69918_Auto_Edited-check.docx

WORD COUNT	5403	TIME SUBMITTED	13-MAY-2022 05:01PM
		PAPER ID	85894636

Name of Journal: *World Journal of Hepatology*

Manuscript NO: 69918

Manuscript Type: MINIREVIEWS

Treatment of advanced hepatocellular carcinoma in the second line: Time for more individualized treatment options?

Rajappa S *et al*. Advanced hepatocellular carcinoma

Abstract

Hepatocellular carcinoma (HCC) is the most frequently diagnosed primary tumor of the liver and is usually detected as advanced disease. It is an aggressive disease that often progresses rapidly when it fails to respond to treatment. As such, patients have limited opportunities to try different subsequent-line treatment regimens. In the last 5 years, the number of agents and/or regimens available for the treatment of advanced HCC has increased significantly, which has made treatment choices for this patient population increasingly complex. In the second-line setting, several phase III trials of regorafenib (RESORCE), ramucirumab (REACH/REACH-2), and cabozantinib (CELESTIAL) have demonstrated clinically meaningful survival benefits in patients with the disease. However, the median overall survival of patients with advanced HCC remains unchanged at approximately 12 mo from the start of systemic second-line therapy, with a limited duration of response. Evidence from the REACH/REACH-2 trials demonstrated for the first time that baseline alpha-fetoprotein (AFP) levels can be used as an identification factor to select those who are likely to benefit the most from ramucirumab treatment. Ramucirumab has been shown to be both well-tolerated and efficacious and to have a clinically acceptable safety profile. Therefore, it should be considered an option for patients with AFP levels ≥ 400 ng/mL.

Key Words: Hepatocellular carcinoma; Alpha-fetoprotein; Prognostic factor; Ramucirumab; Second-line treatment; Survival

Rajappa S, Rau KM, Dattatreya P, Ramaswamy A, Fernandes P, Pruthi A, Cheng R, Lukanowski M, Huang YH. Treatment of advanced hepatocellular carcinoma in the second line: Time for more individualized treatment options? *World J Hepatol* 2022; In press

Core Tip: Hepatocellular carcinoma (HCC) is the most frequently diagnosed primary tumor of the liver and is usually detected as advanced disease. Identifying any

predictive or prognostic factors prior to and during systemic treatment of HCC is critical in determining optimal treatment patterns. Here, we summarize the contributions of the most recently developed treatment options in HCC beyond the first line to improve outcomes for these patients.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequently diagnosed primary liver tumor, the sixth most common neoplasm overall, and the cause of 8.3% of all cancer-related deaths worldwide in 2020[1]. In total, 80% of patients with HCC are diagnosed in developing countries, with the largest burden in Asia, predominantly due to hepatitis B virus (HBV) infection[2,3].

The treatment of HCC is largely influenced by disease stage and usually based on the Barcelona Clinic Liver Cancer model, which accounts for factors used to predict prognosis, such as tumor burden, liver function and performance status[4]. Curative treatment options, such as liver transplant, surgical resection and radiofrequency ablation, are restricted to patients with early-stage HCC. Transarterial therapies, including conventional transarterial chemoembolisation, prolong survival for patients with liver-localised disease for whom surgery is not an option[5,6]. However, not all patients with non-resectable HCC are able to benefit from transarterial chemoembolisation, and this is especially so for patients with multiple and large tumors[7]. Worldwide, the majority of patients with HCC present with advanced disease and are candidates for systemic therapy as opposed to liver-directed approaches[8].

Sorafenib was the first effective first-line treatment approved for advanced HCC after it improved overall survival (OS) in two double-blind, randomized clinical trials (RCTs)[9]. The relative risk of death was reduced by 30% [hazard ratio (HR) = 0.69, 95% confidence interval (CI): 0.55-0.87] compared with best supportive care (BSC) in the larger SHARP study[10,11]. Sorafenib is currently a standard systemic therapy indicated in patients with no chronic liver disease (Child-Turcotte-Pugh class A) and in specific patients with Child-Turcotte-Pugh class B disease with advanced tumors (Barcelona

Clinic Liver Cancer stage C) or tumors that have progressed after locoregional therapy. In 2018, REFLECT, a phase III non-inferiority trial demonstrated that lenvatinib was non-inferior for OS and significantly increased progression-free survival (PFS) relative to sorafenib. Additionally, time to progression (TTP) and objective response rate (ORR) were significantly increased with lenvatinib[12]. Lenvatinib was subsequentially granted approval for the treatment of patients with advanced or unresectable HCC who have received no prior systemic therapy. Recently, the US Food and Drug Administration (FDA) granted approval of atezolizumab in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy. The approval was based upon findings from the phase III IMbrave150 clinical trial, which was the first to demonstrate an improved OS and PFS for immunotherapy *vs* sorafenib in patients with advanced HCC[13]. A 12-mo follow-up demonstrated a median OS of 19.2 mo with atezolizumab plus bevacizumab *vs* 13.4 mo with sorafenib (HR = 0.66; 95%CI: 0.52-0.85; P = 0.0009). At 18 mo, the survival rate was 52% with atezolizumab plus bevacizumab and 40% with sorafenib, which is the longest survival recorded in a front-line phase III study in patients with advanced HCC[13].

There is an unmet need for second- and later-line therapies for patients who experience disease progression or demonstrate intolerance to first-line treatment. In the last 5 years, the number of agents/regimens available for the treatment of advanced HCC have increased significantly, making treatment choices complex for this patient population. HCC is an aggressive disease, often progressing rapidly when it fails to respond to treatment, giving patients limited opportunities to try different treatment regimens. Therefore, identifying any predictive or prognostic factors before and during systemic treatment is critical to the determination of optimal treatment patterns.

It is well accepted that the development of HCC is age dependent. Given the increasing average life expectancy worldwide, the treatment of elderly patients with HCC is becoming a significant global health issue. The likelihood of comorbidities such as diabetes, renal failure, and pulmonary and cardiovascular diseases means that the optimal treatment strategy is often difficult to define in such patients. Consequently,

there is not only a risk for overtreatment in those with inherent fragility, causing severe toxicities, but also a risk of elderly but otherwise fit patients being undertreated. Furthermore, data on the treatment and management of elderly patients with HCC are lacking, and - where data are available - the heterogeneous definitions of elderly make it difficult to interpret the data.

Serum alpha-fetoprotein (AFP) concentrations ≥ 400 ng/mL in patients with HCC have consistently been associated with worse outcomes, including larger tumors, bilobar involvement, portal vein invasion, poorly differentiated histology and decreased median survival[14,15]. Conversely, AFP response, defined as a ≥ 20% decrease in AFP levels, either from baseline or over an 8-wk period[16,17], has been associated with improved survival in patients with HCC treated with locoregional therapies such as chemotherapy, ablation or surgery[18]. AFP response, *i.e.*, changes in AFP at treatment discontinuation, relative to baseline can predict survival of patients with advanced HCC treated with sorafenib with or without transarterial chemoembolisation[19]. Given that roughly half of all patients with advanced HCC have AFP concentrations ≥ 400 ng/mL[20,21], well-tolerated effective treatments are much needed in this population.

HCC incidence and mortality rates vary according to ethnicity, which is mainly attributed to differences in the prevalence of major risk factors such as HBV infection and disparities in access to high-quality medical care. The HCC incidence and mortality rate is particularly high in East and Southeast Asia. In patients with HCC, serum AFP levels can range from normal (0-20 ng/mL) to > 100000 ng/mL[22,23]. Several retrospective reports have noted that AFP levels appear to differ amongst ethnic groups[24,25], with Asian populations consistently being associated with elevated AFP levels when diagnosed with HCC. For example, the median baseline AFP for Asian patients in the pooled analysis of REACH-2 and REACH was more than twice that for non-Asian patients, with a median of 7107 ng/mL *vs* 2801 ng/mL for ramucirumab-treated patients[26]. In Sri Lanka, 23% of patients with HCC had AFP levels > 400 ng/mL[27], whereas 36% of Middle Eastern patients with HCC had levels > 200

ng/mL[28], and raised (20-200 ng/mL) levels have been reported repeatedly in Chinese patients with HCC[29-31].

In this narrative review, we aim to summarize the efficacy and safety of second-line treatments for patients with HCC, and important subgroups of patients with HCC, using OS, PFS and tolerability data from phase III HCC RCTs. Our aim is to evaluate the contributions of second-line treatment options in the improvement of patient outcomes and highlight the importance of ramucirumab in this context.

CURRENT SECOND-LINE OPTIONS FOR PATIENTS WITH HCC: TYROSINE KINASE INHIBITORS

Regorafenib

Regorafenib is an oral multikinase inhibitor that blocks the signalling pathways involved in tumor angiogenesis [vascular endothelial growth factor (VEGF) receptors 1-3 and tyrosine kinase, endothelial], oncogenesis [proto-oncogene c-KIT, rearranged during transfection (RET), Raf-1 proto-oncogene, serine/threonine kinase, and B-Raf proto-oncogene, serine/threonine kinase], metastasis and tumor immunity[32]. Although sorafenib and regorafenib block similar kinases, regorafenib has a broader inhibitory profile and greater pharmacological activity.

RESORCE: In RESORCE (Regorafenib after Sorafenib in Patients with HCC), a randomized, double-blind, placebo-controlled, phase III trial, patients who had tolerated sorafenib treatment but had documented radiographic progression received regorafenib[21]. Tolerance was defined as receiving sorafenib ≥ 400 mg daily for ≥ 20 of a total of 28 d before discontinuation of treatment. Patients were excluded if they had discontinued sorafenib for toxicity reasons, probably because regorafenib has multikinase inhibitory activity similar to that of sorafenib. In the pivotal sorafenib SHARP study, 44% of the patients treated with sorafenib required dose adaptations because they experienced adverse events (AEs)[11]. In RESORCE, patients were randomized to receive once-daily oral regorafenib 160 mg or placebo for the first 21 d of

28-d cycles. Regorafenib improved OS, with a median survival of 10.6 mo (95%CI: 9.1-12.1) compared with 7.8 mo (95%CI: 6.3-8.8) with placebo (HR = 0.63; 95%CI: 0.50-0.79; one-sided $P < 0.0001$); this improvement in OS with regorafenib was maintained in all pre-planned subgroup analyses. An OR was achieved in 40 (11%) regorafenib-treated patients compared with eight (4%) placebo-treated patients. Median PFS by RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 was 3.4 mo (95%CI: 2.9-4.2) with regorafenib and 1.5 mo (95%CI: 1.4-1.5) with placebo (HR = 0.43; 95%CI: 0.35-0.52; one-sided $P < 0.0001$). Median TTP by RECIST 1.1 was 3.9 mo (95%CI: 2.9-4.2) with regorafenib and 1.5 mo (95%CI: 1.4-1.6) with placebo (HR = 0.41; 95%CI: 0.34-0.51). The most frequent clinically relevant grade 3 or 4 AEs in the regorafenib and placebo groups were hypertension [n = 57 (15%) *vs* n = 9 (5%)], palmar–plantar erythrodysesthesia [also known as hand foot skin reaction (HFSR)] [n = 47 (13%) *vs* n = 1 (1%)], fatigue [(n = 34 (9%) *vs* n = 9 (5%)] and diarrhoea [n = 12 (3%) *vs* n = 0 (0%)]. The most common AEs leading to discontinuation more frequently with regorafenib than with placebo were increased aspartate aminotransferase concentrations (8 of 374 patients receiving regorafenib *vs* 3 of 193 patients receiving placebo), HFSR (7 of 374 *vs* none), and increased alanine aminotransferase (4 of 374 *vs* none).

Patient-reported outcomes are an important component of assessing the benefits of treatment in advanced HCC. Health-related quality of life (HRQoL) derived from the Functional Assessment of Cancer Therapy - Hepatobiliary (FACT-Hep) questionnaire is considered a predictor of survival for patients with HCC and also contributes prognostic data to the Eastern Cooperative Oncology Group performance status. Although the FACT-Hep result for regorafenib *vs* placebo was statistically significant, it did not meet the threshold for clinical significance[21]. There were no clinically meaningful differences in HRQoL between regorafenib- and placebo-treated patients with the EQ-5D index or the EQ-5D visual analogue scale, and FACT-General scores were similar between the treatment groups[21,33].

The findings of the RESORCE trial led to the first approval of a drug as a second-line treatment for patients with HCC following sorafenib in the first line. Further

exploratory analyses of the RESORCE trial demonstrated that regorafenib improved clinical outcomes in patients regardless of the speed of their disease progression or their last sorafenib dose, suggesting that sequencing therapy in this manner may extend patient survival[34].

In a separate retrospective analysis, Japanese patients who received lenvatinib as first-line, sorafenib as second-line, and regorafenib as third-line treatment demonstrated a greater PFS, ORR, and disease control rate (DCR) of 3.8 mo, 17.6%, and 41.2%, respectively, compared with 1.8 mo, 1.8%, and 20.8% in patients receiving sorafenib as second-line systemic therapy only[35]. Further clinical trials are warranted to assess the potential of regorafenib as a post-treatment therapy following lenvatinib.

Of the 1142 patients treated with regorafenib in randomized placebo-controlled trials, 40% were aged ≥ 65 years and 10% were aged ≥ 75 years. Although efficacy was similar between those aged ≥ 65 or ≥ 75 years and younger patients, the frequency of grade 3 hypertension (18% *vs* 9%) was higher in patients aged ≥ 65 years than in younger patients. Additionally, one patient aged ≥ 65 years experienced a grade 4 hypertension event, whereas none were reported in younger patients[36].

Post hoc analyses from the RESORCE trial demonstrated higher AFP response rates with regorafenib than with placebo (46% *vs* 11%); median OS was 13.8 mo (95%CI: 11.8-16.5) in AFP responders *vs* 8.9 mo (95%CI: 8.0-9.7) in non-responders (HR = 0.57; 95%CI: 0.40-0.82)[37]. However, AFP response in the RESORCE trial was associated with an increased rate of grade 3 HFSR in the regorafenib-treated group[37].

REFINE: REFINE (Regorafenib Observational Study in HCC; NCT03289273) is a large ongoing multicentric observational study evaluating regorafenib in the real world. Interim analyses suggest that regorafenib performs as expected from RESORCE findings in a real-world setting, with the most common treatment-emergent AEs (TEAEs) similar to those reported in RESORCE.

Cabozantinib

Cabozantinib, an orally bioavailable inhibitor of tyrosine kinases, including the mesenchymal-epithelial transition receptor tyrosine kinase, AXL receptor tyrosine kinase, RET, fms-like tyrosine kinase 3, and VEGF receptors (VEGFRs), was evaluated in a phase II randomized discontinuation study with nine patient cohorts classified by tumor type, including HCC[38]. Favorable clinical outcomes in patients with HCC were observed, including objective tumor responses, disease stabilization, and decreased AFP levels.

CELESTIAL: The subsequent phase III RCT (CELESTIAL) showed positive survival results for cabozantinib, extending OS from 8 mo with placebo to 10.2 mo (HR = 0.76; 95%CI: 0.63-0.93; *P* = 0.005) and PFS from 1.9-5.2 mo (HR = 0.44; 95%CI: 0.36-0.52; *P* < 0.001)[39]. The ORR among patients in the cabozantinib group was 4% (18 of 470 patients experienced a partial response), which differed significantly from the ORR of < 1% (1 in 470 patients experienced a partial response) in the placebo group (*P* = 0.009). The grade 3 or 4 TEAEs occurring more frequently with cabozantinib compared with placebo were HFSR (17% *vs* 0%), hypertension (16% *vs* 2%), increased aspartate aminotransferase level (12% *vs* 7%), fatigue (10% *vs* 4%) and diarrhoea (10% *vs* 2%). These were also the most frequent AEs of any grade that led to dose reductions among patients in the cabozantinib group.

Post hoc subgroup analyses of the CELESTIAL trial demonstrated that elderly patients aged > 65 years derived survival benefit from cabozantinib treatment, with an OS of 11.1 mo for cabozantinib *vs* 8.3 mo for placebo (HR = 0.74; 95%CI: 0.56-0.97) and PFS of 5.4 *vs* 2.0 mo (HR = 0.46; 95%CI: 0.35-0.59). Although the proportion of patients with grade 3 or 4 AEs did not differ by age, patients aged < 65 years had lower AE-related discontinuation rates in the cabozantinib arm than those aged ≥ 65 years (11% *vs* 22%)[40].

A *post hoc* analysis of the CELESTIAL trial assessed quality of life with cabozantinib compared with placebo[41]. During the initial treatment period, cabozantinib was associated with lower EQ-5D scores than was placebo, and - following this early

deterioration - differences between EQ-5D scores for cabozantinib and placebo were numerically smaller but did not reach statistical significance. *Post hoc* analyses of the CELESTIAL trial demonstrated that cabozantinib-treated patients with an AFP response had an OS increase of 7 mo relative to patients without an AFP response (16.1 *vs* 9.1; HR = 0.61; 95%CI: 0.45-0.84) and an increase of 3.3 mo in median PFS (7.3 *vs* 4.0; HR = 0.55; 95%CI: 0.41-0.74)[42].

CURRENT SECOND-LINE OPTIONS FOR PATIENTS WITH HCC: RAMUCIRUMAB

Ramucirumab is a fully human immunoglobulin G1 monoclonal antibody that binds to and selectively inhibits VEGFR2 by preventing the binding of VEGFR ligands VEGF-A, VEGF-C, and VEGF-D. In doing so, ramucirumab inhibits a number of angiogenic pathways involved in tumor development and progression.

REACH-2

Significantly higher microvessel density and VEGF tissue expression have been reported in patients with HCC who have high AFP serum levels, and the cross-talk between AFP and VEGF signalling cascades have been elucidated by *in vitro* studies[43]. The pivotal phase III trial, REACH-2, randomized patients with advanced HCC (who progressed on or were intolerant to sorafenib) and elevated baseline AFP levels (≥ 400 ng/mL) to ramucirumab (n = 197) or placebo (n = 95)[44].

The REACH-2 trial results demonstrated that ramucirumab reduced the risk of death by 29% in patients with HCC, with a median OS of 8.5 *vs* 7.3 mo for the placebo group (HR = 0.71; 95%CI: 0.53-0.95; P = 0.0199). Median PFS was significantly (P < 0.0001) longer in the ramucirumab group (2.8 mo; 95%CI: 2.8-4.1) than in the placebo group (1.6 mo; 95%CI: 1.5-2.7), with an HR of 0.45 (95%CI: 0.34-0.60). Although the proportion of patients with an OR did not differ significantly between treatment arms [9 of 197 (5%) *vs* 1 of 95 (1%); P = 0.1697], the proportion of patients with disease control was significantly higher in the ramucirumab group than in the placebo group (59.9%;

95%CI: 53.1-66.7 *vs* 38.9%; 95%CI: 29.1-48.8; P = 0.0006). Overall, the drug was well tolerated. Hypertension and hyponatraemia were the sole grade 3 or higher TEAEs that occurred in ≥ 5% of patients, with greater occurrence in the ramucirumab group than in the placebo group. Conversely, aspartate aminotransferase concentrations were higher in the placebo group (5%) than in the ramucirumab group (3%). TEAEs resulting in treatment discontinuation were more frequent in the ramucirumab group than in the placebo group (11% *vs* 4%).

***Post hoc* analysis from REACH-2 (AFP response):** In REACH-2, AFP response was significantly higher (P < 0.0001) with ramucirumab (42%) than with placebo (10.5%). OS for patients with and without an AFP response was 13.5 mo *vs* 6.7 mo (HR = 0.470; P < 0.0001)[45]. Furthermore, of the 11 patients who experienced complete normalisation of their AFP levels, eight had received ramucirumab. OS for these patients was significantly longer than for patients who experienced an AFP response without complete normalisation of AFP level (n = 111) (25.6 mo *vs* 10.6 mo, HR = 0.147; P = 0.0019).

REACH

The efficacy and safety of ramucirumab was evaluated in REACH, a phase III RCT[20]. In this trial, second-line treatment with ramucirumab failed to demonstrate an improvement in OS for patients with advanced HCC when compared with placebo in an unselected population; however, a pre-planned subgroup analysis showed that patients with elevated AFP values (≥ 400 ng/mL) benefited from ramucirumab treatment, with such patients experiencing improved outcomes in the ramucirumab arm: Longer median OS (7.8 mo; 95%CI: 5.8-9.3 *vs* 4.2 mo; 95%CI: 3.7-4.8) and PFS (7.8 mo; 95%CI: 5.8-9.3 *vs* 4.2 mo; 95%CI: 3.7-4.8; HR = 0.70; 95%CI: 0.53-0.92) *vs* the placebo arm. A Cox model with baseline AFP fitted as a continuous variable was used to evaluate the interaction between the treatment effect of ramucirumab on survival and baseline AFP concentrations. Results suggested that ramucirumab had an increased

efficacy with increasing values of baseline AFP. This finding ultimately led to the development of the aforementioned REACH-2 study.

***Post hoc* analysis from REACH (AFP response):** Patients with an AFP response in REACH demonstrated significantly longer median OS than patients without an AFP response (13.6 mo *vs* 6.2 mo; HR = 0.46; 95%CI: 0.34-0.62; $P < 0.0001$), irrespective of treatment arm[46]. However, patients in the ramucirumab arm showed an observed benefit in delaying time to AFP progression; 3.5 mo with ramucirumab (95%CI: 2.8-4.5; $n = 283$) and 2.6 mo with placebo (95%CI: 1.6-2.8; $n = 282$; HR = 0.613; $P < 0.0001$).

REACH and REACH-2 pooled analyses: As both REACH and REACH-2 were international trials with similar objectives, eligibility criteria and protocols, data from both trials were combined and pooled for analyses of a larger patient population[44]. This provided greater statistical power, and treatment effects were measured with greater precision for subgroup analyses. The pooled analysis included 542 patients (ramucirumab, $n = 316$; placebo, $n = 226$) with baseline AFP concentrations ≥ 400 ng/mL. Pooled patients in the ramucirumab arm demonstrated a significantly ($P = 0.0002$) longer median OS than those in the placebo arm (8.1 mo; 95%CI: 6.9-9.3 *vs* 5.0 mo; 95%CI: 4.3-6.1; HR = 0.694; 95%CI: 0.571-0.842), which was consistent with the HRs and OS reported in the individual studies.

Improvements in PFS and the proportions of patients achieving responses or disease control in the pooled analysis were also consistent with those in each study. Both the frequency and the type of TEAEs observed in REACH-2 were also reported in the combined population[44]. These AEs are likely on-target effects from VEGFR2 inhibition. A major factor that differentiates ramucirumab from the multi-kinase inhibitors is that it does not seem to cause HFSR, so this may fulfil the need for a second-line treatment for patients with elevated AFP levels for whom first-line therapy failed because of significant HFSR.

Safety and efficacy was assessed in three prespecified age groups (< 65, ≥ 65 to < 75 and ≥ 75 years) in the pooled data of patients participating in REACH and REACH-2 with AFP ≥ 400 ng/mL in a *post hoc* subgroup analysis[47]. Ramucirumab improved median OS in all three age subgroups relative to placebo [< 65 years: 8.18 mo *vs* 4.76 mo (HR = 0.753; 95%CI: 0.581-0.975); ≥ 65 to < 75 years: 7.62 mo *vs* 5.22 mo (HR = 0.602; 95%CI: 0.419-0.866]; ≥ 75 years: 8.87 mo *vs* 6.31 mo (HR = 0.709; 95%CI: 0.420-1.199)]. Additionally, ramucirumab improved PFS relative to placebo in all three age subgroups [< 65 years: 2.73 mo *vs* 1.45 mo (HR = 0.613; 95%CI: 0.472-0.796); ≥ 65 to < 75 years: 2.78 mo *vs* 1.84 mo (HR = 0.563; 95%CI: 0.396-0.802); ≥ 75 years: 4.17 mo *vs* 1.64 mo (HR = 0.480; 95%CI: 0.282-0.817)]. The safety profile, including the incidence of grade 3 or higher AEs, was similar between age subgroups < 65 and ≥ 65 to < 75 years. However, the frequency of grade 3 or higher TEAEs (hypertension and fatigue) was higher for ramucirumab (62%) than for placebo (39%) in the ≥ 75 years subgroup but was similar in the two younger subgroups (54% and 60%). Proteinuria (4.1%) was the most common TEAE resulting in dose adjustment in the ramucirumab arm in patients aged < 65 years, and hypertension was most common in the two older subgroups (7.5% and 5.8%). *Post hoc* analysis indicated that AEs of interest, selected based on the known safety profile of ramucirumab, were similar across all age subgroups.

The Functional Hepatobiliary Symptom Index (FHSI-8) is a patient-administered 5-point Likert-type scale questionnaire focusing on the type and frequency of symptoms experienced by patients with hepatobiliary malignancies. Recent qualitative research supports its validity in patients with HCC and AFP ≥ 400 ng/mL[48]. The FHSI-8 questionnaire comprises eight symptoms: Lack of energy, nausea, pain, weight loss, back pain, fatigue, jaundice and stomach pain or discomfort. These patient-reported outcomes for HRQoL were assessed by age (< 65, ≥ 65 to < 75, and ≥ 75 years) in the pooled REACH/REACH-2 dataset[47,49,50]. Treatment with ramucirumab resulted in a delay in the deterioration of symptoms as measured by FHSI-8 compared with placebo across all subgroups, although this was not significant. Median time to deterioration was also numerically longer with ramucirumab than with placebo in all three age

subgroups. Together, these results support the use of ramucirumab for the treatment of HCC with elevated AFP after prior sorafenib treatment, irrespective of age.

A limitation of the design of both REACH trials was that it excluded patients who received first-line systemic treatment with any drug except for sorafenib, as this was the only therapy associated with an OS benefit at the time. To address this limitation, an ongoing global open-label expansion cohort of REACH-2 is evaluating ramucirumab in patients with advanced HCC and baseline AFP ≥ 400 ng/mL following a non-sorafenib-based systemic therapy[51]. Recently, final results from an expansion cohort of REACH-2 were presented at the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium. Of 47 patients, 51% with second- to third-line or more advanced HCC were classed as Eastern Cooperative Oncology Group performance status 1 at baseline, with a median AFP of 3236 ng/mL. The majority of patients had received lenvatinib (n = 20) as a prior systemic regimen, followed by checkpoint inhibitor (CPI) monotherapy (n = 11), CPI plus an antiangiogenic (n = 15), and CPI plus another CPI (n = 4). Grade 3 or higher TEAEs were reported in 57% (n = 27) of patients, 23% (n = 11) of which were classified as treatment related. The most frequent grade 3 or higher AEs occurring in ≥ 5% of patients were hypertension (11%), followed by proteinuria, hyponatraemia and increased aspartate aminotransferase (6% each). Two deaths associated with treatment-related AEs were reported during treatment or within 30 d following treatment discontinuation. The median OS, PFS and TTP were 8.7 mo (95%CI: 4.6-12.2), 1.7 mo (95%CI: 1.5-4.1) and 2.8 mo (95%CI: 1.5-4.2), respectively. The ORR was 10.6% (95%CI: 1.8-19.5; n = 5), with a median duration of response (DOR) of 8.3 mo (95%CI: 2.4-not reached)[52]. These results indicate that the safety and efficacy of ramucirumab following a non-sorafenib-based systemic therapy was consistent with results of the REACH-2 study in patients following prior sorafenib treatment.

CURRENT SECOND-LINE OPTIONS FOR PATIENTS WITH HCC: IMMUNE CPIS

Immune CPIs are revolutionising the treatment of HCC, and immunotherapy biomarker development to identify patients with the best potential response has

necessarily become a research priority. Whilst persistent HBV and hepatitis C virus infection can contribute to chronic inflammatory conditions in the liver, the immunosuppressive properties of these infections, as well as the inherent unique immunobiology of the liver, are well documented, meaning that HCC is generally not regarded as an immunogenic tumor. Nevertheless, immunotherapy has been explored as both first- and second-line options for patients with advanced HCC.

Nivolumab

Antibodies that disrupt programmed cell death-1 (PD-1) immune checkpoint signalling have the potential to restore the antitumor activity of otherwise suppressed effector T cells. Nivolumab, a fully human immunoglobulin G4 monoclonal antibody, was evaluated for its potential to treat patients with HCC in the second-line setting in the phase I/II dose-escalation and expansion study CheckMate 040, an open-label, non-comparative trial carried out in the United States[53]. In this study, nivolumab treatment resulted in substantial tumor reductions and an ORR of 15% (95%CI: 6-28) in patients with advanced HCC in the dose-escalation phase, with responses occurring early in treatment. The DCR, median TTP and median DOR were 58% (95%CI: 43-72), 3.4 mo (95%CI: 1.6-6.9) and 17 mo (95%CI: 6-24), respectively. OS at both 6 and 9 mo was 66% (95%CI: 51-78). Patients in the dose-escalation phase demonstrated a median OS of 15.0 mo (95%CI: 9.6-20.2), and the median DOR in both phases of the study suggested that nivolumab might offer durable responses hitherto unseen in patients with HCC. Overall, these results were encouraging in the metastatic setting in patients who were previously treated with sorafenib.

Given the favorable ORR and the improved 9-mo OS rates in CheckMate 040[53], the FDA granted nivolumab accelerated approval as a second-line treatment option in the United States despite the study lacking a randomized control arm[54], a major limitation of the study. In the subsequent phase III CheckMate 459 trial, nivolumab failed to significantly improve OS *vs* sorafenib in patients without previous systemic treatment[55].

A randomized cohort expansion phase of the CheckMate 040 study demonstrated that a combination approach may have merit: Nivolumab in combination with ipilimumab resulted in clinically meaningful responses, with an ORR of 31%, DCR of 49%, 24-mo OS of 40% and a more than 2-fold increase in ORR compared with nivolumab monotherapy (31% *vs* 14%)[56]. Although these findings led to FDA approval of the combination of nivolumab plus ipilimumab in a second-line setting for the treatment of advanced HCC, the FDA Oncologic Drug Advisory Committee recently voted 5:4 against the continued accelerated approval of nivolumab[57].

Pembrolizumab

Pembrolizumab, a humanised monoclonal anti-PD1 antibody, showed promising clinical efficacy and manageable safety in patients with advanced HCC in a non-randomized, open-label phase II trial (KEYNOTE-224)[58]. Following these results, accelerated approval of pembrolizumab was granted in November 2018 for patients with HCC who received prior treatment with sorafenib. The randomized, double-blind, placebo-controlled, phase III trial (KEYNOTE-240) evaluated the efficacy and safety of pembrolizumab plus BSC *vs* placebo plus BSC in the second line setting[59,60]. Although PFS and OS were numerically improved *vs* placebo, KEYNOTE-240 did not meet its prespecified statistical dual endpoints of improvements in PFS and OS. Programmed cell death ligand 1 expression in immune and tumor cells in patients enrolled in KEYNOTE-224 was positively associated with response to anti-PD-1 therapy with pembrolizumab[58]. A similar observation in patients enrolled in KEYNOTE-240 is yet to be confirmed. KEYNOTE-394 is another ongoing trial in the same setting, and results are anticipated soon. At the recent Oncologic Drug Advisory Committee meeting, continuing the accelerated approval for pembrolizumab in sorafenib-pre-treated patients with HCC was unanimously sanctioned[61].

Recent real-world evidence from Taiwan demonstrated that patients who received nivolumab or pembrolizumab as second-line therapy for unresectable HCC achieved an ORR of 24.4%, indicating that a certain subset of patients may benefit from

immunotherapy following sorafenib failure[62]. In this study, a novel 10-10 rule (baseline AFP level ≥ 10 ng/mL and 10% reduction within 4 wk of treatment) was proposed to predict survival following immunotherapy in patients with unresectable HCC.

CONCLUSION

Drug-related AEs, complications due to liver disease, the safety profile of the candidate therapy and the patient's QoL all aid in the identification of a suitable second-line drug for patients with advanced HCC after first-line treatment. The role of immune CPIs is somewhat unclear in second-line HCC treatment. Despite being granted accelerated approval by the FDA in the second line setting after failure of sorafenib, both nivolumab and pembrolizumab were recently removed from the European Society for Medical Oncology treatment guidelines because of their failure to demonstrate an improvement in OS and PFS as single agents.

Two tyrosine kinase inhibitors (TKIs), cabozantinib and regorafenib, and one monoclonal antibody, ramucirumab, have been approved for use after sorafenib by the FDA, the European Medicines Agency, and the Japanese Regulatory Agency in the second-line setting for the treatment of patients with advanced HCC. However, regorafenib is only suitable for patients who demonstrated prior tolerance to sorafenib. For sorafenib-intolerant patients, cabozantinib and ramucirumab remain viable treatment options. Treatment choice is also often based on several other factors, including comorbidities and the drug safety profile. For example, in patients with prior HFSR with sorafenib, the risk of recurrence with cabozantinib or regorafenib makes them less rational choices.

Research efforts to identify subgroups of patients with HCC who will benefit from specific therapies are ongoing. Ramucirumab has a very different mechanism of action to the TKIs by virtue of being a monoclonal antibody with a very high specificity for VEGFR2. Data from REACH and REACH-2 support the clinical relevance of this difference, given the contrasting toxicity profile of ramucirumab compared with the TKIs. This may contribute to the tolerability of ramucirumab in a variety of traditionally

hard-to-treat patient subpopulations such as the elderly and patients who do not tolerate or whose disease progresses on sorafenib.

It is well documented that elevated AFP serum levels are associated with a poor prognosis in patients with HCC, and - given that almost half of patients have AFP concentrations ≥ 400 ng/mL following sorafenib treatment - efficacious and well-tolerated options are needed for such patients. Evidence from the REACH-2/REACH trials demonstrated for the first time that baseline AFP levels can be used as an identification factor to select patients who are likely to reap the greatest benefits from ramucirumab treatment. In the face of multiple second-line options for patients with advanced HCC, the onus is on the physician to make a judicious choice. Ramucirumab has been shown to be both well-tolerated and efficacious for patients with baseline AFP ≥ 400 ng/mL and to have a clinically acceptable safety profile.

69918_Auto_Edited-check.docx

ORIGINALITY REPORT

22%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.mdpi.com Internet	132 words — 2%
2	hdl.handle.net Internet	128 words — 2%
3	Ian Chau, Joon Oh Park, Baek-Yeol Ryoo, Chia-Jui Yen et al. "Alpha-fetoprotein kinetics in patients with hepatocellular carcinoma receiving ramucirumab or placebo: an analysis of the phase 3 REACH study", British Journal of Cancer, 2018 Crossref	79 words — 1%
4	Andrew X Zhu, Yoon-Koo Kang, Chia-Jui Yen, Richard S Finn et al. "Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial", The Lancet Oncology, 2019 Crossref	69 words — 1%
5	www.wjgnet.com Internet	54 words — 1%
6	www.nejm.org Internet	47 words — 1%
7	www.dovepress.com Internet	

		46 words — 1%
8	www.nice.org.uk Internet	45 words — 1%
9	f6publishing.blob.core.windows.net Internet	41 words — 1%
10	www.hcp.stivarga-us.com Internet	41 words — 1%
11	link.springer.com Internet	39 words — 1%
12	www.cancer.or.kr Internet	38 words — 1%
13	www.ncbi.nlm.nih.gov Internet	38 words — 1%
14	Nault, Jean-Charles. "The end of almost 10 years of negative RCTs in advanced hepatocellular carcinoma", The Lancet, 2016. Crossref	36 words — 1%
15	Www.dovepress.com Internet	36 words — 1%
16	Lorenza Rimassa, Marcus - Alexander Wörns. "Navigating the new landscape of second - line treatment in advanced hepatocellular carcinoma", Liver International, 2020 Crossref	34 words — 1%
17	www.onclive.com Internet	32 words — 1%

18	Yuji Eso, Hiroyuki Marusawa. "Novel approaches for molecular targeted therapy against hepatocellular carcinoma", Hepatology Research, 2018 Crossref	28 words —	< 1%
19	Nicola Personeni, Lorenza Rimassa, Tiziana Pressiani, Valeria Smiroldo, Armando Santoro. "Cabozantinib for the treatment of hepatocellular carcinoma", Expert Review of Anticancer Therapy, 2019 Crossref	21 words —	< 1%
20	Masatoshi Kudo, Peter R. Galle, Josep M. Llovet, Richard S. Finn et al. "Ramucirumab in elderly patients with hepatocellular carcinoma and elevated alpha-fetoprotein after sorafenib in REACH and REACH-2", Liver International, 2020 Crossref	18 words —	< 1%
21	www.scottishmedicines.org.uk Internet	17 words —	< 1%
22	Andrea Gmür, Philippe Kolly, Marina Knöpfli, Jean-François Dufour. "FACT-Hep increases the accuracy of survival prediction in HCC patients when added to ECOG Performance Status", Liver International, 2018 Crossref	16 words —	< 1%
23	WWW.fda.gov Internet	16 words —	< 1%
24	assets.researchsquare.com Internet	15 words —	< 1%
25	www.targetedonc.com Internet	15 words —	< 1%

26	"Liver Cancer in the Middle East", Springer Science and Business Media LLC, 2021 Crossref	14 words — < 1%
27	issuu.com Internet	14 words — < 1%
28	www.science.gov Internet	14 words — < 1%
29	Pacella, C.M.. "Analysis of factors predicting survival in patients with hepatocellular carcinoma treated with percutaneous laser ablation", Journal of Hepatology, 200605 Crossref	13 words — < 1%
30	intelligencepharma.wordpress.com Internet	13 words — < 1%
31	www.1stoncology.com Internet	13 words — < 1%
32	www.karger.com Internet	13 words — < 1%
33	www.thieme-connect.com Internet	13 words — < 1%
34	Andrew X Zhu, Richard S Finn, Julien Edeline, Stephane Cattan et al. "Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial", The Lancet Oncology, 2018 Crossref	12 words — < 1%
35	Antonella Cammarota, Antonio D'Alessio, Tiziana Pressiani, Lorenza Rimassa, Nicola Personeni.	12 words — < 1%

"Systemic Treatment for Older Patients with Unresectable Hepatocellular Carcinoma", Drugs & Aging, 2021
Crossref

36 Chia-Jui Yen, Masatoshi Kudo, Ho-Yeong Lim, Chih-Hung Hsu et al. "Efficacy and Safety of Ramucirumab in Asian and Non-Asian Patients with Advanced Hepatocellular Carcinoma and Elevated Alpha-Fetoprotein: Pooled Individual Data Analysis of Two Randomized Studies", Liver Cancer, 2020
Crossref
12 words — < 1%

37 Manushi Aggarwal, Abeer Arain, Zhaohui Jin. "Systemic treatment for hepatocellular carcinoma", Chronic Diseases and Translational Medicine, 2018
Crossref
12 words — < 1%

38 Robert J Cersosimo. "Systemic targeted and immunotherapy for advanced hepatocellular carcinoma", American Journal of Health-System Pharmacy, 2020
Crossref
12 words — < 1%

39 jitc.bmj.com
Internet
12 words — < 1%

40 onlinelibrary.wiley.com
Internet
12 words — < 1%

41 www.nature.com
Internet
12 words — < 1%

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON
EXCLUDE SOURCES < 12 WORDS
EXCLUDE MATCHES < 12 WORDS