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## Association of Alpha-Fetoprotein and Clinical Outcomes in Patients with Unresectable Hepatocellular Carcinoma Treated with First-Line Camrelizumab Plus Rivoceranib vs Sorafenib: Post Hoc Exploratory Analysis of the CARES-310 Trial

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*Original Research*

# Association of Alpha-Fetoprotein and Clinical Outcomes in Patients with Unresectable Hepatocellular Carcinoma Treated with First-Line Camrelizumab Plus Rivoceranib vs Sorafenib: Post Hoc Exploratory Analysis of the CARES-310 Trial

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## Abstract

Alpha-fetoprotein is a well-established prognostic biomarker for hepatocellular carcinoma, with elevated levels associated with worse clinical outcomes. We conducted a post hoc exploratory analysis of the CARES-310 trial to evaluate the impact of baseline alpha-fetoprotein levels on efficacy and safety outcomes. CARES-310 (NCT03764293) was a randomized, open-label, phase 3 trial comparing camrelizumab plus rivoceranib with sorafenib as first-line therapy in patients with unresectable hepatocellular carcinoma. Patients were stratified by baseline alpha-fetoprotein (<400 vs ≥400 ng/mL). This analysis assessed overall survival, progression-free survival, objective response rate, disease control rate, and safety by alpha-fetoprotein subgroup in the intent-to-treat and safety populations. Among 543 patients, 347 had alpha-fetoprotein <400 ng/mL and

196 had alpha-fetoprotein ≥400 ng/mL. Camrelizumab plus rivoceranib improved overall survival compared with sorafenib in both the alpha-fetoprotein <400 ng/mL subgroup (30.3 vs 20.2 months; hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.47–0.84) and the alpha-fetoprotein ≥400 ng/mL subgroup (16.6 vs 10.8 months; HR, 0.66; 95% CI, 0.47–0.91). Progression-free survival was also improved in both groups (<400 ng/mL: 7.2 vs 3.8 months [HR, 0.63]; ≥400 ng/mL: 5.5 vs 2.3 months [HR, 0.39]). Objective response rate and disease control rate favored camrelizumab plus rivoceranib across alpha-fetoprotein subgroups. Safety profiles were consistent in patients treated with camrelizumab plus rivoceranib regardless of alpha-fetoprotein level, with no new safety signals identified. Although elevated AFP remains a marker of adverse prognosis, camrelizumab plus rivoceranib demonstrated clinically meaningful efficacy compared with sorafenib irrespective of baseline alpha-fetoprotein level. As a post hoc, exploratory subgroup analysis, this

study was not powered to formally test for differences in treatment effect between alpha-fetoprotein subgroups, and results should be considered hypothesis-generating rather than confirmatory. These findings support the use of camrelizumab plus rivoceranib across alpha-fetoprotein-defined subgroups and highlight the need for validated predictive biomarkers in first-line systemic treatment for patients with advanced hepatocellular carcinoma.

**Keywords:** camrelizumab, rivoceranib, alpha-fetoprotein, hepatocellular carcinoma, sorafenib, CARES-310.

## Introduction

Primary liver cancer, predominantly hepatocellular carcinoma (HCC), is a major and growing contributor to the global cancer burden, ranking as the third leading cause of cancer-related death worldwide and seventh in the United States<sup>1</sup>. Alpha-fetoprotein (AFP) modestly improves sensitivity for early-stage HCC detection<sup>2</sup>; biannual ultrasonography with or without AFP remains the standard surveillance method endorsed by major societies, including the American Association for the Study of Liver Diseases<sup>2,3</sup>. AFP is a glycoprotein that plays an immunoregulatory role during fetal development and is minimally expressed in healthy adults<sup>4</sup>. Elevated AFP levels in adults are associated with pathological conditions involving active liver regeneration, hepatitis, and malignancies, such as HCC and germ cell tumors<sup>4</sup>. AFP synthesis is more prevalent in tumors with large size, poor differentiation, and vascular invasion; therefore, AFP levels can provide important prognostic information for patients with HCC<sup>4</sup>.

The CARES-310 (NCT03764293) trial compared the combination of the anti-PD-1 antibody camrelizumab plus the VEGFR2-targeted tyrosine kinase inhibitor rivoceranib (also known as apatinib) with sorafenib as first-line treatment for unresectable HCC<sup>5</sup>. At the protocol-specified final analysis after an additional follow-up of 22.1 months for camrelizumab plus rivoceranib and 14.9 months for sorafenib, camrelizumab plus rivoceranib continued to show clinically meaningful improved overall survival (OS) and progression-free survival (PFS) compared with sorafenib (median OS, 23.8 months vs 15.2 months; hazard ratio [HR], 0.64 [95% CI, 0.52–0.79]; median PFS, 5.6 months vs 3.7 months; HR, 0.54 [95% CI, 0.44–0.67])<sup>6</sup>. The most common grade  $\geq 3$  treatment-related adverse events (TRAEs) for camrelizumab plus rivoceranib were hypertension (38%) and increased aspartate aminotransferase (AST; 17%) versus palmar-plantar erythrodysesthesia syndrome (16%) for sorafenib.

We hypothesized that the efficacy and safety benefit of camrelizumab plus rivoceranib over sorafenib would be maintained across AFP subgroups. The primary objective of this exploratory post hoc analysis was to evaluate the prognostic association baseline serum AFP levels ( $<400$  ng/mL vs  $\geq 400$  ng/mL) with efficacy and safety outcomes;

because no formal treatment-by-AFP interaction testing was performed, this analysis was not designed to assess the predictive value of AFP for treatment benefit. Given the established association between elevated AFP and poorer prognosis, we considered it clinically relevant to evaluate whether baseline AFP also influenced the safety profile of camrelizumab plus rivoceranib, providing a more complete assessment of the benefit-risk profile of this combination. An AFP level  $\geq 400$  ng/mL was selected based on its established clinical relevance in HCC. This threshold has consistently identified a poorer prognostic subgroup across multiple treatment settings<sup>7,8,9,10</sup> and was recommended as a diagnostic criterion in the 2017 Chinese guidelines for the diagnosis and treatment of primary liver cancer<sup>11</sup>. Separate analyses were performed for the intent-to-treat population and for the safety population.

## Methodology

### Study Design and Patients

CARES-310 was a randomized, open-label, multicenter, phase 3 trial conducted at 95 sites across 13 countries. A detailed description of the study methods, outcomes, statistical analysis, and results has been previously published<sup>5,6</sup>. In brief, the trial enrolled patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C, no prior systemic therapy for advanced disease, Eastern Cooperative Oncology Group performance status of 0 or 1, Child-Pugh class A, and at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Patients were randomized 1:1 to receive camrelizumab 200 mg intravenously every 2 weeks combined with rivoceranib 250 mg orally daily, or sorafenib 400 mg orally twice daily. Patients were stratified by the presence of macrovascular invasion and/or extrahepatic spread (yes vs no), geographical region (Asia vs non-Asia), and baseline serum AFP ( $<400$  vs  $\geq 400$  ng/mL). The co-primary endpoints were PFS by blinded independent review committee (BIRC) per RECIST v1.1 and OS. A key secondary endpoint was objective response rate (ORR) by BIRC per RECIST v1.1. Patients were evaluated until loss of clinical benefits or intolerable toxicity. Treatment beyond progression was allowed if there was evidence of clinical benefits per investigator.

### Post Hoc Exploratory Analysis and Statistical Methods

An entirely post hoc, exploratory analysis of the CARES-310 trial was performed to assess the impact of baseline AFP levels ( $<400$  ng/mL vs  $\geq 400$  ng/mL) on efficacy and safety outcomes, including median OS, median PFS, ORR, disease control rate (DCR), any grade TRAEs, and grade 3-4 TRAEs. This analysis was not prespecified in the statistical analysis plan, no adjustment for multiplicity was performed, and no formal treatment-by-AFP interaction testing was conducted. Accordingly, all analyses were considered descriptive. Kaplan-Meier methods were used to estimate median OS and median PFS. Brookmeyer and Crowley methods were used to calculate confidence

intervals (CI) of the median<sup>12</sup>. Hazard ratios and the corresponding CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence) and geographical regions (Asia vs countries outside of Asia) in the interaction response technology (IRT) system. By contrast, AFP subgroup hazard ratios previously reported in the primary CARES-310 publication were unstratified. One-sided P values were calculated based on log-rank tests. The ORR was calculated based on the number of patients with a complete response and partial response at the corresponding interval divided by the number of patients in the corresponding treatment group. The DCR was calculated based on the percentage of patients with complete response, partial response, or stable disease  $\geq 7$  weeks.

## Results

Of the 272 patients treated with camrelizumab plus rivoceranib in the CARES-310 trial, 176 patients had a baseline AFP level  $<400$  ng/mL, and 96 patients had a baseline AFP level  $\geq 400$  ng/mL. Of the 271 patients treated with sorafenib, 171 patients had a baseline AFP level  $<400$  ng/mL, and 100 patients had a baseline AFP level  $\geq 400$  ng/mL. Most patients were male, BCLC stage C, Child-Pugh class A5, and had received previous local therapy. Baseline characteristics are detailed in Table 1.

<sup>a</sup>BMI was calculated as weight in kilograms divided by height in meters squared. AFP, alpha-fetoprotein; BCLC,

**Table 1: Baseline Characteristics by AFP Subgroup (ITT Population)**

| Characteristic                | AFP $>400$ ng/mL<br>Cam + Rivo<br>(N=176) | AFP $>400$ ng/<br>mL Sorafenib<br>(N=171) | AFP $\geq 400$ ng/<br>mL Cam + Rivo<br>(N=96) | AFP $\geq 400$ ng/<br>mL Sorafenib<br>(N=100) |
|-------------------------------|-------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| EHS, n (%)                    |                                           |                                           |                                               |                                               |
| Absence                       | 60 (34.1)                                 | 56 (32.7)                                 | 37 (38.5)                                     | 35 (35.0)                                     |
| Presence                      | 116 (65.9)                                | 115 (67.3)                                | 59 (61.5)                                     | 65 (65.0)                                     |
| Previous local therapy, n (%) |                                           |                                           |                                               |                                               |
| Yes                           | 103 (58.5)                                | 102 (59.6)                                | 58 (60.4)                                     | 48 (48.0)                                     |
| No                            | 73 (41.5)                                 | 69 (40.4)                                 | 38 (39.6)                                     | 52 (52.0)                                     |
| HCC etiology, n (%)           |                                           |                                           |                                               |                                               |
| HBV                           | 129 (73.3)                                | 120 (70.2)                                | 79 (82.3)                                     | 77 (77.0)                                     |
| HCV                           | 15 (8.5)                                  | 20 (11.7)                                 | 7 (7.3)                                       | 9 (9.0)                                       |
| Nonviral                      | 32 (18.2)                                 | 31 (18.1)                                 | 10 (10.4)                                     | 14 (14.0)                                     |
| BMI, n (%)                    |                                           |                                           |                                               |                                               |
| $<30$                         | 168 (95.5)                                | 160 (93.6)                                | 92 (95.8)                                     | 97 (97.0)                                     |
| $\geq 30$                     | 8 (4.5)                                   | 10 (5.8)                                  | 4 (4.2)                                       | 3 (3.0)                                       |
| Missing                       | 0                                         | 1 (0.6)                                   | 0                                             | 0                                             |

<sup>a</sup>Barcelona Clinic Liver Cancer; BMI, body mass index; Cam, camrelizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; MVI, macrovascular invasion; Rivo, rivoceranib.

## Efficacy

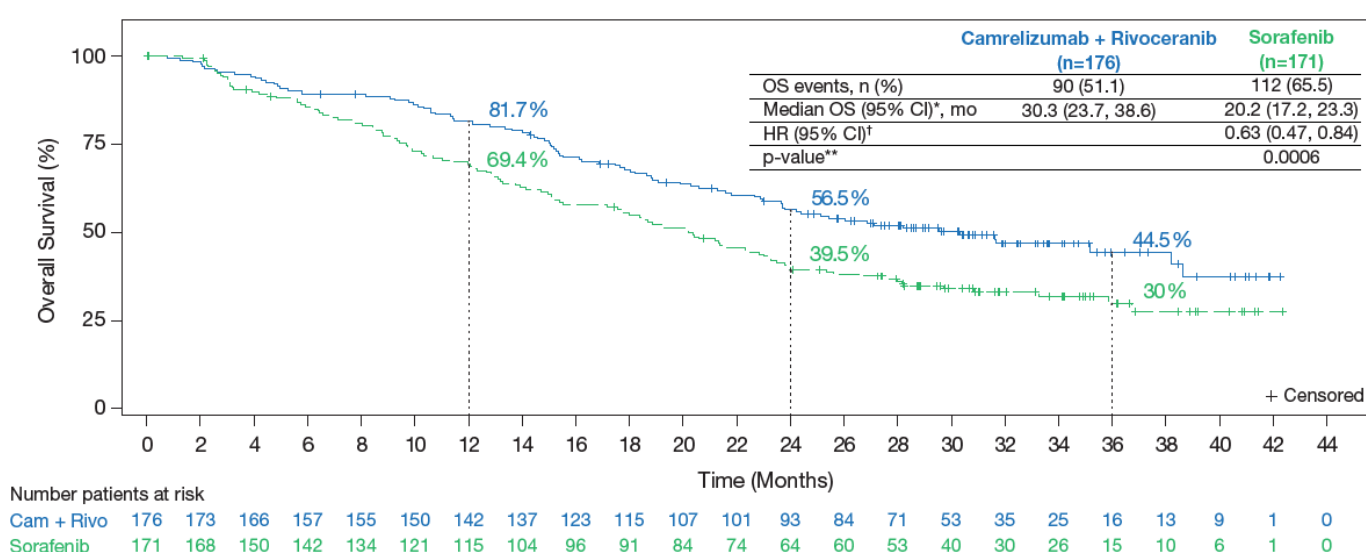
Median OS was 30.3 months with camrelizumab plus rivoceranib and 20.2 months with sorafenib in patients with baseline AFP level  $<400$  ng/mL (HR, 0.63; 95% CI, 0.47–0.84;  $P=0.0006$ ) (Figure 1A). In patients with baseline AFP level  $\geq 400$  ng/mL, median OS was 16.6 months with camrelizumab plus rivoceranib and 10.8 months with sorafenib (HR, 0.66; 95% CI, 0.47–0.91;  $P=0.0055$ ) (Figure 1B). Median PFS per BIRC assessment was 7.2 months with camrelizumab plus rivoceranib and 3.8 months with

sorafenib in patients with baseline AFP level  $<400$  ng/mL (HR, 0.63; 95% CI, 0.49–0.82;  $P=0.0002$ ) (Figure 2A). In patients with baseline AFP level  $\geq 400$  ng/mL, median PFS per BIRC assessment was 5.5 months with camrelizumab plus rivoceranib and 2.3 months with sorafenib (HR, 0.39; 95% CI, 0.27–0.56;  $P<0.0001$ ) (Figure 2B). In patients with baseline AFP  $<400$  ng/mL, ORR was 34.1% with camrelizumab plus rivoceranib and 7.6% with sorafenib. Among those with baseline AFP  $\geq 400$  ng/mL, ORR was 13.5% with camrelizumab plus rivoceranib and 3.0% with sorafenib (Table 2).

**Table 2: Summary of Response Rate by BIRC Assessment (RECIST v1.1) (ITT Population)**

|                                         | AFP >400 ng/mL<br>Cam + Rivo<br>(N=176) | AFP >400 ng/<br>mL Sorafenib<br>(N=171) | AFP ≥400 ng/<br>mL Cam + Rivo<br>(N=96) | AFP ≥400 ng/mL<br>Sorafenib (N=100) |
|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-------------------------------------|
| Objective response rate, n (%) [95% CI] | 60 (34.1) [27.1–41.6]                   | 13 (7.6) [4.1–12.6]                     | 13 (13.5) [7.4–22.0]                    | 3 (3.0) [0.6–8.5]                   |
| Complete response, n (%)                | 5 (2.8)                                 | 2 (1.2)                                 | 0                                       | 0                                   |
| Partial response, n (%)                 | 55 (31.3)                               | 11 (6.4)                                | 13 (13.5)                               | 3 (3.0)                             |
| Stable disease, n (%)                   | 84 (47.7)                               | 90 (52.6)                               | 55 (57.3)                               | 39 (39.0)                           |
| Progressive disease, n (%)              | 26 (14.8)                               | 54 (31.6)                               | 19 (19.8)                               | 46 (46.0)                           |
| Not evaluable, n (%)                    | 6 (3.4)                                 | 14 (8.2)                                | 9 (9.4)                                 | 12 (12.0)                           |
| Disease control rate, a n (%) [95% CI]  | 144 (81.8) [75.3–87.2]                  | 103 (60.2) [52.5–67.6]                  | 68 (70.8) [60.7–79.7]                   | 42 (42.0) [32.2–52.3]               |
| Median time to response, months         | 2                                       | 4                                       | 2                                       | 2                                   |

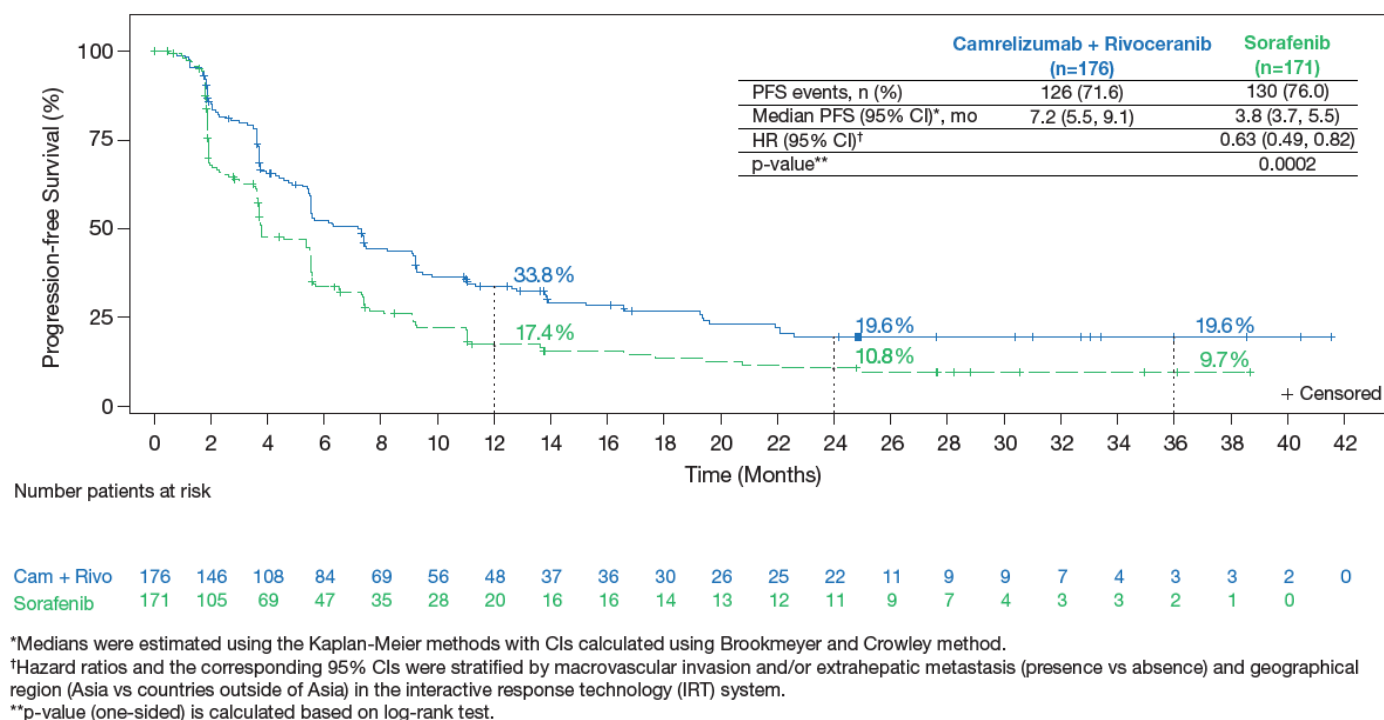
<sup>a</sup>Disease control rate is defined as the percentage of patients with complete response, partial response, or stable disease ≥7 weeks. AFP, alpha-fetoprotein; BIRC, blinded independent review committee; Cam, camrelizumab; ITT, intent-to-treat; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Rivo, rivoceranib.

**Figure 1. Overall Survival. A) Overall Survival for Patients With Baseline AFP <400 ng/mL. B) Overall Survival for Patients With Baseline AFP ≥400 ng/mL. AFP, alpha-fetoprotein; Cam, camrelizumab; HR, hazard ratio; OS, overall survival; Rivo, rivoceranib.**

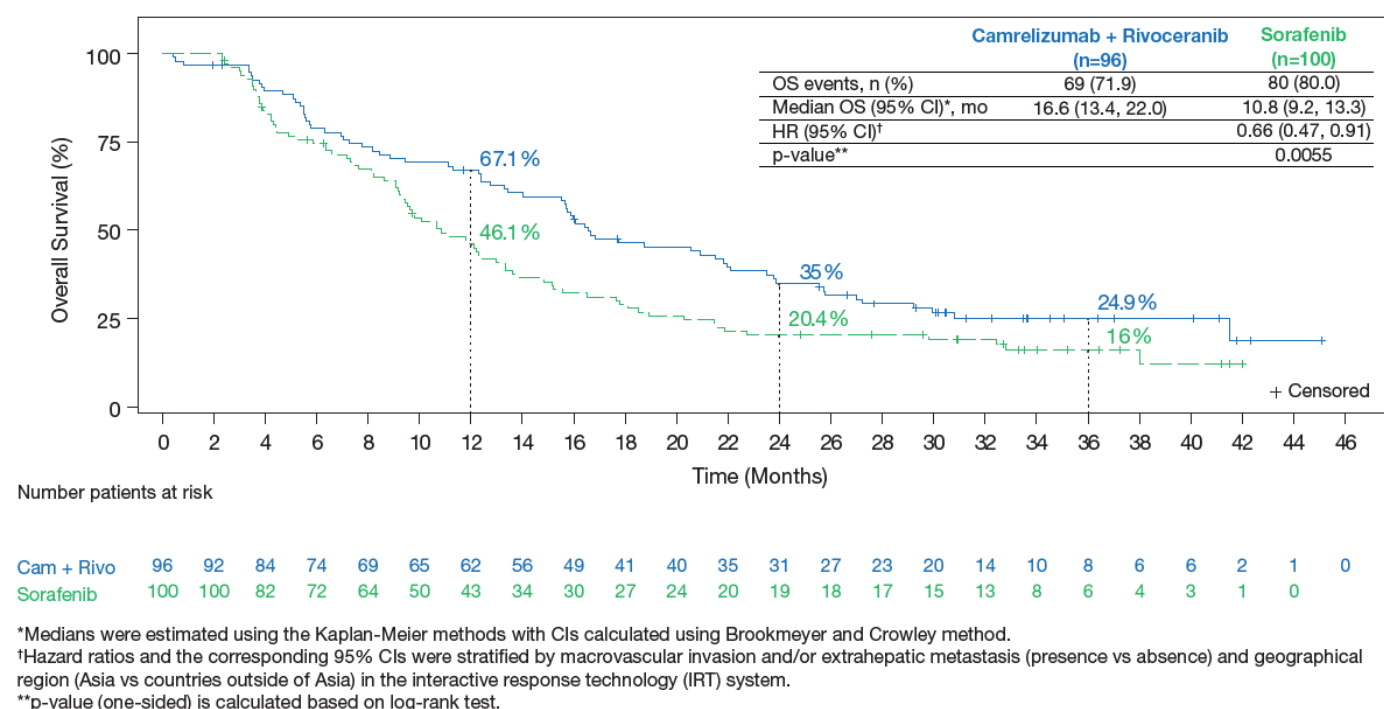
\*Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.

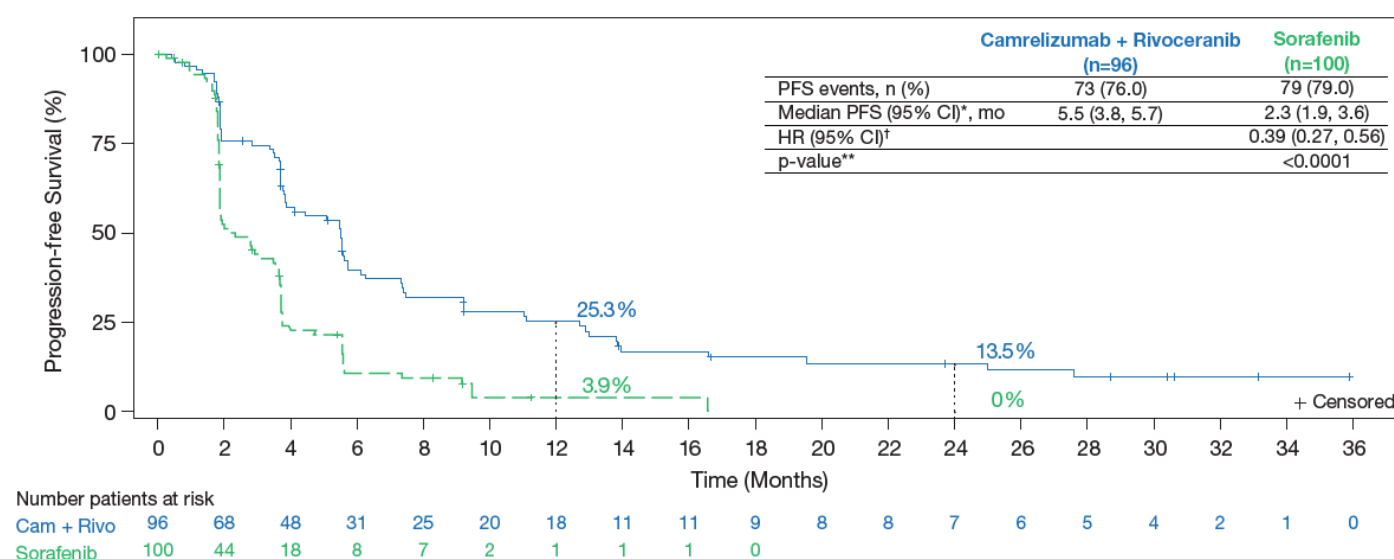
†Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence) and geographical region (Asia vs countries outside of Asia) in the interactive response technology (IRT) system.

\*\*p-value (one-sided) is calculated based on log-rank test.



**Figure 2. Progression-Free Survival. A) Progression-Free Survival for Patients With Baseline AFP <400 ng/mL by BIRC Assessment (RECIST v1.1). B) Progression-Free Survival for Patients With Baseline AFP ≥400 ng/mL by BIRC Assessment (RECIST v1.1).** AFP, alpha-fetoprotein; BIRC, blinded independent review committee; Cam, camrelizumab; HR, hazard ratio; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Rivo, rivoceranib.





\*Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.

†Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence) and geographical region (Asia vs countries outside of Asia) in the interactive response technology (IRT) system.

\*\*p-value (one-sided) is calculated based on log-rank test.

The DCR per BIRC assessment was 81.8% with camrelizumab plus rivoceranib and 60.2% with sorafenib in patients with baseline AFP level <400 ng/mL.

Among those with baseline AFP level ≥400 ng/mL, DCR was 70.8% with camrelizumab plus rivoceranib and 42.0% with sorafenib (Table 2).

## Safety

Among patients treated with camrelizumab plus rivoceranib, the most common TRAEs were similar across baseline serum AFP subgroups. The most common any grade and grade 3–4 TRAEs for patients treated with camrelizumab plus rivoceranib and baseline AFP level <400 ng/mL were increased AST, increased alanine aminotransferase (ALT), and decreased platelet count (Table 3).

**Table 3: Most Common (≥20%) Any Grade or Grade 3–4 (≥5%) TRAEs for Patients Treated With Camrelizumab Plus Rivoceranib and Baseline AFP <400 ng/mL (Safety Population)**

| TRAE, n (%)                      | Cam + Rivo (N=176) Any Grade | Cam + Rivo (N=176) Grade 3–4 | Sorafenib (N=169) Any Grade | Sorafenib (N=169) Grade 3–4 |
|----------------------------------|------------------------------|------------------------------|-----------------------------|-----------------------------|
| AST increased                    | 75 (42.6)                    | 27 (15.3)                    | 67 (39.6)                   | 8 (4.7)                     |
| ALT increased                    | 64 (36.4)                    | 20 (11.4)                    | 56 (33.1)                   | 6 (3.6)                     |
| Platelet count decreased         | 61 (34.7)                    | 21 (11.9)                    | 59 (34.9)                   | 2 (1.2)                     |
| Blood bilirubin increased        | 59 (33.5)                    | 9 (5.1)                      | 49 (29.0)                   | 2 (1.2)                     |
| Proteinuria                      | 40 (22.7)                    | 6 (3.4)                      | 51 (30.2)                   | 3 (1.8)                     |
| White blood cell count decreased | 37 (21.0)                    | 4 (2.3)                      | 21 (12.4)                   | 3 (1.8)                     |
| Neutrophil count decreased       | 36 (20.5)                    | 9 (5.1)                      | 14 (8.3)                    | 0                           |
| GGT increased                    | 35 (19.9)                    | 15 (8.5)                     | 33 (19.5)                   | 14 (8.3)                    |

<sup>a</sup>TRAEs include adverse events related to both camrelizumab plus rivoceranib or sorafenib. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cam, camrelizumab; GGT, gamma-glutamyl transferase; Rivo, rivoceranib; TRAE, treatment-related adverse event.

The most common any grade and grade 3–4 TRAEs for patients treated with camrelizumab plus rivoceranib and

baseline AFP level  $\geq 400$  ng/mL were increased AST, increased ALT, and increased blood bilirubin (Table 4).

**Table 4: Most Common ( $\geq 20\%$ ) Any Grade or Grade 3–4 ( $\geq 5\%$ ) TRAEs for Patients Treated With Camrelizumab Plus Rivoceranib and Baseline AFP  $\geq 400$  ng/mL (Safety Population)**

| TRAE, n (%)               | Cam + Rivo<br>(N=96) Any Grade | Cam + Rivo<br>(N=96) Grade 3–4 | Sorafenib (N=100)<br>Any Grade | Sorafenib (N=100)<br>Grade 3–4 |
|---------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| AST increased             | 37 (38.5)                      | 9 (9.4)                        | 34 (34.0)                      | 6 (6.0)                        |
| ALT increased             | 29 (30.2)                      | 8 (8.3)                        | 25 (25.0)                      | 2 (2.0)                        |
| Blood bilirubin increased | 24 (25.0)                      | 6 (6.3)                        | 26 (26.0)                      | 2 (2.0)                        |
| GGT increased             | 13 (13.5)                      | 6 (6.3)                        | 16 (16.0)                      | 5 (5.0)                        |
| Platelet count decreased  | 23 (24.0)                      | 4 (4.2)                        | 31 (31.0)                      | 2 (2.0)                        |

<sup>a</sup>TRAEs include adverse events related to both camrelizumab plus rivoceranib or sorafenib. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cam, camrelizumab; GGT, gamma-glutamyl transferase; Rivo, rivoceranib; TRAE, treatment-related adverse event.

## Discussion

In this post hoc exploratory analysis of CARES-310, camrelizumab plus rivoceranib was associated with improved OS and PFS versus sorafenib in first-line unresectable HCC, irrespective of baseline AFP level. Although efficacy outcomes by AFP subgroup were previously reported in the primary CARES-310 publication, the present analysis provides a dedicated evaluation of efficacy and safety according to baseline AFP level. These findings suggest that the clinical benefit of camrelizumab plus rivoceranib is maintained across AFP-defined subgroups and support the activity of this combination in patients with both lower and higher AFP levels.

In addition to demonstrating consistent efficacy across AFP subgroups, the safety profile of camrelizumab plus rivoceranib was generally similar regardless of baseline AFP level, with no new safety signals observed. These findings support a consistent benefit-risk profile across AFP-defined patient subgroups.

AFP has long been used as a prognostic marker for HCC, with levels higher than 400 ng/mL generally linked to more aggressive disease and poorer outcomes, although the biological basis for this threshold is unclear<sup>13,14</sup>. In the REACH trial that evaluated ramucirumab versus placebo following first-line sorafenib for advanced HCC, no significant survival benefit was observed in the overall population<sup>15</sup>. However, a greater survival benefit was observed among patients with elevated AFP. This observation led to the REACH-2 trial, which prospectively enrolled patients with advanced HCC and AFP  $\geq 400$  ng/mL and demonstrated significant improvements in both OS and PFS with ramucirumab compared with placebo<sup>16</sup>. These findings established AFP  $\geq 400$  ng/mL as a predictive biomarker for ramucirumab in the second-line

advanced HCC setting.

In contrast, in the frontline setting, our findings demonstrate that the survival benefit of camrelizumab plus rivoceranib is observed regardless of baseline AFP level, with improvements in both OS and PFS across subgroups. Among patients with baseline AFP 15% within 3 months) was strongly associated with disease control and independently predicted improved OS and PFS<sup>7,18</sup>. Similarly, post hoc analyses of the CELESTIAL and REACH trials demonstrated that on-treatment AFP kinetics were associated with clinical outcomes in patients treated with cabozantinib and ramucirumab, respectively, supporting the potential utility of dynamic AFP assessment as a complementary biomarker<sup>19,20</sup>. However, both studies concluded that prospective validation is warranted before AFP kinetics are used to guide clinical decision-making. These findings suggest that serial assessment of AFP during treatment may provide additional prognostic and predictive information beyond baseline AFP. However, AFP kinetics were not evaluated in the present post hoc analysis because longitudinal AFP measurements were not available. Therefore, future prospective studies incorporating both baseline AFP and dynamic AFP changes may further refine patient stratification and improve assessment of treatment benefit of camrelizumab plus rivoceranib.

Despite advances in systemic therapy, there remain no prospectively validated predictive biomarkers for response to immunotherapy-based combinations in the first-line HCC setting. The observation of treatment benefit across both AFP subgroups highlights the need for continued development of validated predictive biomarkers.

This analysis has several limitations, including its post hoc nature and limited power for subgroup comparisons. However, the consistent survival benefit observed across

AFP subgroups aligns with the results of the primary CARES-310 trial. Additional limitations include the absence of formal treatment-by-AFP interaction testing, the use of a single AFP cutoff without assessment of AFP kinetics, and the predominantly Asian/HBV study population, which may limit generalizability to broader patient populations. Given the exploratory post hoc design, these findings are hypothesis-generating rather than confirmatory and should be validated in future prospective studies specifically designed to assess the influence of baseline AFP on treatment outcomes.

AFP remains an important prognostic marker. In this exploratory analysis, clinical benefit with camrelizumab plus rivoceranib versus sorafenib was observed regardless of baseline AFP subgroup. Additional studies specifically designed to evaluate predictive biomarkers are warranted.

## Additional Information

### Acknowledgments

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### Ethics Approval

The study protocol was approved by the Alpha Institutional Review Board and conducted in compliance with the study protocol, the International Standard of Good Clinical Practice, the ethical principles of the Declaration of Helsinki, and applicable regulatory requirements. All patients provided written informed consent prior to enrollment.

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