Patient-reported outcomes (PROs) <65 or ≥65 years old from CARES-310 camrelizumab + rivoceranib vs sorafenib as first-line treatment for patients with unresectable hepatocellular carcinoma

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Abstract # 456

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BACKGROUND

- CARES-310 (NCT03764293) evaluated the combination of the PD-1 inhibitor, camrelizumab (cam), and the VEGFR-2 tyrosine kinase inhibitor, rivoceranib (rivo), compared to standard of care at the time of study initiation, sorafenib, for the treatment of unresectable hepatocellular carcinoma.
- This combination significantly improved overall survival (OS) and progression-free survival (PFS) compared to sorafenib:
  - Median OS: 22.1 months versus 15.2 months; HR 0.62 (95% CI, 0.49, 0.80; one-sided p<0.0001)
  - Median PFS: 5.6 months versus 3.7 months; HR 0.54 (95% CI, 0.44, 0.67; one-sided p<0.0001)
- The most common grade 3 treatment-related adverse events observed with cam + rivo were hypertension (37.5%), hepatotoxicity (33%) and increased AST (16.5%) vs palmar-plantar erythrodysesthesia syndrome (15.2%) and hepatotoxicity (12%) with sorafenib.
- Herein, we present PROs stratified by age: <65 years old (yo) or ≥65 yo from the CARES-310 trial.

METHODS

- In this randomized, open-label, international, multicenter, phase 3 study, patients were randomized 1:1 to receive cam 200 mg IV Q2W + rivo 250 mg PO QD (n=272) or sorafenib 400 mg PO BID (n=271).
- Patients completed the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires at baseline, each visit, and post-last-dose follow-up periods.
- Endpoints included:
  - Time to deterioration (TTD) with a ≥10-point decrease from baseline of patient-reported quality of life (QoL), physical functioning, role functioning, and patient-reported symptoms
  - OS
  - PFS per blinded independent review committee (BIRC)
  - Safety

RESULTS

- As of 8 February 2022, mean completion rates across questionnaires were 98.6% and 96.8% for cam + rivo and 98.9% and 98.8% for sorafenib in the <65 and ≥65 yo age groups, respectively, from baseline through ≥121 weeks of treatment.

Table 1: Baseline Characteristics (Safety Population)

Characteristic	<65 years old		≥65 years old	
	Cam + Rivo (n=191)	Sorafenib (n=210)	Cam + Rivo (n=81)	Sorafenib (n=59)
Median age, years	52.0	52.5	70.0	70.0
Male sex, n (%)	163 (85.3)	182 (86.7)	64 (79.0)	48 (81.4)
Geographic region, n (%)				
Asia	172 (90.1)	187 (89.0)	53 (65.4)	36 (61.0)
Non-Asia	19 (9.9)	23 (11.0)	28 (34.6)	23 (39.0)
BCLC stage, n (%)				
B (middle stage)	22 (11.5)	28 (13.3)	16 (19.8)	11 (18.6)
C (advanced stage)	169 (88.5)	182 (86.7)	65 (80.2)	48 (81.4)
Child-Pugh class, n (%)				
A5	170 (89.0)	175 (83.3)	66 (81.5)	53 (89.8)
A6	21 (11.0)	35 (16.7)	15 (18.5)	6 (10.2)
ECOG PS, n (%)				
0	88 (46.1)	89 (42.4)	32 (39.5)	26 (44.1)
1	103 (53.9)	121 (57.6)	49 (60.5)	33 (55.9)
ALBI grade, n (%)				
1	148 (77.5)	162 (77.1)	52 (64.2)	44 (74.6)
2	43 (22.5)	49 (22.9)	29 (35.8)	15 (25.4)
AFP ≥400 ng/mL, n (%)	72 (37.7)	84 (40.0)	24 (29.6)	16 (27.1)
MVI and/or EHS, n (%)				
MVI	24 (12.6)	43 (20.5)	16 (19.8)	8 (13.6)
EHS	134 (70.2)	143 (68.1)	41 (50.6)	36 (61.0)
Etiology, n (%)				
HBV	165 (86.4)	172 (81.9)	43 (53.1)	25 (42.4)
HCV	9 (4.7)	18 (8.6)	13 (16.0)	9 (15.3)
Non-viral[a]	17 (8.9)	20 (9.5)	25 (30.9)	25 (42.4)

[a]Includes alcohol cirrhosis, genetic, metabolic disorders (such as nonalcoholic steatohepatitis/alcoholic fatty liver disease) and others

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV, hepatitis B; HCV, hepatitis C; MVI, microvascular invasion

RESULTS

- Cam + rivo demonstrated improved TTD in fatigue measured by EORTC-QLQ-C30 in the <65 yo group (**Table 2**).
- In the ≥65 yo group, cam + rivo demonstrated significantly longer median TTD of pain measured by EORTC-QLQ-HCC18 and QLQ-C30 (**Table 3**).
- The median TTD of appetite loss was numerically favorable for cam + rivo in the ≥65 yo group (**Table 3**).
- Median global health status/health-related QoL (GHS/HRQoL) in the ≥65 yo group favored cam + rivo (**Table 3**).
- In both the <65 yo and ≥65 yo age groups, median TTD for jaundice was significant for sorafenib (**Tables 2 and 3**).
- The most common all grade treatment-related adverse events in both the <65 yo and ≥65 yo age groups receiving cam + rivo were hypertension, increased AST, proteinuria, increased ALT, decreased platelet count, and increased blood bilirubin (**Figure 6**).
- The most common all grade treatment-related adverse events in both the <65 yo and ≥65 yo age groups receiving sorafenib were palmar-plantar erythrodysesthesia and hypertension (**Figure 6**).

Table 2: Time to Deterioration in Symptoms (<65 years old)

Scale (Questionnaire)	Median TTD (Months)		HR (95% CI); p-value[c]
	Cam + Rivo (n=191)	Sorafenib (n=210)	
GHS/HRQoL[a]	NR	NR	0.97 (0.69, 1.38); p=0.44
Fatigue[a]	14.8	6.4	0.76 (0.55, 1.05); p=0.05
Pain[a]	NR	12.9	0.91 (0.64,1.30); p=0.30
Appetite loss[a]	NR	NR	0.86 (0.59,1.25); p=0.21
Fatigue[b]	NR	5.6	0.73 (0.53,1.03); p=0.03
Jaundice[b]	15.9	NR	1.78 (1.14, 2.75); p=0.01
Pain[b]	NR	NR	1.10 (0.73, 1.63); p=0.33

[a]EORTC QLQ-C30
[b]EORTC QLQ-HCC18
[c]One-sided p-value calculated based on log-rank test
NR, not reached

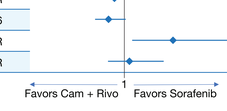


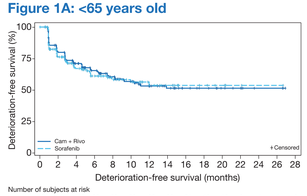
Table 3: Time to Deterioration in Symptoms (≥65 years old)

Scale (Questionnaire)	Median Time to Deterioration (Months)		HR (95% CI); p-value[c]
	Cam+ Rivo (n=81)	Sorafenib (n=61)	
HRQoL/GHS[a]	7.4	6.5	1.09 (0.61, 1.92); p=0.39
Fatigue[a]	3.7	4.6	1.01 (0.60, 1.71); p=0.48
Pain[a]	11.2	4.6	0.56 (0.32, 0.98); p=0.02
Appetite loss[a]	8.3	6.8	0.80 (0.45, 1.41); p=0.22
Fatigue[b]	3.7	4.4	0.92 (0.54, 1.55); p=0.37
Jaundice[b]	6.7	11.1	2.0 (1.06, 3.81); p=0.02
Pain[b]	12.9	6.8	0.47 (0.24, 0.91); p=0.01

[a]EORTC QLQ-C30
[b]EORTC QLQ-HCC18
[c]One-sided p-value calculated based on log-rank test

Figure 1: Time to Deterioration in Quality of Life

Figure 1A: <65 years old

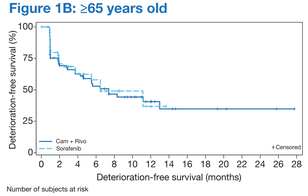


Number of subjects at risk

Cam + Rivo 191	141	109	85	68	56	39	29	21	16	10	8	4	4	0
Sorafenib 210	116	76	57	38	30	18	14	8	7	5	2	1	1	0

<65 years old	Cam + Rivo (n=191)	Sorafenib (n=210)
TTD events, n (%)	74 (38.7)	66 (31.4)
Median[a] TTD, months (95% CI)	NE (9.2, NE)	NE (7.9, NE)
Hazard ratio[b] (95% CI); p value[c]	0.97 (0.69, 1.38); p=0.4415	

Figure 1B: ≥65 years old



Number of subjects at risk

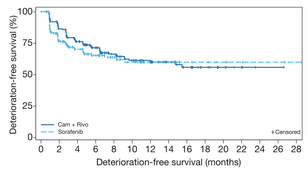
Cam + Rivo 81	46	37	26	20	16	9	6	4	4	3	2	2	1	0
Sorafenib 61	30	20	13	8	4	2	0							

≥65 years old	Cam + Rivo (n=81)	Sorafenib (n=61)
TTD events, n (%)	37 (45.7)	22 (36.1)
Median[a] TTD, months (95% CI)	7.4 (3.7, NE)	6.5 (3.7, NE)
Hazard ratio[b] (95% CI); p value[c]	1.08 (0.62, 1.92); p=0.3898	

[a]Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
[b]Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence), geographical region (Asia vs outside of Asia) and baseline AFP (AFP <400 ng/mL vs AFP ≥400 ng/mL) in the interactive response technology system.
[c]One sided p value is calculated based on log-rank test.
NE, not evaluable

Figure 2: Time to Deterioration in Physical Functioning

Figure 2A: <65 years old

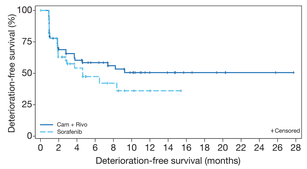


Number of subjects at risk

Cam + Rivo 191	151	118	92	69	57	48	32	24	16	9	5	2	2	0
Sorafenib 210	116	79	55	38	28	17	14	8	7	5	3	2	2	1

<65 years old	Cam + Rivo (n=191)	Sorafenib (n=210)
TTD events, n (%)	63 (33.0)	60 (28.6)
Median[a] TTD, months (95% CI)	NE (14.8, NE)	NE (NE, NE)
Hazard ratio[b] (95% CI); p value[c]	0.77 (0.54, 1.12); p=0.0849	

Figure 2B: ≥65 years old



Number of subjects at risk

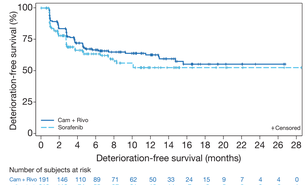
Cam + Rivo 81	46	34	27	21	17	10	9	6	5	4	2	2	1	0
Sorafenib 61	27	16	9	7	3	2	1	0						

≥65 years old	Cam + Rivo (n=81)	Sorafenib (n=61)
TTD events, n (%)	31 (38.3)	26 (42.6)
Median[a] TTD, months (95% CI)	NE (3.7, NE)	4.6 (1.9, NE)
Hazard ratio[b] (95% CI); p value[c]	0.78 (0.45, 1.35); p=0.1854	

[a]Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
[b]Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence), geographical region (Asia vs outside of Asia) and baseline AFP (AFP <400 ng/mL vs AFP ≥400 ng/mL) in the interactive response technology system.
[c]One sided p value is calculated based on log-rank test.
NE, not evaluable

Figure 3: Time to Deterioration in Role Functioning

Figure 3A: <65 years old

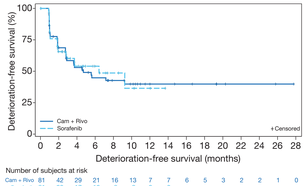


Number of subjects at risk

Cam + Rivo 191	146	110	89	71	62	50	33	24	15	9	7	4	4	0
Sorafenib 210	119	74	55	37	31	18	14	7	6	5	3	2	2	1

<65 years old	Cam + Rivo (n=191)	Sorafenib (n=210)
TTD events, n (%)	65 (34.0)	67 (31.9)
Median[a] TTD, months (95% CI)	NE (14.8, NE)	NE (7.9, NE)
Hazard ratio[b] (95% CI); p value[c]	0.76 (0.54, 1.09); p=0.0649	

Figure 3B: ≥65 years old



Number of subjects at risk

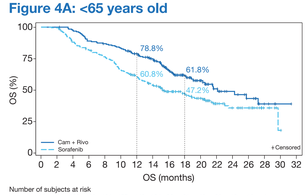
Cam + Rivo 81	42	29	21	16	13	7	7	6	5	3	2	2	1	0
Sorafenib 61	28	17	10	6	3	2	0							

≥65 years old	Cam + Rivo (n=81)	Sorafenib (n=61)
TTD events, n (%)	37 (45.7)	24 (39.3)
Median[a] TTD, months (95% CI)	4.2 (2.8, NE)	6.4 (2.8, NE)
Hazard ratio[b] (95% CI); p value[c]	1.14 (0.66, 1.97); p=0.3202	

[a]Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
[b]Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence), geographical region (Asia vs outside of Asia) and baseline AFP (AFP <400 ng/mL vs AFP ≥400 ng/mL) in the interactive response technology system.
[c]One sided p value is calculated based on log-rank test.
NE, not evaluable

Figure 4: Overall Survival

Figure 4A: <65 years old

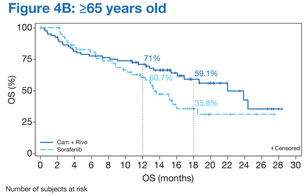


Number of subjects at risk

Cam + Rivo 191	191	185	169	164	157	142	124	90	61	42	26	19	13	4	1	0
Sorafenib 210	209	183	169	157	135	120	104	79	62	50	28	20	16	9	1	0

<65 years old	Cam + Rivo (n=191)	Sorafenib (n=210)
OS events, n (%)	78 (40.8)	118 (56.2)
Median[a] OS, months (95% CI)	22.1 (19.1, NE)	15.2 (12.9, 20.3)
Hazard ratio[b] (95% CI); p value[c]	0.62 (0.47, 0.83); p=0.0006	

Figure 4B: ≥65 years old



Number of subjects at risk

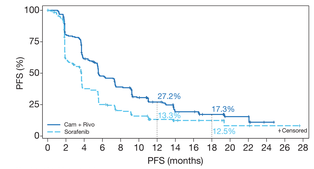
Cam + Rivo 81	74	65	62	60	58	48	41	28	19	15	8	6	5	1	0
Sorafenib 61	59	49	45	41	36	29	20	12	8	3	3	2	1	0	

≥65 years old	Cam + Rivo (n=81)	Sorafenib (n=61)
OS events, n (%)	33 (40.7)	33 (54.1)
Median[a] OS, months (95% CI)	22 (16.1, NE)	13.3 (10.7, 16.0)
Hazard ratio[b] (95% CI); p value[c]	0.62 (0.38, 1.03); p=0.0308	

[a]Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
[b]Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence), geographical region (Asia vs outside of Asia) and baseline AFP (AFP <400 ng/mL vs AFP ≥400 ng/mL) in the interactive response technology system.
[c]One sided p value is calculated based on log-rank test.
NE, not evaluable

Figure 5: Progression-Free Survival

Figure 5A: <65 years old

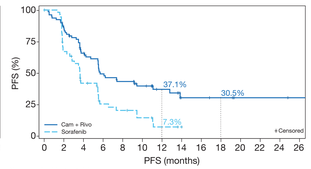


Number of subjects at risk

Cam + Rivo 191	148	111	83	67	49	36	21	21	13	8	8	2	0	
Sorafenib 210	113	66	44	33	25	16	9	8	6	2	2	1	1	0

<65 years old	Cam + Rivo (n=191)	Sorafenib (n=210)
PFS events, n (%)	143 (74.9)	158 (75.2)
Median[a] PFS, months (95% CI)	5.6 (5.5, 7.4)	3.7 (2.8, 3.7)
Hazard ratio[b] (95% CI); p value[c]	0.57 (0.45, 0.72); p<0.0001	

Figure 5B: ≥65 years old



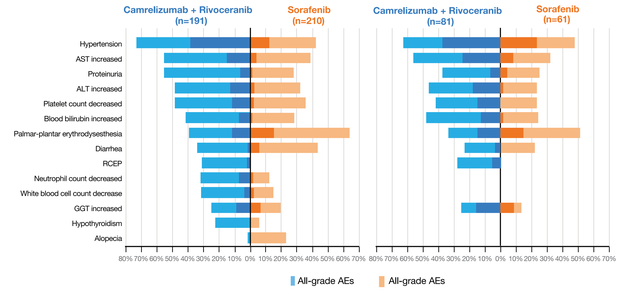
Number of subjects at risk

Cam + Rivo 81	67	46	33	28	21	13	6	6	5	2	2	2	1	
Sorafenib 61	56	20	10	8	5	2	1	0						

≥65 years old	Cam + Rivo (n=81)	Sorafenib (n=61)
PFS events, n (%)	46 (56.8)	44 (72.1)
Median[a] PFS, months (95% CI)	5.7 (4.8, 11.1)	3.6 (2.6, 5.5)
Hazard ratio[b] (95% CI); p value[c]	0.5 (0.32, 0.79); p=0.0012	

[a]Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
[b]Hazard ratios and the corresponding 95% CIs were stratified by macrovascular invasion and/or extrahepatic metastasis (presence vs absence), geographical region (Asia vs outside of Asia) and baseline AFP (AFP <400 ng/mL vs AFP ≥400 ng/mL) in the interactive response technology system.
[c]One sided p value is calculated based on log-rank test.

Figure 6: Most Common (≥20%) Treatment-related Adverse Events



AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysaesthesia; RCEP, reactive capillary endothelial proliferation

CONCLUSIONS

- In the CARES-310 trial, PRO data in adult (<65 years old) and older adult (≥65 years old) patients demonstrated clinically meaningful benefits in key aspects of the patient experience (QoL, functioning, key symptoms) with camrelizumab plus rivoceranib vs sorafenib.
- Although patients treated with camrelizumab plus rivoceranib exhibited a higher rate of treatment-related adverse events, the combination of camrelizumab plus rivoceranib did not adversely impact QoL when compared to sorafenib.
- PRO data stratified by age for adults and older adults further support the positive benefit:risk profile of camrelizumab plus rivoceranib vs sorafenib in patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.

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