**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 69918

**Manuscript Type:** MINIREVIEWS

**Second-line treatment of advanced hepatocellular carcinoma: Time for more individualized treatment options?**

Rajappa S *et al*. Advanced HCC

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**Author contributions:** Pruthi A, Cheng R, and Lukanowski M contributed to the study design; and all authors were involved in the data analysis and interpretation, drafting, review, and approval of the review.

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**Received:** September 6, 2021

**Revised:** November 16, 2021

**Accepted: May 26, 2022**

**Published online:**

**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 significantly increased, 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 is both well tolerated and efficacious and has 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. Second-line treatment of advanced hepatocellular carcinoma: 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 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].

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 chemoembolization, prolong survival for patients with liver-localized disease for whom surgery is not an option[5,6]. However, not all patients with non-resectable HCC are able to benefit from transarterial chemoembolization, especially for patients with multiple and large tumors[7]. Worldwide, themajority of patients with HCC present with advanced disease and are candidates for systemic therapy 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 envatinib 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 envatinib[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 United States 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, 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 of 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 the survival of patients with advanced HCC treated with sorafenib with or without transarterial chemoembolization[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 are 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 are 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 among 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 increased (20-200 ng/mL) levels have been reported repeatedly in Chinese patients with HCC[29-31].

In this narrative review, we 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 was 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 signaling pathways involved in tumor angiogenesis [vascular endothelial growth factor (VEGFreceptors) 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 Regorafenib after Sorafenib in Patients with HCC (RESORCE), 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 8 (4%) placebo-treated patients. Median PFS by Response Evaluation Criteria in Solid Tumors (RECIST) 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 diarrhea [*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 years 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, 1 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%); the 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:** Regorafenib Observational Study in HCC (REFINE; 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 9 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 significantly differed 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 diarrhea (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 mo *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 QoL 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 signaling 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 mo *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 hyponatremia 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)[17]. Furthermore, of the 11 patients who experienced complete normalization of their AFP levels, 8 had received ramucirumab. OS for these patients was significantly longer than for patients who experienced an AFP response without complete normalization 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 were 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 compared with placebo in an unselected population; however, 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. A summary of survival data from phase III randomized controlled trials of second- or later-line treatments in patients with advanced HCC are presented in Table 1.

***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[45]. 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[46]. 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 years 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 years 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 years and ≥ 65 years to < 75 years. However, the frequency of grade 3 or higher TEAEs (hypertension and fatigue) was higher for ramucirumab (62%) than 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[47]. 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 years, ≥ 65 years to < 75 years, and ≥ 75 years) in the pooled REACH/REACH-2 dataset[46,48,49]. 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[50]. 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, hyponatremia 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)[51]. 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.Table 2 summarizes subgroup analyses of randomized controlled trials in HCC.

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

Immune CPIs are revolutionizing 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 signaling 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[52]. 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 United States FDA granted nivolumab accelerated approval as a second-line treatment option in the United States despite the study lacking a randomized control arm[53], 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[54].

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%)[55]. 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[56].

***Pembrolizumab***

Pembrolizumab, a humanized 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)[57]. 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[58,59]. 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[57]. 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[60].

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[61]. 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. Graphical abstract is shown in Figure 1.

**REFERENCES**

1 **World Health Organization**. All cancers Source: Globocan 2020. [cited 19 August 2021]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf

2 **World Health Organization**. CI5 XI: Cancer incidence in five continents volume XI. [cited 19 August 2021]. Available from: https://ci5.iarc.fr/CI5-XI/Default.aspx

3 **Yang JD**, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 589-604 [PMID: 31439937 DOI: 10.1038/s41575-019-0186-y]

4 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999: **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

5 **Raoul JL**, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, Lencioni R. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev* 2011; **37**: 212-220 [PMID: 20724077 DOI: 10.1016/j.ctrv.2010.07.006]

6 **Llovet JM**, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907-1917 [PMID: 14667750 DOI: 10.1016/S0140-6736(03)14964-1]

7 **Piscaglia F**, Ogasawara S. Patient Selection for Transarterial Chemoembolization in Hepatocellular Carcinoma: Importance of Benefit/Risk Assessment. *Liver Cancer* 2018; **7**: 104-119 [PMID: 29662837 DOI: 10.1159/000485471]

8 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/liv.12818]

9 **Ben Mousa A**. Sorafenib in the treatment of advanced hepatocellular carcinoma. *Saudi J Gastroenterol* 2008; **14**: 40-42 [PMID: 19568496 DOI: 10.4103/1319-3767.37808]

10 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

11 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

12 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib *vs* sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

13 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, Lim HY, Kudo M, Breder VV, Merle P, Kaseb AO, Li D, Verret W, Shao H, Liu J, Li L, Zhu AX, Cheng A-L. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2021: **39**: 267 [DOI: 10.1200/JCO.2021.39.3\_suppl.267]

14 **Grizzi F**, Franceschini B, Hamrick C, Frezza EE, Cobos E, Chiriva-Internati M. Usefulness of cancer-testis antigens as biomarkers for the diagnosis and treatment of hepatocellular carcinoma. *J Transl Med* 2007; **5**: 3 [PMID: 17244360 DOI: 10.1186/1479-5876-5-3]

15 **Tangkijvanich P**, Anukulkarnkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P, Poovorawan Y. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol* 2000; **31**: 302-308 [PMID: 11129271 DOI: 10.1097/00004836-200012000-00007]

16 **Personeni N**, Bozzarelli S, Pressiani T, Rimassa L, Tronconi MC, Sclafani F, Carnaghi C, Pedicini V, Giordano L, Santoro A. Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. *J Hepatol* 2012; **57**: 101-107 [PMID: 22414760 DOI: 10.1016/j.jhep.2012.02.016]

17 **Finn RS**, Kudo M, Kang YK, Yen CJ, Galle PR, Llovet J, Assenat E, Brandi G, Lim HY, Pracht M, Rau KM, Merle P, Motomura K, Ohno I, Daniele B, Shin D, Gerken G, Abada P, Hsu Y, Zhu AX. Ramucirumab (RAM) as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline α-fetoprotein (AFP): an analysis of AFP kinetics in the phase III REACH-2 study. *J Clin Oncol* 2019; **37**: 326 [DOI: 10.1200/JCO.2019.37.4\_suppl.326]

18 **Berry K**, Ioannou GN. Serum alpha-fetoprotein level independently predicts posttransplant survival in patients with hepatocellular carcinoma. *Liver Transpl* 2013; **19**: 634-645 [PMID: 23536495 DOI: 10.1002/lt.23652]

19 **He C**, Peng W, Liu X, Li C, Li X, Wen TF. Post-treatment alpha-fetoprotein response predicts prognosis of patients with hepatocellular carcinoma: A meta-analysis. *Medicine (Baltimore)* 2019; **98**: e16557 [PMID: 31374020 DOI: 10.1097/MD.0000000000016557]

20 **Zhu AX**, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Chung HC, Baron AD, Pfiffer TE, Okusaka T, Kubackova K, Trojan J, Sastre J, Chau I, Chang SC, Abada PB, Yang L, Schwartz JD, Kudo M; REACH Trial Investigators. Ramucirumab *vs* placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015; **16**: 859-870 [PMID: 26095784 DOI: 10.1016/S1470-2045(15)00050-9]

21 **Bruix J**, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: 27932229 DOI: 10.1016/S0140-6736(16)32453-9]

22 **Koteish A**, Thuluvath PJ. Screening for hepatocellular carcinoma. *J Vasc Interv Radiol* 2002; **13**: S185-S190 [PMID: 12354835 DOI: 10.1016/s1051-0443(07)61785-0]

23 **Zhou L**, Liu J, Luo F. Serum tumor markers for detection of hepatocellular carcinoma. *World J Gastroenterol* 2006; **12**: 1175-1181 [PMID: 16534867 DOI: 10.3748/wjg.v12.i8.1175]

24 **Wu G**, Wu J, Pan X, Liu B, Yao Z, Guo Y, Shi X, Ding Y. Racial disparities in alpha-fetoprotein testing and alpha-fetoprotein status associated with the diagnosis and outcome of hepatocellular carcinoma patients. *Cancer Med* 2019; **8**: 6614-6623 [PMID: 31517445 DOI: 10.1002/cam4.2549]

25 **Nishioka ST**, Sato MM, Wong LL, Tiirikainen M, Kwee SA. Clinical and molecular sub-classification of hepatocellular carcinoma relative to alpha-fetoprotein level in an Asia-Pacific island cohort. *Hepatoma Res* 2018; **4** [PMID: 29376136 DOI: 10.20517/2394-5079.2017.46]

26 **Yen CJ**, Kudo M, Lim HY, Hsu CH, Vogel A, Brandi G, Cheng R, Nitu IS, Abada P, Hsu Y, Zhu AX, Kang YK. 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; **9**: 440-454 [PMID: 32999870 DOI: 10.1159/000506946]

27 **Chaminda SR**, Suchintha T, Anuk NM, Supun DA, Bhagya GM, Habarakada LCA, Janaka SH. Pre-treatment alphafeto protein in hepatocellular carcinoma with non-viral aetiology - a prospective study. *BMC Gastroenterol* 2017; **17**: 142 [PMID: 29207969 DOI: 10.1186/s12876-017-0710-x]

28 **Sanai FM**, Sobki S, Bzeizi KI, Shaikh SA, Alswat K, Al-Hamoudi W, Almadi M, Al Saif F, Abdo AA. Assessment of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma in Middle Eastern patients. *Dig Dis Sci* 2010; **55**: 3568-3575 [PMID: 20397051 DOI: 10.1007/s10620-010-1201-x]

29 **Tsai JF**, Chang WY, Jeng JE, Ho MS, Lin ZY, Tsai JH. Frequency of raised alpha-fetoprotein level among Chinese patients with hepatocellular carcinoma related to hepatitis B and C. *Br J Cancer* 1994; **69**: 1157-1159 [PMID: 7515263 DOI: 10.1038/bjc.1994.227]

30 **Peng YC**, Chan CS, Chen GH. The effectiveness of serum alpha-fetoprotein level in anti-HCV positive patients for screening hepatocellular carcinoma. *Hepatogastroenterology* 1999; **46**: 3208-3211 [PMID: 10626187]

31 **Furui J**, Furukawa M, Kanematsu T. The low positive rate of serum alpha-fetoprotein levels in hepatitis C virus antibody-positive patients with hepatocellular carcinoma. *Hepatogastroenterology* 1995; **42**: 445-449 [PMID: 8751193]

32 **Wilhelm SM**, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; **129**: 245-255 [PMID: 21170960 DOI: 10.1002/ijc.25864]

33 **Bruix J**, Merle P, Granito A, Huang YH, Bodoky G, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Qin S, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, LeBerre MA, Baumhauer A, Meinhardt G, Han G. Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, double-blind phase 3 RESORCE trial. *Ann Oncol* 2016; **27**: vi564 [DOI: 10.1093/annonc/mdw435.19]

34 **Finn RS**, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Gerolami R, Caparello C, Cabrera R, Chang C, Sun W, LeBerre MA, Baumhauer A, Meinhardt G, Bruix J. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. *J Hepatol* 2018; **69**: 353-358 [PMID: 29704513 DOI: 10.1016/j.jhep.2018.04.010]

35 **Koroki K**, Kanogawa N, Maruta S, Ogasawara S, Iino Y, Obu M, Okubo T, Itokawa N, Maeda T, Inoue M, Haga Y, Seki A, Okabe S, Koma Y, Azemoto R, Atsukawa M, Itobayashi E, Ito K, Sugiura N, Mizumoto H, Unozawa H, Iwanaga T, Sakuma T, Fujita N, Kanzaki H, Kobayashi K, Kiyono S, Nakamura M, Saito T, Kondo T, Suzuki E, Ooka Y, Nakamoto S, Tawada A, Chiba T, Arai M, Kanda T, Maruyama H, Kato J, Kato N. Posttreatment after Lenvatinib in Patients with Advanced Hepatocellular Carcinoma. *Liver Cancer* 2021; **10**: 473-484 [PMID: 34721509 DOI: 10.1159/000515552]

36 **US FDA**. Full prescribing information: Contents\* Warning: Hepatotoxicity. [cited 19 August 2021]. Available from: https://www.accessdata.fda.gov/drugsatfda\_docs/label/2020/203085s011lbl.pdf

37 **Astor L**. RESORCE trial analysis shows higher AFP responses achieved with regorafenib in HCC. [cited 23 August 2021]. Available from: https://www.targetedonc.com/view/resorce-trial-analysis-shows-higher-afp-responses-achieved-with-regorafenib-in-hcc

38 **Kelley RK**, Verslype C, Cohn AL, Yang TS, Su WC, Burris H, Braiteh F, Vogelzang N, Spira A, Foster P, Lee Y, Van Cutsem E. Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study. *Ann Oncol* 2017; **28**: 528-534 [PMID: 28426123 DOI: 10.1093/annonc/mdw651]

39 **Abou-Alfa GK**, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, Merle P, Chen Y, Park JW, Blanc JF, Bolondi L, Klümpen HJ, Chan SL, Zagonel V, Pressiani T, Ryu MH, Venook AP, Hessel C, Borgman-Hagey AE, Schwab G, Kelley RK. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med* 2018; **379**: 54-63 [PMID: 29972759 DOI: 10.1056/NEJMoa1717002]

40 **Rimassa L**, Cicin I, Blanc J-F, Klümpen HJ, Zagonel V, Tran A, Kim SCH, Lin Z-Z, Tam VC, Hazra S, Mangeshkar M, El-Khoueiry A, Cheng A-L, Meyer T, Kelley RK, Abou-Alfa GK. Outcomes based on age in the phase 3 CELESTIAL trial of cabozantinib (C) *vs* placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2018; **36**: 4090 [DOI: 10.1200/JCO.2018.36.15\_suppl.4090]

41 **Abou-Alfa GK**, Mollon P, Meyer T, Cheng AL, El-Khoueiry AB, Kelley RKK, Baron AD, Benzaghou F, Valcheva VV, Hazra S, Mangeshkar M, Freemantle N. Quality-adjusted life years accrued with cabozantinib in patients with advanced hepatocellular carcinoma (aHCC) in the CELESTIAL trial. *J Clin Oncol* 2019; **37**: 207 [DOI: 10.1200/JCO.2019.37.4\_suppl.207]

42 **Kelley RK**, El-Khoueiry AB, Meyer T, Rimassa L, Merle P, Chan SL, Tran A, Parnis F, Tam VC, Cattan S, Markby DW, Clary DO, Cheng AL, Abou-Alfa GK. Outcomes by baseline alpha-fetoprotein (AFP) levels in the phase III CELESTIAL trial of cabozantinib (C) *vs* placebo (P) in previously treated advanced hepatocellular carcinoma (HCC). *Ann Oncol* 2018; **29**: 702P [DOI: 10.1093/annonc/mdy282.085]

43 **Shan YF**, Huang YL, Xie YK, Tan YH, Chen BC, Zhou MT, Shi HQ, Yu ZP, Song QT, Zhang QY. Angiogenesis and clinicopathologic characteristics in different hepatocellular carcinoma subtypes defined by EpCAM and α-fetoprotein expression status. *Med Oncol* 2011; **28**: 1012-1016 [PMID: 20571936 DOI: 10.1007/s12032-010-9600-6]

44 **Zhu AX**, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, Rau KM, Motomura K, Ohno I, Merle P, Daniele B, Shin DB, Gerken G, Borg C, Hiriart JB, Okusaka T, Morimoto M, Hsu Y, Abada PB, Kudo M; REACH-2 study investigators. 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. *Lancet Oncol* 2019; **20**: 282-296 [PMID: 30665869 DOI: 10.1016/S1470-2045(18)30937-9]

45 **Chau I**, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Kudo M, Pfiffer T, Hatano E, Chung HC, Kopeckova K, Phelip JM, Brandi G, Ohkawa S, Li CP, Okusaka T, Hsu Y, Abada PB, Zhu AX. Alpha-fetoprotein kinetics in patients with hepatocellular carcinoma receiving ramucirumab or placebo: an analysis of the phase 3 REACH study. *Br J Cancer* 2018; **119**: 19-26 [PMID: 29808014 DOI: 10.1038/s41416-018-0103-0]

46 **Kudo M**, Galle PR, Llovet JM, Finn RS, Vogel A, Motomura K, Assenat E, Merle P, Brandi G, Daniele B, Okusaka T, Tomášek J, Borg C, Dadduzio V, Morimoto M, Pracht M, Jen MH, Drove Ubreva N, Widau RC, Shinozaki K, Yoshikawa R, Zhu AX. Ramucirumab in elderly patients with hepatocellular carcinoma and elevated alpha-fetoprotein after sorafenib in REACH and REACH-2. *Liver Int* 2020; **40**: 2008-2020 [PMID: 32279446 DOI: 10.1111/liv.14462]

47 **Gable J**, Ayer D, Girvan A, Bowman L, Abada P, Ervin C, Evans E, Cella D. PCN366 - Qualitative patient interviews to support the FACT Hepatobiliary Symptom Index-8 among patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein. *Value Health* 2018; **21**: S76 [abstract] [DOI: 10.1016/j.jval.2018.09.448]

48 **Zhu AX**, Nipp RD, Finn RS, Galle PR, Llovet JM, Blanc JF, Okusaka T, Chau I, Cella D, Girvan A, Gable J, Bowman L, Wang C, Hsu Y, Abada PB, Kudo M. Ramucirumab in the second-line for patients with hepatocellular carcinoma and elevated alpha-fetoprotein: patient-reported outcomes across two randomised clinical trials. *ESMO Open* 2020; **5** [PMID: 32817068 DOI: 10.1136/esmoopen-2020-000797]

49 **Kudo M**, Galle P, Motomura K, Assenat E, Merle P, Brandi G, Daniele B, Okusaka T, Tomasek J, Borg C, Zagonel V, Morimoto M, Pracht M, Finn R, Llovet JM, Homma G, Jen MH, Shinozaki K, Yoshikawa R, Zhu A. 757P Efficacy and safety of ramucirumab (RAM) for advanced hepatocellular carcinoma (HCC) with elevated alpha-fetoprotein (AFP) following first-line sorafenib across age subgroups in two global phase III trials (REACH and REACH-2). *Ann Oncol* 2019; **30**: v253-v324 [DOI: 10.1093/annonc/mdz247]

50 **Finn RS**, De Toni E, Chung Cheung Yau T, Yen C, Hsu C, Chan S, He A, Galle P, Trojan J, Stirnimann G, Baron A, Acosta-Rivera M, Goyal L, Wang C, Abada P, Widau R, Zhu A. Ramucirumab for patients with advanced hepatocellular carcinoma and elevated alpha fetoprotein following a non-sorafenib based systemic therapy: interim results from an expansion cohort of the phase 3 REACH-2 study. *Z Gastroenterol* 2021; **59**: e349-e350 [DOI: 10.1055/s-0041-1734284]

51 **Finn RS**, Yau T, Hsu C-H, De Toni EN, Goyal L, Galle PR, Qin S, Rao S, Sun F, Wang C, Widau RC, Zhu AX. Ramucirumab for patients with advanced hepatocellular carcinoma and elevated α-fetoprotein following a non-sorafenib based first-line therapy: final results from an expansion cohort of REACH-2. *J Clin Oncol* 2022; **40**: 423 [DOI: 10.1200/JCO.2022.40.4\_suppl.423]

52 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]

53 **US Food and Drug Administration**. FDA grants accelerated approval to nivolumab for HCC previously treated with sorafenib. [cited 25 August 2021]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-hcc-previously-treated-sorafenib

54 **Yau T**, Park J, Finn R, Cheng AL, Mathurin P, Edeline J, Kudo M, Han KH, Harding J, Merle P, Rosmorduc O, Wyrwicz L, Schott E, Choo S, Kelley R, Begic D, Chen G, Neely J, Anderson AJ, Sangro B. CheckMate 459: A randomized, multi-center phase III study of nivolumab (NIVO) *vs* sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Ann Oncol* 2019; **30**: v874-v875 [DOI: 10.1093/annonc/mdz394.029]

55 **El-Khoueiry AB**, Yau T, Kang Y-K, Kim T-Y, Santoro A, Sangro B, Melero I, Kudo M, Hou M-M, Matilla A, Tovoli F, Knox JJ, He AR, El-Rayes BF, Acosta-Rivera M, Neely J, Shen Y, Baccan C, Cruz CMD, Hsu C. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Long-term results from CheckMate 040. *J Clin Oncol* 2019; **39**: 269 [DOI: 10.1200/JCO.2021.39.3\_suppl.269]

56 **Karlovitch S**. ODAC opposes ongoing FDA approval of nivolumab for HCC in patients pretreated with sorafenib. [cited 18 August 2021]. Available from: https://www.targetedonc.com/view/odac-opposes-ongoing-fda-approval-of-nivolumab-for-hcc-in-patients-pretreated-with-sorafenib

57 **Zhu AX**, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, Sarker D, Verset G, Chan SL, Knox J, Daniele B, Webber AL, Ebbinghaus SW, Ma J, Siegel AB, Cheng AL, Kudo M; KEYNOTE-224 investigators. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol* 2018; **19**: 940-952 [PMID: 29875066 DOI: 10.1016/S1470-2045(18)30351-6]

58 **Finn RS**, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, Breder V, Edeline J, Chao Y, Ogasawara S, Yau T, Garrido M, Chan SL, Knox J, Daniele B, Ebbinghaus SW, Chen E, Siegel AB, Zhu AX, Cheng AL; KEYNOTE-240 investigators. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. *J Clin Oncol* 2020; **38**: 193-202 [PMID: 31790344 DOI: 10.1200/JCO.19.01307]

59 **Finn RS**, Chan SL, Zhu AX, Knox JJ, Cheng A-L, Siegel AB, Bautista O, Watson P, Kudo M. KEYNOTE-240: Randomized phase III study of pembrolizumab *vs* best supportive care for second-line advanced hepatocellular carcinoma. *J Clin Oncol* 2017; **35**: TPS503 [DOI: 10.1200/JCO.2017.35.4\_suppl.TPS503]

60 **The ASCO Post Staff**. More from the FDA ODAC: Votes on agents for pretreated hepatocellular carcinoma and gastric cancer. [cited 7 May 2021]. Available from: https://ascopost.com/news/april-2021/more-from-the-fda-odac-votes-on-agents-for-pretreated-hepatocellular-carcinoma-and-gastric-cancer/

61 **Lee PC**, Chao Y, Chen MH, Lan KH, Lee CJ, Lee IC, Chen SC, Hou MC, Huang YH. Predictors of Response and Survival in Immune Checkpoint Inhibitor-Treated Unresectable Hepatocellular Carcinoma. *Cancers (Basel)* 2020; **12** [PMID: 31940757 DOI: 10.3390/cancers12010182]

**Footnotes**

**Conflict-of-interest statement:** Mariusz L, and Aarohan P are employees and shareholders of Eli Lilly and Company; Rebecca C is a former employee and a shareholder of Eli Lilly and Company; Philana F is an employee of Eli Lilly and Company. All the authors report no relevant conflicts of interest for this article.

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**Provenance and peer review:** Unsolicited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review started:** September 6, 2021

**First decision:** October 18, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Ireland

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

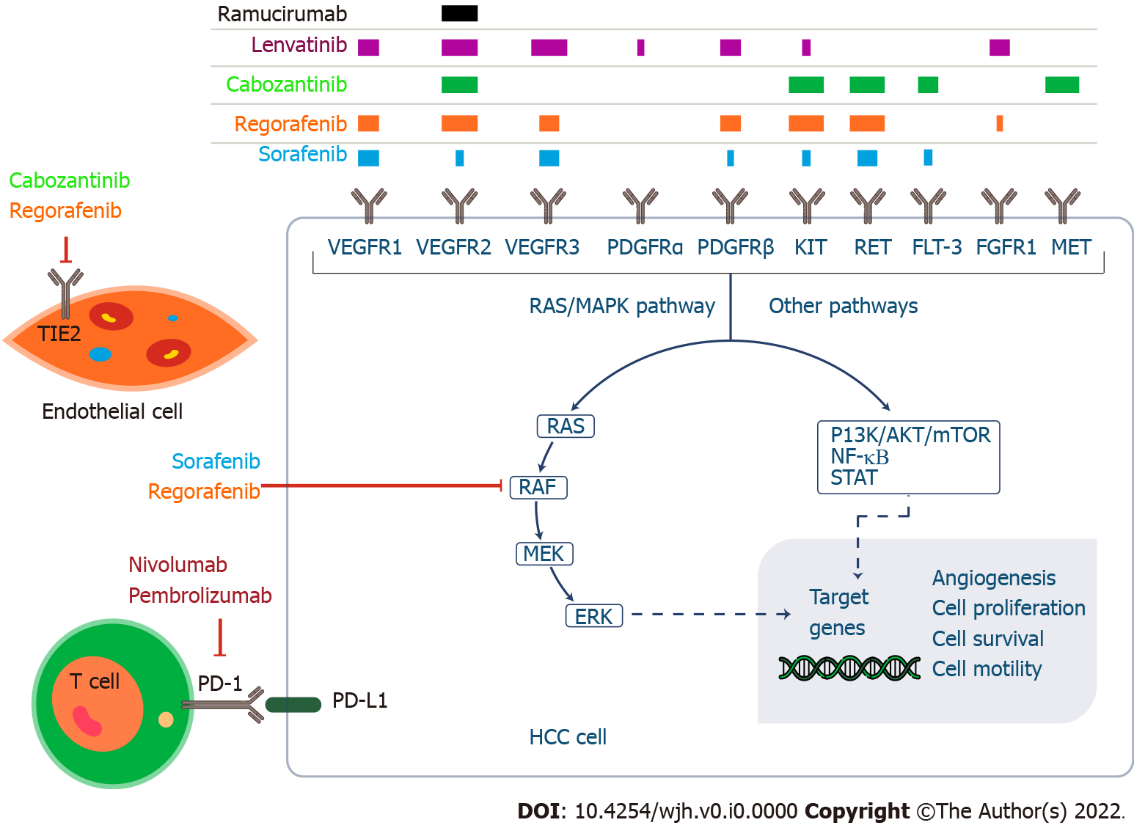
Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Moldogazieva NT, Russia; Shamaa MM, Egypt **A-Editor:** Tajiri K, Japan **S-Editor:** Wang JJ **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**



**Figure 1 Graphical abstract.** ERK: Extracellular receptor kinase; HCC: Hepatocellular carcinoma; FGFR: Fibroblast growth factor receptor; FLT-3: Cytokine Flt3 ligand; KIT: Tyrosine-protein kinase; MEK: Mitogen-activated protein kinase; MET: Mesenchymal epithelial transition factor; mTOR:Mammalian target of rapamycin; NF-kB: Nuclear factor kappa B; PD-1: Programmed cell death 1; PDGFR:Platelet-derived growth factor receptors; PD-L1: Programmed death ligand 1; RAF: Rapidly accelerated fibrosarcoma; RAS: Rat sarcoma virus; RET: Rearranged during transfection; STAT: Signal transducer and activator of transcription; VEGFR: Vascular endothelial growth factor.

**Table 1 Summary of survival data from phase III randomized controlled trials of second- or later-line treatments in patients with advanced hepatocellular carcinoma**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study design** | **Treatment arms** | ***n*** | **Patient population** | **Key findings** |
| Zhu *et al*[20], REACH | Randomized, placebo-controlled, double-blind, multicenter, phase III trial | Ramucirumab or placebo | 565 | Patients with advanced HCC with previous progression or intolerance to sorafenib | Ramucirumab *vs* placebo. Median OS: 9.2 mo (95%CI: 8.0-10.6) *vs* 7.6 mo (95%CI: 6.0-9.3), HR = 0.87 (95%CI: 0.72-1.05) *P* = 0.14. Median PFS: 2.8 mo (95%CI: 2.7-3.9) *vs* 2.1 mo (95%CI: 1.6-2.7), HR = 0.63 (95%CI: 0.52-0.75) *P* < 0.0001 |
| Zhu *et al*[44], REACH-2 | Randomized, placebo-controlled, double-blind, multicenter, phase III trial | Ramucirumab or placebo | 292 | Patients with advanced HCC with previous progression or intolerance to sorafenib, AFP ≥ 400 ng/mL | Ramucirumab *vs* placebo. Median OS (7.6 mo follow-up): 8.5 mo (95%CI: 7.0-10.6) *vs* 7.3 mo (95%CI: 5.4-9.1), HR = 0.710 (95%CI: 0.531-0.949) *P* = 0.0199. Median PFS: 2.8 mo (95%CI: 2.8-4.1) *vs* 1.6 mo (95%CI: 1.5-2.7), HR = 0.452 (95%CI: 0.339-0.603) *P* < 0.0001 |
| Bruix *et al*[33], RESORCE | Randomized, double-blind, parallel-group, phase III trial | BSC + regorafenib or placebo | 573 | Patients with advanced HCC with previous progression or intolerance to sorafenib | BSC + regorafenib *vs* placebo. Median OS: 10.6 mo (95%CI: 9.1-12.1) *vs* 7.8 mo (95%CI: 6.3-8.8), HR = 0.63 (95%CI: 0.50-0.79) one-sided *P* < 0.0001. Median PFS (RESIST 1.1): 3.4 mo (95%CI: 2.9-4.2) *vs* 1.5 mo (95%CI: 1.4-1.5), HR = 0.43 (95%CI: 0.35-0.52) *P* < 0.0001 |
| Abou-Alfa *et al*[39], CELESTIAL | Randomized, double-blind, placebo-controlled, phase III trial | Cabozantinib or placebo | 773 | Patients with advanced HCC with previous progression or intolerance to sorafenib | Cabozantinib *vs* placebo. Median OS: 10.2 mo (95%CI: 9.1-12.0) *vs* 8.0 mo (95%CI: 6.8-9.4), HR = 0.76 (95%CI: 0.63-0.92) *P* = 0.005. Median PFS: 5.2 mo (95%CI: 4.0-5.5) *vs* 1.9 mo (95%CI: 1.9-1.9), HR = 0.44 (95%CI: 0.36-0.52) *P* < 0.001 |

AFP: Alpha-fetoprotein; BSC: Best supportive care; CI: Confidence interval; HCC: Hepatocellular carcinoma; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

**Table 2 Randomized controlled trials in hepatocellular carcinoma: Subgroup analyses[37,40,42,17,48,49]**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ramucirumab (REACH, REACH-2 or AFP ≥ 400 ng/mL pooled population)** | | | | | |
| Patient Reported Outcomes | Pooled population REACH + REACH-2 | Ramucirumab or placebo | 542 | AFP ≥ 400 ng/mL | Ramucirumab *vs* placebo. TtD in FHSI-8 Total Score: 3.3 mo *vs* 1.9 mo, HR = 0.725; *P* = 0.0152 |
| Age | Pooled population REACH + REACH-2 | Ramucirumab or placebo | 542 | AFP ≥ 400 ng/mL | Ramucirumab *vs* placebo. < 65 yr: 8.18 mo *vs* 4.76 mo, HR = 0.716 (95%CI: 0.556-0.922). ≥ 65 to < 75 yr: 7.62 mo *vs* 5.22 mo, HR = 0.593 (95%CI: 0.413-0.851). ≥ 75 yr: 8.87 mo *vs* 6.31 mo, HR = 0.641 (95%CI: 0.390-1.054) |
| AFP dynamics | REACH-2 | Ramucirumab or placebo | 292 | AFP ≥ 400 ng/mL | Ramucirumab *vs* placebo. Time to AFP progression: 2.4 mo *vs* 1.4 mo, HR = 0.422 (95%CI: 0.309-0.576) *P* ≤ 0.0001. Time to radiographic progression: 3.0 mo *vs* 1.6 mo, HR = 0.427 (95%CI: 0.313-0.582) *P* ≤ 0.0001. AFP response: ≥ 20% decrease anytime post-baseline from baseline (% of patients): 42 *vs* 11 *P* ≤ 0.0001. ≥ 20% increase anytime post-baseline from baseline (% of patients): 62 *vs* 79 *P* = 0.0043 |
| **Regorafenib (RESORCE)** | | | | | |
| AFP response | RESORCE | Regorafenib or placebo | 232 | baseline AFP ≥ 20 ng/mL and an AFP measurement at the start of cycle 3 | Regorafenib *vs* placebo. Median OS: 13.8 mo *vs* 8.9 mo, HR = 0.57 (95%CI: 0.40-0.82) |
| **Cabozantinib (CELESTIAL)** | | | | | |
| Age subgroup | CELESTIAL | Cabozantinib or placebo | 707 | Subgroups based on age (< 65 yr and ≥ 65 yr) | Cabozatinib *vs* placebo. Median OS: < 65 yr: 9.6 mo *vs* 7.7 mo (HR = 0.81, 95%CI: 0.62-1.05); ≥ 65 yr: 11.1 mo *vs* 8.3 mo (HR = 0.74, 95%CI: 0.56-0.97). Median PFS: < 65 yr: 5.0 mo *vs* 1.9 mo (HR = 0.45, 95%CI: 0.35-0.57); ≥ 65 yr: 5.4 mo *vs* 2.0 mo (HR = 0.46, 95%CI: 0.35-0.59) |
| AFP | CELESTIAL | Cabozantinib or placebo |  | Baseline AFP < 400 ng/mL | Cabozatinib *vs* placebo. Median OS: 13.9 mo *vs* 10.3 mo (HR = 0.81, 95%CI: 0.62-1.04). Median PFS: 5.5 mo *vs* 1.9 mo (HR = 0.47, 95%CI: 0.37-0.60) |
| Baseline AFP ≥ 400 ng/mL | Cabozatinib *vs* placebo. Median OS: 8.5 mo *vs* 5.2 mo (HR = 0.71, 95%CI: 0.54-0.94). Median PFS: 3.9 mo *vs* 1.9 mo (HR = 0.42, 95%CI: 0.32-0.55) |

AFP: Alpha-fetoprotein; CI: Confidence interval; FHSI: Functional Hepatobiliary Symptom Index; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.