Prognostic and Predictive Factors in Patients with Advanced HCC and Elevated Alpha-Fetoprotein Treated with Ramucirumab in Two Randomized Phase III Trials

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ABSTRACT

Purpose: Ramucirumab is an effective treatment for patients with advanced hepatocellular carcinoma (aHCC) and baseline alpha-fetoprotein (AFP) ≥400 ng/mL. We aimed to identify prognostic and predictive factors of response to ramucirumab in patients with aHCC with AFP ≥400 ng/mL from the phase III REACH and REACH-2 randomized trials.

Patients and Methods: Patients with aHCC, Child-Pugh class A with prior sorafenib treatment were randomized in REACH and REACH-2 (ramucirumab 8 mg/kg or placebo, biweekly). Meta-analysis of individual patient-level data (pooled population) from REACH (AFP ≥400 ng/mL) and REACH-2 was performed. A drug exposure analysis was conducted for those with evaluable pharmacokinetic data. To identify potential prognostic factors for overall survival (OS), multivariate analyses were performed using a Cox proportional hazards regression model. To define predictors of ramucirumab benefit, subgroup-by-treatment interaction terms were evaluated.

Results: Of 542 patients (316 ramucirumab, 226 placebo) analyzed, eight variables had independent prognostic value associated with poor outcome (geographical region, Eastern Cooperative Oncology Group performance score ≥1, AFP >1,000 ng/mL, Child-Pugh >A5, extrahepatic spread, high neutrophil-to-lymphocyte ratio, high alkaline phosphatase and aspartate aminotransferase). Ramucirumab survival benefit was present across all subgroups, including patients with very aggressive HCC [above median AFP; HR: 0.64; 95% confidence interval (CI): 0.49–0.84] and nonviral aHCC (HR: 0.56; 95% CI: 0.40–0.79). While no baseline factor was predictive of a differential OS benefit with ramucirumab, analyses demonstrated an association between high drug exposure, treatment-emergent hypertension (grade ≥3), and increased ramucirumab benefit.

Conclusions: Ramucirumab provided a survival benefit irrespective of baseline prognostic covariates, and this benefit was greatest in patients with high ramucirumab drug exposure and/or those with treatment-related hypertension.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide (1), and accounts for approximately 90% of primary liver cancers (2, 3). Liver cancer is one of the most fatal cancers, with 5-year survival rates generally less than 20%, even in developed countries (4).

Baseline prognostic factors and risk categories in HCC include Barcelona clinic liver cancer (BCLC) stage, Child-Pugh score, elevated neutrophil-to-lymphocyte ratio (NLR), and expression of angiogenic markers (5–10). Serum alpha-fetoprotein (AFP) is the most well-known and studied biomarker in HCC. As sustained inflammation and immunosuppression are common in HCC, NLR is used as a marker of systematic inflammation (11, 12). AFP is a strong negative prognostic factor for survival in HCC (7, 8, 13), and is also a predictive biomarker for ramucirumab survival benefit (14). AFP-expressing HCC is associated with distinct molecular features including high VEGF signaling and increased angiogenesis (14). In addition to baseline factors, on-treatment and/or posttreatment factors such as treatment-related adverse events [e.g., hypertension for bevacizumab (15); skin toxicity for sorafenib (16), and therapeutic drug exposure (17, 18)] are also known to be associated with improved outcomes in several tumor types, including HCC.

Ramucirumab is a human IgG1 VEGFR2 antagonist and was investigated in two global, randomized, double-blind, placebo-controlled phase III trials [REACH (NCT01140347) and REACH-2 (NCT02435433)]. Despite no significant improvement in survival over placebo in patients with advanced HCC (aHCC) during the REACH trial, an overall survival (OS) benefit was observed in the prespecified subgroup of patients with AFP ≥400 ng/mL (19). REACH-2 enrolled only patients with AFP ≥400 ng/mL and demonstrated improved survival when compared with placebo in patients with previously treated aHCC (20).

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Clinical trial registration: REACH (NCT01140347) and REACH-2 (NCT02435433)

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Translational Relevance

Alpha-fetoprotein (AFP) is a biomarker with proven prognostic and predictive value in hepatocellular carcinoma (HCC). REACH-2 is the first positive phase III study demonstrating improved survival with ramucirumab in AFP high HCC. In this *post hoc* analysis, we examined prognostic and predictive factors of response to ramucirumab in patients with advanced HCC with AFP ≥400 ng/mL from REACH and REACH-2. Ramucirumab provided a survival benefit irrespective of baseline prognostic covariates, including aggressive HCC, and nonviral etiologies. While no baseline factors were found to be predictive of a differential overall survival benefit with ramucirumab in patients with AFP ≥400 ng/mL, two treatment-emergent (TE) adverse events were associated with a higher ramucirumab survival benefit: TE hypertension and TE ascites. TE hypertension was associated with higher drug exposure, and higher drug exposure was associated with improved overall survival benefit. These results represent a useful tool for clinical decision-making and will help inform the prognosis of patients with advanced HCC and elevated AFP levels.

In this *post hoc* analysis, we examined prognostic and predictive factors of clinical benefits to ramucirumab in biomarker-enriched (AFP ≥400 ng/mL) population of patients with aHCC from REACH and REACH-2.

Patients and Methods

Study design

REACH and REACH-2 were randomized, double-blind, phase III studies in aHCC (NCT01140347 and NCT02435433). Detailed eligibility criteria have been described previously (19, 20). Patients with HCC, BCLC stage C or B disease not amenable to locoregional therapy or refractory to locoregional therapy, Child-Pugh class A (score <7), Eastern Cooperative Oncology Group performance score (ECOG PS) 0/1, and who had progressed or were intolerant to sorafenib were eligible. REACH enrolled irrespective of AFP level, whereas REACH-2 enrolled patients with elevated AFP (≥400 ng/mL). Patients were randomized (REACH 1:1; REACH-2 2:1) to ramucirumab (8 mg/kg) or placebo every 2 weeks (19, 20). REACH and REACH-2 complied with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable local regulations. Ethics committees at all participating centers approved the protocol, and all patients provided written informed consent.

Prognostic and predictive factors data collection and analysis

A meta-analysis of individual patient-level data from REACH (subset of patients with AFP ≥400 ng/mL) and REACH-2 was carried out (pooled population). The pooling of patient-level data provided a substantially larger patient population, enabling a more precise assessment of prognostic and predictive factors (20).

The following 24 variables at baseline were considered in the statistical analysis to determine prognostic factors for OS and factors associated with improved ramucirumab survival benefit: gender (male vs. female), age (≥65 vs. <65 years), race (Asian vs. non-Asian), geographical region [Region 1: Americas, Europe, Israel, and Australia; Region 2: Asia (except Japan); Region 3: Japan], etiology [viral vs. nonviral; hepatitis B (HBV) vs. Other; hepatitis C (HCV) vs. Other], presence of extrahepatic metastases, presence of macrovascular invasion (MVI), BCLC stage (C vs. B), ECOG PS (≥1 vs. 0), prior locoregional therapy (yes vs. no), reason for sorafenib discontinuation (progressive disease vs. intolerance), baseline AFP (>1,000 vs. 400–1,000 ng/mL), albumin-bilirubin (ALBI) grade (≥2 vs. 1), Child-Pugh score (≥A6 vs. A5), number of sites with extrahepatic spread (0 vs. 1; ≥2 vs. 1), maximum baseline target lesion size (≤50 vs. >50 mm), body mass index (≥25 vs. <25), platelets (<150 vs. ≥150 g/L), time from last sorafenib to randomization (≥1 vs. <1 month), duration of prior sorafenib (≥5 vs. <5 months), baseline NLR (>median vs. ≤median), alkaline phosphatase (ALP; >median vs. ≤median), alanine transaminase (U/L; >median vs. ≤median), and aspartate aminotransferase (AST; U/L) (>median vs. ≤median).

AFP has been the main serologic marker used for diagnosis of HCC, where levels >400 ng/mL are typically considered diagnostic of HCC and have been associated with aggressive disease (3, 21–23). On the basis of these assumptions and data observed in the study, we decided to consider three AFP cutoffs in the analyses: all patients had AFP ≥400 ng/mL as per inclusion criteria, AFP ≥1,000 was used to exclude liver transplantation, while above median AFP (4,081.5 ng/mL) was used to define very aggressive tumors.

For the prognosis analysis, the exploratory *post hoc* analysis was performed using stratified univariate (UV) and multivariate (MV) Cox proportional hazards regression model (stratified by study). Variables with a *P* value lower than 0.1 from UV analysis, irrespective of treatment arm, were included in the MV analysis. A significance level of 0.05 was used to provide a threshold to determine the strength of prognostic value in the MV analysis.

To determine predictors of ramucirumab benefit, subgroup-by-treatment interactions was assessed for each variable using a stratified Cox model (stratified by study). The 24 baseline prognostic variables were analyzed as potential predictive factors of response to ramucirumab. In addition, we also assessed treatment-related adverse events and treatment-emergent (TE) adverse events. Median OS based on Kaplan–Meier estimator and HR based on stratified UV Cox model, were provided across subgroups. The interaction *P* values were derived using Wald test of subgroup-by-treatment interaction from stratified UV Cox model and a threshold of 0.05 was used to determine the strength of the predictive value. To address the potential guarantee-time bias, conditional landmark analysis of OS according to TE hypertension (TE ascites) was carried out at the selected landmark time until death or censoring at the last date the patient was known to be alive (24). Patients who died or discontinued study within the selected landmark time postrandomization were excluded in the conditional landmark analyses of OS.

Exposure-efficacy and safety analyses

To understand whether treatment-related adverse events predicting response to ramucirumab were associated with exposure, exposure-efficacy and exposure-safety analyses were conducted in the pooled population for all patients who had evaluable pharmacokinetic data. Samples for pharmacokinetic analysis from patients in both trials were collected prior to and 1 hour after dose infusions number 1, 4, and 7 and for cycles 1, 2, 4, 7, and 10 (REACH-2). A population pharmacokinetic model (25) was used to predict minimum concentration after first dose administration ($C_{min,1}$) and minimum concentration at steady state ($C_{min,ss}$) for *post hoc* exposure-efficacy and exposure-safety analyses, respectively, in patients with HCC with elevated AFP. MV Cox regression analysis was adjusted for prespecified factors that were found

to be prognostic in REACH-2: ECOG PS (0 vs. 1), presence of MVI, and baseline AFP. In these analyses, $C_{min,1}$ was evaluated as a continuous variable and as a categorical variable using quartiles (Q1–Q4). Minimum concentration after first dose administration ($C_{min,1}$) was used to assess the exposure–response relationship; this approach is supported by review and analysis from the FDA on exposure–response analysis of nivolumab (26).

Data transparency statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Role of funder

The funder of the study designed the trial, in collaboration with all authors and was responsible for data management and statistical analysis. The funder interpreted data in collaboration with all authors and supported development of the report by providing medical writing and editorial assistance. All authors had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Prognostic factors of second-line aHCC

A total of 542 randomized patients (316 ramucirumab, 226 placebo) with AFP ≥400 ng/mL from the two phase III studies were included in the analysis (Supplementary Fig. S1). Patient demographics and baseline characteristics are presented in Supplementary Table S1 and were generally well-balanced across treatment arms, with the median OS for patients treated with ramucirumab ($n = 316$) and placebo ($n = 226$) being 8.1 months (246 deaths) and 5.0 months (190 deaths), respectively (20).

UV analysis was carried out within each arm, and with combined treatment arms to look at all factors separately as potential independent prognostic factors in the whole cohort. Twelve baseline factors were identified as potential independent prognostic factors irrespective of treatment arm: geographic region, presence of MVI, BCLC stage, baseline ECOG PS, baseline AFP (≥1,000 ng/mL), ALBI grade, Child-Pugh score, number of metastatic sites, elevated NLR, ALP, AST, and prior sorafenib duration (Supplementary Table S2). Demographic factors such as gender, race, and age were not identified as prognostic factors.

MV analysis was carried out to determine whether baseline factors first identified in UV analysis would remain prognostic after adjusting for treatment and additional prognostic factors. Most baseline factors identified in UV analysis remained prognostic in the MV adjusted analysis. Aside of treatment allocation, seven variables among demographic and baseline disease characteristics were associated with poor OS in the ramucirumab and overall cohort (geographical region 2, ECOG PS ≥1, AFP ≥1,000 ng/mL, Child-Pugh >A5, extrahepatic sites, elevated NLR and AST), with ALP being an additional prognostic factor within the overall cohort as shown in **Table 1**. ALBI grade, BCLC score, MVI, and prior sorafenib duration did not meet the threshold of statistical significance (Supplementary Tables S3 and S4). Similar results were obtained in additional models that adjusted for potential multicollinearity from BCLC stage (Supplementary Table S3; excluded BCLC stage but included individual components of ECOG PS, MVI, extrahepatic spread, and tumor burden) and ALBI grade (Supplementary Table S4; ALBI grade removed from model because albumin and bilirubin were included in Child-Pugh score).

Predictors of response to ramucirumab

Baseline predictors

A survival benefit favoring ramucirumab was observed across all subgroups, but no baseline variable was found to significantly predict differential response to ramucirumab in terms of OS in the MV analysis (all $P_{interaction}$ values >0.05). Once we established that ramucirumab benefited all subgroups of patients, we focused on analyzing two specific populations: patients with very high AFP, for which we used above the median AFP in the cohort, and patients with nonviral HCC, due to the recent reports suggesting a limited benefit for immunotherapies in those patients as compared with sorafenib (27).

We identified that ramucirumab benefited patients with established thresholds of high AFP levels, that is, patients with AFP ≥1,000 (HR: 0.67, 95% CI: 0.54–0.83), a threshold commonly used to exclude liver transplantation (Supplementary Fig. S2). As elevated AFP in patients with HCC is associated with worse prognosis compared with the general population (28, 29), we next took the median AFP levels as a threshold. Considering that our target population in this study only captures patients with AFP ≥400 ng/mL, this threshold captures the more aggressive cases (40%) of patients included in second-line trials (28, 30, 31), as well as patients above the median AFP level (≥4,081.5 ng/mL) within the pooled population (HR: 0.71, 95% CI: 0.54–0.95; **Fig. 1**). Baseline characteristics for patients with very high (≥4,081.5 ng/mL) and "low" (400–4,081.5 ng/mL) AFP are shown in Supplementary Table S5 and were generally balanced between arms. A numerically higher incidence of HBV (45.4% vs. 37.6%), ALBI grade (grade ≥2: 59.0% vs. 52.8%), and Child-Pugh score (≥A6: 43.2% vs. 36.9%), with more sites of metastases (≥2 sites: 36.2% vs. 29.9%) were noted in the AFP-high compared with -low subgroups.

Regarding ramucirumab effect according to etiology, an OS benefit with ramucirumab was observed in both viral (ramucirumab $N = 200$; placebo $N = 152$) and nonviral (ramucirumab $N = 116$; placebo $N = 74$) etiologies (viral HR: 0.76, 95% CI: 0.60–0.97; nonviral HR: 0.56, 95% CI: 0.49–0.79; $P_{interaction} = 0.29$) with a robust ramucirumab survival advantage compared with placebo in patients with non-viral aHCC (HR: 0.56; 95% CI: 0.49–0.79; **Fig. 2**).

On-treatment predictors of response.

While no baseline factors were found to be predictive of a differential OS benefit with ramucirumab in patients with AFP ≥400 ng/mL, two adverse events were associated with a higher ramucirumab survival benefit: treatment-related hypertension and TE ascites. Hypertension is a well-known adverse drug reaction to antiangiogenic inhibitors, and thus it is considered a treatment-related adverse event (32). Hypertension developed in 68 patients (21.5%) in the ramucirumab group and 20 patients (8.8%) in the placebo group and was predominantly grade 1–2 in severity (Supplementary Fig. S3). The median time to development of hypertension was 26 days

Table 1. Multivariate analysis for identification of potential prognostic factors of OS.

Baseline variable	Subgroup	RAM HR (95% CI)	RAM Wald's *P* value	PL HR (95% CI)	PL Wald's *P* value	Overall HR (95% CI)	Overall Wald's *P* value
Treatment	RAM vs. PL	—	—	—	—	0.72 (0.58–0.90)	0.0029
Geographical region[a]	Region 1 vs. Region 3	0.84 (0.58–1.21)	0.0217	0.94 (0.58–1.53)	0.4279	0.85 (0.64–1.13)	0.0070
	Region 2 vs. Region 3	1.38 (0.91–2.10)		1.28 (0.70–2.34)		1.31 (0.94–1.83)	
Baseline ECOG PS	≥1 vs. 0	1.65 (1.20–2.27)	0.0020	1.21 (0.83–1.77)	0.3163	1.47 (1.16–1.86)	0.0014
Child-Pugh score	≥A6 vs. A5	1.56 (1.12–2.17)	0.0082	1.22 (0.80–1.85)	0.3558	1.34 (1.04–1.72)	0.0221
Number of metastatic sites involved	0 vs. 1	0.82 (0.56–1.19)	0.0164	0.72 (0.44–1.17)	0.0029	0.80 (0.60–1.06)	<0.0001
	≥2 vs. 1	1.45 (1.03–2.06)		1.71 (1.14–2.58)		1.54 (1.19–2.00)	
Baseline AFP (ng/mL)	>1,000 vs. ≤1,000	1.52 (1.05–2.21)	0.0272	1.56 (1.02–2.39)	0.0391	1.52 (1.16–2.00)	0.0026
Baseline NLR	>median vs. ≤median	1.92 (1.43–2.59)	<0.0001	1.47 (1.01–2.12)	0.0440	1.65 (1.33–2.04)	<0.0001
ALP (U/L)	>median vs. ≤median	1.29 (0.92–1.82)	0.1385	1.49 (0.99–2.23)	0.0537	1.43 (1.12–1.83)	0.0049
AST (U/L)	>median vs. ≤median	1.56 (1.12–2.15)	0.0079	1.36 (0.94–1.98)	0.1073	1.43 (1.13–1.83)	0.0034

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PL, placebo; RAM, ramucirumab; tx, treatment.
[a]Geographical regions: Region 1: The Americas, Europe, Israel, and Australia versus Region 2: Asia (except Japan) versus Region 3: Japan.

[interquartile range (IQR): 15–64] in the ramucirumab arm versus 32 days (IQR: 8–55.5) in the placebo arm. The use of antihypertensive agents was greater in patients developing hypertension within the ramucirumab arm compared with placebo. Kaplan–Meier analysis showed improved OS with ramucirumab irrespective of the presence of treatment-related hypertension. However, in patients with treatment-related hypertension, median OS was significantly better in the ramucirumab group ($N = 68$) compared with placebo group ($N = 20$; 14.9 vs. 4.2 months; HR: 0.4, 95% CI: 0.22–0.69; **Fig. 3A** and **B**). In patients without treatment-related hypertension, median OS in the ramucirumab group ($N = 248$) versus placebo group ($N = 206$) was 6.7 versus 5.2 months (HR: 0.8, 95% CI: 0.67–1.02; $P_{\text{interaction}} = 0.0392$; **Fig. 3A** and **B**). Similarly, ramucirumab also had a greater benefit in progression-free survival (PFS) versus placebo in patients with hypertension [4.2 vs. 1.6 months (HR: 0.47, 95% CI: 0.28–0.81)], than those without hypertension [2.7 vs. 1.5 months (HR: 0.63, 95% CI: 0.52–0.77)], $P_{\text{interaction}} = 0.2173$ (**Fig. 3C** and **D**). Higher objective responses rates were observed in patients treated with ramucirumab versus placebo irrespective of hypertension status (with: 9% vs. 0%; without: 4% vs. 1%). For patients treated with ramucirumab, an improvement in OS was per the Kaplan–Meier method (14.9 months compared with 6.7 months). However, the improved OS observed could be biased because patients with TE hypertension were guaranteed to survive at least until the occurrence of TE hypertension while patients without TE hypertension included all patients who died before developing TE hypertension. Conditional landmark analysis is an established method used to address guarantee-time bias (24) in which a fixed time during the course of treatment or follow-up is selected as the landmark, and only the subset of patients still in the study at the landmark time are included in the analysis. In this case, the landmark time is based on the period when the majority of TE hypertension (TE ascites) events occurred from randomization. As the majority of TE hypertension events for patients treated with ramucirumab occurred within the first 2 months from randomization, we selected 2-month as the landmark time. The 2-month conditional landmark analysis demonstrated that patients with TE hypertension had an improved OS compared to those without (14.92 vs. 7.62 months; **Fig. 4**). The results of the original and conditional landmark analyses were comparable, indicating guarantee-time bias has a minimal impact on the hypertension-efficacy relationship.

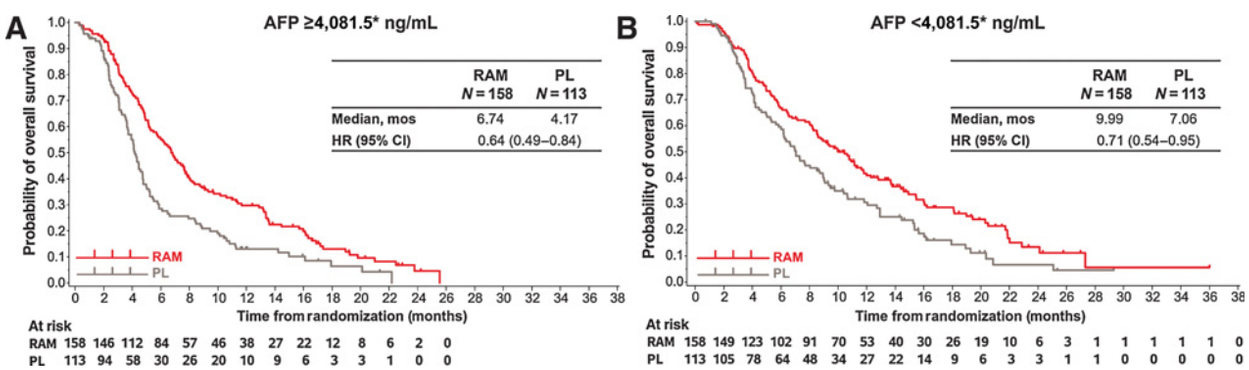

Figure 1.
Kaplan–Meier plots of OS by baseline AFP for ramucirumab versus placebo. Patients with AFP ≥4,081.5 ng/mL (**A**) and AFP <4,081.5 ng/mL (**B**). Kaplan–Meier analysis for OS shown by elevated AFP status (≥4,081.5 vs.<4,081.5 ng/mL) by treatment arm. *Median AFP used to define a very aggressive phenotype in patients with very high AFP. $P_{\text{interaction}} = 0.5106$, not significant. AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; mos, months; *N*, total number of patients; PL, placebo; RAM, ramucirumab.

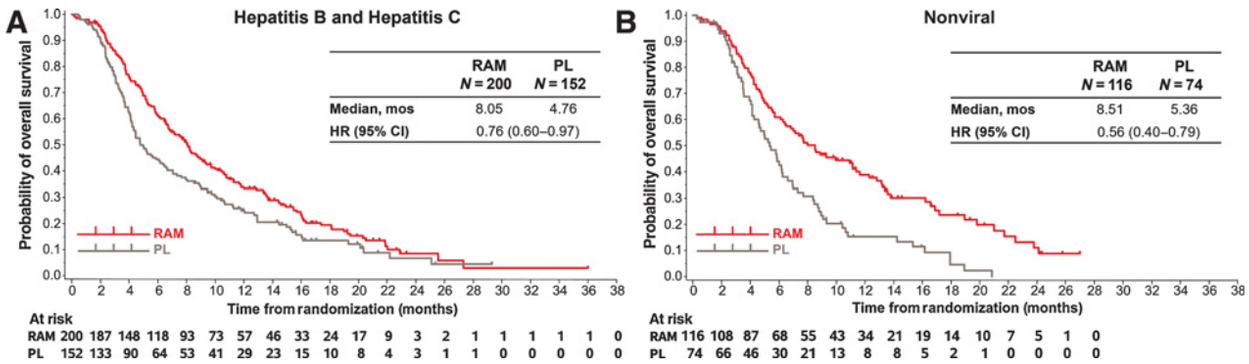

Figure 2.

Kaplan–Meier plots of OS by etiology for ramucirumab versus placebo. Patients with viral etiology (**A**) and nonviral etiology (**B**). Kaplan–Meier analysis for OS shown by etiology status (HBV and HBC vs. nonviral) by treatment arm. $P_{interaction} = 0.2899$, not significant. CI, confidence interval; HR, hazard ratio; mos, months; *N*, total number of patients; PL, placebo; RAM, ramucirumab; PL, placebo.

Ascites is common in patients with HCC and is associated with poor outcomes, but not clearly defined as treatment-related by the investigator assessment. Detailed analyses by TE ascites within the pooled population have been reported previously (33). TE ascites developed in 66 patients (20.9%) in the ramucirumab group and 33 patients (14.8%) in the placebo group and was predominantly grade 1 or 2 in severity. The median time to development of ascites was 43 days (IQR: 29–100) in the ramucirumab arm versus 47 days (IQR: 29–77) in the placebo arm. When adjusted for treatment duration, the incidence of TE ascites was no higher for ramucirumab than placebo as the incidence rates per 100 patient-years of any grade TE ascites were 59.1 and 71.9 for the ramucirumab and placebo groups, respectively, and the incidence of grade ≥3 TE ascites were 13.4 and 19.6, respectively (33). The use of diuretics was greater in patients within the ramucirumab ($n = 170$) arm compared with placebo ($n = 79$). However, higher numbers of patients within the placebo ($n = 7$) arm underwent paracentesis compared with ramucirumab ($n = 3$). Kaplan–Meier analysis showed improved OS with ramucirumab irrespective of the presence of TE

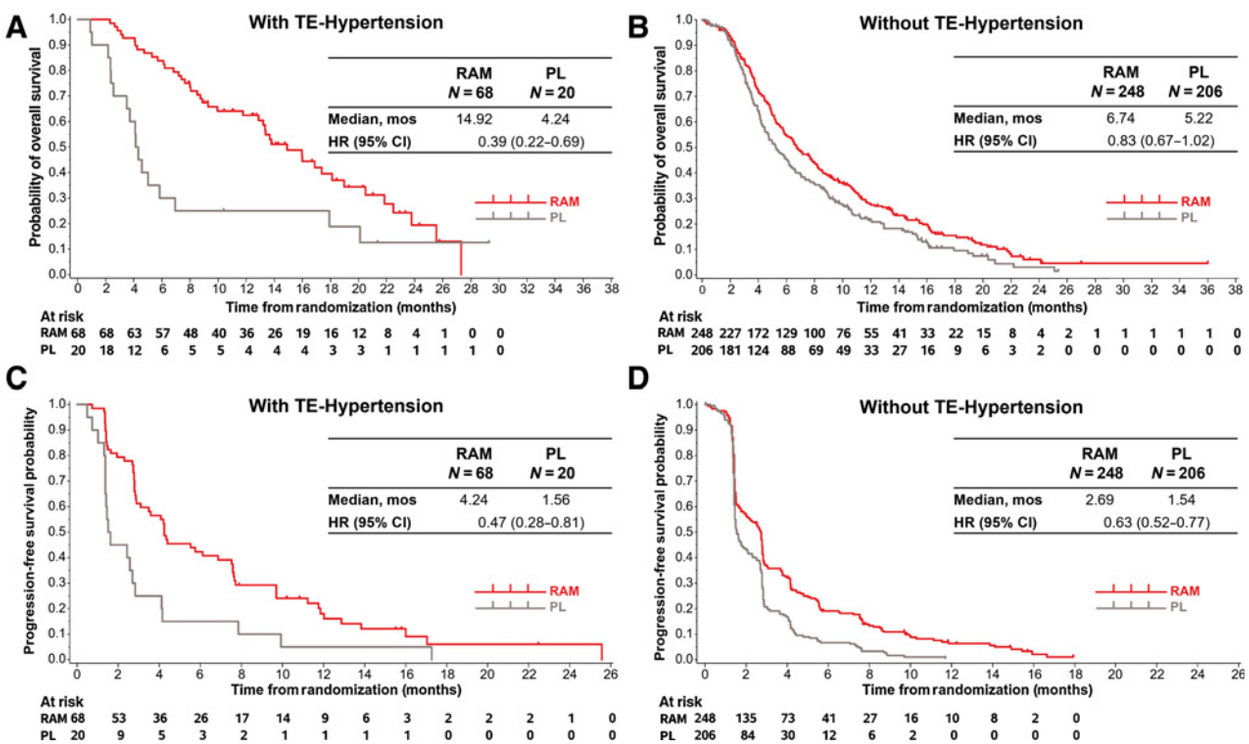

Figure 3.

Kaplan–Meier plots of OS (**A** and **B**) and PFS (**C** and **D**) by TE-hypertension for ramucirumab versus placebo. Kaplan–Meier analysis for OS and PFS shown by TE-hypertension status by treatment arm: ramucirumab (Red) versus placebo (Gray). Patients with (**A** and **C**) and without (**B** and **D**) TE-hypertension. OS $P_{interaction} = 0.0392$, significant. CI, confidence interval; HR, hazard ratio; mos, months; *N*, total number of patients; PL, placebo; RAM, ramucirumab; TE, treatment-emergent.

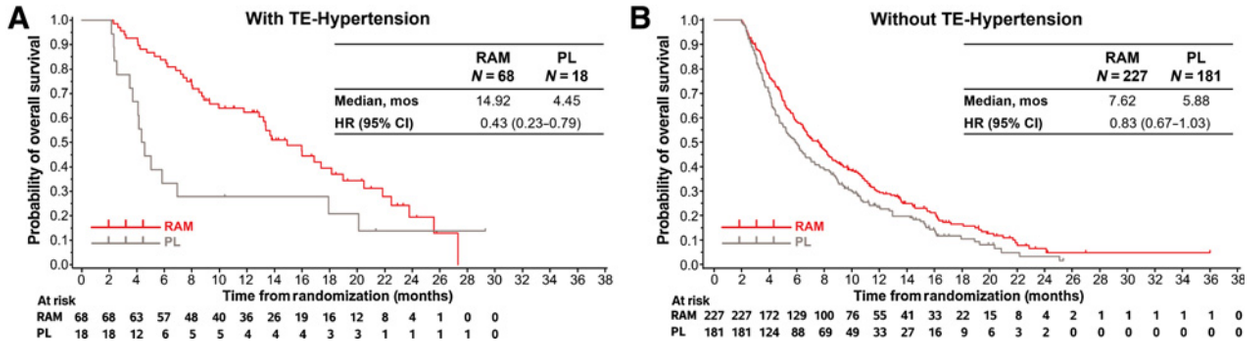

Figure 4.

Conditional landmark analysis for OS according to TE-hypertension ($P_{interaction}$: 0.0942): survival time from 2 months until death. Kaplan–Meier plots of OS shown by TE-hypertension status (survival time from 2 months until death): ramucirumab (red) versus placebo (gray). Patients with (**A**) and without (**B**) TE-hypertension OS $P_{interaction} = 0.0001$, significant. CI, confidence interval; HR, hazard ratio; mos, months; *N*, total number of patients; PL, placebo; RAM, ramucirumab; TE, treatment-emergent.

ascites. In patients with TE ascites, median OS in the ramucirumab group versus placebo group was 6.7 versus 3.4 months (HR: 0.30, 95% CI: 0.18–0.49, $P < 0.0001$), while in patients without TE ascites, median OS was 8.3 versus 5.9 months (HR: 0.77, 95% CI: 0.62–0.95, $P = 0.0155$; Supplementary Fig. S4). An association with greater OS benefit for ramucirumab was observed in patients who developed TE ascites ($P_{interaction} = 0.0001$). During PFS analysis, a significant trend was observed as the median PFS was improved with ramucirumab versus placebo in patients with TE ascites [4.2 vs. 2.0 months (HR: 0.46, 95% CI: 0.29–0.74)], and without TE ascites [2.7 vs. 1.5 months (HR: 0.62, 95% CI: 0.50–0.77); $P_{interaction} = 0.4919$]. Higher objective responses rates were observed in patients treated with ramucirumab versus placebo irrespective of TE ascites status (with TE ascites: 9% vs. 0%; without TE ascites: 4% vs. 1%; ref. 33). For patients treated with ramucirumab, a similar OS was observed in patients with TE ascites compared to those without as per the Kaplan–Meier method (6.7 compared with 8.3 months). To account for the potential guarantee-time bias as described previously, a conditional landmark analysis was conducted. As the majority of TE ascites events for patients treated with ramucirumab occurred within the first 3 months from randomization, 3-month was selected as the landmark time. The 3-month conditional landmark analysis for OS showed similar OS benefit for patients irrespective of TE ascites status (with: 8.51 months; without: 9.99 months; Supplementary Fig. S5). The results of the original and conditional landmark analyses are comparable, indicating that guarantee-time bias has a minimal effect on the ascites-efficacy relationship.

Association between exposure, treatment-related hypertension, and benefit from ramucirumab

Next, we explored whether the association of TE hypertension and benefit of ramucirumab was significantly associated with treatment exposure. For this purpose, we conducted exposure-response (ER) analysis to examine the relationship between ramucirumab exposure in both exposure-efficacy and exposure-safety analyses. Patient demographics and disease characteristics by $C_{min,1}$ quartiles (Q1, lowest exposure, to Q4, highest exposure) of the pooled exposure-efficacy population (Supplementary Fig. S1) are shown in Supplementary Table S6. Several baseline factors associated with poorer prognosis in aHCC, including presence of MVI, higher stage of BCLC (stage C), higher point of Child-Pugh A6, and presence of extrahepatic spread, appeared to be more frequent in lower exposure quartiles. In the UV OS analysis by $C_{min,1}$ quartiles, a separation between the OS curves was observed, indicating a longer survival for patients with ramucirumab exposure corresponding to the higher ramucirumab $C_{min,1}$ quartiles achieved following 8 mg/kg (**Fig. 5**). Median OS from Q1 through Q4 increased (5.7, 7.1, 8.9, and 13.2 months, respectively) and were higher compared with the median OS of 5 months for placebo (**Fig. 5**). After adjusting for prespecified factors that were found to be prognostic in REACH-2 (ECOG PS, MVI, and AFP), the positive association between OS and $C_{min,1}$ remained statistically significant with a decrease in HR from 0.93 (95% CI: 0.70–1.23; Q1), 0.75 (95% CI: 0.56–1.01; Q2), and 0.54 (95% CI: 0.0.40–0.73; Q3) to 0.46 (95% CI: 0.33–0.63; Q4) with increasing ramucirumab exposure (Q1 through Q4) versus placebo. During exposure-safety analysis, significantly higher incidences of grade ≥3 hypertension was observed among patients with increased ramucirumab exposure (12% vs. 4%; Supplementary Table S7), which identified patients with greater benefit from ramucirumab treatment. Unlike hypertension, no significant association between increased ramucirumab exposure and incidences of ascites was observed during ER analysis as shown in Supplementary Table S7.

Discussion

This *post hoc* analysis aimed to identify potential prognostic factors for survival and predictive factors of ramucirumab treatment benefit in a biomarker-enriched (AFP ≥400 ng/mL) patient population from REACH and REACH-2. Many of the known baseline prognostic factors in HCC that have been studied in biomarker unselected trials remained prognostic in our AFP-enriched population, and no baseline factor was identified as predicting a survival advantage for ramucirumab.

After adjusting for treatment and additional prognostic factors, the prognostic factors independently associated with survival in second-line aHCC were geographical region, ECOG PS (0 vs. 1), baseline AFP (>1,000 ng/mL vs. 400–1,000 ng/mL), Child-Pugh score (A5 vs. A6), number of metastatic sites, elevated NLR (>3.2 vs. <3.2), ALP (>146 vs. ≤146), and AST (>57 vs. ≤57). These factors were consistent with prior reports in AFP all comer trials (8, 13, 34–36). Race was found not to be prognostic for OS, and this was consistent with other HCC studies (8, 31).

In recent years, biochemical markers of systemic inflammatory response have been incorporated in prognostic scores for several types of cancer, including HCC. In particular, elevated NLR has been increasingly recognized as an indicator for poor prognosis (37), and is believed to have a potential role in cancer progression (38).

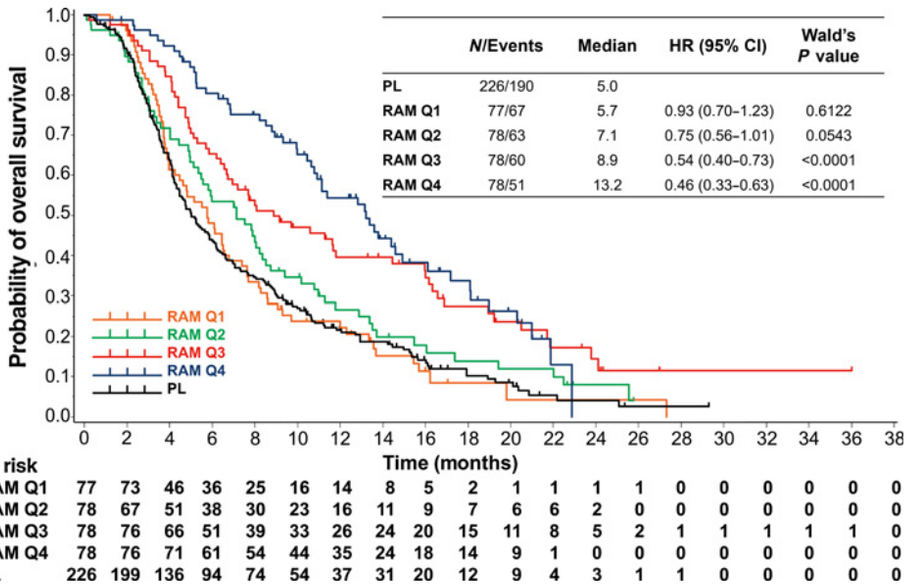

Figure 5.

Kaplan–Meier survival curves for the pooled efficacy population by RAM $C_{min,1}$ quartiles versus PL. Unadjusted data are shown for OS. All included patients had a baseline AFP of ≥400 ng/mL. Patients with missing baseline covariate factors were omitted from the analysis. HRs were adjusted for macrovascular invasion (CRF), ECOG PS at baseline, baseline AFP (ng/mL) (log-transformed). Quartiles: Q1 = <25%; Q2 = 25%–<50%; Q3 = 50%–<75%; Q4 = ≥75%. AFP, alpha-fetoprotein; CI, confidence interval; CRF, case report form; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; *N*, total number of patients; Q1–Q4, quartiles 1 through 4; RAM, ramucirumab.

Consistent with previous studies, elevated NLR remained a poor prognostic factor in our study.

Regarding ramucirumab effect, first we knew that high AFP was not only a poor prognostic factor (7, 8, 13) but also a biomarker that can predict the response to ramucirumab in terms of survival benefit based on data from REACH and REACH-2 trials (14, 19, 20). In the current study, we demonstrate that ramucirumab continues to provide a survival benefit in patients with AFP ≥1,000 ng/mL and in patients where baseline AFP levels are higher than the median (4,081.5 ng/mL) level within the pooled population. Elevated AFP levels are significantly associated with increased mortality (14, 21) and worse prognosis when compared with the general population (21, 23); however, patients with very high AFP (≥4,081.5 ng/mL) also benefit from ramucirumab treatment.

Second, we confirm the effect of ramucirumab across etiologies. HCC commonly occurs as a result of chronic liver disease secondary to viral HBV or HCV infection (39). However, there has been a marked increase in the number of patients with HCC presenting with nonviral etiologies such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH; ref. 40). Approximately one third of patients in the pooled population presented with nonviral etiologies with the majority being significant alcohol use and steatohepatitis (NASH and fatty liver)-related HCC. A limited benefit for immunotherapies in patients with nonviral HCC has been recently suggested in a meta-analysis evaluating effects on OS from three randomized phase III trials: CheckMate-459 (41, 42), IMbrave150 (43), and KEYNOTE-240 (44). A better median OS to PD-1/PD-L1 therapies in patients with virus-induced HCC than in patients with nonviral HCC was observed in the meta-analysis, thus providing the rationale to stratify patients by underlying etiology (27). We herein confirm an OS benefit from ramucirumab treatment among patients with nonviral aHCC, and nonviral aHCC does not represent a predictive factor. A more detailed analysis by disease etiology in the pooled population has been reported separately (45). In the analysis presented here, nonviral etiologies (including ALD and NASH) showed consistent ramucirumab benefit, compared with viral hepatitis.

Although no baseline variables were found to be predictive of a differential OS benefit with ramucirumab in patients with AFP ≥400 ng/mL, we identified hypertension as one treatment-related adverse event associated with better ramucirumab survival benefit. It has been reported that VEGF inhibitors (VEGFI) often cause an elevation in blood pressure, and this class effect has been observed across all VEGFI trials (46–49). Hypertension often occurs rapidly and reflects the effective inhibition of VEGF signaling. This is reflected in our data as higher incidences of hypertension occurred among patients treated with ramucirumab (21.5%) versus placebo (8.8%). Many studies in several tumor types have shown an association with bevacizumab-induced hypertension with improvements in OS, PFS, and overall response rate (15, 47, 50–52). While a ramucirumab survival benefit was observed irrespective of TE hypertension in our study, an association of improved survival was noted in patients who developed hypertension on study. In this sense, median OS of 14.9 months was achieved in those patients, significantly and independently superior to any subgroup. Interestingly, patients with the highest ramucirumab exposure (Q4) were associated with TE hypertension grade >3 and an improved survival response (median 13.2 months) when compared with the rest of the population with lower ramucirumab exposure, as illustrated by the exposure analysis. One potential explanation for the relationship between TE hypertension and efficacy is that both are associated with ramucirumab exposure. This type of link between therapy toxicity and survival is not uncommon, as evidenced by studies of the tyrosine kinase inhibitor, sorafenib (53), as well as immunotherapy (54). To address the potential guarantee-time bias in the predictive effect of TE hypertension on survival impact with ramucirumab, we confirmed the results with a conditional landmark analysis (24).

Finally, TE ascites was also identified as independent predictor of response to ramucirumab, but this result should be interpreted with caution because occurrence of ascites (as opposed to hypertension) occurred throughout the follow-up, and patients on ramucirumab had more time to develop ascites due to a longer survival benefit from treatment. Ascites is common in patients with HCC and is likely caused by either progression of HCC over time or worsening of liver function during the natural course of underlying chronic liver disease. Anti-angiogenic therapies such as ramucirumab have been hypothesized to increase hepatic sinusoidal pressure, leading to increased portal vein pressure and ascites (33, 52). The incidence of ascites in the pooled population was generally consistent with other studies of previously treated aHCC (12%–16%; refs. 28, 31). Because ascites is associated

with disease state, and ramucirumab-treated patients are followed on study longer than placebo-treated patients due to improvement in disease control and survival, exposure-adjusted analysis was conducted in the pooled population and detailed separately. When adjusted for treatment duration, the incidence rates per 100 patient-years of any grade TE ascites were no higher for ramucirumab than placebo (33). In regard to TE ascites association with other TE events, TE ascites was found to be associated with TE hypoalbuminemia, but not TE proteinuria or hypertension (33). In addition, the exposure-safety analysis did not identify a relationship between ramucirumab exposure and incidence rate of ascites as there were no differences noted among patients treated with ramucirumab or placebo.

Certain limitations must be considered in *post hoc* analysis. These results were demonstrated in a biomarker-enriched population (AFP ≥400 ng/mL) well defined by the inclusion and exclusion criteria of the REACH and REACH-2 studies, and so are limited to Child-Pugh A patients who had received prior sorafenib. Furthermore, the treatment-related hypertension and TE ascites results should be interpreted with caution given that TE events are factors only observed after randomization. To account for this, the conditional landmark analyses were used to reduce concern for the guarantee-time bias.

In conclusion, our analysis demonstrated a consistent treatment benefit with ramucirumab for patients with aHCC and AFP ≥400 ng/mL, including patients with aggressive tumors and nonviral etiologies. While no baseline factors predicted response to ramucirumab, TE hypertension was associated with higher drug exposure, and higher drug exposure was associated with improved OS benefit.

Authors' Disclosures

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
2. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7:6.
3. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15:599–616.
4. American Cancer Society. Global cancer facts and figures. 4th ed. Atlanta: American Cancer Society; 2018.
5. Brunetti O, Gnoni A, Licchetta A, Longo V, Calabrese A, Argentiero A, et al. Predictive and prognostic factors in HCC patients treated with sorafenib. Medicina 2019;55:707.
6. Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al. Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions-multicenter analysis. Cancer Med 2019;8:3719–28.
7. Teufel M, Seidel H, Kochert K, Meinhardt G, Finn RS, Llovet JM, et al. Biomarkers associated with response to regorafenib in patients with hepatocellular carcinoma. Gastroenterology 2019;156:1731–41.
8. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: analysis of two phase III studies. J Hepatol 2017;67:999–1008.
9. Personeni N, Giordano L, Abbadessa G, Porta C, Borbath I, Daniele B, et al. Prognostic value of the neutrophil-to-lymphocyte ratio in the ARQ 197–215 second-line study for advanced hepatocellular carcinoma. Oncotarget 2017;8:14408–15.

10. Villanueva A, Llovet JM. Second-line therapies in hepatocellular carcinoma: emergence of resistance to sorafenib. Clin Cancer Res 2012;18:1824.
11. Pinato DJ, Stebbing J, Ishizuka M, Khan SA, Wasan HS, North BV, et al. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). J Hepatol 2012;57:1013–20.
12. Sanghera C, Teh JJ, Pinato DJ. The systemic inflammatory response as a source of biomarkers and therapeutic targets in hepatocellular carcinoma. Liv Int 2019;39: 2008–23.
13. Meyer T, Kelley R, Mangeshkar M, Cheng AL, El-Khoueiry A, Abou-Alfa G. 749P Prognostic and predictive factors from the phase III CELESTIAL trial of cabozantinib (C) versus placebo (P) in previously treated advanced hepatocellular carcinoma (aHCC). Ann Oncol 2019;30:v287–88.
14. Zhu AX, Finn RS, Kang YK, Yen CJ, Galle PR, Llovet JM, et al. Serum alpha-fetoprotein and clinical outcomes in patients with advanced hepatocellular carcinoma treated with ramucirumab. Br J Cancer 2021;124:1388–97.
15. Cai J, Ma H, Huang F, Zhu D, Bi J, Ke Y, et al. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. World J Surg Oncol 2013;11:306.
16. Vincenzi B, Santini D, Russo A, Addeo R, Giuliani F, Montella L, et al. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist 2010;15:85–92.
17. Tabernero J, Ohtsu A, Muro K, Van Cutsem E, Oh SC, Bodoky G, et al. Exposure-response analyses of ramucirumab from two randomized, phase III trials of second-line treatment for advanced gastric or gastroesophageal junction cancer. Mol Cancer Ther 2017;16:2215–22.
18. Nguyen L, Chapel S, Tran BD, Lacy S. Cabozantinib exposure–response analyses of efficacy and safety in patients with advanced hepatocellular carcinoma. J Pharmacokinet Pharmacodyn 2019;46:577–89.
19. Zhu AX, Park JO, Ryoo B-Y, Yen C-J, Poon R, Pastorelli D, et al. Ramucirumab versus 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;16:859–70.
20. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, 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. Lancet Oncol 2019;20:282–96.
21. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379: 1245–55.
22. Sauzay C, Petit A, Bourgeois AM, Barbare JC, Chauffert B, Galmiche A, et al. Alpha-foetoprotein (AFP): a multi-purpose marker in hepatocellular carcinoma. Clin Chim Acta 2016;463:39–44.
23. Song PP, Xia JF, Inagaki Y, Hasegawa K, Sakamoto Y, Kokudo N, et al. Controversies regarding and perspectives on clinical utility of biomarkers in hepatocellular carcinoma. World J Gastroenterol 2016;22:262–74.
24. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol 2013;31:2963–9.
25. O'Brien L, Westwood P, Gao L, Heathman M. Population pharmacokinetic meta-analysis of ramucirumab in cancer patients. Br J Clin Pharmacol 2017;83: 2741–51.
26. Liu C, Yu J, Li H, Liu J, Xu Y, Song P, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. Clin Pharmacol Ther 2017;101:657–66.
27. Pfister D, Núñez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021; 592:450–6.
28. Bruix J, Qin S, Merle P, Granito A, Huang Y-H, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet North Am Ed 2017;389:56–66.
29. Tyson GL, Duan Z, Kramer JR, Davila JA, Richardson PA, El-Serag HB. Level of α-fetoprotein predicts mortality among patients with hepatitis C-related hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:989–94.
30. Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013;31:3509–16.
31. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54–63.
32. Casadei Gardini A, Scarpi E, Marisi G, Foschi FG, Donati G, Giampalma E, et al. Early onset of hypertension and serum electrolyte changes as potential predictive factors of activity in advanced HCC patients treated with sorafenib: results from a retrospective analysis of the HCC-AVR group. Oncotarget 2016;7:15243–51.
33. Kudo M, Ikeda M, Galle PR, Yamashita T, Finn RS, Liang K, et al. Ramucirumab in patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein: outcomes by treatment-emergent ascites. Hepatol Res 2021;51:715–21.
34. Casadei Gardini A, Scarpi E, Faloppi L, Scartozzi M, Silvestris N, Santini D, et al. Immune inflammation indicators and implication for immune modulation strategies in advanced hepatocellular carcinoma patients receiving sorafenib. Oncotarget 2016;7:67142–9.
35. Qi X, Li J, Deng H, Li H, Su C, Guo X. Neutrophil-to-lymphocyte ratio for the prognostic assessment of hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. Oncotarget 2016;7:45283–301.
36. Xue T-C, Zhang L, Xie X-Y, Ge N-L, Li L-X, Zhang B-H, et al. Prognostic significance of the neutrophil-to-lymphocyte ratio in primary liver cancer: a meta-analysis. PLoS One 2014;9:e96072.
37. Mouchli M, Reddy S, Gerrard M, Boardman L, Rubio M. Usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic predictor after treatment of hepatocellular carcinoma. Ann Hepatol 2021;22:100249.
38. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106:dju124.
39. Pascual S, Herrera I, Irurzun J. New advances in hepatocellular carcinoma. World J Hepatol 2016;8:421–38.
40. Negro F. Natural history of NASH and HCC. Liver Int 2020;40:72–6.
41. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. 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–v5.
42. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77–90.
43. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382: 1894–905.
44. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim HY, et al. 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.
45. Galle PR, Kudo M, Llovet JM, Finn RS, Karwal M, Pezet D, et al. Ramucirumab in patients with previously treated advanced hepatocellular carcinoma: impact of liver disease etiology. Liver Int 2021;41:2759–97.
46. Touyz RM, Lang NN. Hypertension and antiangiogenesis: the janus face of VEGF inhibitors. JACC CardioOncol 2019;1:37–40.
47. Hurwitz HI, Douglas PS, Middleton JP, Sledge GW, Johnson DH, Reardon DA, et al. Analysis of early hypertension and clinical outcome with bevacizumab: results from seven phase III studies. Oncologist 2013;18:273–80.
48. Jhaveri KD, Flombaum CD, Kroog G, Glezerman IG. Nephrotoxicities associated with the use of tyrosine kinase inhibitors: a single-center experience and review of the literature. Nephron Clin Pract 2011;117:c312–9.
49. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163–73.
50. Feliu J, Salud A, Safont MJ, García-Girón C, Aparicio J, Losa F, et al. Correlation of hypertension and proteinuria with outcome in elderly bevacizumab-treated patients with metastatic colorectal cancer. PLoS One 2015;10:e0116527.
51. Dionisio de Sousa IJ, Casalta-Lopes J, Rodrigues J, Pais A, Bonito N, Jacinto PS, et al. Association between bevacizumab-related hypertension and response to treatment in metastatic colorectal cancer patients. J Clin Oncol 33: 15s, 2015 (suppl; abstr e14636).
52. Kudo M. Better efficacy of ramucirumab in Japanese patients than in the global population with unresectable hepatocellular carcinoma. Liver Cancer 2020;9:232–44.
53. Pinato DJ, Marron TU, Mishra-Kalyani PS, Gong Y, Wei G, Szafron D, et al. Treatment-related toxicity and improved outcome from immunotherapy in hepatocellular cancer: Evidence from an FDA pooled analysis of landmark clinical trials with validation from routine practice. Eur J Cancer 2021;157:140–52.
54. Rimola J, Diaz-Gonzalez A, Darnell A, Varela M, Pons F, Hernandez-Guerra M, et al. Complete response under sorafenib in patients with hepatocellular carcinoma: relationship with dermatologic adverse events. Hepatology 2018;67:612–22.