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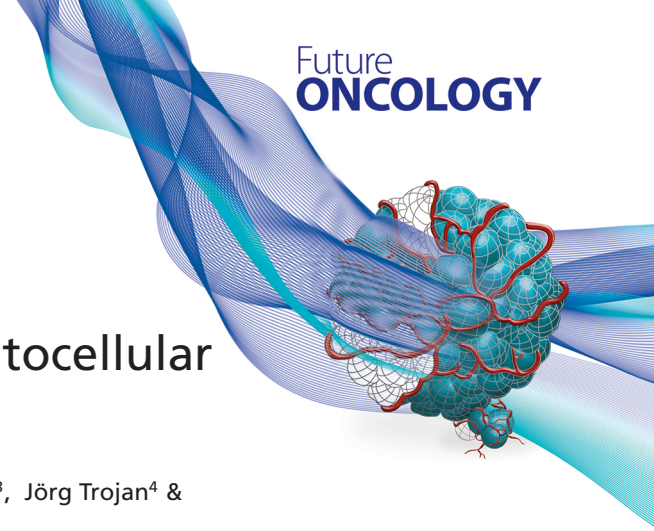

Systemic therapy of advanced hepatocellular carcinoma

Peter R Galle*,[1], Jean-François Dufour[2], Markus Peck-Radosavljevic[3], Jörg Trojan[4] & Arndt Vogel[5]

[1]Department of Internal Medicine, University Medical Center Mainz, 55131, Mainz, Rheinland-Pfalz, Germany
[2]Department of Biomedical Research, University of Bern, Bern, Switzerland
[3]Klagenfurt am Wörthersee Hospital, 3 Internal Medicine & Gastroenterology, Hepatology, Endocrinology, Rheumatology & Nephrology, Klagenfurt, Austria
[4]Hospital of the Goethe University Frankfurt Center of Internal Medicine, Frankfurt am Main, Hessen, Germany
[5]Hannover Medical School, Hannover, Germany
*Author for correspondence: Tel.: +49 061 3117 7275; peter.galle@unimedizin-mainz.de

For a decade, sorafenib remained the only approved first-line treatment and standard of care for advanced hepatocellular carcinoma. The treatment landscape has been evolving rapidly over the past 2 years with the approval of additional first-and second-line systemic treatments, most of which are targeted therapies. The expected approval of immunotherapies constitutes a paradigm shift: for the first time in years, a checkpoint inhibitor in combination with a VEGF antibody recently outperformed sorafenib with regards to efficacy. The wider availability of systemic therapies increases the chance for longer overall survival but raises new questions concerning the role of local options, treatment choice and sequential treatment. Following an expert discussion at the German Cancer Congress 2020 in Berlin, this article aims to summarize the current evidence on and experience of treatment choice and sequence in first- and second-line therapy.

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The past 2 years have seen the approval of numerous targeted first- and second-line therapies for advanced hepatocellular carcinoma (aHCC). Immunotherapeutic concepts are likely to bring about further change in this therapeutic area. These advances pose challenges in real-world clinical practice in terms of treatment choice and optimal sequencing. As a follow-up to a meeting of experts at the 2020 German Cancer Conference in Berlin, these aspects are explored in this article.

For a decade, sorafenib was the only approved first-line treatment and the standard of care in aHCC. However, the treatment landscape is evolving rapidly. For the first time, the combination of a checkpoint inhibitor and a VEGF antibody has outperformed sorafenib with regard to efficacy [1].

A wider variety of systemic therapies provides patients with a better chance of survival. At the same time, the pace of development raises new questions:

1. How will the role of local therapeutic options change?
2. Which first- or second-line therapy is best at the individual patient level, and what is the best treatment sequence?

Given the relative absence of biomarkers in aHCC, real-world treatment choices will have to be informed by other factors. This article aims to provide an overview of available treatments per line of treatment and to provide guidance for sequential therapy based on the latest evidence and practical experience.

Epidemiology & the latest developments

In 2018, almost 23,700 people in Western Europe developed liver cancer (17,300 males and 6400 females) [2], the most common form of which is hepatocellular carcinoma (HCC). The condition mainly affects males with viral, metabolic and/or alcohol-induced cirrhosis of the liver. HCC is the fourth most common cause of cancer death after pulmonary, colorectal and gastroesophageal malignancies [3,4]. The relative 5-year survival rate amounts to approximately 18%. Annual deaths from liver cancer are projected to reach one million by 2030 [4].

The global incidence of hepatitis-related malignancies has declined over the past 3 decades, whereas a continuous increase in liver cancer related to nonalcoholic steatohepatitis has been observed during the same period. The latter trend is probably due to the spread of obesity and diabetes. In Western Europe, the incidence of liver cancer has doubled from 0.14 to 0.28 per 100,000 in men under 30 years of age and has risen from 0.09 to 0.16 per 100,000 among women of the same age group. A significant increase is also evident among men over 60 [5].

Management of HCC

In recent years, important progress has been made in the treatment of HCC. The prognosis of patients with good liver function has improved, mainly due to the availability of new systemic therapies and novel sequential treatment options.

The complexity of HCC demands multidisciplinary patient care, requiring the expertise of (transplantation) surgeons, pathologists, (interventional) radiologists and hepatologists/oncologists. As of October 2020, there are 22 Cancer Society-certified HCC centers in Germany [6]. As well as having to address the given current situation of a patient, a therapeutic concept must anticipate potential outcome, including relapses, progression and treatment failure. The underlying liver condition should be treated wherever possible. Multimodal treatment promises the best results, but continual review and reappraisal of the treatment strategy is imperative.

Staging-led therapy

70–80% of all cases of HCC are attributable to cirrhosis, which in most cases is accompanied by hepatic impairment. Complications such as bleeding esophageal varices, ascites and hepatic encephalopathy contribute to high mortality and morbidity in the patient population. Key risk factors for development of cirrhosis and hence for HCC are [7] as follows:

- chronic alcohol abuse;
- chronic hepatitis B (HBV) or hepatitis C (HCV) virus infection;
- nonalcoholic steatohepatitis.

Various scores such as the gender, age, alpha fetoprotein L3, alpha fetoprotein, des-carboxy-prothrombin (GALAD) score have been developed for better assessment of the HCC risk in patients with chronic liver disease. In addition to the a AFP assay, the GALAD score uses AFP-L3 (lectin-reactive a-fetoprotein) and DCP (des-gamma-carboxy prothrombin) as parameters [8].

The staging system most commonly used in clinical studies as well as the real world is the Barcelona Clinic Liver Cancer System (BCLC), which classifies patients into four stages depending on tumor burden, liver function (Child–Pugh score) and overall health. The pathological diagnosis is based on the tumor–node–metastasis (TNM) classification and staging according to UICC (Union for International Cancer Control) criteria [9–11].

The European Association for the Study of the Liver (EASL) and European Society for Medical Oncology (ESMO) recommendations can be consulted for guidance on treatment decisions [9,10] (Figure 1). In addition, the updated version of the German S3 guideline on the treatment of liver cancer is expected to be published soon.

In addition, over the next years, several clinical trials will mature, investigating the role of systemic therapies such as neoadjuvant and adjuvant approaches in early stages as well as combinations with transarterial chemoembolization (TACE) in intermediate stages. Although initial attempts have yielded negative results, the availability of new treatment options has rekindled hope.

Stage BCLC B: switching from TACE to systemic therapy

TACE is the treatment of choice for tumors confined to the liver, with a maximum diameter of 8 cm and not more than four nodules in BCLC stage B. Various scores provide assistance in selecting eligible patients. The HAP (hepatoma arterial-embolization prognostic) score for instance can be used to estimate the likely benefit of TACE in terms of overall survival (OS) based on liver function and tumor burden [12,13].

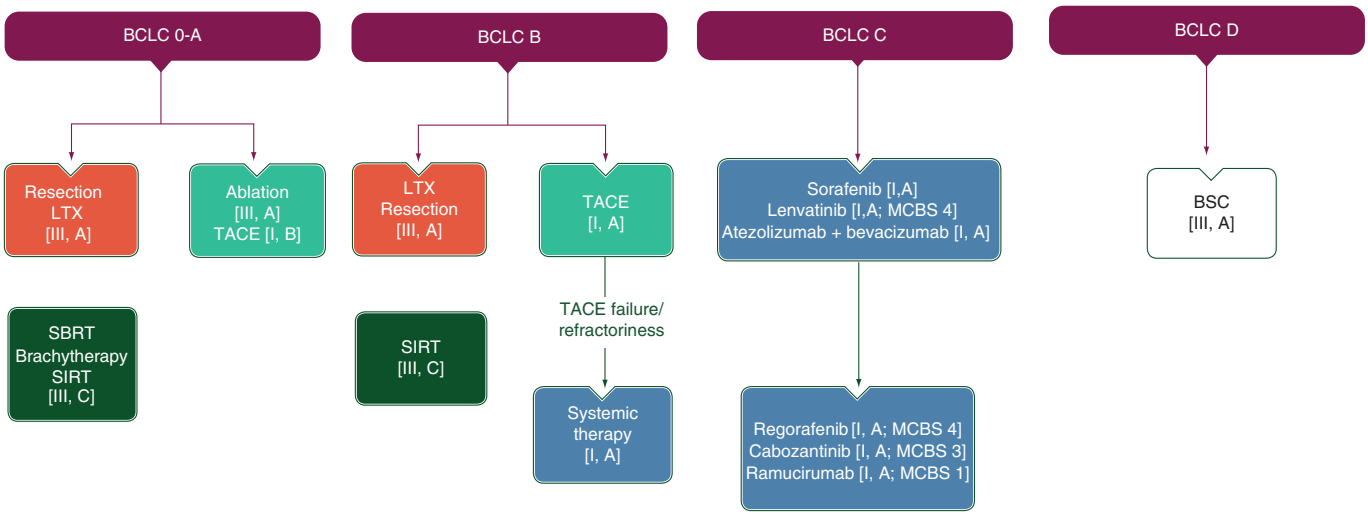


Figure 1. Treatment algorithm by European Society for Clinical Oncology.
BCLC: Barcelona Clinic Liver Cancer; BSC: Best supportive care; EMA: European Medicines Agency; HCC: Hepatocellular carcinoma; LTX: Liver transplantation; MCBS: ESMO-Magnitude of Clinical Benefit Scale; SBRT: Stereotactic body radiotherapy; SIRT: Selective internal radiotherapy; TACE: Transarterial chemoembolisation.
Modified based on [10].

TACE was established 20 years ago at a time when there was no alternative for people with advanced tumors. In the absence of effective systemic treatment options, this resulted in TACE increasingly being used in patients for whom it was not necessarily suited. However, because effective systemic therapies are now available, it is time to revisit TACE's role, especially as it may be linked to impairment of liver function. To complicate matters, several different techniques are available, and the role of cytotoxic drugs is controversial [14].

In addition to rigorous selection of patients for TACE, another important factor is the appropriate time to discontinue local therapies. Both treatment response to TACE and deterioration of liver function are key decision-making criteria: patients with no objective response to treatment after the second TACE have a significantly shorter OS than patients who achieve deep remission. Hence, scrutiny should be exercised before readministering TACE, particularly beyond a second administration [15].

The decision of when TACE therapy should be interrupted is complex. In recent years, several scores have been proposed to guide the retreatment decision (e.g., assessment for retreatment [ART] score with TACE) [16]. According to the EASL guidelines, "their applicability is controversial and such scoring systems probably identify patients who were poor candidates for TACE at baseline, as defined in these guidelines" [9].

Stage BCLC B–C: systemic therapy

First-line treatment

Sorafenib

Sorafenib was the first targeted therapy to show efficacy in patients with aHCC. This multitarget tyrosine kinase inhibitor (TKI) targets VEGF receptor, PDGF receptor, RAF and several other tyrosine kinases. On the basis of a double-blind randomized controlled clinical trial (SHARP; n = 602) and the Asia-Pacific study, sorafenib was the undisputed standard of care in advanced stages for a decade.

The pivotal trial was conducted mainly in European patients (87.5%), approximately one-third of whom had HCC related to hepatitis C. More than half had an Eastern Cooperative Oncology Group performance score (ECOG-PS) score of 0 (54%), almost all had good liver function (Child–Pugh A) and more than 80% were in BCLC stage C. Approximately half of the patient population had extrahepatic metastasis (EHD) and 70% had microvascular invasion (MVI) [17].

Sorafenib treatment significantly extended the mOS of patients in comparison with placebo (10.7 vs 7.9 months; HR = 0.69; 95% CI: 0.55–0.87; $p < 0.001$). Sorafenib treatment benefit was furthermore unrelated to ECOG-PS, MVI or EHD status. The objective response rate (ORR) was low (2%) [17]. Similar results were reported in the Phase III Asia-Pacific study conducted mainly in patients with hepatitis B [18].

Clinical factors predictive of better sorafenib response include chronic hepatitis C infection, a low neutrophil to lymphocyte ratio and liver-confined disease [19,20].

Analysis of GIDEON, a prospective registry study in 3202 patients, suggested that sorafenib could be used to treat Child–Pugh B HCC with no major increase in side effects. However, given the poorer prognosis of patients and in the absence of a proven survival benefit from sorafenib treatment, caution should be exercised when using the TKI to treat individuals with uncompensated cirrhosis [21,22].

The PROSASH score can be used to predict the OS of a patient treated with sorafenib: it considers vascular invasion, age, ECOG-PS, alkaline phosphatase (AP), albumin, creatinine, AST, extrahepatic metastasis and the etiology. An associated online tool calculates the likely OS rate at 6, 12, 24 and 36 months [23,24].

Lenvatinib

After multiple failed studies, lenvatinib was the first drug to show noninferiority to sorafenib with regard to OS (primary end point) in the randomized, open-label, Phase 3 REFLECT trial in 2017. Importantly, this multitarget TKI inhibits FGF receptor, KIT and RET as well as VEGF and PDGF receptor. The study was conducted mainly in Asian patients, all of whom had good liver function (Child–Pugh A); 79% of participants had BCLC stage C disease. In addition, the majority of participants had an ECOG-PS score of 0 (63%), approximately 60% had EHD and about 20% had MVI (with portal vein invasion at the main portal branch and more than 50% liver involvement being exclusion criteria). AFP levels were below 200 ng/ml in 57% of patients [25].

Although lenvatinib was statistically noninferior to sorafenib with regard to OS (13.6 vs 12.3 months; hazard ratio [HR]: 0.92; 95% CI: 0.79–1.06; upper boundary for noninferiority set at 1.08; noninferiority observed across all subgroups). In contrast to the OS results, the TKI was significantly superior to sorafenib with regard to key secondary end points. Investigator-assessed median progression-free survival (PFS) as measured by mRECIST criteria was extended from 3.7 to 7.4 months under lenvatinib (HR: 0.66; 95% CI: 0.57–0.77; $p < 0.0001$). Time to progression (TTP) was 7.4 vs 3.7 months. In nominal terms, these results were consistently better than in the sorafenib SHARP trial, which, however, was not a global study and was mainly conducted in Asian patients [25].

Lenvatinib also significantly outperformed sorafenib in terms of ORR (24.1% vs 9.2%; odds ratio [OR]: 3.13; 95% CI: 2.15–4.56; $p < 0.0001$). This benefit was confirmed by independent review based both on mRECIST and RECIST 1.1 criteria [25].

The most common all-grade adverse events (AEs) included hypertension (42%), diarrhea (39%), reduced appetite (34%) and weight loss (31%) in the lenvatinib arm and hand–foot syndrome (52%), diarrhea (46%), hypertension (30%) and loss of appetite (27%) in the sorafenib arm. At 75% and 67%, respectively, the incidence of grade ≥3 AEs was similar in both arms, with hypertension (lenvatinib vs sorafenib: 23% vs 14%), diarrhea (4% in each arm), reduced appetite (5% vs 1%) and weight loss (8% vs 3%) predominating. Patients receiving lenvatinib benefited from a significantly lower incidence of hand–foot syndrome (3% vs 11%); 9% vs 7% of patients discontinued the study due to treatment-emergent AEs [25].

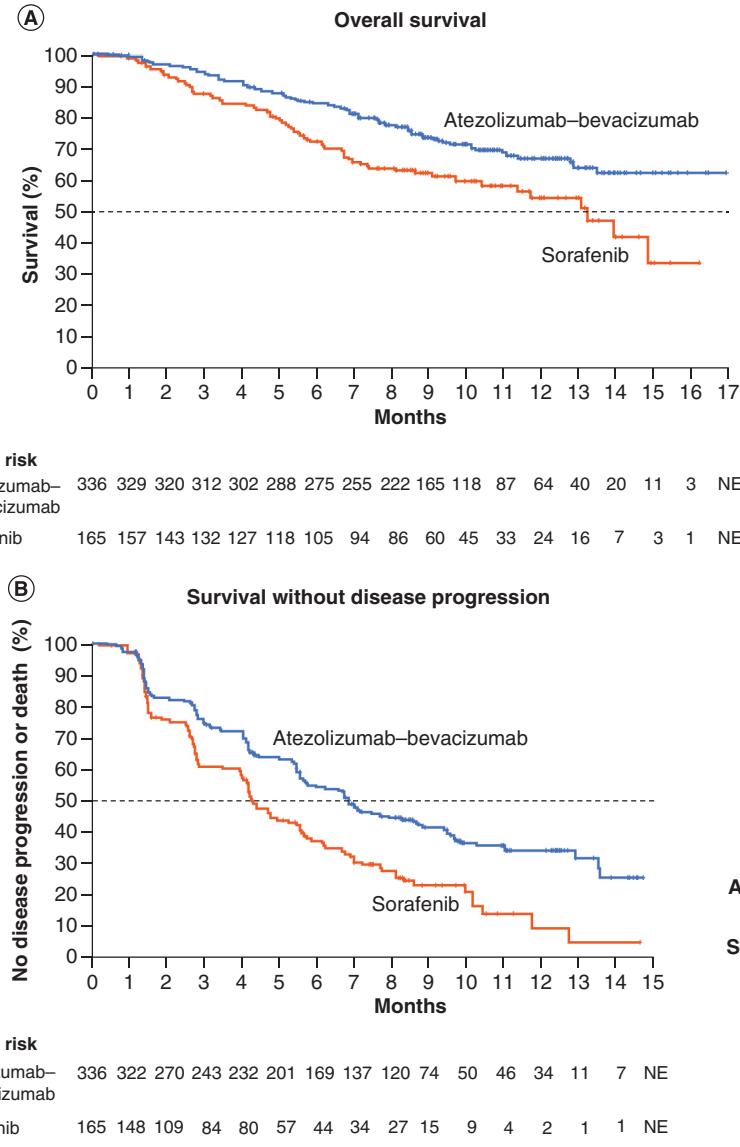
Patient health-related quality of life (HRQoL) worsened in both arms; however, HRQoL deterioration due to symptoms such as pain and diarrhea was less pronounced in patients receiving lenvatinib than in patients receiving sorafenib [26].

For the first time, a retrospective analysis of the REFLECT study enabled investigation of the relevance of treatment response during systemic therapy in a large patient population. Patients achieving partial or complete response during treatment (lenvatinib, n = 115 and sorafenib, n = 44) had an mOS of 22.4 months, whereas nonresponders had an mOS of 11.4 months (HR = 0.61; 95% CI: 0.49–0.76). Importantly, these results confirmed observations that had previously been made in small patient populations only [27,28].

Liver function status at baseline is a well-described prognostic factor. However, a *post hoc* analysis of the REFLECT trial showed that in the lenvatinib arm even patients with poor liver function at baseline benefited versus sorafenib [29].

Atezolizumab + bevacizumab

The IMbrave150 study was the first study in which sorafenib was outperformed in terms of OS. The atezolizumab–bevacizumab combination addresses both (re)activation of immune response to tumor cells and angiogenesis. Preclinical data furthermore indicate that bevacizumab is not only antiangiogenic but also immunomodulatory in its effects in that it reduces VEGF-mediated immunosuppression and improves cancer immunity [30].



	No. of events/ No. of patients (%)	Median overall survival (95% CI) month	Overall survival at 6 month (%)
Atezolizumab–bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4–NE)	72.2

Stratified hazard ratio for death: 0.58 (95% CI: 0.42–0.79)
p < 0.001

	No. of events/ No. of patients (%)	Median progression-free survival (95% CI) month	Progression-free survival at 6 month (%)
Atezolizumab–bevacizumab	197/336 (58.6)	6.8 (5.7–8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0–5.6)	37.2

Stratified hazard ratio for progression or death: 0.59 (95% CI: 0.47–0.76)
p < 0.001

Figure 2. Overall and progression-free survival in the IMbrave150 study.
Mo: Months; NE: Not evaluable.
Modified based on [1].

Initial headline data of a randomized, open-label Phase III trial were presented at ESMO Asia 2019. The anti-VEGF checkpoint inhibitor (CPI) combination was compared to sorafenib in patients with locally advanced or metastatic HCC (n = 501). Only patients with Child–Pugh A cirrhosis were eligible to participate: 81.5% had BCLC stage C disease, 62% had an ECOG-PS score of 0 and 75% had EHD and/or MVI; 62% of participants had AFP levels below 400 ng/ml. HCC patients with autoimmune diseases or immunodeficiency, immunomodulatory therapy, chronic NSAID use, concomitant hepatitis B or C infection or untreated esophageal varices within 6 months before treatment initiation were excluded from the trial. Coprimary end points were OS and PFS [1].

After a median follow-up of 8.6 months, median OS had not yet been reached in the atezolizumab–bevacizumab arm, whereas in patients receiving sorafenib, median OS was 13.2 months (HR: 0.58; 95% CI: 0.42–0.79, p < 0,001). Furthermore, participants treated with the combination remained progression-free for a median of 6.8 months, compared with 4.3 months in the sorafenib arm (HR: 0.59; 95% CI: 0.47–0.76; p < 0.001) (Figure 2) [1].

In this very early analysis with only a small number of events, OS and PFS results were consistent across most of the investigated subgroups; however, the final analysis is yet to be published [1].

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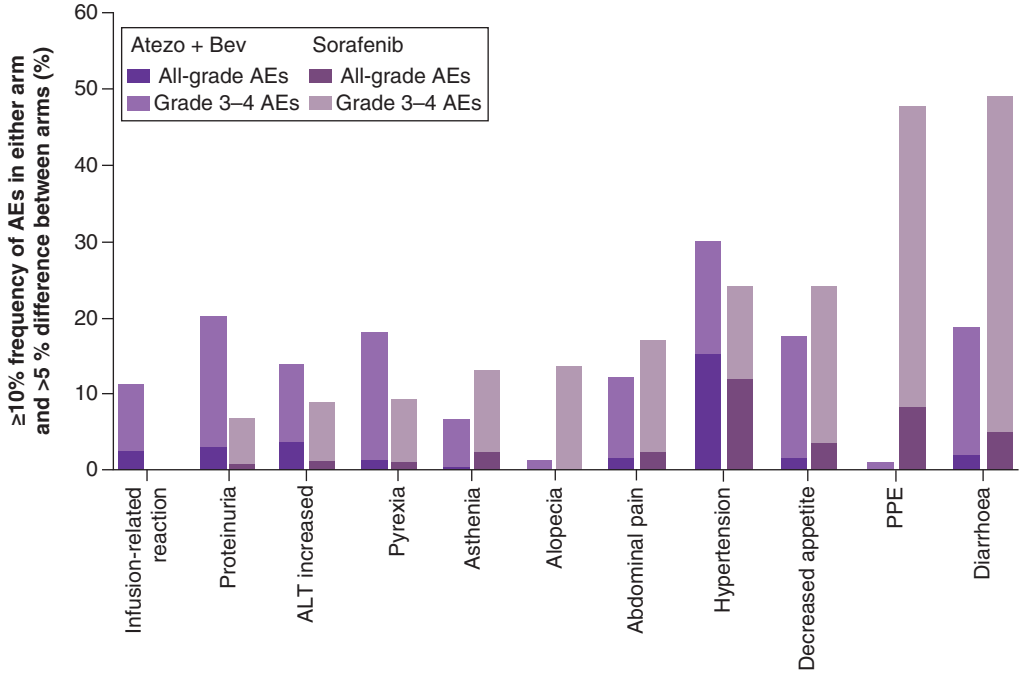

Figure 3. Tolerability in the IMbrave150 study.
AE: Adverse event; Atezo: Atezolizumab; Bev: Bevacizumab; PPE: Palmar-plantar erythrodysesthesia syndrome.
Modified based on [1].

More than twice as many patients in the interventional arm responded to therapy (ORR as per independent review using RECIST 1.1 criteria: 27% vs 12%, $p < 0.0001$; ORR as per mRECIST: 33% vs 13%, $p < 0.0001$). 18 patients (6%) receiving atezolizumab plus bevacizumab achieved complete response and 71 (22%) achieved partial response, compared with 0 and 19, respectively, receiving sorafenib (12%) [1].

Both all-grade AEs and grade 3–4 AEs were similar in both arms, however, treatment in the combination arm went on for considerably longer and the nature of side effects was very different. With regards to the side effects shown in Figure 3, the combination therapy was tolerated significantly better compared with sorafenib. In the atezolizumab–bevacizumab arm, the most common side effect was hypertension; 16% of patients discontinued treatment with either agent and 7% discontinued treatment altogether. In comparison, 10% of patients receiving sorafenib discontinued treatment due to side effects [1].

To minimize the bleeding risk from bevacizumab, esophageal varices were treated before the initiation of therapy. The incidence of bleeding amounted to approximately 20% in both arms and was therefore manageable [1].

The combination also outperformed sorafenib with regard to patient-reported outcomes. At the 2020 Gastrointestinal Cancers Symposium, a prespecified analysis of the IMbrave 150 study showed that clinically meaningful worsening of overall patient HRQoL (11.2 vs 3.6 months; as measured by the EORTC QLQ-C30 questionnaire), role functioning and physical functioning was slower in patients receiving atezolizumab plus bevacizumab and that key symptoms occurred later. In addition, symptoms such as loss of appetite, diarrhea, fatigue, jaundice and pain were less common in the combination arm [31].

Nivolumab

Single-agent CPIs have not significantly prolonged OS in aHCC to date. The Phase III CheckMate 459 study only showed a trend in favor of nivolumab in terms of mOS extension versus sorafenib (16.4 vs 14.7 months, HR: 0.85; 95% CI: 0.72–1.02; $p = 0.0752$). Importantly, however, mOS exceeded 14 months in both arms – a significant achievement for this indication. Nivolumab furthermore doubled the ORR in comparison with sorafenib (15% vs 7%) [32].

First-line treatment decisions

All three first-line therapies (data summarized in Table 1) were evaluated predominantly in patients with good

Table 1. Selected study results of first-line therapies in advanced hepatocellular carcinoma.

End point	Atezolizumab + bevacizumab vs sorafenib (n = 501)†	Lenvatinib vs sorafenib (n = 954)‡	Sorafenib vs placebo (n = 602)§
OS (median, months), [HR; p-value]	NA vs 13.2 [0.58; 0.0006]	13.6 vs 12.3 [0.92; not inferior]	10.7 vs 7.9 [0.69; 0.001]
PFS (median, months) [HR; p-value]	6.8 vs 4.3 [0.59; <0.001]	7.4 vs 3.7 [0.66; <0.0001]	Not studied
ORR (%)	27.3 vs 11.9	24.1 vs 9.2	
CR	5.5 vs 0	1 vs <1	0 vs 0
PR	21.8 vs 11.9	23 vs 9	2 vs 1
SD	46.3 vs 43.4	51 vs 51	71 vs 67
Duration of response (median, months)	NA vs 6.3		

CR: Complete response; NA: Not achieved; ORR: Overall response rate; OS: Overall survival, PFS: Progression-free survival; PR: Partial response; SD: Stable disease.
†Data taken from [1].
‡Data taken from [25].
§Data taken from [17].

overall health and good liver function, the majority of whom had BCLC stage C disease [1,17,25]. The REFLECT study had the largest proportion of Asian participants (approx. 70%) [24]. Regardless of the treatment choice, blood pressure should be managed at initiation or adjusted during treatment if necessary. Liver function status is essential in determining whether patients are eligible for systemic first-line therapy. On the basis of the studies performed, all patients with Child–Pugh A cirrhosis are eligible.

For the first time in more than a decade, the anti-VEGF-checkpoint inhibitor combination significantly prolonged OS in aHCC versus sorafenib. The ORR of 27% might deliver additional benefit in particular to patients with a high tumor burden. Moreover, the combination is considerably less toxic and has less of an impact on patient HRQoL [30]. This is why experts believe approval of the atezolizumab–bevacizumab combination will establish a new standard of care in first-line treatment of this indication.

Given the exclusion criteria in the IMbrave150 study and the mechanism of action underlying immunotherapy, aHCC patients with autoimmune diseases should not receive atezolizumab + bevacizumab. The same is true for patients whose aHCC has relapsed after a liver transplant. To reduce the bleeding risk, eligible patients should undergo endoscopic staging of esophageal varices before initiation of treatment. Appropriate therapy is required before initiating treatment in individuals with clinically significant varices (grade ≥2) [33].

Combination therapy is administered by infusion every 3 weeks. While encouraging good adherence, this means patients need to be sufficiently mobile.

Therapy with a CPI requires careful, long-term patient monitoring, given the risk of potential immune-related side effects because these may occur even after the discontinuation of treatment [34]. Continuous monitoring of laboratory findings – in particular, monitoring of liver function and glucose levels – is recommended during treatment. Close monitoring for potential proteinuria is also advised.

Sorafenib and lenvatinib monotherapies are alternative treatment options where the combination therapy with atezolizumab + bevacizumab is contraindicated. Both drugs are taken orally either once (lenvatinib) or twice a day (sorafenib). This is convenient for patients but also gives them sole responsibility for adherence. Before starting TKIs, careful weighing of the risks as well as benefits is required in individuals with a history of aortic aneurysm. Concomitant use of CYP3A4 inducers should be avoided during therapy [35,36].

Favorable data on the secondary end points PFS, TTP and ORR may be clinically relevant and an argument for the use of lenvatinib. The ORR of 24% observed in the REFLECT trial might be advantageous in certain situations – for instance, if a tumor site in the hepatic hilum is interfering with liver function. However, it is also important to be aware that patients with very advanced disease, including tumor occupation of more than half of the liver, were excluded from the pivotal trial, as were individuals with portal vein invasion at the main portal branch [25].

There are a number of indications demonstrating that lenvatinib may be associated with an increased incidence of hepatic encephalopathy in patients with major portal hypertension. Patients should therefore be informed accordingly [36].

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Table 2. Target structures of tyrosine kinase inhibitor/antibodies approved for advanced hepatocellular carcinoma.

Line	Drug		VEGF	PDGFR	RAF	FGFR	KIT	RET	TIE-2	MET	AXL
1st	Sorafenib	TKI	X	X	x						
1st	Lenvatinib	TKI	X	X		X	X	X			
2nd	Regorafenib	TKI	X	X	X	X		X	X		
2nd	Cabozantinib	TKI	X							X	X
2nd	Ramucirumab	TKI	X								

mAB: Monoclonal antibody; TKI: Tyrosine kinase inhibtor.

Many years of experience with sorafenib have ultimately resulted in optimization of treatment. Noninterventional trials such as the Gideon trial have improved our understanding of side effects and efficacy [21]. Preemptive therapy of hand–foot–skin reactions and monitoring during treatment for the onset of hypoglycemia and bleeding are of great importance [35].

Gastrointestinal problems, mainly diarrhea, can occur with both TKIs [17,25]. Data from a *post hoc* analysis of the REFLECT trial indicate that certain side effects such as hypertension, diarrhea, proteinuria and hypothyroidism during lenvatinib therapy were associated with a longer OS [37]. Similar data exist for sorafenib, where it has been suggested that hand–foot syndrome may also be an indicator of a better OS. Onset of hypertension in the first 2 weeks of sorafenib treatment has furthermore been associated with a better PFS and onset of diarrhea seems to be predictive of a good response to sorafenib [38,39].

Effective side effect management is important for successful treatment, irrespective of the line of treatment. Skin toxicities, hypertension and diarrhea in particular need to be addressed proactively as part of the treatment concept in multitarget TKI therapy. On the basis of observations to date, dose reductions do not seem to have a negative impact on OS during treatment with sorafenib [40]. Very close monitoring of patients with cardiac impairments is imperative during treatment with both TKIs and bevacizumab.

Second-line treatment

Three drugs are currently approved for the second-line treatment of aHCC; these have previously shown benefits in patients pretreated with sorafenib in placebo-controlled trials. Again, only patients with good liver function (Child–Pugh A) and good ECOG-PS (0–1) were enrolled. Regorafenib and cabozantinib are TKIs that primarily target VEGF receptors but also have other target structures; ramucirumab is a monoclonal antibody directed against VEGFR-2 (Table 2 based on [35,36,41–43]).

Regorafenib

Regorafenib target structures in addition to VEGFR include PDGFR, RAF, FGFR, RET, KIT, TIE-2 and others. This multitarget TKI was evaluated in the randomized, double-blind, placebo-controlled, Phase III trial RESORCE (n = 573). Inclusion criteria comprised intact liver function (Child–Pugh A) and progression on adequately tolerated prior sorafenib treatment. More than 60% of patients had an ECOG-PS of 0; more than 80% had MVI or EHD, 44% had AFP levels of ≥400 ng/ml and 87% of participants had BCLC stage C disease [44].

Regorafenib treatment resulted in a significant extension of the mOS relative to placebo from 7.8 to 10.6 months (primary end point; HR: 0.63; 95% CI: 0.50–0.79; $p < 0.0001$). Median PFS as measured by mRECIST criteria was 3.1 versus 1.5 months (HR: 0.46; 95% CI: 0.37–0.56; $p < 0.0001$). TTP was also significantly prolonged in favor of regorafenib (3.2 vs 1.5 months; HR: 0.44; 95% CI: 0.36–0.55; $p < 0.001$). The ORR was 10.6% versus 4.1% ($p = 0.005$), and the tumor control rate amounted to 65.2% versus 36.1% ($p = 0.001$). An efficacy benefit was observed in all subgroups [44].

The most common grade 3–4 AEs in the intervention arm were hypertension (15%), hand–foot syndrome (13%), fatigue (9%) and diarrhea (3%). One in ten patients in the intervention arm and 4% in the placebo arm discontinued treatment due to side effects. The most common reasons for treatment discontinuation were hand–foot syndrome and increased aminotransferase levels. Similar to first-line sorafenib, the occurrence of hand–foot syndrome while receiving regorafenib correlated with a better OS [45].

Cabozantinib

Cabozantinib does not only inhibit VEGF receptor, RET, KIT and FLT3 but also Tyro3, Mer, MET and AXL, which have previously been associated with resistance to sorafenib [46]. The multitarget TKI was evaluated in the randomized, double-blind, placebo controlled, Phase III trial CELESTIAL in patients with progression of unresectable HCC following at least one prior systemic treatment with sorafenib (n = 707). Three-quarters of patients were non-Asian, 53.5% had an ECOG-PS of 0, 78% had EHP and approximately one-third had MVI (84.5% had both). Cabozantinib was the third line of systemic treatment for about one-quarter of the participants [47].

Cabozantinib significantly extended mOS versus placebo (primary end point; 10.2 vs 8.0 months HR: 0.76; 95% CI: 0.63–0.92; p = 0.005) and significantly improved PFS as well (secondary end point; median 5.4 vs 1.9 months; HR: 0.44; 95% CI: 0.36–0.52; p < 0.001). The ORR as measured by RECIST 1.1 criteria was 4% versus 0.4%. Furthermore, the disease control rate (DCR) was 64% in patients receiving cabozantinib – almost twice as high as in the placebo arm (33.4%; p < 0.001) [47].

Data from a *post hoc* analysis indicate that the OS benefit was greater the earlier patients received cabozantinib (second line vs later lines: 11.3 vs 7.2 months; HR: 0.70; 95% CI: 0.55–0.88) [47]. An additional analysis of the CELESTIAL study produced similar results; here, cabozantinib was efficacious irrespective of ALBI (albumin-bilirubin) grades. Median OS was 17.5 months in patients with ALBI grade 1 versus 8.0 months in patients with ALBI grade 2; however, this analysis was not set up to compare efficacy in subgroups stratified by ALBI grade [48]. Time on previous treatment (with sorafenib) had no effect on either OS or PFS in the cabozantinib arm [47].

Grade 3–4 side effects occurred in 68% of patients treated with cabozantinib, the main toxicities being hand–foot syndrome (17% vs 0%), hypertension (12% vs 2%), AST level elevation (12% vs 7%), fatigue (10% vs 4%) and diarrhea (10% vs 2%). The most common reasons for treatment discontinuation (16%) were hand–foot syndrome, fatigue and gastrointestinal problems [47].

Quality-adjusted time without symptoms and toxicity (Q-TWiST) was measured in a retrospective analysis [49]. This method enables an assessment of the benefit–risk ratio of a treatment in the absence of HRQoL data: the relationship between survival benefit and HRQoL being the main interest [50]. Three factors were analyzed: time with grade 3/4 toxicity before progression (TOX), time without grade 3/4 toxicity before progression (TWiST) and survival time after progression or relapse (REL). The analysis showed that patients with aHCC receiving second-line cabozantinib after sorafenib spent significantly more time without disease symptoms and toxicity than those receiving placebo (110.9 vs 78.1 days), despite an increase in days with grade 3/4 toxicity before progression (49.8 vs 9.8 days) [49].

Ramucirumab

Ramucirumab is a monoclonal antibody that is directed against VEGFR-2 and administered by infusion. In the randomized Phase III trial REACH-2 it was compared with placebo in patients whose disease had progressed on or who were unable to tolerate sorafenib. Participants were required to have an unfavorable prognosis as characterized by AFP levels ≥400 ng/mL. Approximately one-third of patients had MIV and about three-quarters had EHD [51].

Median OS was 8.5 versus 7.3 months favoring ramucirumab (primary end point; HR: 0.71; 95% CI: 0.53–0.95; p = 0.0199). The antibody also significantly extended median PFS (secondary end point; 2.8 vs 1.6 months; HR: 0.452; 95% CI: 0.40–0.60; p < 0.0001) [51]. Pooled analysis of REACH-1 and REACH-2 study data confirmed the OS benefit for ramucirumab (8.1 vs 5.0 months; HR: 0.69; 95% CI: 0.57–0.84; p = 0.0002) [52].

Ramucirumab had a more favorable tolerability profile than the TKIs. With regard to grade ≥3 AEs, only hypertension (13% vs 5%), hyponatremia (6% vs 0%) and increased aspartate aminotransferase (3% vs 5%) were more common in the intervention arm than in the placebo arm [51]. Furthermore, pooled analysis of patient-level data from the REACH-1 and REACH-2 studies (same inclusion criteria with AFP levels ≥400 ng/mL, same study design) showed that symptoms such as nausea, fatigue and weight loss worsened later than on placebo [52].

A *post hoc* analysis indicated that liver function correlated with OS in the ramucirumab arm. Patients with ALBI grade 1 lived considerably longer than those with ALBI grade 2 (ramucirumab: 11.4 vs 5.8; placebo: 6.6 vs 4.2 months). Furthermore, a trend toward a better response to ramucirumab was observed in patients with intact liver function [53].

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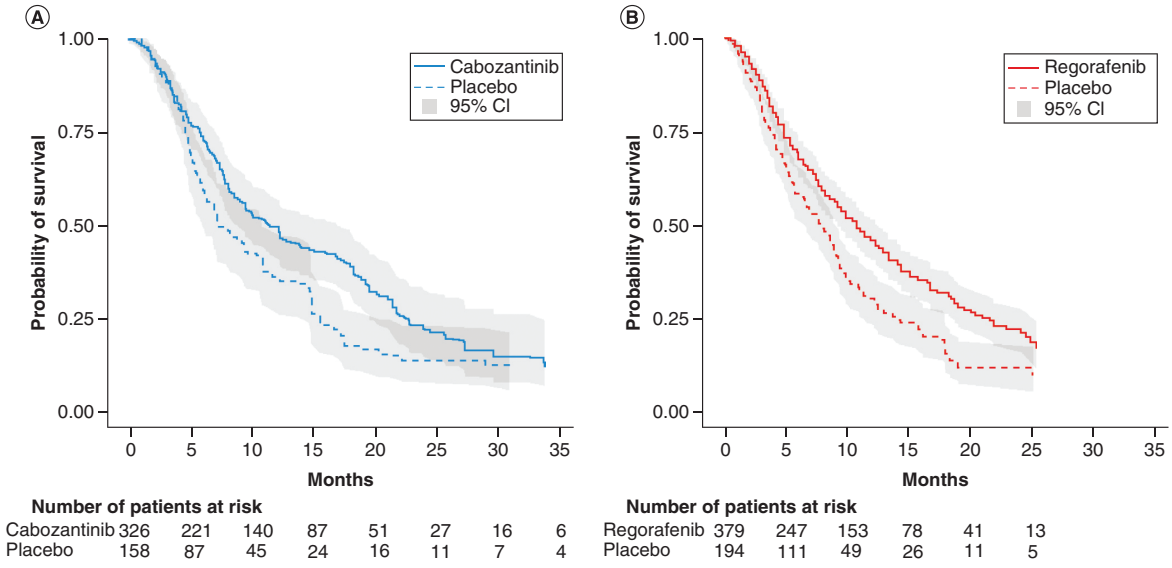

Figure 4. Indirect comparison of patient data listings from Phase III studies of cabozantinib and regorafenib in advanced hepatocellular carcinoma (second line).
Modified based on [55].

Sorafenib

Sorafenib is approved for the treatment of HCC across BCLC stages and treatment lines [35], which may be relevant for sequential treatment and reimbursement. Importantly, second-line efficacy has never been formally demonstrated.

Second-line treatment decisions

As in the first line, the primary goal of second-line aHCC treatment is the extension of OS while maintaining patient quality of life. Unlike in the first line, however, no head-to-head studies evaluating the different treatment options exist; all three agents have been compared with placebo only. Regorafenib and cabozantinib are oral therapies, whereas ramucirumab is administered intravenously.

Several parameters for treatment decision-making have emerged from the pivotal trials. Regorafenib is approved for all HCC patients who have previously received sorafenib [41]. However, the TKI has only ever been studied in patients who had *tolerated* a prior 4-week therapy with ≥400 mg sorafenib [52]. Regorafenib's benefit was unrelated to baseline AFP levels [54].

Regorafenib is an oral therapy comprising four tablets once a day for 3 weeks followed by a 1-week break. Tablets are ingested after a light meal (<600 calories and <30% fat) [41].

Cabozantinib has been studied in patients whose prior sorafenib treatment was discontinued either because of disease progression or because of intolerable toxicity [47].

Results of an indirect comparison of patient-level data from Phase III studies suggest that median PFS may be significantly longer with second-line cabozantinib than with second-line regorafenib (5.6 vs 3.2 months; 95% CI: 4.90–7.26; $p < 0.05$). mOS was not significantly longer (11.4 vs 10.8 months; Figure 4) [55]. It should be noted, however, that interstudy comparisons of disparate studies have various weaknesses.

In comparison with placebo, cabozantinib improved outcomes across a range of baseline AFP levels. AFP response and control rates were higher with cabozantinib than with placebo and were associated with longer OS and PFS [56]. Cabozantinib's efficacy as a second-line treatment was not dependent on the duration of the previous sorafenib therapy; however, the OS tended to be longer if sorafenib had been administered over extended periods of time (up to 6 months) [47].

In the CELESTIAL trial, the incidence of side effects was high, resulting in cabozantinib dose reductions or treatment discontinuation [47]. However, patient HRQoL in the cabozantinib arm was similar to that observed in the placebo arm [49].

Cabozantinib is taken once a day as a tablet [42].

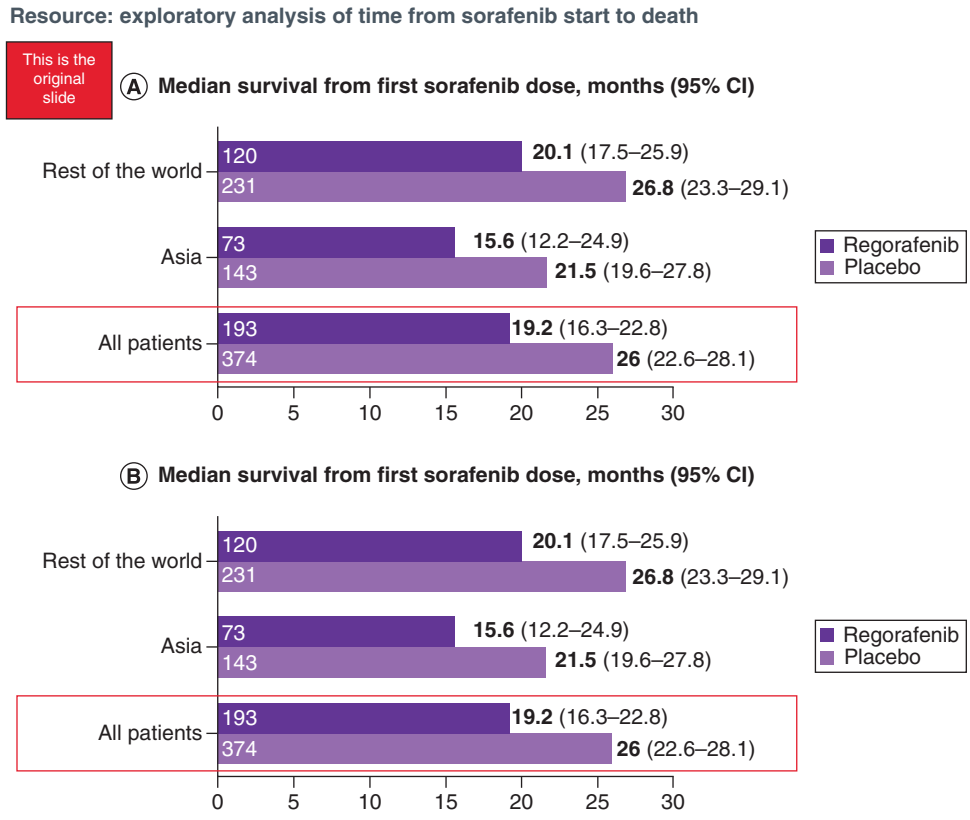

Figure 5. Overall survival of patients receiving sorafenib followed by regorafenib (exploratory analysis). Modified based on [59], reprinted with permission from Clinical Care Options Oncology. Available at www.clinicaloptions.com.

The REACH-2 trial is the first positive biomarker-driven study in aHCC, which is also reflected in the label: ramucirumab treatment is restricted to HCC patients who have been previously treated with sorafenib and who have a serum AFP level of ≥400 ng/ml [43]. The etiology of the condition (HBV vs HCV) does not seem to have an effect on response [57].

Ramucirumab is administered by intravenous infusion every 2 weeks. The dose is based on body weight [43].

Biomarkers

In terms of its clinical and molecular features, HCC is a very heterogeneous condition, which is why predictive biomarkers – other than AFP level for second-line ramucirumab – have not been identified to date. The influence of PD-L1 expression on response to checkpoint inhibitor therapy has not been clarified to date.

Sequential treatment

Sequential treatment offers patients with aHCC a chance of improved long-term survival. Exploratory and *post hoc* analyses indicate that sequential administration of the available first- and second-line monotherapies can result in an OS of about 2 years [58,59]. We can expect survival to improve even further with immunotherapy combinations.

Because all currently available second-line treatments have only ever been tested in patients progressing on or becoming intolerant to prior sorafenib, evidence for the efficacy of second-line treatment options administered after prior lenvatinib is unavailable. A *post hoc* analysis of the REFLECT study demonstrated an OS of 20.8 months in patients who received another systemic therapy after first-line lenvatinib, the most common of which was second-line sorafenib [58].

In a *post hoc* analysis of the RESORCE trial, the OS of patients receiving sorafenib prior to regorafenib was 26 months (Figure 5). Interestingly, the OS benefit observed with second-line regorafenib did not correlate with the time to progression on first-line sorafenib [59].

We expect that, once approved, the combination of atezolizumab and bevacizumab will become the new standard of care in first-line therapy. As a consequence, the future status of sorafenib and lenvatinib as well as their position in a potential treatment algorithm are currently uncertain.

At present, no data exist on the treatment sequencing in this setting. It would make sense to administer the most efficacious current first-line treatment option (lenvatinib) after failure of first-line atezolizumab + bevacizumab; yet, for the time being, the product labels would only allow for the use of sorafenib in the second line.

In the US, nivolumab and pembrolizumab as well as the combination of ipilimumab plus nivolumab have received accelerated US FDA approval in second-line aHCC – however, these options are thus far not available in Europe [60–62].

Future perspective

The pending approval of immunotherapies will change the treatment of aHCC profoundly. In addition, we now have various drugs at our disposal that can significantly prolong patient survival, giving us the opportunity to sequentially apply systemic treatments. In view of further first-line studies investigating immunotherapeutic combinations (e.g., PD-L1-Inhibitor + CTLA4 antibodies: durvalumab plus tremelimumab; HIMALAYA; TKI + PD-1 inhibitor: lenvatinib plus pembrolizumab; TKI + PD-L1 inhibitor: cabozantinib plus atezolizumab; COSMIC-312), identifying the optimal treatment sequence will become increasingly relevant for clinical practice [63–65]. It would be useful to establish clinical features or reliable predictive biomarkers, which could then help to detect patients benefitting the most from the different systemic treatment options. Moreover, we need to promote our knowledge of the development of resistance mechanisms; this will be the key to implementing more personalized approaches in aHCC therapy. The results of several Phase III trials of neoadjuvant and adjuvant immunotherapies (e.g. IMbrave050, CheckMate 9DX and KEYNOTE-937) will further add to the complexity of sequential therapy.

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Executive summary

Transarterial chemoembolization

- Despite major advances in systemic therapies, local options remain an integral part of the treatment of hepatocellular carcinoma (HCC) patients in Barcelona Clinic Liver Cancer System (BCLC) stage B.
- Selecting patients for TACE requires multidisciplinary discussion in a tumor board setting.
- The ideal candidate will have good liver function (ideally albumin-bilirubin [ALBI] grade 1), and one to four tumors measuring not more than 3 to 8 cm (or larger if singular tumors are involved). Liver function should not deteriorate under TACE.
- Switching to systemic therapy should be considered after the second application in the event of poor tolerability, deterioration of liver function or lack of response to TACE.

First-line treatment

- Patients who are not candidates for resection or locoregional therapy, whose liver function is intact (Child–Pugh A) and who are in good overall health (ECOG-PS 0–1) should receive systemic therapy.
- Intravenous treatment with atezolizumab + bevacizumab will establish itself after approval as the new standard of care in systemic first-line therapy.
- Potential contraindications need to be ruled out before initiating combined immunotherapy and antiangiogenesis; esophageal varices and autoimmune diseases in particular.
- Sorafenib and lenvatinib monotherapies are available as alternatives for individuals with contraindications to combination therapy. Oral tyrosine kinase inhibitor (TKI) therapies have somewhat different vascular target structures but a similar side effect profile.
- Lenvatinib's superior efficacy vs sorafenib regarding the secondary end points progression-free survival, time to progression and overall response rate is clinically relevant.
- Sorafenib has been widely established and investigated in clinical practice, especially in patients with Child–Pugh B cirrhosis.
- Comorbidities, side effect profiles, routes of administration and patient preferences need to be taken into account when choosing treatment.

Second-line treatment

- Patient selection, among other factors, is based on the reason for discontinuation of first-line sorafenib (intolerance or progression).
- Regorafenib's efficacy in patients unable to tolerate sorafenib has not been studied.
- Alpha fetoprotein levels are a prognostic biomarker as well as a predictive biomarker for ramucirumab treatment.
- Ramucirumab has a favorable tolerability profile.
- Cabozantinib's efficacy has been demonstrated in both second-line and third-line treatment.
- Whichever second-line treatment is chosen, effective blood pressure control and/or monitoring is required for all patients.

Sequential therapy

- All the currently approved second-line treatments have been investigated in patients progressing on or becoming intolerant to prior sorafenib.
- At present, no data are available for treatment sequences following first-line atezolizumab plus bevacizumab or following first-line lenvatinib.
- The only current treatment option not approved according to treatment line is sorafenib; however, second-line efficacy of the TKI has not been demonstrated in a prospective trial.
- To generate more evidence, subsequent therapies will need to be included in current first-line studies and dedicated sequence studies will need to be initiated.

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