

**Review**

# Systemic Treatment for Advanced Hepatocellular Carcinoma

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**Keywords**

Hepatocellular carcinoma · Patient characteristics · Precision medicine · Targeted therapy · Treatment sequence

**Abstract**

**Background:** Patients with advanced hepatocellular carcinoma (HCC) have a poor prognosis. First-line sorafenib has been the standard of care for a decade, but the treatment landscape is expanding. This review provides a practical overview of current and future systemic treatment options for advanced HCC and their place in clinical practice. **Summary:** First-line sorafenib and lenvatinib have shown to improve the survival of patients with advanced HCC. In the second line, regorafenib provides benefit for patients who previously tolerated sorafenib. Anti-PD1 antibodies, nivolumab and pembrolizumab, recently became available for second-line use in the US. Ramucirumab (for patients with  $\alpha$ -fetoprotein [AFP] levels  $\geq 400$ ) and cabozantinib present potential future second-line treatment options. Combinations of systemic and locoregional treatment, such as radiofrequency ablation or selective internal radiotherapy, require further research. Precision medicine has not yet been translated into clinical practice, as the most common driver mutations (*TERT* promoter, *CTNNB1*, *TP53*, and *ARID1A* mutations) have not yet been shown to be suitable therapeutic targets. However, our growing understanding of signaling pathways and efforts in drug development are expected to pave the way for precision medicine in HCC in the future. Evaluating the place for the current and novel systemic treatment options in clinical practice can be challenging due to the diverse toxicity profiles of the treatment options and characteristics of the patient population.

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Sorafenib data elucidate the effect patient characteristics (such as the performance score, Child-Pugh class, AFP, etiology of the underlying disease, and level of macrovascular invasion and extrahepatic spread) may have on outcomes in advanced stages. **Key Messages:** Lenvatinib is expected to join sorafenib as a preferred first-line treatment in advanced HCC. In the second line, the treatment of choice, regorafenib, is soon expected to be accompanied by cabozantinib and ramucirumab in patients with AFP  $\geq 400$  ng/mL, whereas nivolumab and pembrolizumab present second-line alternatives in the US. © 2019 S. Karger AG, Basel

## Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death [1]. HCC is almost invariably associated with underlying risk factors, such as chronic infections with hepatitis B (HBV) or C (HCV), metabolic syndrome, and alcohol abuse [2]. Many patients present with advanced-stage disease defined as Barcelona Clinic Liver Cancer (BCLC) stage C: cancer-related symptoms (performance status 1–2), preserved liver function, and portal invasion or extrahepatic spread (EHS) [2, 3]. These patients have a poor prognosis. Without treatment, the median overall survival (OS) of patients included in the SHARP trial (mixing BCLC B progressing after TACE and BCLC C patients) is around 8 months [4]. In the SHARP trial, the subgroup of BCLC C patients in the placebo arm had a median OS of 7 months, whereas BCLC B patients had a median OS of 11.4 months [5].

Sorafenib, a multi-kinase inhibitor with anti-proliferative and anti-angiogenic effects, has been the global standard of care for advanced HCC for a decade. First-line sorafenib improved OS in two large, phase 3, randomized controlled trials (RCTs) [4, 6]. In 2017, regorafenib was registered as second-line treatment in the US and Europe, whereas nivolumab and pembrolizumab were registered for second-line use only in the US [2, 7–9]. This review outlines the current data on common questions regarding the systemic treatment of advanced HCC and their practical implications, aiming to assist physicians in making treatment decisions for these patients.

## Questions and Answers on the Systemic Treatment for Advanced HCC

### *What Is the Impact of Patient Characteristics on Outcomes with Sorafenib?*

The main prognostic and predictive studies in advanced HCC have been performed in sorafenib-treated patients. In the general SHARP trial population, first-line sorafenib improved the median OS by nearly 3 months compared with placebo (10.7 vs. 7.9 months; hazard ratio [HR] 0.69;  $p < 0.001$ ). The median time to radiological progression (TTP) improved from 5.5 to 2.8 months ( $p < 0.001$ ) [4]. In the Asia-Pacific (AP) trial, sorafenib was evaluated in China, South Korea, and Taiwan [6]. The survival benefit of sorafenib versus placebo was similar to the SHARP trial (median OS 6.5 vs. 4.2 months; HR 0.68;  $p = 0.014$ ), with a median TTP of 2.8 versus 1.4 months ( $p = 0.0005$ ). Common sorafenib-associated adverse events (AEs) included diarrhea (39/26%; 8/6% grade 3/4), hand-foot-skin reaction (HFSR) (21/45%; 8/11% grade 3/4), and fatigue (22/20%; 4/3% grade 3/4), in the SHARP/AP trials, respectively [4, 6].

The AP and SHARP trials illustrated the impact of patient characteristics on outcomes in advanced stages of HCC [4, 6]. Although the inclusion criteria were similar, there were differences in the etiology of the patient populations. For example, the SHARP trial included patients

from Europe, North America, South America, and Australasia in whom the predominant etiologies were HCV and alcohol abuse, whereas the AP study included an Asian population with HBV as the main etiology. Furthermore, the Asian patients had more advanced disease (EHS, performance score, and number of tumors) than the SHARP population. The absolute OS and TTP were lower in the AP than in the SHARP trial. However, the HRs for survival benefit were similar.

#### (1a) What Is the Impact of Liver Function according to the Child-Pugh Class on Treatment Efficacy?

The majority of patients with HCC have concurrent cirrhosis. The two sorafenib studies only included patients with good liver function (Child-Pugh A), as sorafenib may be deleterious in case of decompensated cirrhosis. Cohort studies have shown that Child-Pugh B patients have a lower OS benefit from sorafenib than Child-Pugh A patients [10, 11]. A phase 2 trial showed more severe liver toxicities (including hyperbilirubinemia, ascites, and encephalopathy) in Child-Pugh B versus Child-Pugh A patients, despite similar pharmacokinetic and toxicity profiles [12]. Sorafenib should be used with caution in Child-Pugh B patients, as there is a narrow margin between an unknown clinical benefit and the risk of toxicities and liver decompensation [13]. In the GIDEON study, some Child-Pugh B and C patients have been treated with sorafenib without obvious deleterious effects on liver function. However, this study was not designed to assess this issue [14]. Consequently, sorafenib is still contraindicated in Child-Pugh C patients, because of the limited life expectancy and the low magnitude of benefit in this population.

#### (1b) What Is the Impact of Macrovascular Invasion and EHS on Treatment Efficacy?

A large proportion of patients with advanced HCC have macrovascular invasion (MVI) and/or EHS, which impacts OS [4, 6]. In the SHARP trial, the median OS was 8.9 months in patients with MVI and/or EHS versus 14.5 months in those without [5]. A combined analysis of the SHARP and AP trials confirmed that patients with EHS have a smaller absolute OS benefit from sorafenib (HR = 0.84 with EHS vs. 0.55 without EHS) [15]. More data are needed about the prognostic value of the extent of MVI and the numbers, size, and location of EHS in patients treated with tyrosine kinase inhibitors (TKIs).

#### (1c) Does the Etiology of the Underlying Disease Impact Treatment Efficacy?

In the SHARP trial, the most frequently reported factors underlying HCC were HCV and alcohol abuse (29 and 26%) [4]. Only 19% of patients were infected with HBV (19%), the major underlying disease in the AP trial (71%) [4, 6]. HBV-positive patients had a lower median OS in the AP trial compared to patients included in the SHARP trial. However, it is not obvious that this difference is strictly due to the HBV infection or more probably related to the difference in baseline characteristics of the patients and tumors [15].

Some data suggest that patients with HBV-related HCC have poorer prognosis and OS than those infected with HCV [16]. A meta-analysis of three RCTs suggested that the effect of sorafenib was not significant in patients with HBV [17]. The efficacy in patients with HCV-related HCC was confirmed by a subset analysis from the SHARP trial, showing an OS of 14.0 months with sorafenib versus 7.4 months with placebo (HR 0.50) [5]. However, the AP trial also showed a significantly increased OS for sorafenib versus placebo (HR 0.74), while more than 70% of patients were HBV positive [6, 15]. Cross-trial comparisons should be interpreted with caution. Interestingly, the phase 3 REFLECT trial has shown somewhat more survival benefit from lenvatinib versus sorafenib in patients with HBV (13.4 vs. 10.2 months; HR 0.83) [18]. However, this study was designed as a noninferiority trial and superiority over sorafenib was not reached. Overall, treatment choice cannot be solely based on the etiology of the underlying liver disease, as these data are derived from post hoc subgroup analysis of RCTs.

### (1d) What Is the Impact of $\alpha$ -Fetoprotein Levels on Treatment Efficacy?

A multivariate subgroup analysis of the SHARP and AP studies showed that  $\alpha$ -fetoprotein (AFP) levels  $>200$  ng/mL were a strong prognostic factor of poor OS with sorafenib [15]. In the REFLECT study, patients with baseline AFP levels  $<200$  ng/mL had a longer OS than those with AFP levels  $\geq 200$  ng/mL, both in the lenvatinib and sorafenib group, confirming a prognostic value of this biomarker in each treatment arm [18]. Conversely, a post hoc subgroup analysis showed that ramucirumab significantly increased OS in patients with high AFP levels (7.8 vs. 4.2 months,  $p = 0.006$ ) [19]. The phase 3 REACH-2 trial has compared second-line ramucirumab with placebo in patients with a serum AFP  $\geq 400$  ng/mL (NCT02435433). Presentation of results at the ASCO meeting showed an increased OS in the ramucirumab trial, suggesting that the AFP level is a predictive marker of response to ramucirumab [20].

### (2) What Are the Approved Second-Line Treatment Options for Advanced HCC?

A phase 2 RCT showed no benefit of dose escalation of sorafenib in progressive patients [21]. In the last decade, several phase 3 RCTs testing novel, mainly targeted therapies in advanced HCC, failed to show improved OS due to toxicity or, more frequently, absence of efficacy (Table 1) [4, 6, 19, 20, 22–32]. However, regorafenib (FDA and EMA) and nivolumab in 2017 and pembrolizumab in 2018 were approved (by the FDA and EMA and by the FDA alone, respectively) for second-line use in patients previously treated with sorafenib.

#### (2a) What Is the Role of Regorafenib in the Second-Line Treatment of Advanced HCC?

In December 2016, regorafenib ended the succession of negative results in advanced HCC [8, 33]. Regorafenib is an anti-angiogenic TKI that also targets stroma and oncogenic signaling, such as the mitogen-activated protein kinase pathway [8]. In the phase 3 RESORCE RCT, second-line regorafenib increased the OS by 2.8 months versus placebo (10.6 vs. 7.8 months;  $p < 0.0001$ ; HR 0.63) in patients with radiological progression on sorafenib. However, this study included a selected patient population, consisting of patients with Child-Pugh A cirrhosis and Eastern Cooperative Oncology Group performance status (ECOG-PS) scores  $\leq 1$ , who tolerated sorafenib  $\geq 400$  mg/day for  $\geq 20$  of the last 28 days of treatment. Interestingly, patients receiving second-line placebo in the RESORCE trial had the same OS (7.8 months) as patients receiving first-line placebo in the SHARP trial [33]. This illustrates the more indolent patient population included in second-line trials. Furthermore, experience with subgroups not included in the RESORCE study is limited. Sequential treatment with sorafenib followed by regorafenib led to a median OS of 26 months [34]. However, liver function impairment or poor performance status prevented some patients from benefitting from a second-line treatment.

The main AEs of regorafenib were similar to sorafenib and occurred frequently, with HFSR reported in 53% (13% grade 3), diarrhea in 41% (3% grade 3), fatigue in 40% (9% grade 3), and hypertension in 31% (15% grade 3/4) of patients [8]. Grade 3/4 AEs occurred in 67% of patients under regorafenib versus 39% under placebo and called for dose reductions or interruptions in 54 and 10% of patients, respectively.

Regorafenib was approved by the FDA and EMA as second-line treatment after sorafenib failure in patients with advanced HCC and is currently the recommended second-line treatment in Child-Pugh A patients with an ECOG-PS score of 0–1 who tolerated sorafenib in the first line. Currently, patients with Child-Pugh B cirrhosis, significant comorbidities or sorafenib intolerance have been excluded from the RESORCE trial and should not be treated with regorafenib [35]. In these populations, efficacy and tolerance are still unknown. Careful evaluation of second-line regorafenib in the real-world setting is required; a noninterventional study is currently ongoing (NCT03289273).

## (2b) What Is the Role of Nivolumab and Pembrolizumab in the Second-Line Treatment of Advanced HCC?

Immunotherapy aims to unleash the immune response against cancer cells. The monoclonal antibodies directed against programmed cell death protein 1 (PD1), nivolumab, and pembrolizumab were recently approved by the FDA for the second-line treatment of advanced HCC. The FDA approval of nivolumab in 2017 was based on a nonrandomized, open-label, phase 1/2 study (CheckMate-040), in which nivolumab showed a median OS of 15 months, an overall response rate (ORR) of 19%, and a median duration of response of 9.9 months in the overall population [9]. The main AEs included pruritus (19%), rash (16%), and diarrhea (14%). Autoimmune AEs were rare. In 2018, second-line pembrolizumab showed promising data from an ongoing phase 2 trial (Keynote-224), with an ORR of 17%, a median progression-free survival (PFS) of 4.9 months and a median OS of 12.9 months and was approved by the FDA [36].

Although data from these studies were encouraging enough for the FDA to approve nivolumab and pembrolizumab, the CheckMate-040 study was an early-stage study with a heterogeneous population, mixing sorafenib-naïve and pretreated patients. Moreover, neither CheckMate-040 nor Keynote-224 included a control arm. Continued approval may depend on confirmation of the results and clinical benefit in the phase 3 RCTs expected for 2019.

### *What Will Be the Place of Novel Compounds in the Treatment of Advanced HCC?*

Several novel systemic therapies are currently evaluated in RCTs, including targeted therapies and immunotherapy.

#### Lenvatinib

Lenvatinib is a multi-target kinase inhibitor directed against receptors for vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), platelet-derived growth factor, and the proto-oncogenes Kit and RET [37]. It was first evaluated in a Japanese phase 2 study. The majority of patients (59%) were HCV-positive and 59% had BCLC stage C HCC. Lenvatinib showed an ORR of 37% and an OS of 18.7 months. Drug-related AEs seemed manageable and included arterial hypertension (76%), HFSR (65%), anorexia (61%), and proteinuria (61%). A total of 11 fatal AEs were reported, including hepatic failure and cerebral hemorrhage.

In February 2018, data from the phase 3, open-label, noninferiority RCT REFLECT, comparing first-line lenvatinib with sorafenib in patients with advanced HCC without MVI, were published [18]. Patients with main portal vein invasion, biliary invasion, and a tumor burden of more than 50% of the liver were excluded from this trial. Lenvatinib was noninferior to sorafenib (median OS 13.6 vs. 12.3 months; HR 0.92, 95% confidence interval [CI] 0.79–1.06) and was associated with a significantly higher PFS (7.4 vs. 3.7 months;  $p < 0.00001$ ), time to progression (8.9 vs. 3.7 months  $p < 0.0001$ ) and ORR (24.1% vs. 9.2%;  $p < 0.00001$ ) compared with sorafenib. Moreover, lenvatinib was associated with a higher ORR according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria (from 24.1% in investigator review to 40.6% in masked independent review) than sorafenib (from 9.2% in investigator review to 12.4% in masked independent review). This was offset by an increased rate of treatment interruptions and discontinuations due to AEs with lenvatinib (40 vs. 32% and 9 vs. 7%). The most common AEs in the lenvatinib group included hypertension (42%), diarrhea (39%), and decreased appetite (34%). The OS of lenvatinib seemed to be consistent across subgroup analyses, including Western versus Eastern patients and patients with HBV versus HCV. Lenvatinib seemed to be more effective than sorafenib in the subgroup of HBV-infected patients. However, no definitive conclusions can be drawn from a subgroup analysis of an RCT.

**Table 1.** Phase 3 randomized controlled trials in advanced HCC

Treatment	S/NI	n per arm	Median OS, months	Median TTP, months	Median PFS, months	ORR, %	Comments
<b>First-line trials</b>							
Sorafenib vs. placebo [4]	S	299/303	10.7 vs. 7.9 ( <i>p</i> < 0.001)	5.5 vs. 2.8 ( <i>p</i> < 0.001)	NR	2 vs. 1* RECIST	
Sorafenib vs. placebo [6]	S	150/76	6.5 vs. 4.2 ( <i>p</i> = 0.014)	2.8 vs. 1.4 ( <i>p</i> = 0.005)	NR	3.3 vs. 1.3*	Patients from the Asia-Pacific region
FOLFOX4 vs. doxorubicin [22]	S	184/187	6.4 vs. 4.97 (NS)	NR	2.93 vs. 1.77 ( <i>p</i> < 0.001)	8.2 vs. 2.7* ( <i>p</i> = 0.02)	Open-label study
Sunitinib vs. sorafenib [23]	S	530/544	7.9 vs. 10.2 ( <i>p</i> = 0.0014)	4.1 vs. 3.8 ( <i>p</i> = 0.3082)	3.6 vs. 3 ( <i>p</i> = 0.22)	7.2 vs. 6.9*	More AEs in the sunitinib arm
Brivanib vs. sorafenib [24]	NI	577/578	9.5 vs. 9.9 (NI not met)	4.2 vs. 4.1 ( <i>p</i> = 0.85)	NR	12 vs. 9** ( <i>p</i> = 0.56)	
Sorafenib + erlotinib vs. sorafenib + placebo [25]	S	362/358	9.5 vs. 8.5 (NS)	3.2 vs. 4 ( <i>p</i> = 0.18)	NR	6.6 vs. 3.9* ( <i>p</i> = 0.102)	Higher OS in patients with HBV
Linifanib vs. sorafenib [26]	NI	514/521	9.1 vs. 9.8 (NI not met)	5.4 vs. 4 ( <i>p</i> = 0.001)	NR	13 vs. 6.9*	More AEs in the linifanib arm
Lenvatinib vs. sorafenib [18]	NI	478/476	13.6 vs. 12.3 (NI met)	8.9 vs. 3.7 ( <i>p</i> < 0.0001)	7.4 vs. 3.7 ( <i>p</i> < 0.0001)	24.1 vs. 9.2** ( <i>p</i> < 0.0001)	
Doxorubicin + sorafenib vs. sorafenib [29]	NR	173/173	9.3 vs. 10.5 (NS)	NR	3.6 vs. 3.2 (NS)	NR	Unpublished data Study halted for futility

**Table 1** (continued)

Treatment	S/NI	n per arm	Median OS, months	Median TTP, months	Median PFS, months	ORR, %	Comments
<b>Second-line trials</b>							
Brivanib vs. placebo [27]	S	263/132	9.4 vs. 8.2 (NS)	4.2 vs. 2.7 ( $p < 0.001$ )	NR	10 vs. 2* ( $p = 0.003$ )	
Everolimus vs. placebo [28]	S	362/184	7.6 vs. 7.3 (NS)	3 vs. 2.6 (NS)	NR	2.2 vs. 1.6*	Increased survival in patients with HBV
Ramucirumab vs. placebo [19]	S	283/282	9.2 vs. 7.6 (NS)	3.5 vs. 2.6 ( $p < 0.0001$ )	2.8 vs. 2.1 ( $p < 0.0001$ )	8 vs. 1* ( $p < 0.0001$ )	Higher OS in patients with AFP $\geq 400$ ng/mL
Ramucirumab vs. placebo [20]	S	197/95	8.5 vs. 7.3 ( $p = 0.0199$ )	NR	2.8 vs. 1.6 ( $p < 0.0001$ )	4.6 vs. 1.1* (NS)	Unpublished data Patients with elevated AFP ( $\geq 400$ ng/mL)
Regorafenib vs. placebo [8]	S	379/194	10.6 vs. 7.8 ( $p < 0.0001$ )	1.4 vs. 1.4	3.1 vs. 1.5 ( $p < 0.0001$ )	11 vs. 4** ( $p < 0.0001$ )	Patients tolerant to sorafenib
Cabozantinib vs. placebo [38]	S	470/237	10.2 vs. 8.0 ( $p = 0.0049$ )	NR	5.2 vs. 1.9 ( $p < 0.0001$ )	4 vs. 0.4 ( $p = 0.0086$ )*	
S-1 vs. placebo [30]	S	223/111	11.1 vs. 11.2 (NS)	2.6 vs. 1.4 ( $p < 0.0001$ )	2.6 vs. 1.4 ( $p < 0.0001$ )	5 vs. <1 (NS)	Patients from Japan
Tivantinib vs. placebo [31]	S	226/114	8.4 vs. 9.1 (NS)	2.4 vs. 3.0 (NS)	2.1 vs. 2.0 (NS)	0 vs. 0*	Patients with high MET expression (staining intensity score $\geq 2$ in $\geq 50\%$ of tumor cells)
ADI-PEG 20 vs. placebo [32]	S	424/211	7.8 vs. 7.4 (NS)	NR	2.6 vs. 2.6 (NS)	NR	

ORR was assessed at imaging, either using traditional RECIST (\*) or mRECIST (\*\*) criteria. AE, adverse event; AFP,  $\alpha$ -fetoprotein; FOLFOX4, oxaliplatin, folinic acid and 5-fluorouracil; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; mRECIST, modified RECIST; NI, noninferiority; NR, not reported; NS, not significant; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; S, superiority.

In 2018, lenvatinib was approved in the US and Japan. Further analysis of the phase 3 RCT data will be needed to elucidate the potential of lenvatinib as an alternative for sorafenib and to decide how to choose between lenvatinib and sorafenib. However, as the OS of lenvatinib is similar to sorafenib and no tumor biology-based biomarkers are available to guide treatment, the discussion on lenvatinib versus sorafenib may focus on toxicity and drug costs.

#### Cabozantinib

Cabozantinib is a multi-kinase inhibitor, targeting MET, AXL, and VEGF receptors, that was associated with a median OS of 11.5 months and an ORR of 5% in a phase 2 study [38]. The main AEs were diarrhea (63%), HFSR (56%), and thrombocytopenia (37%). The phase 3 CELESTIAL RCT showed an OS of 10.2 versus 8.0 months for cabozantinib versus placebo (HR 0.76;  $p = 0.005$ ) in the second or third line [39]. PFS was 5.2 versus 1.9 months (HR 0.44;  $p < 0.0001$ ). Although in favor of cabozantinib, the ORR was relatively limited in both groups (4 vs. 0.4%;  $p < 0.001$ ). However, cabozantinib almost doubled the disease control rate compared with placebo (partial response or stable disease; 64 vs. 33%). The main grade 3/4 AEs were HFSR (17%) and hypertension (16%). Cabozantinib is expected to be approved for second- or third-line use in 2018.

#### Immunotherapy

Cancer uses multiple mechanisms to evade the host immune response. Many novel compounds targeting different immune evasion mechanisms are being tested, as well as regimens combining immunotherapy with chemotherapy, targeted therapy, radiation, or another immunotherapy. These ongoing studies will bring more clarity on the role of immunotherapy in the treatment of HCC.

Phase 3 studies in patients with advanced HCC without major portal vein invasion comparing nivolumab to sorafenib in the first line and comparing pembrolizumab to placebo in the second line are ongoing (NCT02576509, NCT02702401). Tremelimumab, a blocker of cytotoxic T-lymphocyte-associated protein 4 (CTLA4), showed a partial response rate of 18% and a TTP of 6.5 months in a phase 2 study in HCV-related HCC [40]. A phase 3 RCT comparing durvalumab (anti-PDL1) plus tremelimumab (anti-CTLA4) versus sorafenib in patients with advanced HCC is currently underway (NCT032988451). In a phase 1 study in patients with advanced HCC, the combination of atezolizumab and VEGF inhibitor bevacizumab was safe and well tolerated, with promising early efficacy; the confirmed ORR per RECIST v1.1 was 61% by investigator assessment and 65% by independent review facility assessment (NCT02715531) [41]. Responses were observed in all subgroups, including patients with different etiologies, geographic regions, and baseline AFP levels. Responses were durable, with 10 responses ongoing for  $\geq 6$  months and 3 of these ongoing for  $\geq 1$  year per investigator assessment (median follow-up: 10.3 months). Median OS, PFS, and duration of response had not been reached at the clinical cutoff date (NCT02715531). The phase 3 RCT IMbrave150, comparing atezolizumab plus bevacizumab with sorafenib in patients with locally advanced or metastatic HCC, is ongoing (NCT03434379) [42]. The combination of the PD1 inhibitor pembrolizumab and the VEGFR/FGFR inhibitor lenvatinib is currently tested in a 2-part, phase 1b trial (NCT03006926) [43]. It induced a confirmed ORR of 27% (95% CI 12–48) in patients with unresectable HCC; when investigators included unconfirmed responses, the ORR was 42% (95% CI 23–63).

#### Ongoing Phase 3 Trials with Targeted Therapies

Two other targeted drugs are currently being investigated in phase 3 trials in advanced HCC: ramucirumab and apatinib. Second-line ramucirumab, a monoclonal antibody targeting the VEGF receptor 2, failed to increase OS compared with placebo in the phase 3 REACH study



(9.2 vs. 7.6 months,  $p = 0.14$ ) [19]. However, a post hoc analysis suggested that patients with AFP levels  $\geq 400$  ng/mL could benefit from ramucirumab. A new phase 3 RCT is now comparing ramucirumab with placebo in this subgroup and presentation at the ASCO Annual Meeting reported an increased OS in the ramucirumab arm compared to the placebo arm (NCT02435433) [20]. Apatinib is a TKI, mainly directed against the VEGF receptor, that is currently tested in a phase 3, placebo-controlled RCT in Asia (NCT02329860).

#### *What Toxicity Profiles Can Be Expected When Using Targeted Therapy or Immunotherapy?*

The currently available therapies have different toxicity profiles and specific AEs can arise at different stages, even if most of AEs of tyrosine kinase inhibitors occur in the first month of treatment. During the first month of treatment with targeted therapies (sorafenib, regorafenib, lenvatinib), arterial hypertension, diarrhea, asthenia, and HFSR may occur. HFSR can emerge several months after the beginning of treatment, but interestingly, retrospective data indicate that early skin toxicity and diarrhea may predict clinical benefit from sorafenib [44, 45]. After the first month, rash and dry skin are more frequent. Later in the course of treatment, more rare AEs may be seen, such as cardiovascular events and thrombosis. Immunotherapy has a completely different safety profile, mainly consisting of rash and rare, but sometimes severe, immune-mediated AEs including immune-mediated hypothyroidism, adrenal insufficiency, colitis, hepatitis, and acute renal injury. Figure 1 outlines suggested management options for the main AEs related to sorafenib, lenvatinib, regorafenib, and anti-PD1 inhibitors such as nivolumab and pembrolizumab.

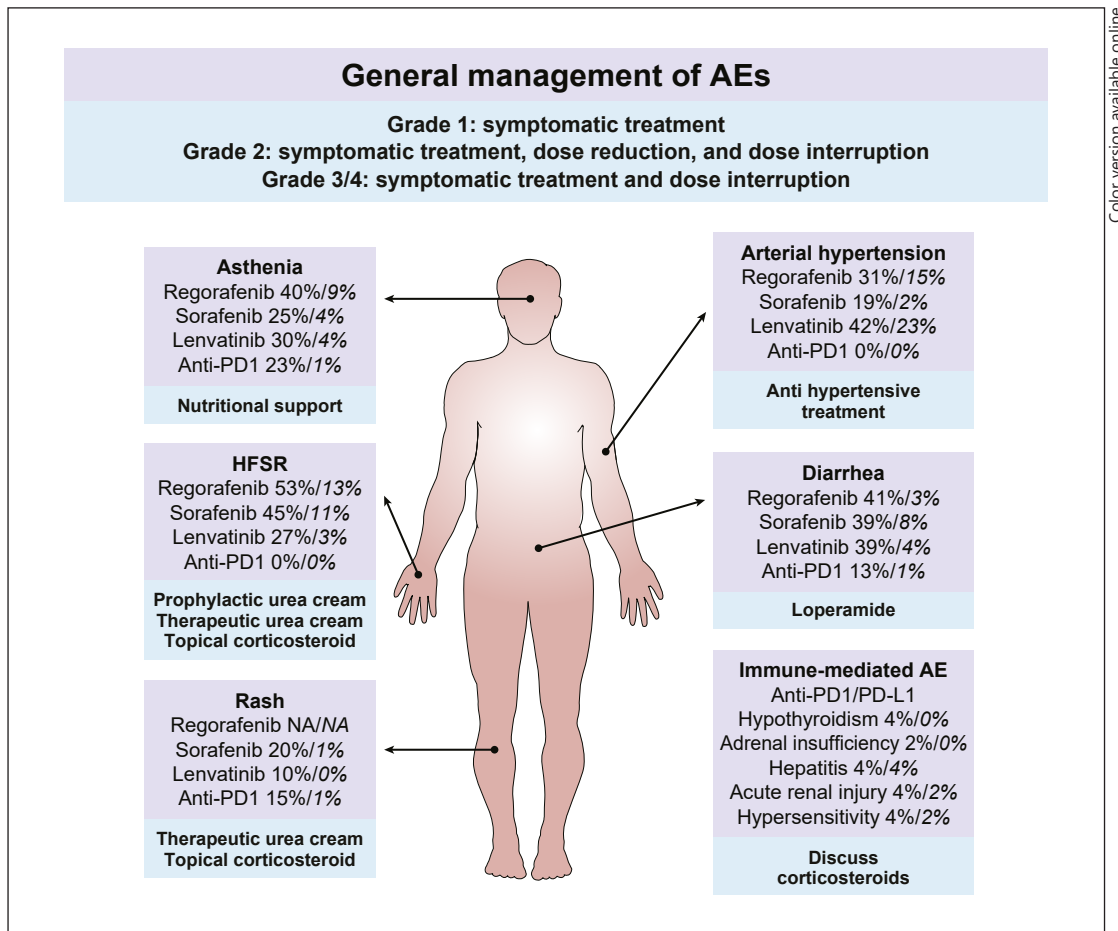
#### *What Is the Role of Driver Mutations and Precision Medicine in the Field of HCC?*

Important advances have been made in our understanding of the pathophysiology of HCC and signaling pathways involved in hepatocarcinogenesis, including the identification of driver mutations and key signaling pathways (Fig. 2) [46–50]. Promoter mutations in the telomere maintenance gene telomerase reverse transcriptase (*TERT*) are the most frequent genetic alteration in HCC, occurring in 40–60% of patients [49]. Mutations in *TP53* (25–40%), *CTNNB1* (11–37%), chromatin remodeling complex (*ARID1A*, 4–17%; *ARID2*, 3–18%), and the oxidative stress pathway (*NFE2L2*, 3–6%; *KEAP1*, 2–8%) are also common in HCC.

Most approved treatments in advanced HCC are TKIs targeting multiple targets. However, phase 3 RCTs did not include biomarker enrichment, except for those on ramucirumab and tivantinib. The concept of precision medicine has been built on our knowledge about the cancer genome. Biomarkers derived from tumor analysis have been suggested as potential predictors of response to sorafenib, such as VEGFA amplification and FGF3/4 amplification. However, these biomarkers have only been analyzed in retrospective studies and lack prospective validation [51]. Overall, compared to other types of solid tumors, precision medicine in HCC is still at the embryonic stage.

Another example of precision medicine in HCC is the use of c-Met inhibitors in patients harboring high expression of *MET* [52]. Unfortunately, nonselective kinase inhibitors with c-Met activity, such as tivantinib, have not shown efficacy in advanced HCC [31]. This might be due to incomplete understanding of the mechanism of action of the drug (preclinical data has recently suggested that tivantinib is not a potent Met inhibitor after all) and the limited value of *MET* overexpression as a surrogate marker of oncogene addiction [53]. Another example is the FGFR4 inhibitor BLU-554. Preliminary phase 1 data with BLU-554 in patients with *FGF19* overexpression show limited toxicity and promising clinical activity [54].

Precision medicine in HCC has several limitations. Potential targetable alterations (e.g., *FGF19* amplifications, *PTEN* deletion, and *RPS6KA3* inactivation) have a frequency of less than 5–10% in the HCC population [55]. The most frequent genetic alterations in HCC currently



**Fig. 1.** Managements of AEs of systemic treatments for HCC. The purple boxes contain the main AEs related to sorafenib, lenvatinib, regorafenib, and anti-PD1 antibodies, with the percentages of any grade AEs/grade 3–4 AEs (italics). The blue boxes contain suggestions for the management of the AEs. AE, adverse event; NA, not applicable; HFSCR, hand-foot-skin reaction; PD1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand.

have no available treatment options and tumor heterogeneity could decrease the efficacy of targeted therapy [56]. Moreover, primary or secondary resistance invariably occurred [57]. Additional knowledge about tumor heterogeneity and plasticity of cancer cells and further efforts on drug development will be required to bypass these drawbacks and lead HCC into the era of precision medicine. In the design of new clinical trial in HCC, biomarker enrichment and tumor biopsies should be mandatory prior to inclusion in order to give access to material that can be used to identify biomarkers of response.

*What Are the Consequences of Recent Developments for the Design of Future Clinical Trials?*

In future phase 3 RCTs, sorafenib or lenvatinib should be the first-line comparators. However, availability of several second-line treatments could lead to an increased post-progression survival after first-line treatment, leading to more difficulties to assess OS in the first line [58]. Regorafenib and cabozantinib should be second-line comparators in patients who previously tolerated sorafenib. Once approved, cabozantinib should be the comparator in

second-line treatment of sorafenib-intolerant patients (as defined in the RESORCE trial: sorafenib  $\geq 400$  mg/day for  $\geq 20$  of the last 28 days of treatment). Placebo-controlled trials can be acceptable in the third line. Further data from phase 3 RCTs with nivolumab and pembrolizumab in the first and second line are needed to determine their place in future RCTs.

Controversies exist about the use of surrogate endpoints, including TTP, PFS, or ORR, in patients with advanced HCC. ORR by the mRECIST has been suggested as a validated surrogate endpoint, but this remains controversial [59, 60]. Phase 3 studies have shown discrepancies between OS and proposed surrogate endpoints, including increases in ORR, PFS or TTP without an increased OS (Table 1). This could be explained by a conceivably higher toxicity of the novel agents or increased tumor aggressiveness after progression [61]. Currently, OS remains the primary endpoint in phase 3 RCTs in advanced HCC.

### Patient Scenarios and Treatment Proposals

For a decade, sorafenib was the only approved treatment for advanced HCC, with no other approved options for sorafenib-intolerant and/or progressive patients. Positive results of novel compounds in first, second and even further lines of treatment prompt physicians to question the position of new treatment options and develop tailored treatment strategies, taking into account clinical characteristics, underlying disease, HCC stage, and reimbursement status. However, clinicians have to interpret the results of subgroup analysis from RCTs with caution. This section contains suggested scenarios, treatment proposals, and sequences to aid the physician's decision-making process around the treatment of advanced HCC (Fig. 3). We discuss these scenarios as clinicians could discuss treatment options in different clinical situations in a multidisciplinary tumor board. However, most data come from subgroup analyses that cannot provide definitive proof for each scenario.

#### *First-Line Treatment*

##### HCV-Infected Patients with Advanced HCC

Sorafenib has shown a clear efficacy and safety benefit in HCV-infected patients with advanced HCC [17]. A subgroup analysis of the SHARP and AP trials showed that HCV-positive patients were more likely to benefit from sorafenib [15]. Sorafenib could be suggested as a first-line option in this population.

Nivolumab showed impressive efficacy results in a phase 1/2 study in the second line, but adequate data is lacking to recommend nivolumab as a first-line treatment option [9]. Final results of the phase 3 head-to-head RCT comparing nivolumab and sorafenib can shed light on possible advantages in survival and cost-effectiveness.

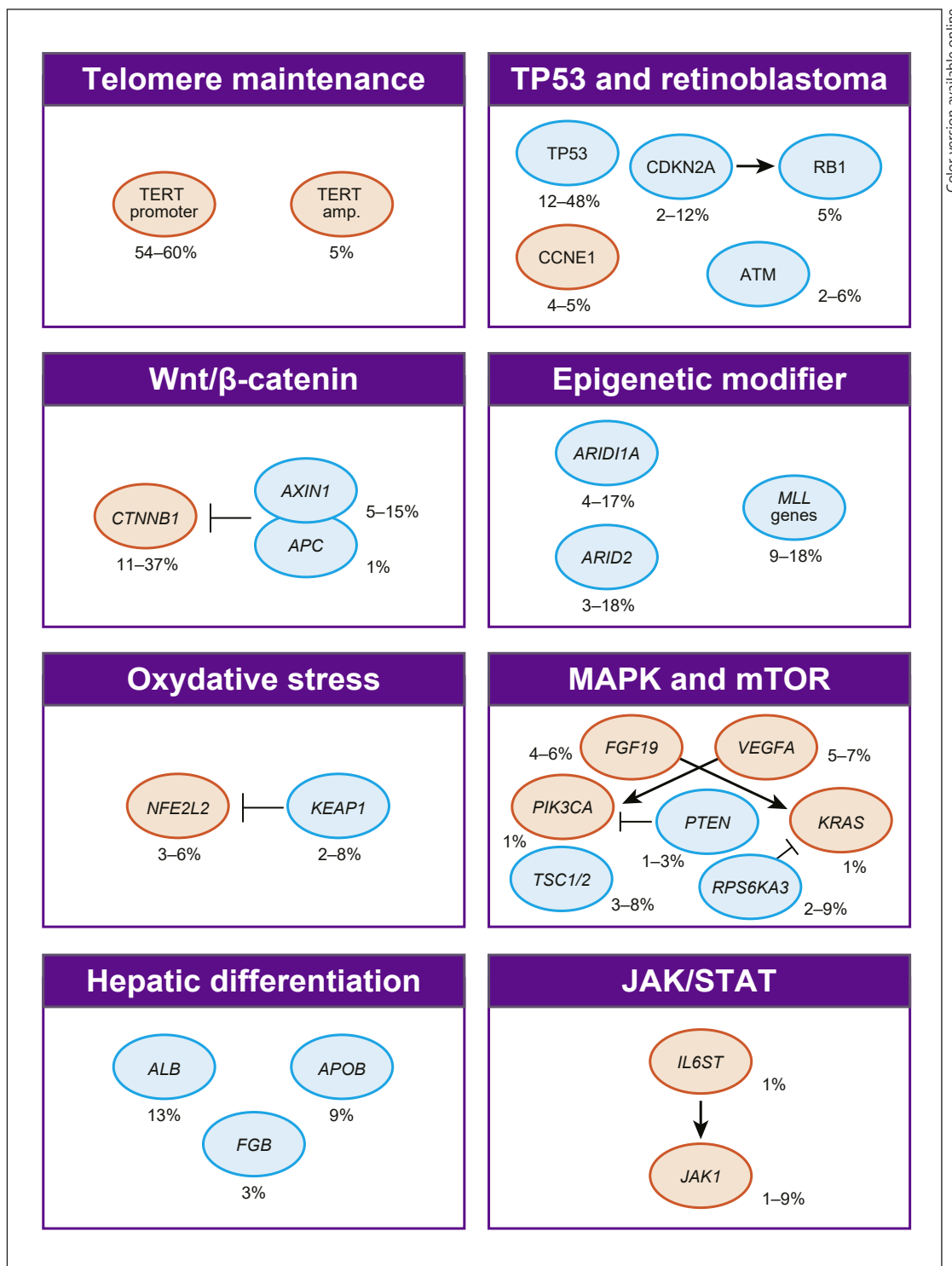
##### HBV-Infected Patients with Advanced HCC

Sorafenib has shown a clear benefit compared with placebo in HBV-infected patients with advanced HCC [6, 15]. However, a recent meta-analysis of three RCTs with sorafenib ( $n = 1,643$ ) indicated lower benefit of sorafenib in this population [17]. Despite the contravened conclusion of this study, this finding needs to be considered when treating HBV-infected patients [62].

Phase 3 data indicate that lenvatinib may have more benefit than sorafenib in HBV-infected patients, but this assumption is only based on a subgroup analysis of the phase 3 RCT [18]. Lenvatinib seemed to have a manageable toxicity profile. Furthermore, costs are

currently lower than that of sorafenib, which is relevant considering HBV infections are more frequent in developing countries.

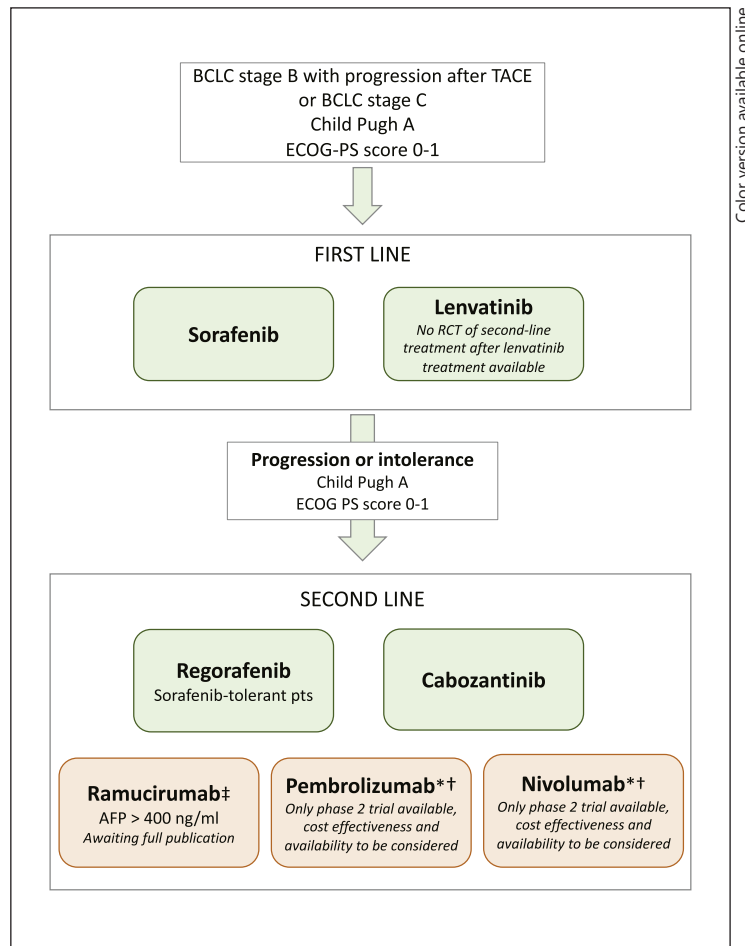
The subgroup analysis of the REFLECT trial could permit starting with first-line lenvatinib (where approved) in HBV-positive patients with advanced HCC to optimize their chance of



Color version available online

(For legend see next page.)

**Fig. 3.** Current and future treatment options by line of therapy and patient subgroup. The green boxes contain recommended (future) therapies. The orange boxes contain alternative future treatments, not recommended as first choice based on the current knowledge. No studies on second-line treatment after progression/intolerance to lenvatinib are currently available. \* Insufficient data for robust recommendation. † Only registered in the US. ‡ Not registered. BCLC, Barcelona Clinic Liver Cancer; ECOG-PS, Eastern Cooperative Oncology Group performance status; pts, patients; RCT, randomized controlled trial.



**Fig. 2.** Mutational landscape of HCC. This figure depicts the main signaling pathways mutated in liver carcinogenesis. The main driver genes mutated in HCC in each signaling pathway are shown with the percentages of somatic mutations in each gene. Oncogenes are presented in red and tumor suppressor genes in blue. *TERT*, *CCNE1*, and *MLL4* are also targeted by recurrent somatic HBV insertions. The *TERT* gene was either mutated in its promoter or amplified (*TERT* amp.). ALB, albumin; APC, adenomatosis polyposis coli tumor suppressor; APOB, apolipoprotein B; ARID2, AT-rich interactive domain-containing protein 2; ARID1A, AT-rich interactive domain-containing protein 1A; ATM, ataxia-telangiectasia mutated; CCNE1, cyclin E1; CDKN2A, cyclin-dependent kinase inhibitor 2A; CTNNB1, Catenin (cadherin-associated protein) beta 1; FBG, fibrinogen beta chain; FGF19, fibroblast growth factor 19; IL6ST, glycoprotein 130; JAK, janus kinase; KEAP1, kelch-like ECH-associated protein 1; MLL, mixed-lineage leukemia; mTOR, mechanistic target of rapamycin; NFE2L2, nuclear factor (erythroid-derived 2)-like 2; RB1, retinoblastoma protein; PIK2CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RPS6KA3, ribosomal protein S6 kinase, 90kDa, polypeptide 3; STAT, signal transducer and activator of transcription; TERT, telomerase reverse transcriptase; TP53, tumor protein p53; TSC1/2, tuberous sclerosis 1/2; VEGFA, vascular endothelial growth factor A.

response, survival, and treatment cost. It is also possible to treat HBV-positive patients with sorafenib, as the AP trial included a large proportion of HBV-infected patients and showed benefit. Sorafenib could be a treatment option for patients with comorbidities, especially arterial hypertension, bearing in mind the relatively high incidence of this disease as a lenvatinib-related AE. While awaiting the final phase 3 data, nivolumab will be not suggested for first-line use.

#### Patients with Locally Advanced HCC

The subgroup of patients with locally advanced HCC (BCLC stage C with portal vein invasion, without metastases or BCLC stage B progressive after TACE) was the target of two open-label phase 3 RCTs evaluating sorafenib versus selective internal radiation therapy (SIRT) (SARAH and SIRVENIB) [63, 64]. Despite a lower rate of AEs, a better quality of life, and higher ORR, survival benefit was not significantly higher in the SIRT groups and OS was slightly lower in the SIRT group compared with the sorafenib arm in patients with portal vein thrombosis. Sorafenib therefore remains the standard of care in this setting.

#### *Second and Further Lines of Treatment*

##### Patients with Progression under Sorafenib

For many years, patients who progressed under sorafenib had no other options than to continue sorafenib, receive best supportive care, or participate in (few) clinical trials. Nowadays, it is estimated that around 50% of patients are candidates for second-line treatment [65].

Regorafenib has shown a clear benefit in progressive patients, decreasing the risk of death by 37% versus best supportive care, provided sorafenib was well tolerated (sorafenib  $\geq 400$  mg/day for  $\geq 20$  of the last 28 days of treatment in the RESORCE trial) [8]. However, the number of treatment options is increasing, as exemplified by the FDA approval of nivolumab and pembrolizumab. In our opinion, regorafenib and, after approval and publication of the full data, cabozantinib should be the second-line treatment options of choice, pending the final survival data from nivolumab and pembrolizumab (expected in 2019) and the publication on ramucirumab in patients with AFP  $\geq 400$  ng/mL. The efficacy of nivolumab and pembrolizumab should be balanced by the costs, patient preference (oral vs. intravenous administration), and reimbursement.

A small proportion of patients will be eligible for third-line treatment. Cabozantinib may be a future treatment option in this subgroup. Finally, no results of phase 3 trials are available for second-line treatment after lenvatinib, resulting in the absence of a robust recommendation in this setting.

##### Sorafenib-Intolerant Patients

When no second-line therapies were available, intolerant patients continued sorafenib with adapted doses. Currently, nivolumab and pembrolizumab could be considered in the US. Cabozantinib and ramucirumab (in patients with AFP  $\geq 400$  ng/mL) may present future alternatives but are not yet approved. Regorafenib should generally be avoided in sorafenib-intolerant patients, but if no alternative options are available, regorafenib could be administered with caution, on a case-by-case basis, depending on the toxicities patients experienced with sorafenib. Close monitoring would be essential, as these patients were excluded from the RESORCE trial.

#### **Conclusion**

After 10 years, sorafenib is still the first-line standard of care for many patients with advanced HCC, including patients with locally advanced HCC and HCV-related advanced HCC. Lenvatinib may present an alternative for patients. Regorafenib is the treatment of choice for progressive patients, although nivolumab and pembrolizumab is available in the US based on

the results of a phase 2 study. Ramucirumab (in patients with AFP  $\geq 400$  ng/mL) and cabozantinib (in an unselected population) may present future second-line treatment options. In the near future, more data will be published on immunotherapy that will possibly affect the herein proposed recommendations. In the more distant future, precision medicine may come into play in the treatment of advanced HCC.

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