Liver Cancer

Research Article

Liver Cancer
DOI: 10.1159/000551156

Received: August 22, 2025
Accepted: February 13, 2026
Published online: February 23, 2026

Impact of Age on Patient-Reported Outcomes with First-Line Camrelizumab plus Rivoceranib versus Sorafenib in Adults with Unresectable Hepatocellular Carcinoma: Post Hoc Analyses of the CARES-310 Open-Label, Randomized, Phase 3 Trial

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Keywords
Hepatocellular carcinoma · Camrelizumab · Patient-reported outcomes · Overall survival · Progression-free survival

Abstract
Introduction: The CARES-310 randomized, open-label, international phase 3 trial reported improved overall survival and progression-free survival with camrelizumab-rivoceranib compared with sorafenib in adults with unresectable hepatocellular carcinoma (uHCC). ***Methods:*** We performed a post hoc analysis of data from CARES-310 to evaluate patient-reported outcomes (PROs), survival, and safety in adults <65 years and ≥65 years. PRO endpoints included time to deterioration with a ≥10-point decrease from baseline of health-related quality of life (HRQoL), physical functioning, role functioning, and symptoms. ***Results:*** PRO data for these age cohorts demonstrated clinically meaningful benefits with camrelizumab-rivoceranib versus sorafenib in key aspects of the patient experience such as HRQoL, functioning, pain, and fatigue. Similarly, both age groups had a significant survival outcome advantage on camrelizumab-rivoceranib versus sorafenib. Although patients treated with camrelizumab-rivoceranib had higher rates of treatment-related adverse events versus sorafenib, this did not adversely affect HRQoL as assessed by PROs. The most common ≥20% grade ≥3 treatment-related adverse events in the

ClinicalTrials.gov identifier: NCT03764293

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camrelizumab-rivoceranib arm were hypertension and increased AST versus palmar-plantar erythrodysesthesia syndrome in the sorafenib arm. ***Conclusion:*** These results support the favorable benefit-risk profile of camrelizumab-rivoceranib in patients <65 years and ≥65 years as a first-line therapy in patients with uHCC who have not received prior systemic therapy.

Introduction

Globally, primary liver cancer ranks as the sixth most common cancer and the third leading cause of cancer-related deaths [1]. Unless the incidence and mortality rates improve, the number of new diagnoses and deaths from primary liver cancer may increase by over 50% in the next 2 decades [2]. Most primary liver cancers (75% to 85%) are hepatocellular carcinoma (HCC) [1]. A recent analysis of US cancer statistics reported 5-year relative survival rates of 33.6% for adults with localized HCC, 12.0% for regional disease, and 3.5% for distant disease [3]. The incidence of HCC is rising in Europe and North America and decreasing in part of Asia [4]. In addition to the risk of mortality, patients with advanced HCC are burdened by symptoms and comorbidities, primarily caused by liver cirrhosis and worsening liver function [5], that can severely impact their health-related quality of life (HRQoL) and psychosocial wellbeing. Also, the treatments patients receive for HCC can cause toxicities that can affect their physical health and quality of life (QOL). Thus, in the clinical trial setting, it is critical to assess the impact of investigational therapies on daily activities and QOL of patients with HCC. The responses to HRQoL questionnaires provided by these patients reflect the impact from their cancer, ensuing hepatic damage, and treatment-related toxicities [5].

Camrelizumab, an anti-programmed cell death-1 humanized monoclonal antibody, has shown efficacy and a manageable safety profile in patients with advanced HCC when used in combination with rivoceranib, a vascular endothelial growth factor receptor tyrosine kinase inhibitor also known as apatinib [6, 7]. In the CARES-310 trial, camrelizumab-rivoceranib combination therapy statistically significantly improved progression-free survival (PFS) and overall survival (OS) compared with sorafenib monotherapy in adults with unresectable HCC (uHCC), reducing the relative risk of progression by 36% and the risk of progression or death by 48% [8, 9].

As exploratory endpoints, CARES-310 assessed time to first deterioration (defined as a decrease of ≥10 points from baseline) in global health status (GHS), physical functioning, and role functioning assessed using the validated and reliable European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) and the EORTC Quality-of-Life Questionnaire Hepatocellular Carcinoma 18 (QLQ-HCC18) [8]. As previously published [8], at baseline, mean scores in both treatment arms, camrelizumab-rivoceranib and sorafenib, on the functioning, GHS/QOL, and symptom scales were comparable. Patients treated with camrelizumab-rivoceranib had numerically lower risk of deterioration in physical functioning (hazard ratio [HR] = 0.775) and role functioning (HR = 0.887) compared with patients in the sorafenib arm. GHS/QOL were maintained in the camrelizumab-rivoceranib arm, with the median time to deterioration (TTD) 11.2 months compared to sorafenib 7.4 months. Treatment with camrelizumab-rivoceranib had a longer TTD in diarrhea (one-sided $p = 0.0046$) and had numerically lower risk of deterioration in fatigue (HR = 0.862) and pain (HR = 0.828) compared with sorafenib. The compliance rates for patient-reported outcome (PRO) questionnaires were high for both treatment arms. Analysis of symptoms showed statistically significant less deterioration in pain (two-sided $p = 0.0262$), diarrhea (two-sided $p = 0.0350$), and fatigue (two-sided $p = 0.0068$), favoring camrelizumab-rivoceranib. Physiological changes, the increased presence of comorbidities, and frailty factors associated with aging expose patients with HCC to higher risk of drug toxicities. Older adults (age ≥65 years old) may have a lower tolerance for certain therapies. To evaluate the impact of age on outcomes with camrelizumab-rivoceranib treatment versus sorafenib in HCC patients, we performed this post hoc analysis of PROs, survival, and safety in adults 18 to <65 years of age and adults ≥65 years enrolled in CARES-310.

Methods

Study Design

The CARES-310 study design, methods, and protocol were previously published [8]. An independent data monitoring committee regularly monitored safety and reviewed efficacy from all preplanned analyses. We performed post hoc analyses of PROs, survival, and safety to evaluate outcomes in 2 cohorts of adult patients enrolled in the CARES-310 study: adults 18 to <65 years old (referred to as <65 years in this manuscript) and adults ≥65 years old.

Patients

The study design, methods, and results of primary, secondary, and some exploratory endpoints for the CARES-310 have been published [8]. In brief, the study included adults (≥18 years) with a cytologically or histopathologically confirmed HCC diagnosis, Barcelona Clinic Liver Cancer (BCLC) stage B or C disease, Child-Pugh A5 and A6, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, not amenable to surgical or locoregional therapy or with progression after such therapy, and no prior systemic therapy.

Randomization and Masking

As previously published [8], for randomization, patients were stratified based on the presence or absence of macrovascular invasion or extrahepatic metastasis, geographic region defined as Asia (i.e., China, Hong Kong, South Korea, Taiwan) or non-Asia (i.e., Belgium, Germany, Italy, Poland, Russia, Spain, Turkey, Ukraine, USA), and baseline alpha-fetoprotein (AFP) concentration <400 ng/mL or ≥400 ng/mL. Using a randomization sequence generated by an independent third party, eligible patients were randomized 1:1 to treatment with camrelizumab-rivoceranib or sorafenib; the study was open label.

Procedures

As previously reported [8], patients in the CARES-310 study received camrelizumab 200 mg intravenously every 2 weeks plus rivoceranib 250 mg orally once daily or sorafenib 400 mg orally twice daily in 28-day cycles. Treatment continued until unacceptable toxicity, withdrawal of informed consent, disease progression confirmed by blinded independent review committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or investigator's decision. Treatment could continue beyond disease progression if the investigator found that the patient had evidence of clinical benefit and tolerance to treatment. Dose modifications were allowed. Patients who experienced treatment-related adverse events (TRAEs) that led to dose modification or permanent discontinuation of camrelizumab or rivoceranib could continue to receive the other agent as monotherapy.

Outcomes

As previously reported [8], the primary endpoints in the CARES-310 study were PFS (defined as time from randomization to the first radiographic tumor progression or death assessed by the BIRC) per RECIST v1.1 and OS (defined as time from randomization to death from any cause). Safety was regularly monitored until 90 days after the last dose of camrelizumab or 30 days after the last dose of rivoceranib or sorafenib. Adverse events were graded by the investigators according to the Common Terminology Criteria for Adverse Events, v4.0.3.

The EORTC QLQ-C30 and QLQ-HCC18 were administered on day 1 of each 28-day cycle, at the end of treatment, and at the first safety follow-up visit which occurred 30 days after the last dose [8]. The EORTC QLQ-C30 asks patients to self-assess their functioning (i.e., physical, emotional, role, cognitive, and social), QOL, and general cancer symptoms (i.e., fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) in the previous week [10, 11]. The EORTC QLQ-HCC18 asks patients to self-assess their HCC-specific symptoms (i.e., fatigue, body image, jaundice, nutrition, fever, pain, abdominal swelling, and sex life) in the previous week [12, 13].

Patients completed validated versions of both questionnaires electronically at the clinic site on day 1 of treatment 28-day cycle one (i.e., baseline) and of each subsequent cycle, including the treatment discontinuation visit. Patients completed both questionnaires at the beginning of their visit before discussion of the patient's health state, laboratory test results, or health record; before administration of study treatment; and before any other study assessments. After treatment discontinuation or disease progression, whichever came first, questionnaires were completed electronically or via telephone every 3 months for 1 year unless the patient withdrew consent.

Patient responses on all items of the EORTC QLQ-C30 and EORTC QLQ-HCC18 were scored according to the EORTC guidelines [13]. This scoring included linearly transforming all raw scores onto a 100-point scale. A higher scale score (e.g., closer to 100) denotes better functioning and QOL, but worse symptoms. Thus, a higher QOL or function score relative to baseline reflects improved QOL or functioning, and a higher symptom score relative to baseline reflects worsening of symptoms. These analyses conformed with published international recommendations for analyses of PRO and QOL endpoints [14].

Statistical Analysis

Details of the primary analyses have been previously described [8]. Efficacy was analyzed in the intention-to-treat population (all randomized patients), and safety was analyzed in patients who received ≥1 dose of study drug. The Kaplan-Meier method was used for survival estimates and the log-rank test for survival distribution

comparisons. Prespecified TTD in HRQoL outcomes was analyzed by the Kaplan-Meier method; changes from baseline in HRQoL outcomes were analyzed using the mixed model for repeated measures. Mean score change from baseline was assessed by a constrained longitudinal data analysis model with PRO score as the response variable, and treatment, time, treatment by time interaction, stratification factors used for randomization as covariates (two-sided). For time to true deterioration analyses, the magnitude of treatment difference was assessed using a stratified Cox proportional hazard model with the Efron method of tie handling (two-sided). No formal hypothesis tests were performed for the PRO analyses, and all p values are nominal. SAS (v9.4) was used for all statistical analyses.

Results

Baseline Characteristics by Age Cohort

The CARES-310 trial recruited, screened, and randomized 543 patients between June 28, 2019, and March 23, 2021. For the primary analysis [8], all 272 patients randomized to camrelizumab-rivoceranib received treatment and 269 of 271 patients randomized to sorafenib received treatment. In this CARES-310 post hoc analysis, we used data from the 541 patients who received ≥1 dose of study medication. The age <65-year cohort comprised 401 patients, 191 randomized to camrelizumab-rivoceranib and 210 randomized to sorafenib, and the age ≥65-year cohort comprised 140 patients, 81 randomized to camrelizumab-rivoceranib and 59 randomized to sorafenib. Although the age-treatment subgroups had similar baseline demographic characteristics and distributions of ECOG performance status, AFP concentrations, and prevalence of macrovascular invasion, there were differences in some other baseline disease characteristics (Table 1). For example, the hepatitis B virus etiology was more prevalent in the <65-year cohort than in the ≥65-year cohort for both the camrelizumab-rivoceranib (165 [86%] of 191 patients vs. 43 [53%] of 81 patients) and sorafenib (172 [82%] of 210 patients vs. 25 [42%] of 59 patients) treatment arms, respectively. Conversely, the hepatitis C virus (HCV) and nonviral etiologies were less prevalent in the <65-year cohort than in the ≥65-year cohort for both the camrelizumab-rivoceranib (HCV: 9 [5%] vs. 13 [16%]; nonviral: 17 [9%] vs. 21 [31%]) and sorafenib (HCV: 18 [9%] vs. 9 [15%]; nonviral: 20 [10%] vs. 25 [42%]) treatment arms, respectively.

PROs by Age Cohort

As of the August 2023 data cutoff for the final analysis, the median OS and median follow-up for OS in the camrelizumab-rivoceranib arm were 23.8 months and 22.1 months, respectively. In the sorafenib arm, the median OS was 15.2 months, with a median follow-up for OS of 14.9 months. Mean completion rates across PRO questionnaires from baseline through the ≥185-week study period ranged from 83.3% to 100% for patients in the camrelizumab-rivoceranib arm (n = 272) and from 50.0% to 100% of patients in the sorafenib arm (n = 271). Treatment with camrelizumab-rivoceranib was associated with numerically lower risks of deterioration in physical functioning (HR 0.775; 95% CI: 0.574–1.047) and role functioning (HR = 0.887; 95% CI: 0.663–1.186) compared with sorafenib. Patients treated with camrelizumab-rivoceranib had numerically lower risks of deterioration in fatigue (EORTC QLQ-C30; HR = 0.862; 95% CI: 0.661–1.124) and pain (EORTC QLQ-C30; HR = 0.828; 95% CI: 0.621–1.105) compared with sorafenib. Patients treated with sorafenib had a longer TTD in jaundice (EORTC QLQ-HCC18; median not reached vs. 12.9 months; HR = 1.830; 95% CI: 1.288–2.599; one-sided p = 0.0004) and a numerically lower risk of abdominal swelling (EORTC QLQ-HCC18; HR = 1.328; 95% CI: 0.875–2.015) compared with camrelizumab-rivoceranib.

As of the August 2023 data cutoff, mean completion rates across PRO questionnaires from baseline through ≥185 weeks of treatment for the respective camrelizumab-rivoceranib and sorafenib treatment arms were 96.8% and 98.9% for patients <65 years and 96.8% and 98.49% for patients ≥65 years. In the <65-year age cohort (Table 2), patients in the camrelizumab-rivoceranib arm had a numerically longer median TTD of fatigue measured by EORTC QLQ-C30 (HR = 0.79; 95% CI: 0.57–1.08; p = 0.07), and a shorter median TTD of jaundice measured by EORTC QLQ-HCC18 (HR = 1.61; 95% CI: 1.06–2.47; p = 0.01) compared with the sorafenib arm. In both treatment arms in this age cohort, the median TTD was not reached for appetite loss, assessed by EORTC QLQ-C30, and pain assessed by EORTC QLQ-HCC18.

In the ≥65-year age cohort (Table 2), patients in the camrelizumab-rivoceranib arm had a numerically shorter median TTD of fatigue measured by EORTC QLQ-C30 (HR = 1.01; 95% CI: 0.60–1.71; p = 0.48), a shorter median TTD of jaundice measured by EORTC QLQ-HCC18 (HR = 2.2; 95% CI: 1.15–4.05; p = 0.01), and a longer median TTD of pain measured by EORTC QLQ-HCC18 (HR = 0.50; 95% CI: 0.26–0.95; p = 0.02).

Table 1. Baseline characteristics (safety population)

	Age <65 years		Age ≥65 years		*p* value*
	camrelizumab-rivoceranib (*n* = 191)	sorafenib (*n* = 210)	camrelizumab-rivoceranib (*n* = 81)	sorafenib (*n* = 59)	
Age, years	52 (23–64)	52 (23–64)	70 (65–83)	70 (65–82)	<0.0001
Sex, *n* (%)					0.0896
Female	28 (15)	28 (13)	17 (21)	11 (19)	
Male	163 (85)	182 (87)	64 (79)	48 (81)	
Geographic region, *n* (%)					<0.0001
Asia	172 (90)	187 (89)	53 (65)	36 (61)	
Non-Asia	19 (10)	23 (11)	28 (35)	23 (39)	
BCLC stage, *n* (%)					0.0469
B	22 (12)	28 (13)	16 (20)	11 (19)	
C	169 (88)	182 (87)	65 (80)	48 (81)	
ECOG PS, *n* (%)					0.5774
0	88 (46)	89 (42)	32 (40)	26 (44)	
1	103 (54)	121 (58)	49 (60)	33 (56)	
AFP, *n* (%)					0.0286
<400 ng/mL	119 (62)	126 (60)	57 (70)	43 (73)	
≥400 ng/mL	72 (38)	84 (40)	24 (30)	16 (27)	
Extrahepatic metastasis or macrovascular invasion, *n* (%)					
Extrahepatic metastasis	134 (70)	143 (68)	41 (51)	36 (61)	0.0026
Macrovascular invasion	24 (13)	43 (20)	16 (20)	8 (14)	0.9058
Etiology, *n* (%)					<0.0001
HBV	165 (86)	172 (82)	43 (53)	25 (42)	
HCV	9 (5)	18 (9)	13 (16)	9 (15)	
Nonviral[a]	17 (9)	20 (10)	25 (31)	25 (42)	
Hepatic cirrhosis, *n* (%)	7 (4)	8 (4)	6 (7)	3 (5)	0.1836
Child-Pugh score in patients with hepatic cirrhosis, *n* (%)					
Class A (5 points)	4 (57)	6 (75)	6 (100)	3 (100)	
Class A (6 points)	3 (43)	2 (25)	0	0	

Data are median (range) or *n* (%). AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; PS, performance status. [a]Includes alcohol cirrhosis, genetic disorders, metabolic disorders (e.g., nonalcoholic steatohepatitis/alcoholic fatty liver disease), and others. *p values were calculated using the chi-square test for categorical variables and t test for continuous variables.

Although not statistically significant, the median TTD of appetite loss numerically favored the camrelizumab-rivoceranib arm compared with the sorafenib arm (median, 8.3 vs. 6.8 months; HR = 0.83; 95% CI: 0.48–1.46; $p = 0.26$).

Efficacy by Age Cohort

By Kaplan-Meier analyses, both age <65-year and ≥65-year cohorts showed similar patterns of deterioration-free survival with no significant differences between camrelizumab-rivoceranib and sorafenib treatment arms for GHS/HRQoL (Fig. 1a, b), physical functioning (Fig. 1c, d), and role functioning (Fig. 1e, f). The TTD in physical functioning for the ≥65-year age cohort Kaplan-Meier plot was the only one to show consistent separation between the camrelizumab-rivoceranib and sorafenib deterioration-free survival curves starting around 4 months (Fig. 1d). In the age <65-year cohort, patients in the camrelizumab-rivoceranib treatment arm had longer median PFS (5.6 vs. 3.7 months; HR = 0.56; 95%

Table 2. TTD in symptoms by age cohort

Median (95% CI)	TTD, months		HR (95% CI), *p* value
	Camrelizumab-rivoceranib	Sorafenib	
Age <65 years	*n* = 191	*n* = 210	
Fatigue[a]	13.3 (6.5–NR)	6.4 (3.6–NR)	0.79 (0.57–1.08), *p* = 0.07
Appetite loss[a]	NR (15.0–NR)	NR	0.88 (0.60–1.28), *p* = 0.25
Jaundice[b]	20.2 (12.9–NR)	NR (15.7–NR)	1.61 (1.05–2.47), *p* = 0.01
Pain[b]	NR	NR (11.1–NR)	1.11 (0.75–1.66), *p* = 0.30
Age ≥65 years	*n* = 81	*n* = 61	
Fatigue[a]	3.7 (1.9–10.2)	4.6 (1.8–NR)	1.01 (0.60–1.71), *p* = 0.48
Appetite loss[a]	8.3 (4.6–17.4)	6.8 (2.8–12.1)	0.83 (0.48–1.46), *p* = 0.26
Jaundice[b]	6.7 (4.6–9.4)	11.1 (6.4–NR)	2.15 (1.15–4.05), *p* = 0.01
Pain[b]	12.9 (8.3–NR)	6.8 (3.8–NR)	0.50 (0.26–0.95), *p* = 0.02

Data are median (95% CI). EORTC, European Organization for Research and Treatment of Cancer; NR, not reached; QLQ-C30, Quality-of-Life Questionnaire-Core 30; QLQ-HCC18, Quality-of-Life Questionnaire Hepatocellular Carcinoma 18; TTD, time to deterioration. [a]EORTC QLQ-C30. [b]EORTC QLQ-HCC18.

CI: 0.44–0.71; $p < 0.0001$; Fig. 2a) and median OS (23.8 vs. 15.6 months; HR = 0.65; 95% CI: 0.51–0.84; $p = 0.0003$; Fig. 2c) compared with sorafenib. Patients aged <65 years in the respective camrelizumab-rivoceranib and sorafenib treatment arms had 1-year PFS of 28.6% versus 13.8% (Fig. 2a) and 1-year OS of 78.9% versus 60.9% (Fig. 2c). Similarly, in the age ≥65-year cohort, patients in the camrelizumab-rivoceranib treatment arm had longer median PFS (5.7 vs. 3.6 months; HR = 0.49; 95% CI: 0.32–0.75; $p = 0.0005$; Fig. 2b) and median OS (23.9 vs. 13.6 months; HR = 0.57; 95% CI: 0.37–0.89; $p = 0.0059$; Fig. 2d) compared with sorafenib. Patients aged ≥65 years in the respective camrelizumab-rivoceranib and sorafenib treatment arms had 1-year PFS of 36.7% versus 8.8% (Fig. 2b) and 1-year OS of 71.2% versus 61.0% (Fig. 2d).

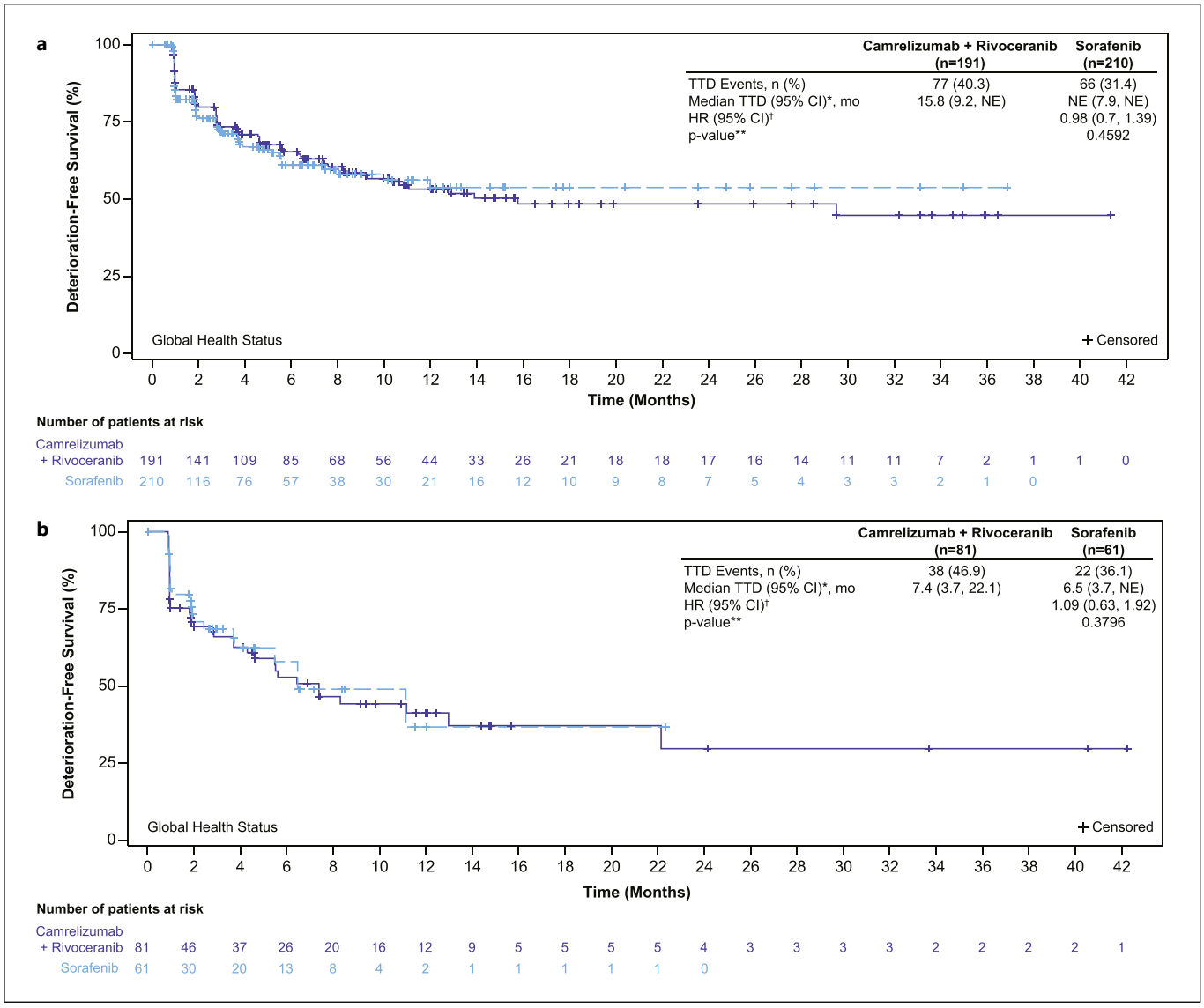
Safety by Age Cohort

In the age <65-year cohort, the three most common grade 3–4 TRAEs were hypertension (38.2%), aspartate aminotransferase (AST) increased (14.7%), and alanine aminotransferase increased (12.6%) in the camrelizumab-rivoceranib arm, and palmar-plantar erythrodysesthesia syndrome (16.2%), hypertension (12.4%), gamma-glutamyl transferase increased (7.1%) in the sorafenib arm (Table 3). In the age ≥65-year cohort, the three most common grade 3–4 TRAEs were hypertension (38.3%), AST increased (24.7%), and alanine aminotransferase increased (17.3%) in the camrelizumab-rivoceranib arm, and hypertension (23.7%), palmar-plantar erythrodysesthesia syndrome (15.3%), and AST and gamma-glutamyl transferase increased (both 8.5%) in the sorafenib arm.

Camrelizumab discontinuation due to TRAEs was reported in 29 (15.2%) of patients in the age <65-year cohort and 29 (35.8%) patients in the age ≥65-year cohort. Rivoceranib discontinuation due to TRAEs was reported in 32 (16.8%) of patients in the age <65-year cohort and 24 (29.6%) patients in the age ≥65-year cohort. Sorafenib discontinuation due to TRAEs was reported in 16 (7.6%) in the age <65-year cohort and 6 (10.2%) patients in the age ≥65-year cohort.

Discussion

To evaluate the potential impact of older age on outcomes in the CARES-310 trial, we performed a post hoc analysis of PROs, survival, and safety data for adults <65 years and ≥65 years randomized to camrelizumab-rivoceranib or sorafenib treatment for uHCC. PRO data in adults <65 years and ≥65 years demonstrated clinically meaningful benefits with camrelizumab-rivoceranib compared with sorafenib in key aspects of the patient experience such as HRQoL, functioning, pain, and fatigue. Patients in both the <65-year and ≥65-year age cohorts had improved PFS and OS with camrelizumab-rivoceranib compared with sorafenib, consistent with the findings of the primary analysis [8]. In both age cohorts, although patients treated with camrelizumab-rivoceranib had higher rates



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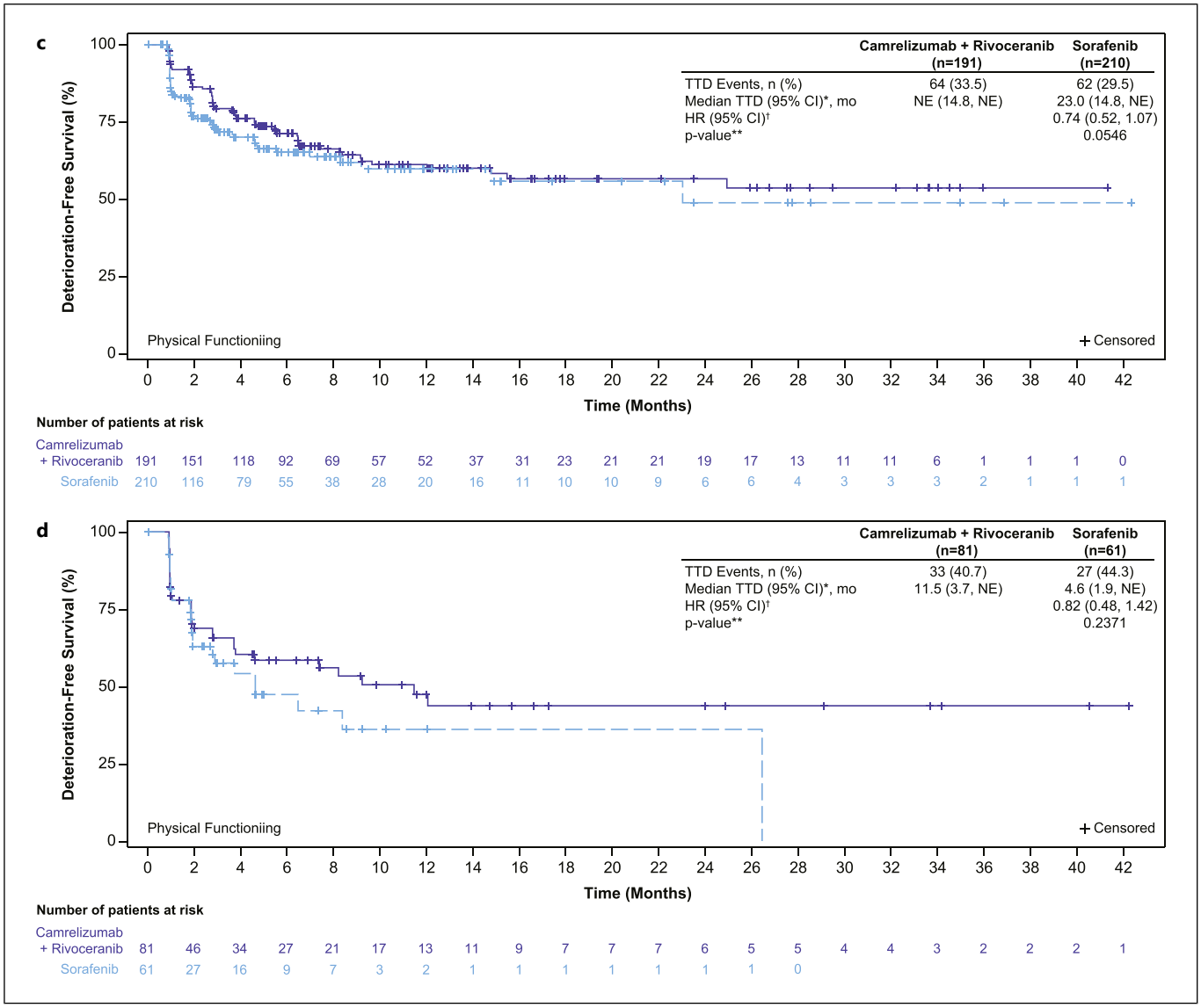
of some TRAEs compared with sorafenib, the combination therapy did not adversely impact HRQoL as indicated by comparable PROs.

Considering the limitations of cross-trial comparisons, the PRO results from the CARES-310 OS primary analysis [8] align with those reported in other first-line phase 3 trials in patients with uHCC (Table 4). The IMbrave150 trial (NCT03434379) of atezolizumab-bevacizumab versus sorafenib used the EORTC QLQ-C30 to assess PROs [15–17]. For QOL, the median TTD was 11.2 months for atezolizumab-bevacizumab versus 3.6 months for sorafenib (HR = 0.63; 95% CI: 0.46–0.85). For physical functioning, the median TTD was 13.1 versus 4.9 months for atezolizumab-bevacizumab versus sorafenib (HR = 0.53; 95% CI: 0.39–0.73), respectively. For role functioning, the median TTD was 9.1 versus 3.6 months for atezolizumab-bevacizumab versus sorafenib, respectively (HR = 0.62; 95% CI: 0.46–0.84). A post hoc analysis of IMbrave150 evaluated results in adults aged 18 to <65 years, ≥65 to <75 years, and >75 years [18]. Similar to the CARES-310 post hoc analysis, hepatitis B virus infection was more common in the 18 to <65-year age cohort than in the older age cohorts in IMbrave150. For all three age cohorts, patients in the atezolizumab-bevacizumab arm compared with the sorafenib arm had longer TTDs for



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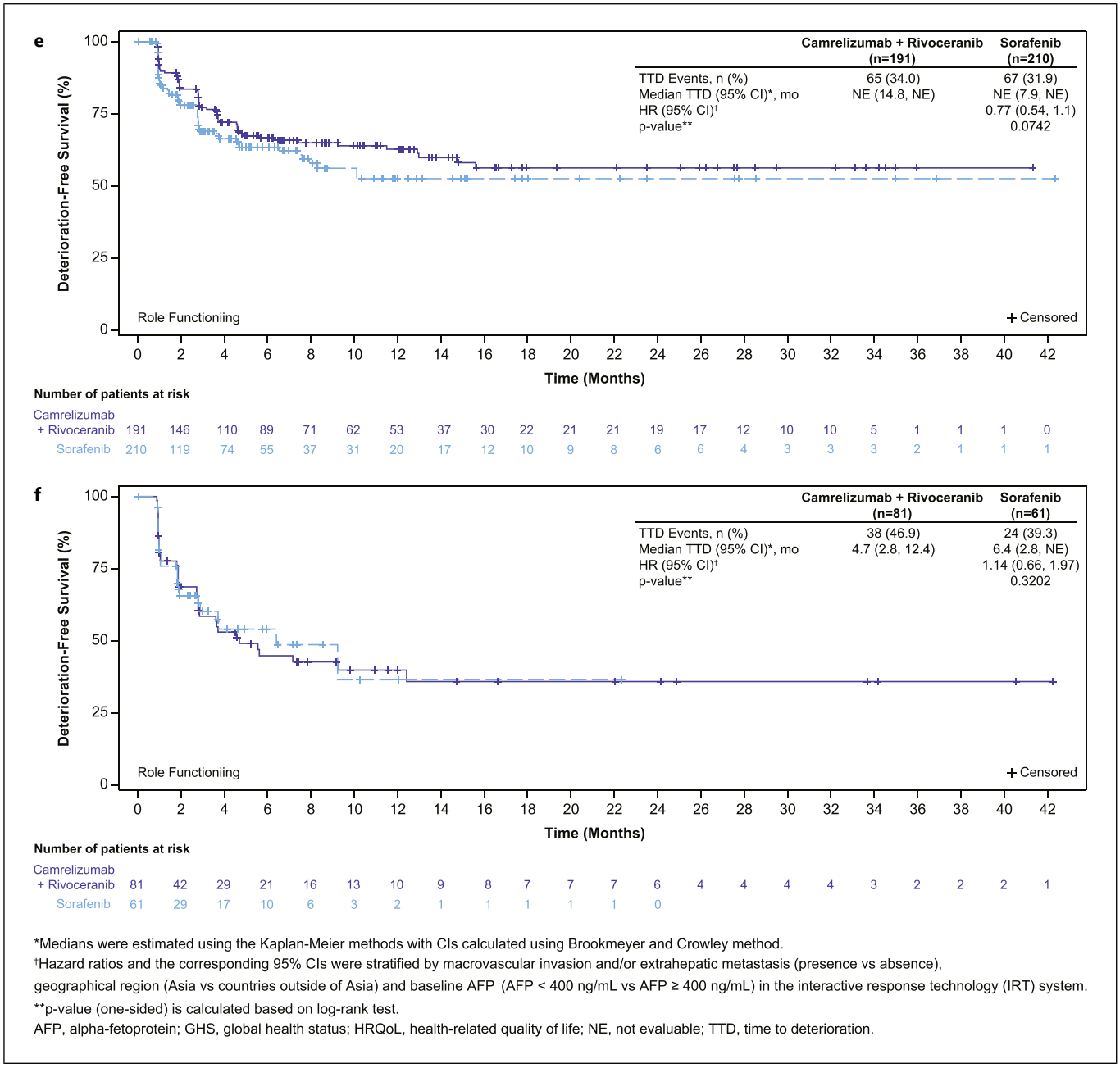
PROs assessed by EORTC QLQ-C30 and EORTC QLQ-HCC18.

The HIMALAYA (NCT03298451) trial compared tremelimumab-durvalumab (STRIDE regimen) versus sorafenib in terms of superiority and durvalumab single-agent versus sorafenib in terms of non-inferiority [19, 23, 24]. For GHS or QOL evaluated by EORTC QLQ-30, the median TTD was 7.5 months (HR = 0.76; 95% CI: 0.61–0.96), 7.4 months (HR = 0.77; 95% CI: 0.62–0.96), and 5.7 months (HR not reported) for STRIDE, durvalumab, and sorafenib, respectively [20]. For physical functioning and role functioning, the respective median TTDs were 12.9 months (HR = 0.68; 95% CI: 0.53–0.87) and 9.3 months (HR = 0.70; 95% CI: 0.55–0.88) for STRIDE, 14.1 months (HR = 0.66; 95% CI: 0.51–0.83) for durvalumab, and 7.4 months (HR not reported) and 7.1 months (HR not reported) for sorafenib.

The CheckMate 9DW (NCT04039607) trial compared nivolumab-ipilimumab with investigator's choice of lenvatinib or sorafenib monotherapy [21]. Compared with the monotherapy arm, patients in the combination arm had reduced risk of HRQoL deterioration evaluated by Functional Assessment of Cancer Therapy Hepatobiliary Cancer (FACT-Hep) total score (HR = 0.69; 95% CI: 0.55–0.87) and FACT-Hep hepatobiliary cancer subscale (HR = 0.71; 95% CI: 0.55–0.92), and reported a

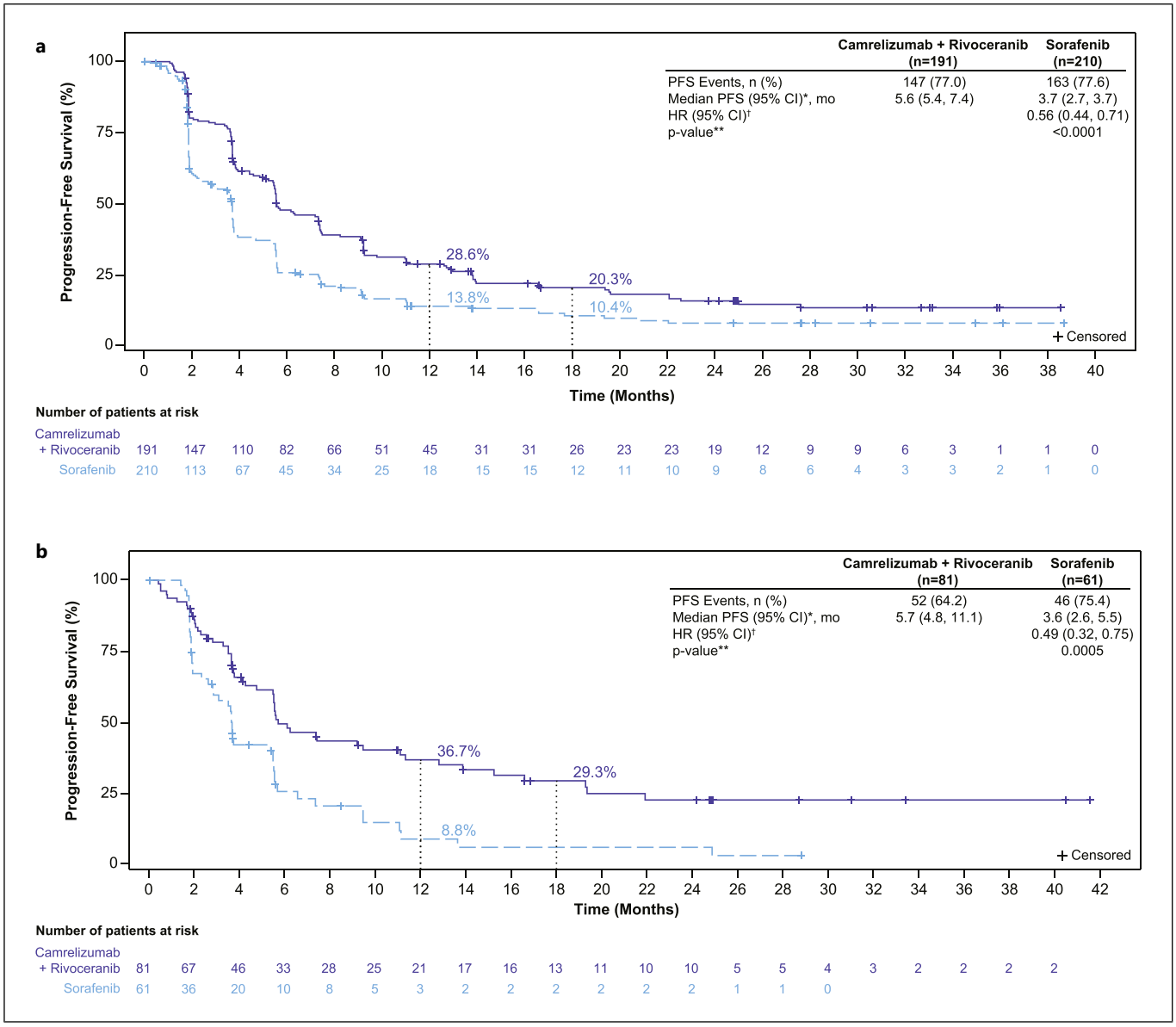


*Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
†Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence), geographical region (Asia vs countries outside of Asia) and baseline AFP (AFP < 400 ng/mL vs AFP ≥ 400 ng/mL) in the interactive response technology (IRT) system.
**p-value (one-sided) is calculated based on log-rank test.
AFP, alpha-fetoprotein; GHS, global health status; HRQoL, health-related quality of life; NE, not evaluable; TTD, time to deterioration.

Fig. 1. Kaplan-Meier plots of TTD of GHS/HRQoL, physical functioning, and role functioning by age cohort. **a** GHS/HRQoL <65 years. **b** GHS/HRQoL ≥65 years. **c** Physical functioning <65 years. **d** Physical functioning ≥65 years. **e** Role functioning <65 years. **f** Role functioning ≥65 years.

lesser impact from side effects (odd ratio 0.56; 95% CI: 0.44–0.71) [22].

The CARES-310 trial used the EORTC QLQ-C30 and the EORTC QLQ-HCC18 scales to assess QOL of patients with HCC [8]. The median TTD of GHS was 11.2 months (95% CI: 7.6–not reached) in the camrelizumab-rivoceranib treatment arm and not reached (95% CI: 7.4–not reached) in the sorafenib arm (HR = 1.02; 95% CI: 0.77–1.36). For physical functioning, median TTD was not reached in both treatment arms and there was no significant difference in risk of deterioration with camrelizumab-rivoceranib (HR =



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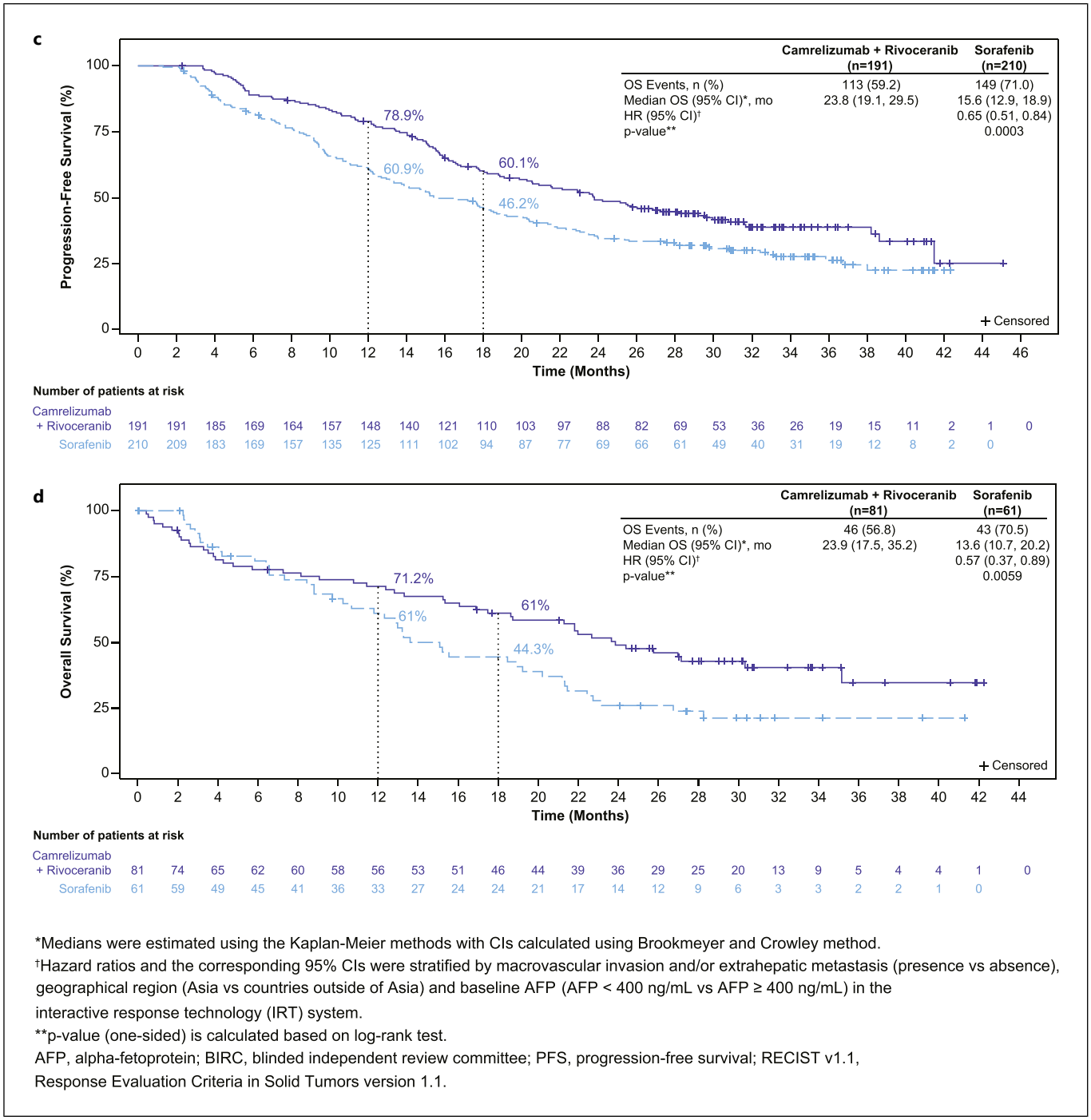
0.78; 95% CI: 0.58–1.06). For role functioning, the median TTD was not reached (95% CI: 11.5–not reached) for camrelizumab-rivoceranib and was 10.1 months (95% CI: 7.6–not reached) for sorafenib (HR = 0.88; 95% CI: 0.66–1.18). Compared with sorafenib, camrelizumab-rivoceranib showed an improvement in most symptoms and nonstatistically significant numerical trends in improved physical and role functioning.

This post hoc analysis of CARES-310 PRO data was not powered to detect significant differences between the two age cohorts. Thus, the reported *p* values are nominal. It is important to note that the age <65-year cohort was nearly 3 times the size of the age ≥65-year cohort (401 vs. 140 patients, respectively). Another study limitation is that there were imbalances in PRO survey completion rates between the treatment groups (minimum completion rate: 50% with sorafenib vs. 83% with camrelizumab-rivoceranib) that could have affected overall estimates.

The analysis of CARES-310 PRO data for the <65 and ≥65-year cohorts revealed clinically meaningful benefits



*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), geographical region (Asia vs countries outside of Asia) and baseline AFP (AFP < 400 ng/mL vs AFP ≥ 400 ng/mL) in the interactive response technology (IRT) system.
**p-value (one-sided) is calculated based on log-rank test.
AFP, alpha-fetoprotein; BIRC, blinded independent review committee; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Fig. 2. Kaplan-Meier plots of PFS and OS by age cohort. **a** PFS age <65 years. **b** PFS age ≥65 years. **c** OS age <65 years. **d** OS age ≥65 years.

with camrelizumab-rivoceranib versus sorafenib in key aspects of the patient experience such as HRQoL, functioning, pain, and fatigue. Although patients treated with camrelizumab-rivoceranib had higher rates of some TRAEs versus sorafenib, this did not adversely impact their HRQoL as indicated by comparable PRO results. These PRO results provide evidence supporting the favorable clinical benefit of camrelizumab-rivoceranib

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Table 3. Most common TRAEs[a] by age cohort

n (%)	Age <65 years				Age ≥ 65 years			
	all grade		grade 3–4		all grade		grade 3–4	
	camrelizumab-rivoceranib (*n* = 191)	sorafenib (*n* = 210)	camrelizumab-rivoceranib (*n* = 191)	sorafenib (*n* = 210)	camrelizumab-rivoceranib (*n* = 81)	sorafenib (*n* = 59)	camrelizumab-rivoceranib (*n* = 81)	sorafenib (*n* = 59)
Hypertension	138 (72.3)	89 (42.4)	73 (38.2)	26 (12.4)	51 (63.0)	28 (47.5)	31 (38.3)	14 (23.7)
AST increased	104 (54.5)	82 (39.0)	28 (14.7)	9 (4.3)	46 (56.8)	19 (32.2)	20 (24.7)	5 (8.5)
Proteinuria	104 (54.5)	59 (28.1)	11 (5.8)	3 (1.4)	31 (38.3)	15 (25.4)	5 (6.2)	2 (3.4)
ALT increased	92 (48.2)	67 (31.9)	24 (12.6)	7 (3.3)	38 (46.9)	14 (23.7)	14 (17.3)	1 (1.7)
Platelet count decreased	92 (48.2)	76 (36.2)	21 (11.0)	4 (1.9)	34 (42.0)	14 (23.7)	12 (14.8)	0
Blood bilirubin increased	78 (40.8)	60 (28.6)	13 (6.8)	3 (1.4)	39 (48.1)	15 (25.4)	11 (13.6)	1 (1.7)
PPE syndrome	75 (39.3)	134 (63.8)	21 (11.0)	34 (16.2)	27 (33.3)	30 (50.8)	12 (14.8)	9 (15.3)
Diarrhea	65 (34.0)	93 (44.3)	3 (1.6)	14 (6.7)	19 (23.5)	13 (22.0)	3 (3.7)	0
Neutrophil count decreased	62 (32.5)	25 (11.9)	13 (6.8)	3 (1.4)	13 (16.0)	3 (5.1)	4 (4.9)	0
Reactive capillary endothelial proliferation	61 (31.9)	0	4 (2.1)	0	23 (28.4)	0	4 (4.9)	0
White blood cell count decreased	61 (31.9)	32 (15.2)	7 (3.7)	4 (1.9)	14 (17.3)	7 (11.9)	1 (1.2)	0
GGT increased	46 (24.1)	42 (20.0)	16 (8.4)	15 (7.1)	21 (25.9)	8 (13.6)	13 (16.0)	5 (8.5)
Hypothyroidism	42 (22.0)	14 (6.7)	0	0	16 (19.8)	3 (5.1)	0	0
Fatigue	35 (18.3)	18 (8.6)	4 (2.1)	1 (0.5)	21 (25.9)	3 (5.1)	4 (4.9)	0
Bilirubin conjugated increased	31 (16.2)	24 (11.4)	8 (4.2)	6 (2.9)	15 (18.5)	12 (20.3)	5 (6.2)	2 (3.4)
Rash	33 (17.3)	42 (20.0)	2 (1.0)	1 (0.5)	12 (14.8)	8 (13.6)	4 (4.9)	2 (3.4)
Hypophosphatemia	16 (8.4)	34 (16.2)	1 (0.5)	12 (5.7)	2 (2.5)	6 (10.2)	1 (1.2)	0
Lipase increased	16 (8.4)	8 (3.8)	12 (6.3)	4 (1.9)	4 (4.9)	4 (6.8)	1 (1.2)	1 (1.7)
Asthenia	15 (7.9)	1 (0.5)	12 (5.7)	0	17 (21.0)	3 (5.1)	2 (2.5)	0
Alopecia	3 (1.6)	46 (21.9)	0	0	1 (1.2)	6 (10.2)	0	0

Data are *n* (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase increased; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event. [a]Defined as all-grade adverse events reported in ≥20% of patients and grade 3–4 adverse events in >5% of patients.

Table 4. Summary of PRO outcomes reported in CARES-310, IMbrave150, and HIMALAYA studies

	CARES-310 (NCT03764293) [8]	IMbrave150 (NCT03434379) [16–18]	HIMALAYA (NCT03298451) [19, 20]	CheckMate 9DW (NCT04039607) [21, 22]
Study design	Randomized (1:1), open-label, phase 3 trial	Randomized (2:1), open-label, phase 3 trial	Randomized (1:1:1), open-label, phase 3 trial	Randomized (1:1), open-label, phase 3 trial
Key inclusion criteria	Age ≥18 years HCC (confirmed histologically or cytologically)	Age ≥18 years Locally advanced metastatic and/or uHCC (confirmed histologically, cytologically, or clinical features per AASLD criteria)	Age ≥18 years HCC (confirmed histologically or cytologically)	Age ≥18 years Advanced HCC (histologically confirmed) ineligible for curative surgical or locoregional therapy or progressed after such therapy
	BCLC stage B or C disease not amenable to or progressing after surgical or locoregional therapy	No previous systemic therapy for liver cancer	Ineligible for locoregional therapy	No previous systemic therapy for advanced HCC
	No previous systemic therapy ≥1 measurable lesion per RECIST v1.1	Measurable disease per RECIST v1.1 not amenable to curative or locoregional therapies or progressed despite them	No prior systemic therapy ≥1 measurable lesion per RECIST v1.1	≥1 measurable lesion per RECIST v1.1
	Child-Pugh class A liver function ECOG PS 0–1	Child-Pugh class A liver function ECOG PS 0–1	Child-Pugh class A liver function ECOG PS 0–1	Child-Pugh score of 5 or 6 ECOG PS 0–1
Treatment groups	Camrelizumab plus rivoceranib (*n* = 272) vs. sorafenib (*n* = 271)	Atezolizumab plus bevacizumab (*n* = 336) vs. sorafenib (*n* = 165)	Tremelimumab plus durvalumab (*n* = 393) vs. durvalumab (*n* = 389) vs. sorafenib (*n* = 389)	Nivolumab plus ipilimumab (*n* = 335) vs. investigator's choice of lenvatinib or sorafenib (*n* = 333)
Primary endpoints	PFS and OS	PFS and OS	OS for tremelimumab plus durvalumab vs. sorafenib	OS
PRO measures	GHS, function, and QOL: EORTC QLQ-C30 Symptoms: EORTC QLQ-C30, EORTC QLQ-HCC18	EORTC QLQ-C30	EORTC QLQ-C30	QOL: FACT-Hep total score and HCS, and EQ-5D-3L utility index Symptom TTD: HCS FACT-Hep
Selected PRO results (TTD), months	GHS: 11.2 (7.6–NR) vs. NR (7.4–NR) (HR = 1.02; 95%: CI, 0.77–1.36)	QOL: 11.2 (6.0–NE) vs. 3.6 (3.0–7.0) (HR = 0.63; 95% CI: 0.46–0.85)	GHS/QOL: 7.5 (5.8–10.8) vs. 7.4 (5.7–9.3) vs. 5.7 (4.8–7.4) (combination HR = 0.76; 95% CI: 0.61–0.96)	QOL total score: favored combination therapy (HR = 0.71; 95% CI: 0.55–0.92)
	Physical functioning: NR (12.0–NR) vs. NR (8.3–NR) (HR = 0.78; 95% CI: 0.58–1.06)	Physical functioning: 13.1 (9.7–NE) vs. 4.9 (3.5–6.2) (HR = 0.53; 95% CI: 0.39–0.73)	Physical functioning: 12.9 (9.2–16.8) vs. 14.1 (9.2–18.5) vs. 7.4 (5.7–10.2) (combination HR = 0.68; 0.53–0.87)	QOL HCS: favored combination therapy (HR = 0.71; 95% CI: 0.55–0.92)
	Role functioning: NR (11.5–NR) vs. 10.1 (7.6–NR) (HR = 0.88; 95% CI: 0.66–1.18)	Role functioning: 9.1 (6.5–NE) vs. 3.6 (2.2–6.0) (HR = 0.62; 95% CI: 0.46–0.84)	Role functioning: 9.3 (7.4–13.9) vs. 9.1 (6.3–11.3) vs. 7.1 (5.6–9.2) (combination HR = 0.70; 0.55–0.88)	Median symptom TTD, months: 2.6 (95% CI: 2.0–3.9) vs. 2.1 (95% CI: 1.6–2.8) (HR = 0.76; 95% CI: 0.62–0.93)

Data are median (95% CI) or HR (95% CI). AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-3L, European Quality-of-Life 5 Dimensions 3 Level; FACT-Hep, Functional Assessment of Cancer Therapy Hepatobiliary Cancer; GHS, global health status; HCC, hepatocellular carcinoma; HCS, hepatobiliary cancer subscale; NE, could not be evaluated; NR, not reached; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; PS, performance status; QLQ-HCC18, Quality-of-Life Questionnaire Hepatocellular Carcinoma 18; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TTD, time to deterioration; v, version.

treatment in adults, including those ≥65 years, with uHCC who have not received prior systemic therapy. Because many patients with HCC are >60 years, we encourage inclusion of this type of analysis as a secondary objective in future HCC clinical trials.

Acknowledgments

We thank all the patients and their caregivers, and all the investigators and personnel at study sites for participating in the CARES-310 study. Medical writing support was provided by Monica Nicosia and Olivia Adams (Phillips Group Oncology Communications Inc.) funded by Elevar Therapeutics.

Statement of Ethics

As noted in the published primary analysis [8], Local or Central Institutional Review Boards or Ethics Committees reviewed and approved the CARES-310 study protocol and the study was in compliance with the ethical principles of the Declaration of Helsinki, the guidelines of Good Clinical Practice, and local regulatory requirements. All patients provided written informed consent to participate in the CARES-310 study.

Conflict of Interest Statement

Stephen Lam Chan declares grants or contracts from MSD, Eisai, Ipsen, Sirtex, and Zai Lab – payments were made to institution; consulting fees from AstraZeneca, MSD, Eisai, Elevar, Roche, Ipsen, and Hengrui – payments were made to individual; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Eisai, Roche, Ipsen, and MSD – payments were made to individual; and support for attending meetings and/or travel from Eisai, Roche, Ipsen, and Novartis – payments were made to institution. Ahmed Omar Kaseb declares consulting fees from Roche/Genentech, Merck, BMS, Eisai, and Exelixis; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche/Genentech, Merck, BMS, Eisai, and Exelixis. Laura Alexander, Xianzhang Meng, and Kristin Ryan declare employment with Elevar Therapeutics. Wei Shi declares employment with Jiangsu Hengrui Pharmaceuticals. Arndt Vogel declares consulting fees from Roche, AstraZeneca, Boehringer Ingelheim, Ipsen, Incyte, Cogent, Eisai, Zymeworks, Biologix, BMS, Terumo, Elevar, Servier, MSD, Tahio, Jazz Pharmaceuticals, Medivir, AbbVie, Tyra, Falk, Janssen, and Lilly; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, AstraZeneca, Boehringer Ingelheim, Ipsen, Incyte, Cogent, Eisai, Zymeworks, Biologix, BMS, Terumo, Elevar, Servier, MSD, Tahio, Jazz Pharmaceuticals, Medivir, AbbVie, Tyra, Falk, Janssen, and Lilly; support for attending meetings and/or travel from Roche, MSD, and Astellas; and participation on a data safety monitoring board or advisory board for Roche, AstraZeneca, Boehringer Ingelheim, Ipsen, Incyte, Cogent, Eisai, Zymeworks, Biologix, BMS, Terumo, Elevar, Servier, MSD, Tahio, Jazz Pharmaceuticals, Medivir, AbbVie, Tyra, Falk, Janssen, and Lilly. Stephen Lam Chan and Arndt Vogel were members of the journal's Editorial Board at the time of submission.

Funding Sources

The CARES-310 study was sponsored by Jiangsu Hengrui Pharmaceuticals and was co-funded by Elevar Therapeutics. For the report of this post hoc analysis, Elevar Therapeutics collaborated with academic authors regarding the study design, data collection, data analysis, data interpretation, and writing.

Author Contributions

S.L.C. contributed to the study design. X.M. was responsible for directing statistical analysis. The manuscript was drafted by S.L.C., A.O.K., L.A., K.R., W.S., and A.V. S.L.C. and A.V. directly accessed and verified the underlying data reported in this manuscript. All authors participated in data interpretation, reviewed and revised the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon request.

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