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REVIEW

Regorafenib in hepatocellular carcinoma: latest evidence and clinical implications

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Abstract

Over the past ten years, sorafenib, a multikinase inhibitor, has been the only systemic agent approved for first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). Whereas only recently lenvatinib was shown to be noninferior to sorafenib, in terms of survival, all other agents previously tested failed to prove noninferiority (or superiority) when compared with sorafenib. Similarly, in a second-line setting, most investigational drugs have failed to provide better survival outcomes than placebo. However, in 2016, data from the RESORCE trial, a phase 3 study evaluating regorafenib in HCC patients who experience disease progression after first-line treatment with sorafenib, have shown a 2.8-month median survival benefit over placebo (10.6 versus 7.8 months). Overall, side-effects were in line with the known safety profile of regorafenib. More recently, the survival benefits of a sustained anti-angiogenic inhibition were demonstrated also with cabozantinib in the frame of the phase 3 CELESTIAL trial. As HCC seems to be an attractive target for immunotherapy, a phase 1/2 trial reported promising efficacy signals from nivolumab, and results of a larger phase 3 trial with another checkpoint inhibitor, namely, pembrolizumab, are still pending. After nearly a decade of a certain degree of stagnation, we are now witnessing a period of novel therapeutic advances with multikinase inhibitors and immunotherapy that will likely change the treatment scenario of HCC.

Keywords: advanced, angiogenesis, hepatocellular carcinoma, immunotherapy, metastatic, multikinase inhibition, regorafenib, second-line.

Citation

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver worldwide. It is the fifth most common cancer in men and seventh among women, and the third leading cause of cancer-related mortality in the world, with a rising incidence, particularly in Western countries [1,2].

Chronic liver disease due to hepatitis B virus (HBV) or hepatitis C virus (HCV) accounts for the majority of HCC cases; alcohol intake, steatosis, diabetes, exposures to toxic agents and genetic and metabolic diseases are risk factors further increasing in incidence [1]. A common pathway for these varied etiologies may involve chronic inflammation recognized as a procarcinogenic condition [3].

Surgical resection, liver transplantation, and ablation are treatments that offer a high rate of complete excision of disease and, thus, potential for cure [2]. However, the disease frequently relapses or is diagnosed at an advanced stage when curative treatments are no longer available. Furthermore, no adjuvant therapy has been demonstrated to improve recurrence-free survival after curative treatments [4]. Currently, treatment with the multikinase inhibitor sorafenib is the only approved first-line systemic therapeutic option in Western countries for patients with unresectable HCC and well-preserved liver function (Child–Pugh class A) [5]. Sorafenib was approved in 2007 based on the results of the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, which reported a significant increase in overall survival (OS) and time to radiological progression over placebo [5]. Similar results were achieved in another double-blind, randomized, phase 3 trial in patients from the Asia-Pacific region [6]. The most frequent adverse events (AEs) were diarrhea, hand-foot skin reaction (HFSR), fatigue, and weight loss, all of which were often manageable [5]. Recently, the REFLECT trial, a global randomized open-label phase 3 noninferiority study, demonstrated that lenvatinib, a different multikinase inhibitor, is noninferior compared to sorafenib in terms of OS in untreated patients with advanced

HCC [7]. Furthermore, lenvatinib achieved statistically significant improvement in progression-free survival (PFS), time to progression (TTP), and overall response rate (ORR) compared to sorafenib. The safety profile of the two drugs was consistent with what observed in previous studies [7]. Based on these results, lenvatinib has been approved in Japan as a new therapeutic option for patients with unresectable HCC. Finally, in the first-line setting, two recently published phase 3 randomized studies, the European SARAH trial [8] and SIRveNIB study, conducted in the Asia-Pacific region [9], failed to show an improvement in OS with selective internal radiation therapy (SIRT) with yttrium-90 resin microspheres compared to sorafenib even if SIRT appeared to achieve a better local control and to be associated with less AEs.

In the second-line setting, in the randomized double-blind phase 3 RESORCE trial, regorafenib achieved improved OS, PFS, TTP, ORR and disease control rate (DCR) compared to placebo [10]. In the second- and third-line setting, the CELESTIAL trial, a recently presented randomized double-blind phase 3 trial, demonstrated statistically significant improved OS, PFS and ORR with cabozantinib versus placebo [11].

However, in the last decade, 11 phase 3 trials, evaluating tyrosine-kinase inhibitors (TKIs), monoclonal antibodies (moAbs), chemotherapy and other molecules, as monotherapy or in combination, in first- and second-line setting, failed to demonstrate any advantage over sorafenib or placebo, respectively [12–22]. Even if safety was not a major problem in the development of some new agents, for other compounds toxicities related to the concomitant liver cirrhosis may represent a significant hurdle for clinical development. Furthermore, efficacy may also depend on patient's characteristics and geographical region.

Negative studies for second-line treatment of HCC

Previous studies with several drugs designed to inhibit different pathways important in HCC pathogenesis and progression have been evaluated for second-line treatment with disappointing results. Phase 3 trials of brivanib, a small-molecule TKI targeting vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR) [17], everolimus, a mammalian target of rapamycin (mTOR) inhibitor [18], pegylated arginine deiminase (ADI-PEG) 20, an arginine degrading enzyme [19], and ramucirumab, a moAb against VEGFR2 [20], did not meet their primary endpoint of improved OS versus placebo. Noteworthy, in the ramucirumab study the predefined subgroup of patients with elevated baseline alpha-fetoprotein (AFP) levels showed a statistically significant benefit in terms of OS, and it has been recently announced that a phase 3 trial enrolling patients with high baseline AFP levels met its primary endpoint of OS [23].

While prognostic and predictive biomarkers are already used in clinical practice in several tumor types, biomarker research has still to produce conclusive results in the field of HCC [24].

Tivantinib – a small-molecule, adenosine triphosphate (ATP) independent inhibitor of MET, the hepatocyte growth factor (HGF) receptor – demonstrated statistically significant and clinically meaningful increase in OS, PFS, TTP, and DCR over placebo in patients with high MET expression detected by immunohistochemistry (IHC) on tumor cells in a second-line randomized double-blind placebo-controlled phase 2 study [25]. Initial tumor biomarker analysis from this study showed the prognostic value and the predictive value of MET expression as a marker of benefit from tivantinib [25]. Further biomarker analyses from the same study suggested that tumor MET levels were higher in patients previously treated with sorafenib, circulating biomarkers such as MET and HGF might be prognostic in second-line HCC [26], and baseline neutrophil-to-lymphocyte ratio was an independent prognostic biomarker [27]. Based on the phase 2 results, tivantinib has been evaluated in two phase 3 trials in previously treated patients with high tumor MET expression, the METIV-HCC trial in western countries [21], and the JET-HCC trial in Japan [22]. To the best of our knowledge, these trials were the first biomarker-driven trials in HCC. However, both studies were negative and did not confirm that tivantinib would improve OS and PFS compared to placebo in patients with high tumor MET expression detected by IHC. Although the METIV-HCC study was negative, with more than 1100 biopsies analyzed, this trial demonstrated the feasibility of conducting large tissue biomarker studies in advanced HCC. Furthermore, paired biopsy results confirmed that MET expression is more frequently high in patients treated with sorafenib (35% of patients were MET-high when biopsied before sorafenib, and 69% of patients were MET-high when biopsied after sorafenib), highlighting MET plasticity and the importance to biopsy at the appropriate time.

Regorafenib for second-line treatment of HCC

Regorafenib has been studied in the advanced HCC setting in a multicenter single-arm phase 2 study that enrolled 36 patients with well-preserved liver function (Child–Pugh class A) who progressed on prior sorafenib therapy [28]. Patients who discontinued sorafenib for toxicity were not eligible for the study, due to the partially overlapping safety profiles. Patients received regorafenib at the dose of 160 mg orally once daily in cycles of 3 weeks on/1 week off treatment. The primary endpoint was safety, the secondary endpoints were efficacy, according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) [29], and pharmacokinetics (PK). The median duration of treatment was 19.5 weeks (range 2–103). Thirty-five patients (97%) required dose reductions, interruptions, and/or delays, in most of cases due to AEs. All patients reported at least one treatment-emergent AE (TEAE), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Most common AEs included diarrhea (53%), fatigue (53%), HFSR (53%), hypothyroidism (42%), anorexia (36%), hypertension (36%),

Table 1. Efficacy results of the RESORCE phase 3 trial [10].

Outcome	Regorafenib (n=379)	Placebo (n=194)	Hazard ratio (95% CI)	*p*-value
Response				
Complete	2 (1%)	0	-	NR
Partial	38 (10%)	8 (4%)	-	NR
Overall response rate	40 (11%)	8 (4%)	-	0.0047
Stable disease	206 (54%)	62 (32%)	-	NR
Disease control rate	247 (65%)	70 (36%)	-	<0.0001
Overall survival (months)			0.63 (0.50–0.79)	<0.0001
Median	10.6	7.8		
95% CI	9.1–12.1	6.3–8.8		
Progression-free survival (months)			0.46 (0.37–0.56)	<0.0001
Median	3.1	1.5		
95% CI	2.8–4.2	1.4–1.6		
Time to progression (months)			0.44 (0.36–0.55)	<0.0001
Median	3.2	1.5		
95% CI	(2.9–4.2)	(1.4–1.6)		

CI, confidence interval; NR, not reported.

nausea (33%), and voice change (28%); most frequent grade 3/4 AEs were fatigue (17%) and HFSR (14%); 5 patients (14%) experienced serious AEs (SAEs) considered related to the study drug. DCR was achieved in 72% of patients, with stable disease in 25 patients (69%) and partial response in 1 (3%). Median TTP was 4.3 months (95% CI: 2.9–13.1). The 3-month PFS rate was 65% (95% CI: 45–79) and the 6-month PFS rate 44% (95% CI: 26–60). Median OS was 13.8 months (95% CI: 9.3–18.3). The 3-month OS rate was 88% (95% CI: 72–95) and the 6-month OS rate 79% (95% CI: 61–89) [28].

Based on the phase 2 results, regorafenib has been further evaluated in the multicenter, randomized, double-blind, placebo-controlled RESORCE phase 3 trial [10]. The RESORCE trial enrolled HCC patients with Barcelona clinic liver cancer (BCLC) stage B or C, preserved liver function (Child–Pugh class A), and good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] 0 or 1). Patients had to have tolerated treatment with sorafenib ≥400 mg daily for at least 20 of the last 28 days of treatment, and the reason for permanent discontinuation of sorafenib had to be documented radiological progression. Patients had to be enrolled in the trial within 10 weeks after the end of sorafenib treatment. Patients who discontinued sorafenib due to toxicity were not allowed to be enrolled in the study. Between May 2013 and December 2015, 573 patients were randomized (2:1 ratio) to receive regorafenib (n=379) or placebo (n=194). Randomization was stratified by geographical region (Asia versus rest of world), macrovascular invasion (yes versus no), extrahepatic disease (yes versus no), AFP levels (<400 versus ≥400 ng/mL), and ECOG PS (0 versus 1). The percentage of patients enrolled from Asia was 38% (n=216). Baseline patient characteristics were well-balanced between the two treatment groups. Patients received 160 mg regorafenib (four 40 mg tablets) orally or matching placebo once daily for 21 consecutive days, followed by 7 days off treatment in 28-day cycles. Treatment continued until disease progression according to mRECIST, clinical progression, death, unacceptable toxicity, or decision by the investigator. The primary endpoint of the study was OS in the intent-to-treat population, further endpoints included PFS, TTP, ORR, and DCR assessed by the investigators using mRECIST and RECIST v.1.1, safety, and quality of life. Of the patients who started treatment, 309 (83%) in the regorafenib arm and 183 (95%) in the placebo arm discontinued study treatment. The most common reason for discontinuation was disease progression. Median treatment duration was 3.6 months with regorafenib and 1.9 months with placebo.

After a median follow-up of 7 months, median OS was 10.6 months in the regorafenib arm versus 7.8 months in the placebo arm, with a hazard ratio (HR) of 0.63 (95% CI: 0.50–0.79; $p<0.0001$). Regorafenib was superior to placebo in all the efficacy endpoints (Table 1). An updated OS analysis, performed almost 1 year after the primary analysis, confirmed the previously reported results (10.7 versus 7.9 months, HR 0.61, $p<0.0001$) [30]. Both predefined and exploratory analyses confirmed the superiority of regorafenib compared to placebo in all subgroups of patients. The efficacy of regorafenib was confirmed regardless of the pattern of progression on prior sorafenib [31] and regardless of last sorafenib dose [32]. The development of new distant metastases or vascular invasion was confirmed to be associated with worse survival. However, despite the strong prognostic impact, regorafenib provides significant survival benefits irrespective of the pattern of disease progression on prior sorafenib [31]. Further exploratory data showed that in the selected population for the study, treatment with the

sequence of sorafenib followed by regorafenib resulted in an unprecedented median OS of 26 months [32]. Also, a negative correlation between baseline AFP and circulating MET levels and prognosis was confirmed regardless of treatment [33]. Finally, HFSR has been shown to be associated with a better OS with regorafenib [34], and this result, even if retrospectively observed, is in line with the prospectively demonstrated correlation between HFSR and OS with sorafenib [35]. Significantly, more patients on regorafenib compared to placebo experienced an objective response by mRECIST criteria. However, similar outcomes, in terms of PFS and TTP, were observed using mRECIST and RECIST v.1.1. The prognostic impact of the objective response as a surrogate marker of outcome and the best radiological criterion to assess responses are still matters of debate. Indeed, in a retrospective analysis of patients treated with sorafenib, the survival associated with disease control was not significantly different from the survival associated with progressive disease according to RECIST criteria [36].

Of the 573 randomized patients, 567 patients (99%) started treatment (374 in the regorafenib group and 193 in the placebo group) and were included in the safety analysis. All patients who received regorafenib and 93% of patients who received placebo had at least one TEAE (graded using NCI-CTCAE version 4.03), considered possibly related to the study drug in 93% of patients on regorafenib and 52% of patients on placebo (Table 2). Most commonly reported grade 3/4 AEs were hypertension (15% of patients on regorafenib versus 5% of patients on placebo), HFSR (13 versus 1%), fatigue (9 versus 5%), and diarrhea (3% versus none). When analyzed by the last sorafenib dose during prior treatment, only grade ≥3 HFSR, fatigue, anorexia, and increased bilirubin were slightly higher in the group that received <800 mg compared with 800 mg, while no difference was observed in rates of other TEAEs. Therefore, the last sorafenib dose may not predict the onset of TEAEs occurring with regorafenib [32]. SAEs and death rates were similar in the two study arms; SAEs were deemed related to the study drug in 10% of patients on regorafenib and 3% of patients on placebo. Interruptions/dose reductions and discontinuations due to AEs were reported in 68 and 25% of patients on regorafenib and in 31 and 19% of patients on placebo, respectively. Drug-related AEs leading to interruptions/dose reductions and to discontinuations were reported in 54 and 10% of patients on regorafenib and 10 and 4% of patients on placebo, respectively. Of note, quality of life was similar in the two treatment groups [10]. Based on the results of the phase 3 RESORCE study, regorafenib has been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with advanced HCC previously treated with sorafenib.

Other second-line trials with positive results

In addition to the RESORCE study, recent second-line trials investigating checkpoint inhibitors and multikinase inhibition pathways have provided encouraging results, which may potentially expand the landscape of second-line treatments.

In fact, HCC immunogenicity and the concomitant immune suppression represent the ideal frame for immunotherapy interventions aiming to restore the otherwise 'exhausted' effector T cells functions. Several studies previously described different oncofetal and cancer/testis proteins, which in turn make up the so-called tumor-associated antigens able to elicit CD8+ T-cell responses, though often impaired in HCC patients [37]. Furthermore, the appearance of neo-antigens resulting from nonsynonymous tumor mutations might itself contribute to HCC immunogenicity. Nevertheless, immune surveillance is generally eluded by diverse mechanisms, including programmed cell death ligand 1 (PD-L1) upregulation [38], that eventually lead to HCC progression [39]. In this context, the immunotherapy armamentarium currently available with antiprogrammed cell death 1 receptor (PD-1), anti-PD-L1, and anticytotoxic T lymphocyte antigen-4 (CTLA-4) blocking antibodies constitutes a rational strategy to efficiently stimulate anticancer immune responses. This approach has been proven successful in several tumor types, including melanoma, refractory Hodgkin's lymphoma, renal cell carcinoma, nonsmall cell lung cancer, Merkel cell carcinoma, urothelial carcinoma, head and neck cancers, and in a broad group of cancers displaying microsatellite instability.

Early results with immune checkpoint blockade in HCC stem from a pilot study with an anti-CTLA-4 antibody, namely, tremelimumab, where 43% of the patients were Child–Pugh class B. Despite these poor prognostic characteristics, tremelimumab, even though administered at a dose that is now considered subtherapeutic, exhibited a satisfactory safety profile, and the survival outcomes were in line with other contemporary studies for second-line treatment of HCC enrolling only Child–Pugh A patients [40].

More recent studies have been also focusing on the PD-1/PD-L1 immune checkpoint pathway, which is felt to contribute to liver immune tolerance. Specifically, nivolumab, which is a fully human IgG4 moAb blocking the PD-1 interaction with PD-L1 and PD-L2, is currently investigated in a HCC-specific multicohort phase 1/2 trial (CheckMate 040, NCT01658878). The first two phases of this trial consist in a dose-escalation phase and a dose-expansion phase designed to estimate ORR and duration of response with nivolumab monotherapy, according to patients' viral status and prior sorafenib exposure. The final results pertaining to these two phases of the CheckMate 040 study were reported in The Lancet, in 2017 [41]. With more than 60% of patients being previously exposed to sorafenib, a major finding emerging from the dose-escalation and the dose-expansion phases was an impressive median OS reaching 28.6 months in sorafenib-naïve patients and 15.6 months in patients who were previously exposed to sorafenib [42]. Based on these findings, the FDA has granted the approval of nivolumab as second-line treatment agent for HCC on September 22, 2017.

Table 2. Treatment-emergent adverse events in the RESORCE phase 3 trial – safety population. Adapted from: Bruix J et al. Lancet 2017 [10].

	Treatment-emergent						Treatment-emergent drug-related					
	Regorafenib (n=374)			Placebo (n=193)			Regorafenib (n=374)			Placebo (n=193)		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	374 (100)	208 (56)	40 (11)	179 (93)	61 (32)	14 (7)	346 (93)	173 (46)	14 (4)	100 (52)	31 (16)	1 (1)
HFSR	198 (53)	47 (13)	NA	15 (8)	1 (1)	NA	196 (52)	47 (13)	NA	13 (7)	1 (1)	NA
Diarrhea	155 (41)	12 (3)	0	29 (15)	0	NA	125 (33)	9 (2)	0	18 (9)	0	0
Fatigue	151 (40)	34 (9)	NA	61 (32)	9 (5)	NA	110 (29)	24 (6)	NA	37 (19)	3 (2)	NA
Hypertension	116 (31)	56 (15)	1 (<1)	12 (6)	9 (5)	0	87 (23)	48 (13)	1 (<1)	9 (5)	6 (3)	0
Anorexia	116 (31)	10 (3)	0	28 (15)	4 (2)	0	88 (24)	10 (3)	0	12 (6)	0	0
Increased bilirubin	108 (29)	37 (10)	2 (1)	34 (18)	15 (8)	6 (3)	70 (19)	24 (6)	1 (<1)	7 (4)	4 (2)	0
Increased AST	92 (25)	37 (10)	4 (1)	38 (20)	19 (10)	3 (2)	48 (13)	16 (4)	3 (1)	15 (8)	9 (5)	1 (1)
Fever	72 (19)	0	0	14 (7)	0	0	14 (4)	0	0	4 (2)	0	0
Nausea	64 (17)	2 (1)	NA	26 (13)	0	NA	40 (11)	1 (<1)	NA	13 (7)	0	NA
Increased ALT	55 (15)	10 (3)	2 (1)	22 (11)	5 (3)	0	29 (8)	6 (2)	2 (1)	8 (4)	2 (1)	0
Weight loss	51 (14)	7 (2)	NA	9 (5)	0	NA	27 (7)	4 (1)	NA	3 (2)	0	NA
Oral mucositis	47 (13)	4 (1)	0	6 (3)	1 (1)	0	42 (11)	4 (1)	0	5 (3)	1 (1)	0
Vomiting	47 (13)	3 (1)	0	13 (7)	1 (1)	0	27 (7)	1 (<1)	0	5 (3)	0	0
Cough	40 (11)	1 (<1)	NA	14 (7)	0	NA	4 (1)	0	NA	2 (1)	0	NA
Hypophosphatemia	37 (10)	30 (8)	2 (1)	4 (2)	3 (2)	0	22 (6)	16 (4)	2 (1)	2 (1)	1(1)	0
Hoarseness	39 (10)	0	NA	1 (1)	0	NA	34 (9)	0	NA	0	0	NA

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HFSR, hand-foot skin reaction; NA, not applicable.

Interestingly enough, response rates in PD-L1-positive and PD-L1-negative tumors were similar, as were according to viral and nonviral etiologies. Still pending are the results from two other cohorts, respectively, evaluating nivolumab plus an anti-CTLA-4 antibody (ipilimumab), and nivolumab monotherapy in patients with Child–Pugh B7 or B8 scores. While the aforementioned cohorts have left the enrollment open to either patients sorafenib-naïve or previously exposed, a 'first-line only' cohort has been designed for patients naïve from systemic treatments, who are randomized in a 1:1 manner to receive sorafenib or nivolumab. Of note, results gained from nivolumab across these different cohorts might potentially expand treatment perspectives for patients usually excluded from clinical trials due to their Child–Pugh score. It is also predicted that sorafenib-intolerant patients, who therefore might not be optimal candidate for regorafenib, could derive benefit from immunotherapy. Such patients, experiencing an AE during sorafenib, roughly represent 30% of patients who have to discontinue first-line treatment [43].

Importantly, the PD-1 receptor and the CTLA-4 play together complementary and nonredundant roles in regulating adaptive immunity and maintaining peripheral tolerance. In particular, whereas PD-1 contributes to T-cell anergy and exhaustion, the engagement of CTLA-4 rather inhibits T-cell activation. In preclinical models, a combined blockade of PD-1 and CTLA-4 achieved more profound antitumor activity than blockade of either pathway alone [44]. Given these premises, a nivolumab plus ipilimumab cohort in the CheckMate 040 study is of interest since it may provide useful results to gauge the value of such an additive to synergistic approach, already tested in other disease settings [45].

In the second-line setting, the RESORCE study has demonstrated the efficacy of multikinase inhibition mediated by regorafenib. Novel data now suggest a possible role even for another

multikinase inhibitor with nonselective anti-MET activity, namely, cabozantinib, that shares with regorafenib a certain degree of potent angiogenic inhibition [46]. A phase 3 double-blind placebo-controlled trial randomizing 773 HCC patients to cabozantinib or placebo in the second- or third-line setting has been recently reported under the name of CELESTIAL trial [11]. With primary endpoint OS, the trial was a positive one, since median OS was 10.2 months in the cabozantinib group, as compared with 8.0 months in the placebo group, and HR for death with cabozantinib versus placebo was 0.76 (p=0.0049). Interestingly, MET overexpression as detected by IHC was a stringent inclusion criterion for enrollment onto the HCC tivantinib trials [21,22] but not in CELESTIAL trial. Though cabozantinib is a MET inhibitor, this implies that MET expression, as detected by IHC at least, might not be necessary to select patients who might benefit from cabozantinib. Further developments of cabozantinib might be foreseen also in combination with checkpoints inhibitors. Indeed, in preclinical investigations, treatment of tumor cells with cabozantinib leads to increased tumor-cell expression of major histocompatibility complex class 1 antigen and greater sensitivity of tumor cells to T-cell-mediated killing [47]. On these grounds, possible synergistic activities of cabozantinib plus nivolumab (with or without ipilimumab) are currently explored within an additional cohort of the aforementioned CheckMate 040 trial.

Ongoing phase 3 studies for second-line treatment of HCC: ramucirumab and pembrolizumab

Despite the negative results of the phase 3 REACH study in the intent-to-treat population [20], a test for interaction indicated a significant and meaningful survival benefit from ramucirumab over placebo in the prespecified subgroup of patients with baseline AFP ≥400 ng/mL. Since the REACH study did not stratify patients according to AFP concentration, a prospective confirmation of these findings has been conducted in the frame of a new phase 3 trial. It has been recently announced that this trial met its primary endpoint of OS as well as the secondary endpoint of PFS, thus being the first positive phase 3 biomarker-driven trial in HCC [23]. However, in contrast to ramucirumab, in prespecified subgroup analyses of RESORCE, regorafenib equally benefitted patients with AFP levels ≥400 ng/mL as well as patients with lower AFP levels.

Consistent with findings from dose-escalation and dose-expansion phases of CheckMate 040 trial, the results of a phase 2 study (KEYNOTE-224) with another anti-PD-1 antibody, namely, pembrolizumab, have confirmed the role of checkpoint blockade in HCC in patients progressing after sorafenib. Indeed, among the most remarkable findings of this trial are an ORR as high as 17% and a median OS not reached by the time of presentation [48]. Moreover, the overall safety profile of pembrolizumab was comparable to that observed in patients in the dose-escalation and dose-expansion phase of the CheckMate 040, although a full report is still pending. Currently, pembrolizumab plus best supportive care (BSC) is being studied against placebo plus BSC in a phase 3 trial as second-line therapy [49].

Conclusions

While previous efforts to develop new therapies for HCC have failed, both in first-line and in second-line setting, the results of RESORCE definitely represent significant advances in the treatment of HCC.

However, the current landscape of available treatment options is expanding and it is becoming increasingly more articulated. Despite such encouraging data, because of a lack of molecular and clinical predictors of efficacy, it remains currently unknown how to best select in the future a second-line treatment for patients able to tolerate prior sorafenib. Similarly, the same questions remain open also for patients intolerant to sorafenib, who nevertheless are logically excluded from further treatment with regorafenib.

From a clinical standpoint, several data gleaned in recent years have turned the attention to patterns of progression on sorafenib and reasons for sorafenib discontinuation [43,50]. In fact, these data allow to dissect advanced HCC into clinically defined categories and provide valuable prognostic information that should be acknowledged for stratification within next trials for second-line treatment of HCC. For the time being, additional considerations pertain to the optimization of radiologic criteria currently used to assess tumor response, especially in view of mounting evidences highlighting the discordance between TTP and OS [51]. In this context, a thorough analysis of AFP kinetics would be still of interest, owing to earlier works [36] indicating a role for AFP response as a surrogate endpoint of survival, worth to be considered in conjunction with radiologic assessments.

Finally, as current data with regorafenib and cabozantinib suggest a benefit from a sustained anti-angiogenic strategy, it is too early to define how this will compare in a clinical scenario that is witnessing the emergence of immune-oncology. Reasonably, in the absence of other decision-making parameters, differences in tolerability and previous sorafenib exposure will be major drivers favoring the choice of a specific drug.

Whereas for other solid malignancies, prognostic and predictive molecular biomarkers are ready for clinical practice, the METIV-HCC and CheckMate 040 trials indirectly teach that the quest for reliable biomarkers in HCC is far from being concluded.

Traditionally, the virtual lack of biological specimens from the majority of HCC patients has been one of the major hurdles for biomarker discovery in this disease [24]. Although the search of predictive markers for anti-angiogenic therapies, including regorafenib, has been rather elusive thus far, a novel generation of clinical trials is hopefully setting the stage for the development of precision medicine in the field of HCC.

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