenib [6], lenvatinib provides a non-inferior OS compared to sorafenib [2], and nivolumab failed to demonstrate that it prolongs OS compared to sorafenib but showed a non-significant trend with improved long-term survival rates [19].

The IMbrave 150 trial confirmed that atezo-bev is superior to sorafenib in prolonging both OS (with a HR of 0.58) and PFS (with a HR of 0.59) [6]. IMbrave 150 was an open label phase 3 trial that randomized 501 patients with a 2:1 ratio to either the standard dose of Sorafenib (400 mg bid) or the combination of a flat dose of atezolizumab (1,200 mg) plus a weight-based dose of bevacizumab (15 mg/Kg) given IV every 3 weeks. The combination also resulted in objective remissions that were more frequent (27.3% vs 11.9%) and more durable (duration > 6 months in 87.6% vs 59.1%), and a longer time until deterioration of health-related quality of life (HRQoL) (median time 11.2 vs 3.6 months) despite an increased number of patients with serious AEs (38.0% vs 30.8%) and AEs leading to discontinuation of any agent (15.5 vs 10.3%). The trial was interrupted at the first interim analysis after a short follow-up of 8.6 months, when median OS was not reached among patients treated with atezo-bev. With a longer follow up, median OS was 19.2 months with atezo-bev arm compared to 13 months with sorafenib [20]. In addition, a network metaanalysis has suggested the superiority of atezo-bev over lenvatinib and nivolumab [21].

The REFLECT trial showed that lenvatinib is non-inferior to sorafenib in terms of OS (HR of 0.92) but failed to show that it is superior [2]. REFLECT was an open label phase 3 trial that randomized 954 patients with a 1:1 ratio to continuous treatment with the standard dose of Sorafenib (400 mg bid) or a weight-adjusted dose of lenvatinib (12 mg/day if ≥60 kg or 8 mg/day if <60 kg). Lenvatinib therapy resulted in a slightly longer OS (13.6 vs 12.3 months), higher ORR by RECIST 1.1 (18.8% vs 6.5%), and a longer TTP (7.4 vs. 3.7 months) and PFS (7.3 vs 3.6 months), plus an increased number of patients with serious treatment-related AEs (TRAE)(43% vs 30%) and AEs leading to treatment

discontinuation (40% vs 32%). This may explain that time on treatment in the trial was shorter than TTP, thus suggesting treatment interruption prior to disease progression.

The CheckMate 459 trial failed to show that nivolumab is superior to sorafenib in terms of OS (with a HR of 0.85 [95% CI 0.72-1.02]) [19]. CheckMate 459 was an open label phase 3 trial that randomized 743 patients with a 1:1 ratio to the standard dose of Sorafenib (400 mg bid) or a flat dose of nivolumab (240 mg every 2 weeks). Nivolumab therapy resulted in a longer median OS (16.4 vs 14.7 months), higher proportion of patients alive at 33 months (29 vs 21%), higher ORR by RECIST 1.1 (15% vs 7%), similar median TTP (3.7 vs. 3.8 months), reduced number of patients with severe TRAEs grade 3 or 4 (22% vs 50%) and TRAEs leading to treatment discontinuation (8% vs 11%), and better preservation of HRQoL over time.

Second and further line settings

For patients who progress or do not tolerate sorafenib (and eventually other systemic therapies), regorafenib [3], cabozantinib [4] and ramucirumab [5] prolong OS compared to placebo. For regorafenib, the benefit has only been shown for patients that stably tolerate 400 mg of sorafenib daily; for ramucirumab, the benefit is restricted to patients that have serum alpha-fetoprotein (AFP) levels ≥400 ng/ml.

RESORCE was a double-blind phase 3 trial that randomized 573 patients with a 2:1 ratio to regorafenib (160 mg daily for the first 3 weeks of each 4-week cycle) or placebo [3]. Eligible patients must have had documented radiological progression within the last 2 months during sorafenib treatment as defined in study-specific

criteria in order to avoid indolent disease, must have tolerated at least 400 mg daily of sorafenib for 20 or more of the 28 days before discontinuation, and must have received their last sorafenib dose within 10 weeks of randomisation. In this population, regorafenib resulted in longer median OS (10.6 vs 7.8 months), with 46% of patients experiencing TRAEs grade 3 or 4 and 10% discontinuing therapy because of TRAEs. ORR by RECIST was 7% and median duration of response (DOR) was 3.5 months.

CELESTIAL was a double-blind phase 3 trial that randomized 707 patients with a 2:1 ratio to cabozantinib (60 mg daily) or placebo [4]. Eligible patients had received prior sorafenib and had disease progression after at least one and up to two systemic treatments for HCC. Cabozantinib resulted in longer median OS (10.2 vs 8 months in the entire cohort, 11.3 vs 7.2 months in second-line patients), with 68% of patients experiencing AEs grade 3 or 4 of any causality and 16% discontinuing therapy because of TRAEs. ORR by RECIST 1.1 was 4%.

REACH-2 was a double-blind phase 3 trial that randomized 292 patients with a 2:1 ratio to ramucirumab (8 mg/kg every 2 weeks) or placebo [5]. Eligible patients had serum AFP levels ≥400 ng/mL and had received prior sorafenib as the only systemic therapy (discontinued because of intolerance or tumour progression). Ramucirumab resulted in longer median OS (8.5 vs 7.3 months), with 35% of patients experiencing serious AEs of any causality and 11% discontinuing therapy because of TRAEs. ORR by RECIST 1.1 was 5%. A previous trial testing this agent in patients with any level of AFP failed to produce superior OS compared to placebo [22].

The approval of nivolumab [23], pembrolizumab [24] and the combination of nivolumab and ipilimumab [25] for second line therapy in the USA and other countries is based on single arm trials. In the case of pembrolizumab, the superiority over placebo in terms of OS was not confirmed in a randomized trial [10].

CheckMate 040 was a basket trial that included 6 different patient cohorts. In cohorts 1 and 2, 262 patients in first or further lines received escalating doses (cohort 1) or 3 mg/kg of nivolumab (cohort 2) every 2 weeks [23]. Among 154 patients in the second line post-sorafenib, median OS was 15 months, ORR by RECIST 1.1 was 15%, 18% of patients experienced TRAEs grade 3 or higher and 3% discontinued therapy because of TRAEs. In cohort 4, 120 patients in second line after sorafenib were randomised to three different regimes of the combination of ipilimumab and nivolumab [25]. Among 50 patients receiving 3 mg/kg of ipilimumab and 1 mg/kg of nivolumab every 2 weeks, median OS was 22.8 months, ORR by RECIST 1.1 was 32%, 53% of patients experienced TRAEs grade 3 or higher and 18% discontinued either agent because of TRAEs. In cohort 5 [26], 49 patients in Child-Pugh B class received a flat dose of 240 mg of nivolumab every 2 weeks and median OS was 7.6 months, ORR by RECIST 1.1 was 12.2%, 24.5% of patients experienced TRAEs grade 3 or higher and 4% discontinued therapy because of TRAEs. In cohort 6, patients in first or second line were randomised to receive one of two different combinations, nivolumab plus cabozantinib or nivolumab plus ipilimumab plus cabozantinib [27].

Keynote 224 was a single arm trial that recruited 104 sorafenib-experienced patients who received 200 mg of pembrolizumab every 3 weeks [24]. Median OS was 12.9

months, ORR by RECIST 1.1 was 17%, 25% of patients experienced TRAEs grade 3 or higher and 5% discontinued therapy because of TRAEs. The controlled trial Keynote 240 failed to show that pembrolizumab is superior to placebo in terms of OS (with a HR of 0.78 [95% CI 0.61-0.99]) [10]. Keynote 240 was a double-blind phase 3 trial that randomized 413 patients with a 2:1 ratio to pembrolizumab (200 mg every 3 weeks) or placebo [10]. Pembrolizumab resulted in longer median OS (13.9 vs 10.6 months) and higher ORR by RECIST 1.1 (18.3% vs 4.4%), higher number of patients with AEs of any causality grade 3 or higher (52.7% vs 46.3%) and with AEs of any causality leading to treatment discontinuation (17.2% vs 9%).

Patient candidates for systemic therapy.

Systemic therapy is the mainstay of the treatment of HCC patients in the advanced stage of the Barcelona Clinic Liver Cancer (BCLC) classification [28]. However, some patients diagnosed at the early or intermediate stages present a profile that prevents the indication of the first treatment option to be considered for such stages. In this scenario, the treatment stage migration concept moves the treatment selection to that corresponding to the next evolutionary stage. Same concept applies to patients in whom initial treatment fails and still remains at the early or intermediate stages. This is particularly relevant in patients at the intermediate stage in whom response to treatment has been suboptimal and/or present liver function impairment or disease progression not amenable to further chemoembolization sessions. Current guidelines recommend chemoembolization for patients with liver only disease suitable for selective approach, in whom liver function is preserved and are free of cancer

symptoms [9]. Same criteria should be met when considering new chemoembolization sessions. If this is not the case, patients have reached the untreatable progression stage and should be considered for systemic therapy [29]. Probably, patients naïve to locoregional treatment should be considered separately in terms of prognosis from those presenting post-treatment progression and not being suitable for retreatment. Life expectancy may be different and such characteristic has to be considered in trials design and analysis [18].

Treatment recommendations for patients naïve to systemic therapy

When systemic therapy is deemed appropriate in a patient with HCC, atezo-bev should be considered the preferred option (figure 1). Alternative therapies should be considered when the risk of using atezo-bev is high or unknown based on patient or tumour characteristics that are summarized in table 3. Attention should be payed to the specific inclusion and exclusion criteria for each agent in registration trials. Risk of bleeding, comorbidities such as arterial hypertension and cardiovascular disease, and prior autoimmune conditions may become limiting parameters for the indication of atezo-bev.

A preserved liver function has been a pre-requisite in all phase 3 trials. The specific cohort recruiting Child B patients in CheckMate 040 has shown that nivolumab monotherapy is safe in this population [30]. Small real-life cohorts also support the safety of sorafenib [31,32] and nivolumab [33] in early Child B (7 points) patients. Such

evidence is lacking for atezo-bev. However, wide variations of impaired liver function fall within the Child-Pugh class B and even within the Child-Pugh class A, where ascitic decompensation may be present. An individualised case-by-case evaluation based on the evidence mentioned above is recommended for patients with mildly abnormal liver function or decompensated cirrhosis. There is no scientific support for treating patients with severely compromised performance status (ECOG 2 or beyond).

Systemic treatment of HCC has evolved from absence of active agents with survival benefit, to oral TKIs which are easy to administer, and currently to intravenous drugs. Any treatment requires specific training and expertise and demands the availability of facilities to apply them. Hence, liver cancer groups should secure an adequate setting to provide optimal care, including drug delivery, management of adverse events and management of complications of the underlying liver disease that most patients present.

Contraindications to first-line agents and alternative options

Absolute and relative contraindications to ICIs, antiangiogenics and multi-TKIs define treatment indication in a patient naïve to systemic therapies, based on prior or current medical conditions or the need to receive certain concomitant medications, as summarized in table 3.

The two main concerns with ICIs are autoimmune diseases and liver transplantation. Regarding the former, target organ and current disease activity should be taken into account. Autoimmune disorders that do not result in organ dysfunction, that have already abolished organ function, or when organ dysfunction can be easily controlled should not contraindicate ICIs. Such conditions comprise hypothyroidism, type 1 diabetes, vitiligo, skin diseases with limited involvement including psoriasis, pernicious anaemia, resolved childhood asthma or atopy. On the other end, any prior autoimmune damage to the central nervous system or the heart are absolute contraindications. For other relatively common disorders like Graves' disease, rheumatoid arthritis or systemic lupus erythematosus, individual decisions should be taken and the need for immunosuppression make TKIs a better option. The safety of ICIs in patients with prior autoimmune diseases has only been studied in small retrospective studies with intrinsic patient selection bias. Although a metanalysis reported that flares and immune-mediated AEs in patients with autoimmune diseases were generally manageable, some events were lethal [34]. Caution is therefore an obligation until prospective studies supporting such approach are available, particularly regarding HCC patients with autoimmune hepatitis or primary biliary cholangitis. The presence of autoantibodies (anti-nuclear, anti-thyroid, anti-smooth muscle or others), or the presence of cryoglobulins in patients with HCV or HBV infection are not per se a contraindication to ICIs.

In patients with a contraindication to atezolizumab, either sorafenib or lenvatinib should be considered next (figure 1). When choosing between lenvatinib or sorafenib, factors that may be considered are the lack of evidence of non-inferiority of lenvatinib

for patients with main portal vein invasion or extensive (≥ 50%) tumour liver involvement, lack of evidence-based support for the available second line therapies after lenvatinib, and superiority of lenvatinib over sorafenib in secondary endpoints in the REFLECT trial. Besides, differences in safety profile may also be important in individual patients, with weight loss, proteinuria, hypertension, and vomiting being more common after lenvatinib; while hand-foot skin reaction, rash, diarrhoea, and alopecia being more common with sorafenib.

The main contraindication to antiangiogenics, including bevacizumab and multi-TKIs, is a history of bleeding, thrombotic or cardiovascular disorders. In large metanalyses, high-dose bevacizumab (10-15 mg/kg) has been associated with an increased risk of cardiac ischemia (relative risk [RR] 4.4), cerebral ischemia (RR 6.67), bleeding (RR 3.32), and arterial hypertension (RR 7.11)[35]; and sunitinib and sorafenib with an increased risk of atherothrombotic events (RR 3.02) and bleeding (RR 2.0)[36,37]. Any recent major bleeding event contraindicates atezo-bev and TKIs, in particular haemoptysis or gastrointestinal bleeding. In addition, untreated oesophageal varices at risk of bleeding also contraindicate atezo-bev. Cardiovascular events that contraindicate antiangiogenics comprise cerebral vascular accidents (transient or not); ischemic heart disease, particularly after acute myocardial infarction or unstable angina; moderate to severe congestive heart failure (NYHA class 2 or higher); poorly controlled arterial hypertension, especially in the presence of prior hypertensive crisis or hypertensive encephalopathy; peripheral arterial thrombosis; and significant arrhythmias. When thrombotic or cardiovascular events are not recent, the need for therapeutic (not

prophylactic) antiaggregation or anticoagulation indicates a substantial contraindication.

In HCC patients, the risk of variceal bleeding has to be specifically addressed. Bevacizumab does not increase portal pressure, at least in animal models. But it can interfere with clotting and wound healing and result in more severe variceal bleeding. For atezo-bev, a recent (within the last 6 months) evaluation of oesophageal and gastric varices is mandatory. For TKIs, it is at least highly recommended. Patients with varices should be managed as per local practice guidelines and no specific counsel was given in the IMbrave150 trial. Following general recommendations in non-HCC patients, those with small varices may be treated with beta-blockers or not treated, while in those with medium-large varices the choice of beta-blockers or endoscopic band ligation should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events [38]. The efficacy of beta-blockers may be lower in patients with HCC [39] but prospective evidence is lacking. If endoscopic ligation is performed, the goal is almost complete eradication of varices and a safety window of around one month should be opened between the last endoscopic session and initiation of antiangiogenic therapy with atezo-bev or TKIs.

Because of the effect of antiangiogenics on wound healing, atezo-bev and TKIs should not be started in the presence of non-healing or dehiscing wounds, active ulcers, or unresolved bone fractures. There is no evidence of the safe use of atezo-bev or TKIs in patients with proteinuria ≥ 1 g /24 h.

In patients with a contraindication to bevacizumab and TKIs, participation in clinical trials with novel agents is recommended. When clinical trials are not available or for those patients who are not candidates or refuse participation, treatment options like ICIs could be considered under a compassionate use policy but physicians should share with patients the decision of using agents with an unknown benefit (figure 1).

When to switch to second or further line therapies

During treatment with first- or second-line agents and where multiple agents are available, physicians may feel impelled to switch to a different option in the presence of any sign of moderate toxicity or any direct or indirect sign of tumour progression. This, however, may not play in the best interest of the patient. Actually, a number of factors can aid on patient monitoring including the appearance and management of specific AE, changes in AFP levels over time, and imaging evaluation of tumour response.

The decision to interrupt treatment is easy in the presence of life-threatening (CTCAE grade 4) AEs. The mechanism of toxicity should be taken into account when choosing the next therapy in such cases. On the other hand, some AEs are actually indicating a treatment benefit. Such correlation between AEs and positive outcomes has been shown for TKIs like sorafenib (and skin toxicity) [40], lenvatinib (hypertension, diarrhea, proteinuria and hypothyroidism) [41], regorafenib (skin toxicity) [42] and cabozantinib (skin toxicity and hypertension) [43]. Therefore, TKI-induced AEs should

be managed appropriately to reduce their negative impact on HRQoL, and at the same time avoid treatment discontinuation and maximize treatment benefits [44]. Most common AEs related to TKIs are chronic and symptomatic including hand-foot skin reaction, diarrhoea, fatigue, decreased appetite, and weight loss, while ramucirumab is mostly associated with hypertension. ICIs are better tolerated than TKIs and a correlation between immune-mediated AEs and better prognosis has also been suggested [45]. ICIs interruption, steroids and/or other immunosuppressive agents may be needed, and it is still uncertain whether treatment re-challenge could be done with acceptable risks [46,47]. Therefore, appropriate preventive and management strategies should also be employed with ICIs to mitigate tolerability issues and to help distinguish intolerance from inadequate management of AEs.

Another important aspect to consider is that not all progression events are prognostically equal [11]. The pattern of progression to sorafenib impacts prognosis, with new vascular invasion or new extrahepatic lesions being correlated to the worst prognosis [11]. More recently, this has been confirmed for patients treated with ramucirumab [48], and even for locoregional therapies [49]. Although we still lack information about the influence of the pattern of progression on survival after progression to atezo-bev, it seems judicious to extrapolate from all these experiences. Therefore, limited intrahepatic progression may be an insufficient reason to switch from first- to second-line therapy [18]. Clinical decisions should not only consider radiological response but also liver function, general condition and pattern of progression. In regard to ICIs, initial pseudoprogression related to the mechanism of action of this drug class may be misclassified as progressive disease, and progression

should be confirmed after 4 weeks before deciding a treatment switch [50]. Pseudoprogression is rare, occurring in less than 10% of patients across tumour types [51]. Progression in the form of small new lesions that do not grow significantly thereafter do not call for a switch in treatment. AFP responses predict outcome of patients treated with atezo-bev [52], sorafenib [53], regorafenib [54], cabozantinib [55] and ramucirumab [56]. Contrary, increased AFP levels in the absence of radiological should not be taken as an unequivocal sign of tumour progression and lead to treatment discontinuation. In summary, with the help of these aids and sound clinical judgement, clinicians should not switch treatment prematurely to avoid losing sequential treatment benefits and involve the patient in any decision. On the other hand, hyperprogression (a flare-up of tumour growth) may occur in up to 12.7% of patients treated with nivolumab [57] and the occurrence and incidence should be explored during atezo-bev to inform practice.

Treatment recommendations after first-line therapy

Approximately one-quarter to one-third of patients with advanced HCC are eligible for second-line systemic treatment, based on preserved liver function, performance status, and comorbidities [58]. Regorafenib, cabozantinib, and ramucirumab (for patients with AFP ≥400 ng/mL) are widely available and reimbursed. In contrary, nivolumab, pembrolizumab and the combination of ipilimumab and nivolumab are not approved or reimbursed for HCC in several countries and regions (Table 4), as strong scientific evidence of efficacy based on randomised trials is not available. There are no meaningful differences in efficacy between TKIs and ramucirumab given the

comparable HRs for OS. Matching-adjusted indirect comparisons of second-line cabozantinib vs. regorafenib [59] and cabozantinib vs. ramucirumab [60] yield similar OS for any given pair of agents. Other studies have analysed patient outcomes under specific sequences like sorafenib-regorafenib [61], sorafenib-cabozantinib [62], or lenvatinib-other drugs including sorafenib [63]. These are exploratory analyses and straight comparisons between the various sequences cannot be done. Moreover, no data on sequences after atezo-bev are available and therefore one may argue that the hierarchy established before atezo-bev may no longer be maintained.

Besides label issues, this lack of supporting evidence makes it difficult to provide strong recommendations on how to sequence drugs after atezo-bev. Factors to consider when selecting a second-line systemic treatment include patient characteristics and comorbidities, adverse events during first-line treatment, safety profile of second-line agents and associated HRQoL, route and schedule of administration. Contrary, aetiology of the underlying liver disease, tumour stage, and response to prior sorafenib are not useful. If ultimately proven to provide survival benefit, the high ORR reported with the combination of ipilimumab plus nivolumab may favour this option for patients with the kind of progression associated with worse prognosis such as high-burden or extrahepatic disease. Of note, none of the available agents are approved after lenvatinib or atezo-bev and access may be restricted on this basis. Additionally, regorafenib has been tested only in sorafenib-tolerant patients). With the exception of ramucirumab, provision of second-line therapies is not based on predictive biomarkers. The restriction of ramucirumab to patients with AFP ≥400 ng/ml does not mean that this should be the agent of choice for that population. Indeed,

subgroup analyses for the other second-line agents reveal that treatment benefit is similar in patients with high or low AFP levels. Data supporting the use of ramucirumab after bevacizumab are lacking, even if antiangiogenics beyond progression are commonly used in other tumour types as colorectal cancer [64]. In any case, individual preferences should be a key part of the discussion with patients.

Treatment recommendations in special populations.

High-quality data on approved drugs in HCC patients with comorbidities are missing, and medical conditions, such as prior transplant, human immunodeficiency virus (HIV) infection, and haemodialysis pose concrete challenges in daily practice [65]. HCC relapse occurs in 10-16% of liver transplant recipients, a population with an increased incidence of cardiovascular and other comorbidities [66]. A median OS of 12 months (range 1.45-20.1) has been reported with sorafenib along with reassuring safety data [67], and a retrospective study of regorafenib in sorafenib-tolerant patients provided the first rationale for sequential therapy [68]. ICIs are contraindicated in patients with relapsed HCC after liver transplantation. PD-L1 has a key role in the prevention of graft rejection, and PD-1 inhibitors have been implicated in severe rejection leading to death of liver transplant patients [69].

In people living with HIV, HCC represents an increasing cause of morbidity and mortality, and is frequently diagnosed at a younger age and at an advanced stage [70]. Systemic treatments raise significant challenges such as drug-drug interactions, and

potential synergistic toxicity with concomitant antiretroviral therapy [71]. Although evidence is limited to retrospective studies or case reports of sorafenib and regorafenib, efficacy and safety data seem similar to those reported in non-HIV patients [72].

Patients on haemodialysis are at risk of HCC and are often diagnosed with an advanced stage resulting in a poor prognosis [73]. While a phase I study of sorafenib in patients with hepatic or renal dysfunction did not help in drawing specific conclusions for patients with HCC [74], a large European and Latin American retrospective real-world study reported sorafenib efficacy and safety data similar to those in patients without haemodialysis [75]. Furthermore, based on data on renal cell cancer, it seems that sorafenib, nivolumab, and bevacizumab can be safely used in patients undergoing haemodialysis [76]. Importantly, while waiting for dedicated clinical trials, careful monitoring is recommended in these special populations [65].

The safe use of ICIs in patients with coinfection by HBV and HCV or by HBV and HDV has not been established. Nevertheless, there is no strong reason to deny treatment to these patients provided they meet the criteria of being under concomitant treatment with direct antiviral agents against HBV with HBV viral load lower than 100-500 IU/ml. In patients with subtypes such as fibrolamellar and other histologic subtypes including mixed tumours (hepato-cholangiocarcinoma), the recommendation of any specific agent or combination of agents has to be decided on a case-by-case basis since the information is limited and frequently, such tumours have been systematically excluded from recent clinical trials.

Geographic variations in approvals and reimbursements.

Evidence of medical benefit from clinical trials, approval status and reimbursement issues regulate access to medication in general and in systemic therapy of HCC in particular. Accelerated approval may be granted by agencies as a result of persuasive data in surrogate endpoints or intermediate clinical endpoints that are reasonably likely to predict clinical benefit to support drug approval in an unmet clinical need. Validation of benefit should be confirmed after accelerated approval and if benefit is not confirmed, approval may be withdrawn [77]. In fact, the Oncologic Drugs Advisory Committee of the US Food and Drug Administration met in April 2021 to review a number of accelerated approvals for immunotherapy agents where the clinical benefit was not verified in confirmatory trials, including Nivolumab and Pembrolizumab in HCC. The Committee voted 5 to 4 against the continued accelerated approval of nivolumab for the treatment of HCC patients with who were previously treated with sorafenib, and 8 to 0 in favour of the continued accelerated approval of pembrolizumab for the same indication. No further decision has been adopted by the FDA after these recommendations.

In the end, different interpretation of evidence and availability of resources in different health care systems result in significant disparities with respect to available systemic treatment of HCC worldwide. Table 4 lists the approval status as of February 2021 for systemic agents in HCC. Approval does not warrant reimbursement. For instance, cabozantinib is approved in many regions (Australia, European Union, Hong

Kong, Israel, Jordan, Korea, Lebanon, Panama, Peru, Russian Federation, Saudi Arabia, Serbia, Switzerland, Singapore, Taiwan, Turkey, Ukraine, United Arab Emirates, and US) but reimbursed only in a few (Sweden, Germany, Austria, Luxembourg, Netherlands, France, Italy, Lithuania and Russia). In some countries like Spain, none of the second line options are currently reimbursed.

A perspective on clinical trial design and data analysis.

HCC poses a unique challenge on clinical trial design due to the combination of a very heterogeneous, variably aggressive tumour and a similarly heterogeneous chronic liver disease with variably impaired liver function. Anti-tumour efficacy may not be captured in patients with poor liver function and, conversely, it may be overestimated in patients with good liver function and indolent tumours.

The effectiveness of any new agent, alone or in combination, has to be supported by substantial evidence from adequate and well-controlled clinical investigations. As previously mentioned, OS is the only true robust endpoint and surrogates lack adequate validation [13,14]. Yet, OS has some limitations. It might require a long follow-up to capture enough number of events due to improved OS, and it can be affected by downstream therapies with a positive impact on OS. Valid surrogate endpoints are therefore an unmet need.

As known, PFS is a composite endpoint that captures death and evidence of radiological progression. Previous guidelines discouraged PFS due to the competitive risk effect of dying due to the natural history of cirrhosis despite a relevant anti-tumour benefit. This is currently mitigated by restrictive inclusion criteria which only allow recruitment of Child-Pugh A patients without ascites [9]. In such patients, the likelihood of death as a result of liver decompensation (GI bleeding, encephalopathy or infections) is low (around 5% at 1 year [78]). On the other hand, not all progression patterns have the same impact in outcome [16]. At the end of the day, surrogate validation has specific rules that have not been fulfilled in HCC under systemic treatment. Indeed, response and PFs have failed as surrogates for survival in other cancer types [79–81]. The suggested validation of response in the brivanib trial did not show a high correlation and the 95% confidence interval discarded clinical and statistical significance [82]. Suggestions for PFS value have been raised at the trial level and not at the individual level. At the same time, the suggestions for specific cut-offs at the trial level have not considered the inference from the worst bound of the 95% prediction intervals [16]. This would result in a more stringent limit that would likely prevent the recognition of an OS benefit of less magnitude.

Evaluation of tumour growth and remission are also challenging in HCC. Challenges stems from the methods to propose response criteria and their stretched use along the years. Tumour burden reduction or growth criteria were the result of an interobserver agreement study using rubber balls covered by a blanket [83]. This established the cut-offs for the WHO criteria [84], ultimately incorporated into RECIST[85]. At that time systemic therapy was cytotoxic and patient's prognosis was

dismal, as diagnosis was achieved at advanced stage. In such setting, response or stabilization were associated to better outcome, as progression meant death at short term. With earlier diagnosis and sustained disease stabilization being frequently achieved with sorafenib, TTP and PFS were introduced in the assessment of efficacy. At the same time, it was assumed that progression reflects treatment resistance, and thus, requires treatment interruption. However, the RECIST consortium has stressed that they did not advocate the use of TTP or PFS and that progression should not mandate treatment interruption[86,87], an idea accepted under immunotherapy too [50,88].

The validity of the RECIST criteria is controversial in HCC. Effective locoregional treatments induce major tumour necrosis that may not run in parallel with a reduction in tumour diameter [89]. Indeed, necrosis of the surrounding tissue may be read as progression when it could be classified as CR. This primed the development of the EASL criteria [90], later on integrated in modified RECIST (mRECIST) [91]. Both offer the same assessment after locoregional procedures where the goal is to achieve CR or extensive partial response. The key differences with RECIST affect the definition of progression and how should activity be assessed under systemic therapy. In mRECIST, new intrahepatic nodules only determine progressive disease when they exceed 10mm, present arterial contrast enhancement and late wash-out, or show subsequent growth. Tumour washout was not requested for the refined RECIST charter applied in the SHARP trial [92]. However, TTP does not differ between both systems, and mRECIST may simply delay confirmation of progression [3]. At the same time, ORR by mRECIST under agents that induce intense arterial vasoconstriction (TKIs and anti-

VEGF antibodies) may prime an overestimation of response due to the reading of less contrast uptake as necrosis [15]. This does not occur under ICI, but necrosis in such instance is not a frequent observation. Finally, immunotherapy has further complicated imaging evaluation because pseudoprogression due to tumour infiltration by immune cells has to be discarded and response may be highly discordant across tumour sites [93]. As a whole, the use of response evaluation other than RECIST criteria or any parameter as surrogate for OS has to be properly validated in the setting of systemic therapies before it can become widely accepted.

Finally, sustained symptomatic improvement is always a clinical benefit. Regulatory agencies increasingly consider patient reported outcomes as important efficacy endpoints and they should be integrated in any pivotal clinical trial. However, there is need for improvement so that outcomes through PROs are aligned with data from adverse events registration according to CTCAE [94]. At the same time, it would be worth to refine this terminology to that conventionally used and established for liver toxicity [95].

In view of the increasingly high numbers of systemic agents or combinations for the treatment of HCC, a head-to-head comparison and a defined analysis on sequential treatments is unlikely. Biomarker definition of subgroups with the potential of high response rates and/or improved survival is urgently needed and encouraged. Furthermore, the assessment of the role of systemic therapies in stages beyond advanced stage HCC (early and intermediate stage) will be relevant to discover the full potential of systemic agents. Last but not least, the investigation of systemic agents in

previously neglected patient subgroups with poor liver function, comorbidities etc. should be encouraged.

In summary, advances in the field of systemic therapy for HCC emerge at a constant rate and in the near future, these comments and recommendations will have to be updated according to the scientific evidence derived from the currently ongoing investigations.

Tables.

Table 1: Summary of efficacy and toxicity of systemic therapies approved by regulatory agencies for HCC

Study	Accrual period	Treatment line	Sample size	Study arm	Median OS (months)	Median PFS/TTP (months)	ORR (RECIST)	Rate of CTC AEs grade ≥3 for the investigational agent	Subsequent systemic treatment
Multi-targeted tyrosine kinase inhibitors									
SHARP [1]	Mar 05-Apr 06	1L	299 303	Sorafenib Placebo	10.7 7.9	5.5 (TTP) 2.8	2% 1%	HFSR 8%; diarrhoea 8%; fatigue 3.4%	NA
SHARP-AP [96]	Sept 05-Jan 07	1L	150 76	Sorafenib Placebo	6.5 4.2	2.8 (TTP) 1.4	3.3% 1.1%	HFSR 10.7%; diarrhoea 6.0%; fatigue 4%	NA
REFLECT [2]	Mar 13-July 15	1L	478 476	Lenvatinib Sorafenib	13.6 12.3	7.3 (PFS) 3.6	18.8% 6.5%	Hypertension 23%; increased bilirubin 7%; proteinuria 6%	32.6% 38.7%
RESORCE [3]	May 13-Dec 15	2L (post-SOR)	379 194	Regorafenib Placebo	10.6 7.8	3.1 (PFS) 1.5	11% 4%	Hypertension 16%; HFSR 13%; increased bilirubin 11%	NA
CELESTIAL [4]	Sept 13-Sept 17	2L or 3L (post-SOR)	470 237	Cabozantinib Placebo	10.2 8.0	5.2 (PFS) 1.9	4% <1%	HFSR 17%; hypertension 17%; diarrhoea 17%	NA
Antiangiogenic antibodies									
REACH-2 [5]	July 15-Aug 17	2L (post-SOR) & hAFP	197 95	Ramucirumab Placebo	8.5 7.3	2.8 (PFS) 1.6	4.6% 1.1%	Liver failure 18.3%; hypertension 12.7%; bleeding 5.1%	26.9% 28.4%
Immune checkpoint inhibitors (monotherapy)									
Checkmate 459 [19]	Jan 16-May 17	1L	371 372	Nivolumab Sorafenib	16.4 14.7	3.7 (PFS) 3.8	15% 7%	Increased AST 6%; diarrhoea 0.8%; fatigue 0.8%	39% 47%

Keynote 240 [10]	Mar 16-Nov 17	2L (post-SOR)	278 135	Pembrolizumab Placebo	13.9 10.6	3.0 (PFS) 2.8	18.3% 4.4%	Increased AST 13.3%; increased bilirubin 7.5%; increased ALT 6.1%	41.7% 47.4%
Immune checkpoint inhibitors (combinations)									
IMbrave 150 [6,20]	Mar 18-Jan 19	1L	336 165	Atezolizumab & Bevacizumab Sorafenib	19.2 13.4	6.9 (PFS) 4.3	30% 11%	Hypertension 15.2%; increased AST 7.0%; increased ALT 3.6%	36% 52%
Checkmate 040 cohort (Phase II) [25]	Jan 16-Sept 16	2L (post-SOR)	50	Ipilimumab & Nivolumab	22.8m	NA	32%	Hepatitis 20%; rash 6%; diarrhoea/colitis 6%; pneumonitis 6%	NA

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTC: Common Toxicity Criteria; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; NA, not available; NR, not reached; OS, overall survival; PD-1; programmed cell death protein 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; SOR: sorafenib; TTP, time-to-progression.

Table 2: Summary of background of study populations in stratified randomized clinical trials on systemic agents in HCC

Study	Stage	MVI	EHD	ECOG PS	Child-Pugh A	Stratification factors
SHARP [1]	BCLC B (18%) BCLC C (82%)	36%	53%	ECOG 0 (54%) ECOG 1 (38%) ECOG 2 (8%)	98%	Geography (Europe/Australia vs. USA) ECOG PS (0 vs. 1-2) MVI or EHD or both (Present vs. Absent)
SHARP-AP [96]	BCLC B (4.7%) BCLC C (95.3%)	36%	68.7%	ECOG 0 (25.3%) ECOG 1 (69.3%) ECOG 2 (5.3%)	97.3%	Geography (China vs. Taiwan vs. South Korea) ECOG PS (0 vs. 1-2) MVI or EHD (Present vs. Absent)
REFLECT [2]	BCLC B (22%) BCLC C (78%)	23%	61%	ECOG 0 (64%) ECOG 1 (36%)	99%	Geography (Asia-Pacific vs. Western) MVI, EHD or both (Present vs. Absent) Body weight (<60kg or ≥60kg)
RESORCE [3]	BCLC A (<1%) BCLC B (14%) BCLC C (86%)	29%	70%	ECOG 0 (65%) ECOG 1 (35%)	98%	Region (Asia vs. Rest of world) ECOG PS (0 vs. 1) MVI (Present vs. Absent) EHD (Present vs. Absent) AFP (<400ng/ml vs. ≥400ng/ml)
CELESTIAL [4]	BCLC B (9%) BCLC C (91%)	27%	79%	ECOG 0 (52%) ECOG 1 (48%)	98%	Aetiology (HBV vs. HCV vs. others) Geography (Asia vs. Other) MVI or EHD or both (Present vs. Absent)
REACH-2 [5]	BCLC B (17%) BCLC C (83%)	36%	72%	ECOG 0 (57%) ECOG 1 (43%)	100%	Geography (Asia vs. Japan vs. Rest of world) MVI (Present vs. Absent) ECOG PS (0 vs. 1)
Keynote 240 [10]	BCLC B (20.1%) BCLC C (79.9%)	12.9%	70.1%	ECOG 0 (58.3%) ECOG 1 (41.7%)	99.6%	Geography (Asia vs. non-Asia including Japan) MVI (Present vs. Absent)

						AFP (<200 vs. ≥200ng/ml)
IMbrave 150 [6]	BCLC A (2%) BCLC B (15%) BCLC C (82%)	38%	63%	ECOG 0 (62%) ECOG 1 (38%)	100%	Geography (Asia except Japan vs. Rest of world) ECOG PS (0 vs. 1) MVI or EHD (Present vs. Absent) AFP (<400 vs. ≥400ng/ml)
Checkmate 459 [19]	BCLC A (4%) BCLC B (14%) BCLC C (82%)	75% (EHD or MVI or both)		ECOG 0 (73%) ECOG 1 (27%)	100%	Geography (Asia vs. non-Asia) Aetiology (HCV vs. non-HCV) MVI or EHS or both (Present vs. Absent)

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer stage; ECOG PS, Eastern Cooperative Oncology Group performance status; EHD, extra-hepatic disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MVI, macrovascular invasion.

Table 3. Requirements specific to first-line agents considered as inclusion or exclusion criteria in pivotal clinical trials.

ATEZOLIZUMAB + BEVACIZUMAB	**LENVATINIB or SORAFENIB**
Requirements regarding concomitant medications	
Patients with HBV infection should be under antiviral therapy with a viral load < 500 IU/mL	
Patients should not be in need of full-dose anticoagulants or antiaggregants (prophylactic doses are allowed).	Patients should not be in need of anticoagulants, except low molecular weight heparin
Treatment with strong CYP3A4 inducers or chronic daily treatment with a NSAID should be avoided.	
Contraindications based on current or prior acute events or chronic conditions	
Thrombocytopenia with platelets < 75 × 10^9/L Severe chronic hepatitis with AST, ALT > 5 × ULN Renal insufficiency (Creatinine clearance < 50 mL/min) Proteinuria ≥ 1 g /24 h	Thrombocytopenia with platelets < 75 × 10^9/L Severe chronic hepatitis with AST, ALT > 5 × ULN Renal insufficiency (Creatinine clearance < 40 mL/min) Proteinuria ≥ 1 g /24 h
Untreated or incompletely treated gastric or oesophageal varices with high-risk for bleeding (assessed by esophagogastroduodenoscopy within the last 6 months)	Gastric or oesophageal varices that require treatment
Current or past autoimmune diseases, with the following exceptions: hypothyroidism, type 1 diabetes, skin diseases with limited involvement. Any condition that requires chronic systemic immunosuppression. Inhaled or topical steroids and adrenal replacement doses < 10 mg/day prednisone equivalents are usually permitted.	
Inadequately controlled blood pressure Prior history of hypertensive crisis or hypertensive encephalopathy. Chronic heart failure of NYHA class > I, myocardial infarction, or stroke within 3 months. Unstable angina. Unstable arrhythmia Significant vascular disease (including recent peripheral arterial thrombosis) within 6 months	Inadequately controlled blood pressure or the need of >1 antihypertensive medication Chronic heart failure of NYHA class > II, unstable angina, myocardial infarction or stroke within 6 months Arrhythmia requiring medical treatment QTc > 480 ms
Bleeding diathesis or significant coagulopathy Recent GI bleeding or haemoptysis	Bleeding or thrombotic disorders Recent GI bleeding or haemoptysis
Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture	

Populations with unknown benefit	
HBV-HCV coinfection	
HIV infection	HIV infection
ECOG performance status > 1	ECOG performance status > 1
Liver transplantation	Liver transplantation
Child-Pugh class B or C	Child-Pugh class B or C
Current moderate to severe ascites or any history of hepatic encephalopathy	
	HCC with ≥ 50% liver occupation, invasion into the bile duct, or invasion of the main portal branch (only for lenvatinib)
Fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC	
Brain or leptomeningeal metastasis	Brain or leptomeningeal metastasis

Data for Atezolizumab + Bevacizumab were obtained from the Imbrave 150 trial [6] and those for Sorafenib and Lenvatinib from the SHARP [1] and REFLECT [2] trials.

Table 4. Regulatory situation of the different agents approved for HCC worldwide (as of February 2021).

	First Line			**Second Line** (after Sorafenib)					
	Sorafenib	Lenvatinib	Atezolizumab + Bevacizumab	Regorafenib	Ramucirumab	Cabozantinib	Nivolumab	Nivolumab + Ipilimumab	Pembrolizumab
US	X	X	X	X	X	X	*	*	*
EU	X	X	X	X	X	X			
Japan	X	X	X	X	X				
China	X	X	X	X					
Australia	X	X	X	X		X	*		*
Middle East	X	X	X	X	X	X	*	*	*
Southeast Asia	X	X	X	X	X	X	*	*	*
India	X	X		X	X		*		
Russia	X	X	X	X	X	X	*	*	*
South America	X	X	X	X	X	X	*	*	*

X Approval based on positive randomized controlled trials. * Approval based on single-arm trials. For regions, a marked cell represents approval in any country within that region.

Figure legend

Figure 1. Treatment algorithm for HCC candidates to systemic therapy. HCC, hepatocellular carcinoma.

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First Line Therapy

Atezolizumab-Bevacizumab

Sorafenib or Lenvatinib
(if contraindications to atezolizumab- bevacizumab)

Second Line Therapy

Multi-TKI and VEGFR2 inhibitor as per off-label availability

Regorafenib
Cabozantinib
Ramucirumab