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Anti-Tumour Treatment

Current strategies for the treatment of intermediate and advanced hepatocellular carcinoma

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A B S T R A C T

Hepatocellular carcinoma (HCC) ranks among the most common cancers worldwide and remains to be a major global health care problem. Until 2007, no effective therapies were available for patients after failure of locoregional approaches, and the approval of sorafenib as the first systemic agent with efficacy in patients suffering from advanced HCC marked a new era in the treatment of this deadly disease. However, it took nearly 10 years until the portfolio of effective drugs finally expanded and additional substances showed activity in both first and further lines of treatment. Since their recent approval, these novel substances have substantially changed the field of palliative treatment strategies in patients with advanced HCC, and their sequential application has demonstrated their potential to significantly prolong patient survival in the palliative setting. With the recently communicated data from the first positive immuno-oncology trial in HCC, it appears highly likely that the implementation of IO concepts will result in a further improvement of patient prognosis. Although locoregional approaches remain an integral component of meaningful treatment concepts for patients with BCLC-B stage HCC, repetitive interventions bear the risk of a progressive deterioration of liver function. More than ever, in order to implement long-term therapeutic concepts and exploit the full potential of systemic treatment strategies, it is of utmost importance to maintain a fine balance between anti-tumor activity and toxicity.

With an emphasis on the systemic treatment options, this review provides a summary of the most recent results from large phase III clinical trials and discusses their clinical implications.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadliest cancers worldwide with a rising incidence in the Western world [1]. These phenotypically and molecularly heterogeneous tumors are characterized by a pronounced intrinsic resistance to systemic chemotherapies. For almost 10 years, the tyrosine kinase inhibitor (TKI) sorafenib was the only approved treatment for advanced HCCs in patients with preserved liver function, and until 2016, none of the compounds tested in both first and second line setting in large phase-III studies led to a survival benefit. The TKI regorafenib was the first substance that significantly improved overall survival after failure of sorafenib treatment, which subsequently led to regulatory approval in a second line setting in 2017. In addition, the non-inferiority of lenvatinib in comparison to sorafenib opened another therapeutic first-line option in the same year. Subsequently, cabozantinib showed convincing anti-tumor efficacy in recent phase-III studies in second- and third line approaches, and ramucirumab is now the first biomarker-guided therapy that gained approval in the second line setting for patients with AFP values exceeding 400 ng/ml. Promising early reports from the checkpoint inhibitors nivolumab and pembrolizumab paved the way for immuno-oncological (IO) interventions for HCC, and the combination of atezolizumab and bevacizumab is the first IO combination with statistically and clinically meaningful activity in advanced HCC.

Thus, a sequential treatment approach of systemic therapies is now feasible and should be implemented to improve survival of HCC patients.

Transition from local therapies to systemic therapies

HCC is a malignancy that requires interdisciplinary evaluation to develop individualized and tailored treatment concepts. The reasonable combination of appropriate surgical approaches, interventional/loco-regional treatment strategies and various lines of systemic therapies is required to achieve the best possible patient survival. Although locoregional therapies will remain a mainstay of HCC therapy, recent studies advocate for a more cautious use. Many patients who receive repeated loco-regional treatments regardless of tumor stage experience a progressive impairment of liver function, rendering the initiation of effective systemic therapies impossible [2,3]. In line with this, several single center retrospective studies have shown that in clinical routine less than 20% of patients have received systemic treatment in the past [4]. Similar observations were reported from the large BRIDGE study, a multiregional, longitudinal cohort study to document real-life management of patients with HCC to provide a better understanding of global treatment patterns in HCC. Based on data from more than 18,000

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patients diagnosed with HCC between 2005 and 2012, this retrospective study confirmed that TACE was the most frequent first-line treatment across all stages and that the use of systemic therapies was extremely low despite a high number of patients with advanced disease [5]. In current guidelines, TACE is recommended for intermediate stage HCC patients with well-preserved liver function and multinodular HCC without vascular invasion. In light of increasing evidence that survival with TACE in unselected patient populations is significantly worse compared to the results reported in the pivotal phase-III study, the extended use of local, intraarterial therapies demands a critical re-evaluation [6]. In contrast to the survival of 28 months in the phase-III study, a recent meta-analysis across 101 studies, including more than 10,000 patients, revealed a mOS of only 18 months in patients treated with TACE [7]. Despite the low mOS, 5-year survival rate was remarkably high with 32.5% highlighting the anti-tumor efficacy of TACE in well selected patients. In order to identify those patients with long-term benefit within the heterogeneous cohort of intermediate stage HCCs, as well as to prevent the widespread use of TACE outside treatment recommendations, scoring systems have been developed that can reliably predict survival after TACE on the basis of baseline clinical features. Among the first prognostic scores was the hepatoma arterial-embolization prognostic (HAP) score, which is based on 4 factors that are considered significant predictors of overall survival: albumin and bilirubin level as markers of liver function and α-fetoprotein level and tumor size as markers of tumor burden. The HAP score is calculated as the sum of points allocated to each factors, and patients are then classified into four distinct prognostic groups with respect to overall survival (HAP A = 0 points; HAP B = 1 point; HAP C = 2 points; HAP D- ≥ 3 points) [8,9]. The score has been internationally validated and bears the advantage of easy applicability and simplicity. A limitation of the score is that it does not permit patient-level prognostication; this limitation was recently met by Johnson and colleagues who developed a TACE-specific model based on routinely available clinical features [10]. In addition to the parameters included in the HAP score, this score considers further factors that influence survival, such as tumor number, vascular invasion and etiology of the underlying liver disease. The proposed model shows superior predictive accuracy compared to existing models and allows for patient stratification into four distinct risk categories with a clinically meaningful survival range between 7 months and more than 4 years.

One of the key factors in HCC treatment is the preservation of liver function and several trials have observed acute and chronic liver injury in patients treated with TACE, especially with less selective or repeated TACE procedures [2,11,12]. In addition to the development of criteria to identify the best TACE candidate, there is thus a need to define unresponsiveness or refractoriness to TACE to avoid possible unnecessary harm to the liver. Retrospective studies have identified increased liver injury, deterioration of liver function and absence of radiological tumor response as prognostic factors for overall survival [13,14]. While it is widely accepted that repeated TACE sessions should be avoided in patients with prolonged liver injury or with any deterioration of liver function, the role of response assessment is still evolving. Several studies have shown that complete and partial responses assessed by mRECIST or RECIST1.1 is a strong predictor for overall survival [15,16]. The optimal number of TACE sessions to reach the best response in an individual is not well defined and in clinical practice it is recommended that two TACE sessions can be performed based on observations that patients who do not respond to the first TACE may achieve a response after a second course [17,18]. In contrast to patients who experience a response after TACE, there is meanwhile convincing evidence that patients that only achieve disease stabilization have a poor prognosis and will not benefit from additional TACE treatments [10]. A switch to systemic therapies should therefore be considered in patients whose disease is refractory to TACE and/or with an early recurrence of new lesions. In line with this recommendation, intermediate HCC patients whose disease was refractory to TACE and who were switched to systemic therapy experienced an increase in survival and better preservation of liver function compared to those who continued TACE in several observational and retrospective studies [2,11,12,18].

In recent years radioembolization (SIRT) has been positioned between TACE and systemic therapy in the treatment algorithms of many centers, mainly based on real world data [19]. Recently, three prospective, randomized phase-III trials have evaluated the activity of SIRT in HCC. Two of these trials (SARAH trial in France and the SIRveNIB trial in Asia-Pacific) randomised intermediate stage patients with preserved liver function to sorafenib or SIRT. Both trials failed to meet the primary endpoint to improve OS compared to sorafenib [20,21]. In addition, based on the data from the SORAMIC phase-II trial, the addition of SIRT to sorafenib treatment does not improve survival compared to sorafenib alone in patients with advanced HCC [22]. SIRT is therefore not recommended for HCC patients in intermediate stage who are refractory to TACE and for patients in advanced stage HCC.

In conclusion, potential benefits of locoregional treatment need to be critically weighted against potential adverse effects, especially on liver function, which will seriously affect the prognosis of the patients. An interdisciplinary dialogue of all disciplines involved in the treatment of HCC patients is imperative to select the best possible treatment algorithm. Several recently published scores allow prediction of expected survival before and after first TACE based on clinical features and response assessment, and should be implemented in daily decision making to select the patients for either local or systemic therapies.

Systemic therapies

First line therapies

Sorafenib – The gold standard in first line for 10 years

Until 2007, no effective treatment for patients diagnosed with advanced HCCs or patients who progressed into this stage after failure of other therapies was available. The positive results of the randomized, controlled phase-III SHARP trial evaluating sorafenib, an oral multi-TKI with activity against Vascular Endothelial Growth Factor Receptor (VEGFR), Platelet-derived Growth Factor Receptor (PDGFR) and RAF Kinase, for advanced HCC in a mainly Western cohort provided first evidence for the efficacy of of small molecule inhibitors in advanced HCCs [23]. Median OS in the sorafenib arm was 10.7 months vs. 7.9 month in placebo-treated patients (Hazard ratio (HR), 0.69; 95% CI 0.55–0.87; p = 0.00058). Similar results were not only demonstrated in a parallel phase-III study involving mainly Asian, predominantly hepatitis B-infected patients [24], but also in 8 subsequent phase-III studies in which sorafenib served as control treatment. On the basis of the positive results from the two initial phase-III trials, sorafenib was approved and became the systemic standard of care in HCC. Although currently no predictive biomarkers for response exist, clinical factors such as chronic hepatitis C infection, a low neutrophil to lymphocyte ratio and a liver limited disease appear to favor a better response to the treatment with sorafenib [25]. Because VEGF receptor-2 is considered a key target of sorafenib, its ligand VEGF-A has been studied as a potential biomarker for sorafenib efficacy. In the translational programm of the SHARP study, baseline plasma VEGF-A concentration exhibited no predictive value, but high plasma VEGF-A level were associated with a poor prognosis [26]. Similarely, high baseline plasma Ang-2 level was an independent marker for poor OS but not for sorafenib efficacy. Although the SHARP study demonstrated that sorafenib improves survival by about 3 months, survival varies significantly between patients treated with the multi-TKI. Recently, a multivariable model was developed to predict survival following sorafenib treatment based on baseline clinical features, which may help clinical decision making. The variables influencing overall survival in the PROSASH score were vascular invasion, age, ECOG score, AFP, albumin, creatinine, AST, extrahepatic spread and aetiology. Corresponding data can be entered into an online tool that calculates the respective survival percentage at

6, 12, 24 and 36 months (https://jscalc.io/calc/oGSDLHDsDg9g2XBF) [27].

Despite its approval for all stages of liver disease, large non-interventional observational studies have shown that the survival of patients with CHILD B cirrhosis under treatment with sorafenib is significantly shorter when compared to sorafenib-treated CHILD A patients. Since these studies did not provide conclusive evidence for a benefit in CHILD B patients, the use of sorafenib should in general be limited to patients with compensated stages of cirrhosis [28]. The spectrum of adverse effects of sorafenib is well described and requires close monitoring of the patients, specifically during the first weeks of treatment. For instance, diarrhea, hypertension and hand-foot syndrome occur in a number of patients, but the majority of these adverse effects can be controlled and attenuated by supportive measures and frequently also dose reductions. Of note, dose reductions (i.e. < 800 mg/d) do not seem to impair overall outcome of patients [29]. Interestingly, paralleling observations in patients treated with EGFR-targeted agents, early skin reactions and diarrhea seem to be predictors of a favorable therapy response [30].

Lenvatinib – REFLECT trial

Lenvatinib is an oral multi-TKI with activity against VEGFR1-3, FGFR1-4, PDGF, RET und KIT. The recent open-label phase-III study REFLECT involving mainly Asian patients demonstrated non-inferiority of lenvatinib in comparison to sorafenib in a first line setting [31]. The study achieved its primary endpoint with a mOS of 13.6 months in the experimental lenvatinib arm versus 12.3 months in the sorafenib arm (HR: 0.92; 95% CI 0.79–1.06). An interesting observation of this trial was the high objective response rate (ORR) for lenvantinib with 24.1% vs 9.2% for sorafenib (independent review: ORR mRECIST 40.6% vs. 12.4%, ORR RECIST1.1: 18.8% vs. 6.5%). In order to assess the association between OR and OS irrespective of the treatment, mOS of responders was compared to that of non-responders using landmark analysis. Interestingly, mOS was 22.4 months for responders and 11.4 months for non-responders and OS was significantly prolonged for patients who achieved an objective response at the 2-, 4- and 6-months landmark. Moreover, an exploratory multivariate Cox regression analysis provided first time robust evidence that response is an independent predictor of OS in HCC patients under systemic therapy [32]. Further, surrogate characteristics for survival such as progression free survival (PFS) and time-to-progression (TTP) were consistently higher in the lenvatinib group than in the sorafenib group (PFS: 7.4 months vs. 3.7 months; TTP: 8.9 months vs. 3.7 months). Adverse effects were overall slightly more pronounced in lenvatinib-treated patients, particularly hypertension and thrombocytopenia. However, time on treatment was also significantly longer in the experimental arm (5.7 months for lenvatinib vs. 3.7 months for sorafenib) and time on treatment-adjusted adverse event rates were similar in both arms. Another secondary endpoint of the REFLECT study was the assessment of quality of life over the course of the study. Quality of life scores declined with both treatments, however treatment with lenvatinib delayed deterioration of several QLQ-C30 domains such as role function, pain and diarrhea [33]. Similar to the findings in the SHARP study, the biomarker program of the REFELCT study has so far not identified any clinical useful markers to select for either treatment, with the exception that in the small subgroup of patients with high baseline FGF21 OS was longer for lenvatinib compared to sorafenib. Higher VEGF, ANG2, and FGF21 baseline levels were associated with worse OS in both arms [34].

The study excluded patients with adverse prognostic tumor characteristics, e.g. main branch portal vein thrombosis or greater than 50% tumor occupation of the liver, which should be considered in routine clinical decision making. Nevertheless, results from the trial encourage the use of lenvatinib as an effective first line therapy in advanced HCC leading to inclusion in recent EASL and ESMO guidelines [35,36]. Consequently, approval for lenvatinib in first line was recently granted by the FDA and EMA.

Nivolumab – Checkmate-459 trial

Initial clinical immunotherapy trials in HCC were performed with nivolumab: the large dose-escalation and expansion study Checkmate-040 for patients with advanced hepatocellular carcinomas demonstrated both safety and efficacy of the anti-PD-1 antibody [37]. High disease control rates and ORR were observed across all investigated subgroups, including patients with impaired liver function, extrahepatic tumor burden, or in patients after treatment with sorafenib. Results from the dose-escalation phase also indicated that nivolumab is safe in patients with chronic hepatitis C and B infections. Based on these findings, nivolumab was granted accelerated approval by the FDA for second-line therapy of advanced HCC. Subsequently, the efficacy of nivolumab was tested in first line to show superiority over sorafenib. Overall, 643 patients were randomized to either treatment with a minimum follow-up of 22.8 months [38]. Unfortunately, nivolumab did not significantly improve mOS according to the predefined threshold of statistical significance (HR 0.84, p = 0.0419). mOS was remarkably long in both arms with 16.4 months for nivolumab and 14.7 months for sorafenib (HR 0.85 [95% CI: 0.72–1.02]; p = 0.0752). Clinical benefit was observed across predefined subgroups, including hepatitis infection status, presence of vascular invasion and/or extrahepatic spread, and region. In agreement with previous studies, ORR was 15% for nivolumab and 7% for sorafenib and mPFS was very similar between both arms with 3.7 months vs 3.8 months. Grade 3/4 treatment-related adverse events were significantly lower in the nivolumab arm compared to the sorafenib arm and QoL scores were clearly in favor of nivolumab. Overall, the study revealed an improvement in mOS for patients with advanced HCC in both treatment arms, but failed to show a superiority of immunotherapy over sorafenib indicating that either better patient selection or combination therapies are required to significantly improve mOS with immunotherapy in advanced HCC.

AtezoBev – IMbrave150 trial

Several promising combinatorial treatment strategies involving immune checkpoint inhibitors are currently under investigation both for concurrent and sequential use. These include dual checkpoint inhibition, combination with kinase inhibitors or loco-regional therapies, such as RFA, TACE and irradiation. Very recently, convincing data for the combination of atezolizumab and bevacizumab has been published. Bevacizumab has demonstrated only modest single-agent activity in HCC in small phase-II studies. The rationale for combining an angiogenesis inhibitor and a PD-L1 inhibitor is based on the hypervascularity that many HCC tumors exhibit and the overexpression of VEGF and PD-L1. Preclinical evidence suggests that VEGF inhibition may not only have direct antiangiogenic effects, but also helps to reverse VEGF-mediated immunosuppression and enhance anticancer immunity - a concept that has already shown clinical benefit in other tumor types. In the initial IMbrave phase-Ib study, 36% of patients had confirmed responses with atezolizumab and bevacizumab, including 12 complete responses. An additional 37 patients had stable disease, resulting in a disease control rate of 71%. mPFS was 7.3 months and mOS was 17.1 months with a 12-month OS of 63%. In the second part of the study, patients were randomized to the combination vs. atezolizumab alone. In this part, primary endpoints were safety and PFS by independent review. After a median follow-up of 6.6 months, the combination arm had a median PFS of 5.6 months versus 3.4 months for the atezolizumab control group, providing additional evidence for the superior performance of the combination approach in advanced HCC. The combination was subsequently evaluated in the randomized phase-III IMbrave150 study in comparison to sorafenib. mOS had not yet been reached for atezolizumab plus bevacizumab compared to 13.2 months for patients randomized to sorafenib after a median follow-up of 8.6 months (HR: 0.58 (95% CI 0.42, 0.79, p = 0.0006). mPFS was also significantly increased with 6.8 vs 4.3 months (HR: 0.59, 95% CI 0.47, 0.76, p < 0.0001). Further underscoring the superior performance of the combination therapy, overall response rate more than doubled in

the atezolizumab plus bevacizumab arm compared to sorafenib alone (27% vs 12%, p < 0.0001) based on independent assessment using RECIST 1.1 criteria, with comparable results when HCC mRECIST criteria were applied (33% vs 13%, p < 0.0001). Importantly, the increased efficacy of atezolizumab plus bevacizumab was accompanied by a significantly delayed deterioration in quality of life compared to sorafenib. Grade 3/4 adverse events matched the previously reported side effect profiles of the respective drugs and occurred with similar frequencies in both arms. In contrast to the characteristic TKI side effects of sorafenib, the most frequent grade 3/4 adverse events for atezolizumab plus bevacizumab were hypertension and proteinuria.

Together, after 12 phase-III trials with sorafenib as control arm during the last 11 years, IMbrave150 was the first positive phase-III study showing a clinically meaningful overall survival benefit compared to sorafenib. Based on these data the combination of atezolizumab plus bevacizumab will become the next standard of care in first line HCC.

Second line therapies

Regorafenib – RESORCE trial

Regorafenib is an oral fluorinated sorafenib analog with a similar spectrum of molecular targets. Besides a profound anti-proliferative effect on the tumor cells, regorafenib significantly inhibits neo-angiogenesis and, thus, modulates the tumor microenvironment. The randomized controlled RESORCE phase-III trial evaluated the role of regorafenib in patients with advanced HCC that progressed under sorafenib therapy [39]. Main inclusion criteria were a preserved liver function (CHILD A), progressive disease under sorafenib as well as tolerability to sorafenib (defined as receiving sorafenib ≥400 mg for at least 20 days of the last 28 days of treatment). Patients were rigorously stratified for region, portal-vein thrombosis, AFP levels and extrahepatic tumor manifestation. The median duration on prior sorafenib was identical in both study cohorts, but with 7.8 months notably longer compared to unselected patient populations. The trial reached its primary endpoint and demonstrated a significantly improved OS for regorafenib vs. placebo (10.6 vs 7.8 months, HR 0.63; 95% CI 0.50–0.79 m p < 0,0001) as well as an increase in the median TTP (3.2 months vs. 1.5 months; HR 0.44; 95% CI 0.36–0.55; p < 0.001). In addition, regorafenib significantly extended the tumor control (65.2% vs. 36.1% (p < 0.001)) as well as objective response rate (10.6% vs. 4.1% (p = 0.005)). The spectrum of adverse events was comparable to side-effects described for sorafenib, including hypertension, hand-foot-syndrome, fatigue and diarrhea, but was overall manageable. In the translational program of the RESORCE study, archived tumor tissues and baseline plasma sample were analyzed to identify predictive and prognostic biomarkers. In agreement with previous studies, plasma levels of AFP and c-MET were associated with poor overall survival. Interestingly, among 266 analyzed proteins, the decreased level of 5 proteins was identified as predictive for regorafenib treatment benefit regarding OS in the regorafenib arm (angiopoietin 1, cystatin B, the latency-associated peptide of trans-forming growth factor beta 1, oxidized low-density lipoprotein receptor 1, C-C motif chemokine ligand 3). None of these potentially predictive proteins were found to be prognostic for OS [40]. Based on the results of the RESORCE trial, regorafenib was approved by the FDA and the EMA for treatment of patients with advanced HCCs who tolerated but progressed on sorafenib.

Cabozantinib – CELESTIAL trial

Cabozantinib is a multi-TKI with activity against MET, VEGFR2 and RET. Following its approval for the treatment of thyroid and renal cell carcinomas, cabozantinib has most recently been granted approval as a second line treatment in HCC Child Pugh A patients by EMA and FDA. The phase-III CELESTIAL trial compared cabozantinib vs. placebo in second- and third line treatment for advanced HCC with preserved liver function and good performance status (i.e. Child-Pugh A, ECOG PS 0/1). The study was terminated after the second interim analysis due to proven efficacy [41]. Overall, an improvement in OS from 8.0 months to 10.2 months could be demonstrated for cabozantinib compared to placebo. Mean PFS was 5.4 months versus 1.9 months (HR 0.44, 95% CI 0.36–0.52, p < 0.001). Further, the disease control rate was 64% for cabozantinib vs. 33.4% in placebo (p < 0.001) with a low ORR rate of 4% vs. 0.4% according to RECIST 1.1 (p = 0.0086). 28% of the patients in the cabozantinib arm had received more than one previous line of therapy. According to a subsequent post-hoc analysis, mOS was improved from 7.2 months to 11.3 months in patients that had received only sorafenib as previous therapy (HR 0.70, 95% CI 0.55–0.88). A multivariate analysis identified high baseline values of AFP, alkaline phosphatase, ALBI grade, neutrophil to lymphocyte ratio, and number of disease sites as prognostic factors for shorter OS [42]. Interestingly, in the cabozantinib arm mOS was 17.5 months in patients with an ALBI grade 1 compared to 8.0 months for patients with an ALBI grade 2, thus confirming the high prognostic relevance of liver function in HCC. Efficacy of cabozantinib was independent of liver function, but there was a trend for a higher efficacy in patients with better liver function [43].

Similar to the other TKIs, grade 3/4 side effects occurred in 68% of patients and predominantly involved hand-foot syndrome, hypertension, transaminase elevation and fatigue. In order to assess the impact of cabozantinib on QoL, a post-hoc analysis compared patient experience of three discrete health states: time with grade 3/4 toxicity before progression (TOX), time without grade 3/4 toxicity before progression (TWiST) and survival time after progression (REL) [44]. Despite an increase in days with grade 3/4 toxicity before progression, patients treated with cabozantinib spent significantly more time without disease symptoms and toxicity than those receiving placebo. In the translational program of the CELESTIAL study, plasma samples were analyzed for the prognostic and predictive impact of 13 biomarkers. Analyses comparing high vs low biomarker levels identified MET, HGF, GAS6, ANG2, IL-8, and IGF-1 as prognostic factors for OS in both treatment arms whereas VEGF-A was only in the placebo and AXL and EPO only in the cabozantinib arm prognostic. No baseline biomarkers were found to be predictive of an OS benefit with cabozantinib [45].

Together, the results of the CELESTIAL study confirm that cabozantinib has a place in second and further lines of therapy of advanced HCC independent of sorafenib tolerability and previous systemic therapies.

Ramucirumab – REACH-2 trial

Ramucirumab is a recombinant monoclonal antibody that specifically binds to the VEGFR2 domain, thereby preventing the binding of VEGF ligands. Similar to other compounds, ramucirumab initially showed promising results in a small phase-II study for advanced HCC. Based on these results, the randomized controlled phase-III REACH study was initiated as a second-line therapy after sorafenib failure [46]. However, the REACH study failed to demonstrate a significant improvement in mOS for all patients and did not meet its primary endpoint. Despite these initial discouraging results, a subgroup analysis suggested that ramucirumab improves survival in patients with elevated baseline AFP levels above 400 ng/ml. Subsequently, the REACH II study was initiated in this patient population. In this selected cohort of patients, ramucirumab improved the mOS from 7.3 months in the placebo arm to 8.5 months in the treatment arm (HR 0.710; 95% CI 0.53–0.95; p = 0.019) and PFS from 1.6 months to 2.8 months (HR 0.452; 95% CI 0.40–0.60; p < 0.0001) [47]. A combined analysis of the REACH I and II study confirmed the survival benefit of ramucirumab compared to placebo (Delta: 3.1 months, HR 0.69; 95% CI 0.57–0.84; p = 0.0002). The side effect spectrum deviates substantially from TKIs. With respect to grade 3/4 side effects, only hypertension (12.7% vs. 3.8%) and proteinuria (1.3% vs. 0%) occurred more frequently with ramucirumab compared to placebo. In agreement with the favorable side effect profile, a pooled meta-analysis of individual

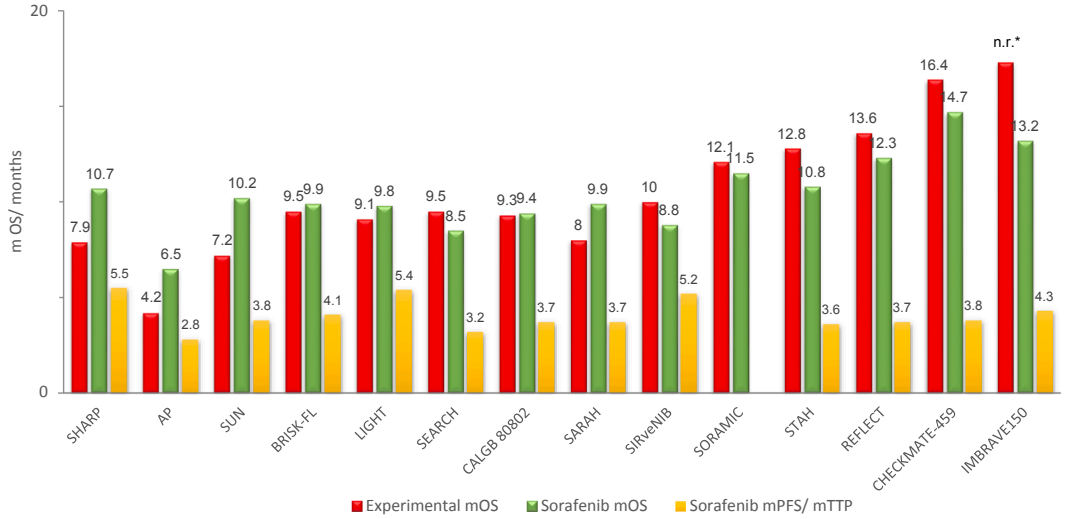

Fig. 1. mOS of patients treated with sorafenib (green) or the respective experimental compound (red) in recent phase-III trials. mPFS or mTTP under sorafenib is depicted in yellow. n.r.*: not reached.

Table 1
Overview of post-study treatments received by patients from REFLECT and CHECKMATE-459.

	REFLECT		CHECKMATE-459	
Medications, n (%)	Lenvatinib (n = 478)	Sorafenib (n = 476)	Sorafenib (n = 372)	Nivolumab (n = 371)
Patients with any anticancer medication	156 (32.6%)	184 (38.7%)	196 (53%)	181 (49%)
Sorafenib	121 (25.3%)	56 (11.8%)		
Cabozantinib	0 (0%)	11 (2.3%)		
Tyrosine kinase inhibitor			86 (23%)	132 (36%)
Investigational drug	15 (3.1%)	45 (9.5%)	40 (11%)	10 (3%)
IO			76 (20%)	7 (2%)
Chemo	73 (15%)	115 (24%)	25 (7%)	15 (4%)

patient data regarding disease symptoms revealed a statistically significant benefit with ramucirumab treatment compared to placebo. A delay in deterioration was observed for nausea and fatigue, weight loss, and pain [48]. In a post-hoc analysis, the impact of liver function measured by CP and ALBI on outcome in both studies was evaluated. ALBI-1 or CP-5 were both associated with better ECOG performance status, less macrovascular invasion, and a higher proportion of hepatitis B compared to ALBI-2 or CP-6. In agreement with previous studies, mOS of patients with better liver function (ALBI-1: 10.8 months/CP-5: 10.6 months) was longer compared to patients with more advanced liver disease (ALBI-2: 5.3 months/CP-6: 5.9 months). Efficacy of ramucirumab was shown in both groups of patients with a trend to a higher efficacy in patients with better preserved liver function (Brandi et al. EASL 2019).

Thus, ramucirumab is a viable second line option in patients with high AFP levels. Notably, ramucirumab is the first intravenous, non-TKI with proven anti-angiogenetic efficacy in advanced HCC.

Pembrolizumab – Keynote-240 trial

In contrast to nivolumab, pembrolizumab has been primarily developed in the second line setting in advanced HCC. The results of the phase-II KEYNOTE-224 study were very promising with a mOS of 12.9 months, a mPFS of 4.9 months and a disease control rate of 61%, which led to an accelerated approval of pembrolizumab in second line for advanced HCC by the FDA [49]. KEYNOTE-240 was subsequently a randomized, placebo controlled, phase-III study, in which 413 patients previously treated with one line of systemic therapy were randomized 2:1 to receive either pembrolizumab or placebo. Consistent with the results of the KEYNOTE-224 study, pembrolizumab improved mOS by 3.3 months to 13.9 months (HR: 0.78; one sided p = 0.0238; to be positive, it had to be 0.017) and PFS by 0.2 months to 3 months (HR: 0.78; one sided p = 0.0209) compared to placebo. Due to the statistical design of the study, these differences however did not meet the level of prespecified significance. ORR was 16.9% (95% CI 12.7–21.8%) for pembrolizumab compared 2.2% (95% CI 0.5–6.4%) for placebo (p = 0.00001). Patients who responded had an exceptionally long duration of response with a median of 13.8 months. Unfortunately, tissue for translational analysis was only available for a small subset of patients, and PD-L1 CPS or TPS was not significantly associated with treatment efficacy of pembrolizumab as previously suggested in the KEYNOTE-224 study. The safety profile including incidence of hepatitis and other immune mediated events was generally comparable with previous reports. Overall, the data from the Keynote-224 and 240 studies with pembrolizumab in HCC were consistent and clinically meaningful but did not reach the level of prespecified significance in the phase-III study. Based on these results it remains speculative whether the approval of pembrolizumab will be retracted by the FDA, but it appears highly unlikely that pembrolizumab will be approved as monotherapy in advanced HCC by EMA.

Sequential systemic treatment for advanced HCC

The approval of regorafenib in 2016 enabled HCC patients to continue systemic therapy after progression on sorafenib. Within the last 3 years additional compounds have entered the clinic and are available for first- and second line treatment. Exploratory analyses of the reported first- and second-line trials indicate that the sequential use of these drugs can achieve cumulative OS of over 20 months in BCLC C patients with maintained liver function. A retrospective evaluation of the sequential treatment effect of sorafenib followed by regorafenib from the RESORCE study revealed a median OS from the beginning of systemic therapy of 26 months vs. 19.6 months for placebo [50]. These data obtained in a well selected patient population provided for the first-time evidence that sequential application of systemic therapies in BCLC C patients can result in a mOS of over 2 years. Subsequently, the effect of sequential therapy on overall survival was evaluated in a post-hoc analysis of the REFLECT study. The mOS in the sorafenib arm of 12.3 months was already longer than in all previous phase-III studies, in which sorafenib was the experimental or control arm (Fig. 1). In REFLECT, 32.6% of patients in the lenvatinib arm and 38.7% in the

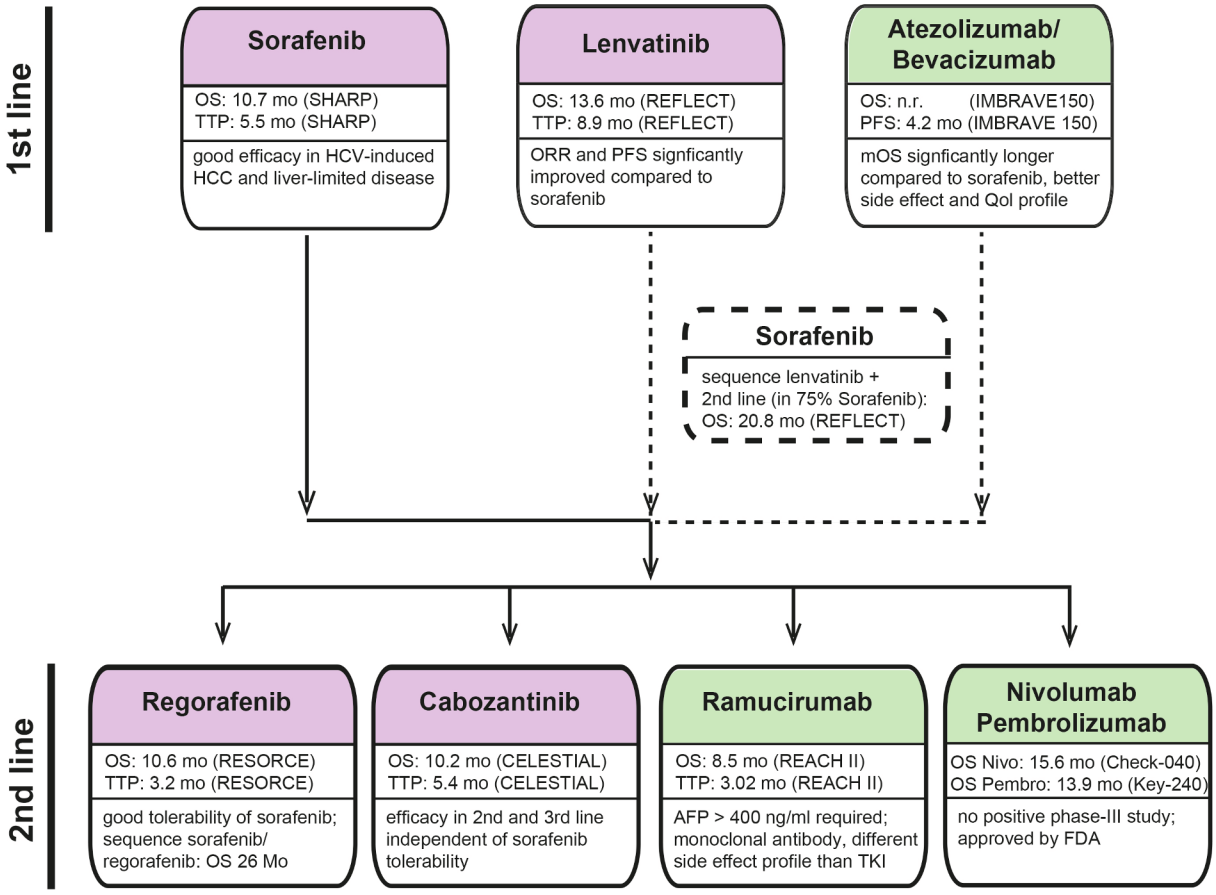

Fig. 2. Current treatment options for advanced HCC in 1st and 2nd line.

sorafenib arm received further anti-cancer medication during the survival follow-up period, which likely contributed to the long survival in both arms. Among patients who did not receive subsequent anticancer medication, the mOS for patients who received first-line lenvatinib versus first-line sorafenib was 11.5 months versus 9.1 months. Among patients who received subsequent treatment, mOS for patients treated with lenvatinib in first line was 20.8 months versus 17.0 months for those patients who started treatment on sorafenib. Similarly, in the CHECKMATE-459 study, a high number of patients was able to receive second line treatment (38% in the nivolumab arm and 46% in the sorafenib), and consistent with the data from REFLECT, mOS further increased in the sorafenib arm to 14.6 months.

Importantly, not only patients in first line studies but also patients treated in recent second line studies were able to receive subsequent therapies. In the KEYNOTE-240, 42% of patients treated with pembrolizumab and 47% treated with placebo received further lines of therapy. Similarly, 25% of patients in the cabozantinib and 30% of patients in the control arm in the CELESTIAL study were subsequently treated with additional systemic therapies.

A more detailed analysis of the drugs used during the follow-up periods of the clinical trials reveals that not only the number, but also the type of second-line therapy has changed. In the early trials, due to a lack of alternative effective treatment options, most patients were treated beyond progression with sorafenib or switched to cytotoxic chemotherapy (Table 1). Now, the majority of patients is treated with approved drugs or with immunotherapy in further treatment lines. These data provide compelling evidence for the important implications of sequential systemic treatment on OS in HCC.

Conclusions and outlook

Sorafenib was the standard of care and the only systemic treatment of advanced HCC for many years. Following the failure of several large phase-III clinical trials, lenvatinib, regorafenib, cabozantinib and ramucirumab are now available and viable options in first as well as second line setting (Fig. 2). Importantly, with IMbrave150, the first positive immunotherapy phase-III study has been presented after two failed phase-III studies with IO monotherapy. The combination of atezolizumab with bevacizumab will be practice changing regarding the first line treatment of advanced HCC.

All recent studies underlined that a well-preserved liver function is pivotal for a successful sequential administration of systemic therapies. A fine balance between an efficient anti-tumor activity and acceptable toxicity needs to be maintained during the treatment with local therapies as well as with new therapeutic compounds. Convincing results in the field of immuno-oncology will become increasingly important in this context and there is early evidence not only for a superior benefit of combinations between systemic treatments, but also regarding the combination of checkpoint inhibition with local or ablative therapies.

For the first time, we now have several drugs at our disposal that can significantly prolong survival of patients suffering from advanced HCC. However, it is still unclear which patients benefit the most from which drug, and furthermore, what is the optimal therapeutic sequence. With the exception of high AFP values for ramucirumab, the field still lacks predictive biomarkers that can be used to guide proper choice of therapy in routine clinical practice. In order to improve patient stratification with respect to the existing therapeutic options, but also to advance inclusion criteria for future clinical trials, the identification of reliable biomarkers will be crucial. Translational programs, but also retrospective real-world data, matched with tissue and liquid-based

biomarker analysis, will be key to implement more personalized approaches in HCC therapy.

In summary, the availability of new active compounds profoundly extended the “continuum-of-care” in HCC across different stages of disease. In contrast to the mOS of 10.7 months under Sorafenib in the SHARP study, most recent data indicates that a mOS of more than two years is now feasible for patients with advanced stage HCC through a sequential application of the available systemic treatment options. The possibility of this sequential approach, however, crucially depends on a preserved liver function. Therefore, repetitive locoregional therapies that may affect liver function need to be critically evaluated, and a switch towards systemic therapy should not be considered the “final straw” but regarded as a viable therapeutic option to significantly improve patient outcome.

Disclosures

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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