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Systemic therapy in advanced-stage hepatocellular carcinoma

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Summary Hepatocellular carcinoma (HCC) is a complex disease, since both choice of treatment and prognosis depend not only on tumor-specific but also on liver-related characteristics. Therefore, a multidisciplinary approach in specialized clinics is required for the optimal management of HCC patients. Almost half of patients present with advanced-stage tumor with no curative therapeutic options. According to international guidelines, palliative systemic therapy is recommended in these patients. The multikinase inhibitor sorafenib was the first drug to show antitumor efficacy and was the only approved treatment for almost a decade, as several other agents failed to improve patient survival. In recent years, treatment practices have changed with lenvatinib as another first-line treatment choice and regorafenib, cabozantinib, and ramucirumab as second-line therapeutic options. However, only patients with preserved liver function (Child-Pugh-Turcotte [CPT]-A) were enrolled in these studies and are consequently suitable for these drugs. After promising phase-1 and phase-2 studies, subsequent phase-3 trials evaluating the immune checkpoint inhibitors (ICIs) nivolumab and pembrolizumab have failed to demonstrate a significant improvement in patient survival. Ongoing trials are evaluating the combination of ICIs with tyrosine kinase inhibitors or vascular endothelial growth factor (VEGF) inhibitors. Recently, in a phase-3 trial, the combination therapy atezolizumab and bevacizumab led to a significantly improved overall survival compared to sorafenib in the first-line setting. Further studies are needed to determine how best to select between the growing number of therapeutic options.

Keywords Sorafenib · Lenvatinib · Regorafenib · Cabozantinib · Ramucirumab

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Introduction

Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers. Worldwide, liver cancers are the fourth most common cause of cancer-related death and rank sixth in terms of incident cases [1]. Whereas in Asia the global burden of HCC is declining, it is still increasing in the US and Europe [2]. Liver cancer is the second most lethal tumor. In the majority of cases, HCCs occur in patients with advanced-stage chronic (cirrhotic) liver disease, mostly as a result of hepatitis B (HBV) and C virus (HCV) infection and alcohol abuse [3, 4]. Due to the universal availability of HBV vaccination and the wide implementation of direct antiviral therapy for HCV, virus-related HCCs will decrease, whereas HCC due to non-alcoholic fatty liver disease (NAFLD) together with metabolic syndrome will become a leading cause of HCC in western countries. Despite the fact that surveillance programs lead to early detection in up to 51.6% of patients, at a point when curative treatment options are applicable, more than half of patients present with advanced-stage tumor and ultimately receive palliative therapies [5]. According to several international guidelines, systemic therapies are recommended for patients with advanced disease (Barcelona Clinic Liver Cancer [BCLC] stage C) or who have intermediate-stage disease (BCLC-B) and progression with transarterial therapies [6, 7].

Systemic chemotherapies that were used in the past, such as fluorouracil (5-FU), doxorubicin, and gemcitabine, as well as anti-hormonal therapies,

failed to show any benefit in several randomized controlled trials [8–10]. Progress in the understanding of hepato-carcinogenesis has led to the development of molecular targeted therapies. Sorafenib, a multitarget tyrosine kinase inhibitor (TKI), was the first drug to demonstrate antitumor efficacy in patients with advanced-stage HCC with well-preserved liver function [11].

First-line therapy

In 2008, the pivotal Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial showed that, in comparison to placebo, **sorafenib** (400 mg BID) led to a significant improvement in both overall median survival (mOS) (10.7 vs. 7.9 months) as well as median progression free survival (mPFS) (5.5 vs. 2.8 months) [11]. The safety and efficacy of this agent were validated in patients from the Asian-Pacific region [12]. Sorafenib was consequently approved for the treatment of advanced-stage HCC and has remained the gold standard for over a decade. In these studies, however, only patients with preserved liver function (Child-Pugh-Turcotte [CPT] A) were included. A retrospective Austrian study as well as a large international observational study demonstrated that patients with mildly decompensated cirrhosis (CPT-B [7 points]) might also benefit from sorafenib [13, 14]. Due to the overall poor prognosis of decompensated cirrhosis, sorafenib did not show any survival benefit in these patients and, therefore, treatment should be avoided. Moreover, the typical side effects of sorafenib, mainly diarrhea, hand-foot syndrome (HFS), and hypertension, are aggravated in patients with advanced-stage liver cirrhosis [14]. Due to the potential of adverse events, one should consider commencing sorafenib at a lower dose (e.g., 200 mg BID), especially in patients with CPT-B.

After negative results in several randomized controlled trials (RCTs), including erlotinib, brivanib, sunitinib, and linifanib, **lenvatinib** proved in 2018 to be non-inferior to sorafenib in the first-line setting. Median survival in the lenvatinib and sorafenib groups was 13.6 months and 12.3 months, respectively [15]. Grade 3 or 4 adverse events with lenvatinib included hypertension (23% vs. 14% receiving sorafenib), weight loss (8% vs. 3%), and HFS (3% vs. 11%). Based on this study, lenvatinib received Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the first-line treatment of HCC in 2018. Interestingly, lenvatinib showed a statistically significant improvement compared with sorafenib for all secondary efficacy endpoints (progression-free survival, time to progression, and objective response) as determined by investigator tumor assessments based on modified response evaluation criteria in solid tumors (mRECIST). mPFS was 8.9 months in the lenvatinib cohort compared to 3.7 months in the sorafenib group.

More recently, the data from a phase-3 RCT (IMbrave 150) were presented at the European Society for Medical Oncology (ESMO) Asia meeting showing a significant improvement for atezolizumab in combination with bevazizumab compared to sorafenib with regard to mOS (NE vs. 13.2 months) and mPFS (6.8 vs. 4.3 months) [16]. However, the publication of the full paper needs to be awaited in order to draw conclusions for daily clinical practice.

Second-line therapy

Based on promising phase-2 studies, several drugs, such as brivanib, everolimus, and tivantinib, have been tested in RCTs in patients experiencing tumor progression or intolerance of first-line sorafenib. However, all these agents failed to show any benefit in overall survival compared to placebo and best supportive care.

In 2017, **regorafenib** was the first drug to demonstrate a significant survival benefit in patients with HCC progression receiving sorafenib therapy. In the RESORCE trial, regorafenib led to an increase in both mOS from 7.8 (placebo) to 10.6 months and median time to tumor progression (mTTP) according to mRECIST from 1.5 to 3.2 months [17]. Again, only patients with preserved liver function (CPT-A) were included. As for safety, more patients in the regorafenib arm had treatment interruption or dose reduction (50% vs. 10%) and discontinuation due to drug-related adverse events (10% vs. 4%). The safety profile was similar to that of sorafenib with hypertension, HFS, and diarrhea as the most common clinically relevant grade 3 and 4 events. Based on this study, regorafenib became the first drug to be approved for second-line treatment. An additional, exploratory analysis investigated the outcome of sequential treatment with sorafenib followed by regorafenib [18]. The sequence sorafenib-regorafenib yield an mOS of 26.0 months compared to 19.2 months for sorafenib-placebo. The survival benefit was independent of the pattern of disease progression during prior sorafenib therapy and of the last sorafenib dose (800 mg vs. <800 mg). However, the data need to be interpreted with caution, as patients who died during sorafenib therapy or showed a deterioration in liver function to CPT B were not included in this analysis. Thus, it represents a positive selection of the very best patients.

Based on the positive phase-3 data from a large RCT (CELESTIAL trial), **cabozantinib** received approval for second-line treatment at the end of 2018. Eligible patients had a diagnosis of HCC not amenable to curative treatment but with preserved liver function (CPT-A). They had previously received sorafenib, but additionally they could have also received up to two previous systemic therapies with progression on at least one of them [19]. Compared to placebo, cabozantinib improved the mOS from 8.0 to 11.3 months in the overall cohort and from 7.2 to 11.3 in the sub-

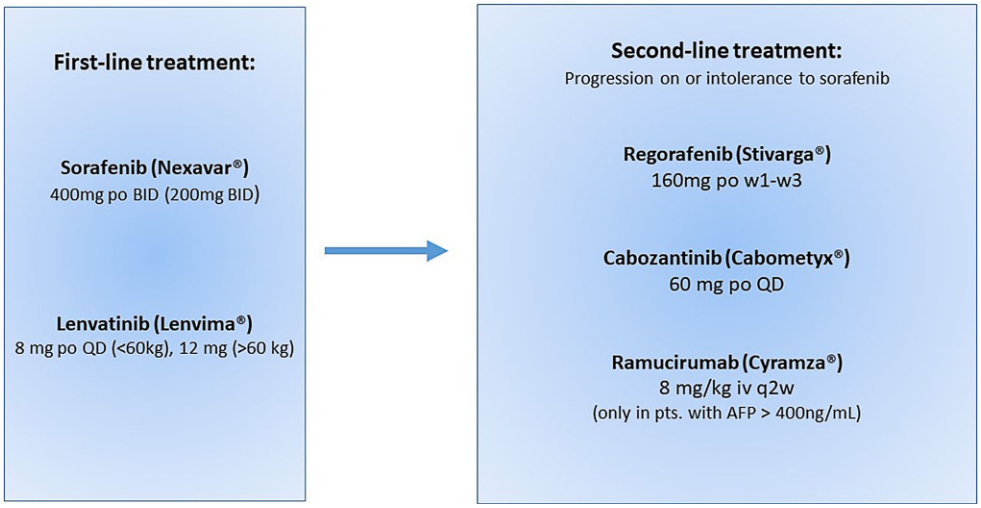

Fig. 1 Approved agents for the treatment of advanced-stage HCC. *po* Per os; *iv* intravenously; *QD* once daily; *BID* twice daily; *q2w* every second week; *q3w* every third week; *AFP* alpha-fetoprotein

group of patients that previously only received sorafenib. In addition, the mPFS was significantly better in the cabozantinib group compared to placebo (5.2 vs. 1.9 months). Regarding safety, more patients in the experimental arm needed dose reduction (62 vs. 13%) or discontinuation due to drug-related adverse events (16 vs. 3%). The most common grade 3 and 4 side effects were HFS, hypertension, increased serum aspartate aminotransferase (AST), fatigue, and diarrhea.

The REACH-1 study failed to demonstrate any benefit for **ramucirumab** in the second-line setting after progression under sorafenib therapy. In a post-hoc subgroup analysis, however, ramucirumab led to a significant survival benefit in patients with an alpha-fetoprotein >400 ng/mL [20]. This finding was validated in the subsequent REACH-2 trial. In comparison to placebo, ramucirumab increased mOS (8.5 vs. 7.3 months) as well as mPFS (2.8 vs. 1.6 months) with manageable side effects [21].

Bangaru et al. have proposed a possible algorithm for the second-line therapy for advanced-stage HCC based on first-line TKI tolerance and alpha-fetoprotein levels (above or below 400 ng/mL) [22].

Table 1 Efficacy data from phase-3 trials for the first- and second-line therapy of hepatocellular carcinoma

Trial	Drugs	HR (OS) *p*-value	Median OS (months) *p*-value	Median PFS (months) *p*-value	ORR
First-line treatment					
SHARP [11] ($n=602$)	Sorafenib vs. Placebo	0.69 (95% CI 0.55–0.87)	10.7 vs. 7.9 $p<0.001$	5.5 vs. 2.8 $p<0.001$	RECIST: 2% vs. 1%
Asia-Pacific [12] ($n=226$)	Sorafenib vs. Placebo	0.68 (95% CI 0.50–0.93) 0.014	6.5 vs. 4.2 $p=0.014$	2.8 vs. 1.4 $p=0.005$	RECIST: 3.3 vs. 1.3%
REFLECT [15] ($n=954$) Non-inferiority trial	Lenvantinib vs. Sorafenib	0.92 (95% CI 0.79–1.06)	13.6 vs. 12.3 $p=$ n. s.	7.5 vs. 3.6 $p<0.0001$	RECIST: 18.8% vs. 6.5% mRECIST: 40.6 vs. 12.4%
[a] IMBrave 150 [16] ($n=501$)	Atezolizumab + Bevacizumab vs. Sorafenib	0.58 (96% CI 0.42–0.79)	NE vs. 13.2 $p=0.0006$	6.8 vs. 4.3 $p<0.0001$	RECIST: 27% vs. 12% mRECIST: 33 vs. 13%
[a] CHECKMATE 459 [27] ($n=726$)	Nivolumab vs. Sorafenib	0.84 (95% CI 0.72–1.02)	16.4 vs. 14.7 $p=0.0752$	3.7 vs. 3.8 $p=$ n. s.	RECIST: 15% vs. 7%
Second-line treatment					
RESORCE [17] ($n=573$)	Regorafenib vs. Placebo	0.63 (95% CI 0.50–0.79)	10.6 vs. 7.8 $p<0.0001$	3.1 vs. 1.5 $p<0.0001$	RECIST: 6.6% vs. 2.6% mRECIST: 10.6 vs. 4.1%
CELESTIAL [19] ($n=760$)	Cabozantinib vs. Placebo	0.76 (95% CI 0.63–0.92)	10.2 vs. 8.0 $p=0.005$	5.2 vs. 1.9 $p<0.001$	RECIST: 4 vs. 0.4%
REACH-2 [21] ($n=292$) pts. with AFP >400 ng/mL	Ramucirumab vs. Placebo	0.71 (95% CI 0.53–0.95)	8.5 vs. 7.3 $p=0.0199$	2.8 vs. 1.6 $p<0.0001$	RECIST: 5 vs. 1%
KEYNOTE 240 [29] ($n=413$)	Pembrolizumab vs. Placebo	0.78 (95% CI 0.61–0.99)	13.9 vs. 10.6 $p=0.0238$	3.0 vs. 2.8 $p=0186$	RECIST: 18.3 vs. 4.4%

HR hazard ratio; *n.s.* not statistically significant; *NE* not evaluated; *OS* obverall survival; *PFS* progression-free survival; *ORR* objective response rate; *AFP* alpha-fetoprotein; *(m)RECIST* (modified) response evaluation criteria in solid tumors
[a]Trial not yet published as full paper; meeting abstract available

In recent years, new agents have been introduced and approved for the treatment of advanced-stage HCC. However, it should be pointed out that in these trials almost only patients with preserved liver function (CPT-A) were enrolled, which is not representative for all patients with advanced tumor stage. Unfortunately, scientific evidence for the efficacy and safety in patients with CPT-B is limited to observational or retrospective series. In the majority of patients, advanced tumor stage and/or tumor progression are associated with progressive liver disease, a contraindication for the use of the abovementioned antitumor drugs. In a recently presented real-life experience after first-line treatment with sorafenib, only a small, proportion of patients (13.1%) actually met the inclusion criteria for the RESORCE, CELESTIAl and REACH-2 trials [23]. Expanding the inclusion criteria, such as enrolment of CPT-B7 patients, would have led to a significant impairment of mOS mainly due to an increase in severe adverse events.

All approved agents for the treatment of advanced-stage HCC are shown in Fig. 1; the efficacy data from phase-3 trials for the first- and second-line therapy for HCC are summarized in Table 1.

Immunotherapy: immune checkpoint inhibitors

Immunotherapy has been the breakthrough in cancer treatment in recent years and has revolutionized the cure strategy, with continuous advances and evidence of efficacy in several types of cancer. It has been shown that expression of programmed cell death ligand 1 (PD-L1) and upregulation of programmed cell death (PD) 1 on CD8(+) T cells correlated with poorer prognosis in patients with HCC [24]. The clinical benefit of immune-based therapies for HCC are emerging.

The CheckMate 040 trial was designed as a multicenter, open-label, phase-1 and -2 trial to evaluate the safety and efficacy of PD-1 immune checkpoint inhibitor (ICI) **nivolumab** in patients with advanced-stage HCC [25]. In contrast to other studies, patients with CPT-B (7 points) were also enrolled. *Disease control* could be observed in 64% of patients (1% complete response [CR], 18% partial response [PR], 45% stable disease [SD]) mainly within 3 months after treatment. In contrast, around 25% of patients developed rapid progression. Unfortunately, no specific marker could be found for this cohort. Survival outcomes were encouraging with a 6- and 9-month survival of 83% and 74%, respectively, and an mTTP of 4 months. In a recent follow-up study, 18-month OS was 57% in sorafenib-naïve patients and 44% in sorafenib-experienced patients with mOS of 28.6 and 15.6 months, respectively [26]. The most common adverse events of any grades were fatigue, pruritus, rash, and grade 3/4 increase in serum transaminases. However, phase-3 data (CheckMate 459 trial) recently reported no significant improvement in mOS with nivolumab compared to sorafenib in the first-line setting [27].

The results for pembrolizumab, another PD-1 inhibitor, in the treatment of advanced-stage HCC were reported in the non-randomized phase-2 KEYNOTE-224 trial. A total of 114 patients that had either progressed on (80%) or were intolerant to (20%) sorafenib were included. After a median follow-up of 12.3 months, tumor response was seen in 17% of patients (1% CR, 16% PR) and 44% of patients had SD [28]. Similar to nivolumab, the response generally occurred at the first radiologic assessment. The mTTP was 4.9 months and mOS 12.9 months. The most frequent serious adverse events were increased serum transaminases and adrenal insufficiency. The final analyses of the phase-3 RCT KEYNOTE-240 evaluating pembrolizumab versus placebo as a second-line treatment in western HCC patients showed an improvement in the co-primary endpoints OS and PFS; however, these differences did not reach statistical significance per specified criteria [29].

As already mentioned, the IMbrave 150 study comparing atezolizumab (anti-PD-L1 antibody) in combination with bevacizumb was the first positive immunotherapy phase-3 trial demonstrating a significant improvement in OS and PFS compared to sorafenib in the first-line setting [16].

Ongoing trials and the future of liver cancer treatment

There are other ongoing trials evaluating the safety and efficacy of anti-PD-1 monotherapy for advanced-stage HCC patients either in the first- or second-line setting. In addition, other strategies are being pursued to maximize the potential of immunotherapy; in particular, some trials are exploring the combination with anti-PD1/PD-1L with TKIs, anti-vascular endothelial growth factor (VEGF) or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) drugs. Immunotherapeutic agents may be promising for combination therapy with sorafenib and other anti-angiogenetic drugs, since the major toxicity profiles of TKIs and immunotherapeutic drugs do not overlap. Results from phase-1 and -2 studies are already available and show potential benefit compared to anti-PD1 monotherapy [30, 31]. In addition, the adverse events in these combination treatments were manageable.

Several other combination therapies are still ongoing and will hopefully further increase objective response, improve survival, and their results may reshape the treatment landscape.

Take home message

- Sorafenib and lenvatinib are approved for the first-line therapy of patients with advanced-stage hepatocellular carcinoma.

- Regorafenib, cabozantinib, and ramucirumab are therapeutic options for the second-line setting.

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