Impact of Baseline Liver Function on Survival Outcomes in Patients with Unresectable Hepatocellular Carcinoma (uHCC) Treated with Camrelizumab + Rivoceranib vs Sorafenib: A Post Hoc Analysis of Study CARES-310

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BACKGROUND

- The CARES-310 (NCT03764293) trial evaluated the combination of the PD-1 inhibitor, camrelizumab (cam), and the VEGFR-2 tyrosine kinase inhibitor, rivoceranib (rivo), compared to sorafenib for the treatment of unresectable hepatocellular carcinoma.
- This combination therapy 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 the results of a post-hoc analysis evaluating the impact of baseline albumin-bilirubin (ALBI) grade and Child-Pugh (CP) class on survival outcomes.

METHODS

- CARES-310 was a 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).
- In this post-hoc analysis, median overall survival (mOS), median progression free survival (mPFS), objective response rate (ORR) and disease control rate (DCR) were assessed by baseline ALBI grade 1 vs 2 and CP class A5 vs A6
  - Safety and time to deterioration to CP class B was assessed by baseline ALBI grade.

RESULTS

Table 1: Baseline Characteristics by Baseline ALBI Grade

Category	ALBI Grade 1		ALBI Grade 2	
	Cam + Rivo (n=200)	Sorafenib (n=206)	Cam + Rivo (n=72)	Sorafenib (n=63)
Median age, years	56.5	56.0	63.0	57.0
Age group, n (%)				
<65 years	148 (74.0)	162 (78.6)	43 (59.7)	48 (76.2)
≥65 years	52 (26.0)	44 (21.4)	29 (40.3)	15 (23.8)
Male sex, n (%)	166 (83.0)	178 (86.4)	61 (84.7)	52 (82.5)
Geographic region, n (%)				
Asia	172 (86.0)	174 (84.5)	53 (73.6)	49 (77.8)
Non-Asia	28 (14.0)	32 (15.5)	19 (26.4)	14 (22.2)
ECOG PS, n (%)				
0	91 (45.5)	90 (43.7)	29 (40.3)	25 (39.7)
1	109 (54.5)	116 (56.3)	43 (59.7)	38 (60.3)
CP class, n (%)				
A5	189 (94.5)	188 (91.3)	47 (65.3)	40 (63.5)
A6	11 (5.5)	18 (8.7)	25 (34.7)	23 (36.5)
BCLC stage, n (%)				
B (middle stage)	26 (13.0)	32 (15.5)	12 (16.7)	7 (11.1)
C (advanced stage)	174 (87.0)	174 (84.5)	60 (83.3)	56 (88.9)
AFP ≥400 ng/mL, n (%)	67 (33.5)	75 (36.4)	29 (40.3)	25 (39.7)

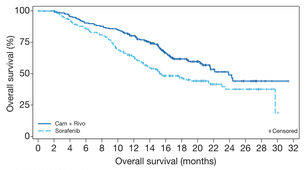
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.

- mOS, mPFS, DCR, and ORR improved with cam + rivo vs sorafenib regardless of baseline liver function (**Figures 1-4, Tables 2-4**).
  - The hazard ratios (HRs) for mOS in the cam + rivo arm were consistent for both ALBI grade 1 and grade 2, mirroring the HR observed in the intention-to-treat (ITT) population (0.62). This pattern persisted when the analysis was stratified by baseline CP class A5 and A6 (**Table 4**).
- Median time to deterioration to CP B was similar between treatment arms for ALBI grade 1 and grade 2 (**Figure 5**).
- Rates of all grade adverse events (AEs) and treatment-related AEs (TRAEs) were similar for patients with ALBI grade 1 and grade 2, although SAEs occurred at a greater rate in ALBI grade 2 vs grade 1, as did AEs leading to discontinuation or dose interruptions (**Table 5**).
- In patients with post-baseline grade 3/4 hepatoxicity, 58.2% of patients treated with cam + rivo vs 14.2% of patients treated with sorafenib were alive at last follow-up, with a mOS of 19.2 months vs 6.3 months (**Table 2**).

RESULTS

Figure 1: Overall Survival by Baseline ALBI Grade

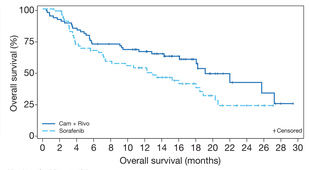
Figure 1A: ALBI Grade 1



ALBI Grade 1	Cam + Rivo (n=200)	Sorafenib (n=206)
OS events, n (%)	78 (39.0)	112 (53.8)
Median OS,[a] months (95% CI)	23.9 (20.3, NE)	15.4 (13.3, 21.6)
Hazard ratio[b] (95% CI)	0.62 (0.47, 0.83)	

[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 estimated using an unstratified Cox proportional hazard model.
CI, confidence interval; NE, not evaluable; OS, overall survival.

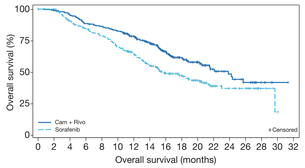
Figure 1B: ALBI Grade 2



ALBI Grade 2	Cam + Rivo (n=72)	Sorafenib (n=63)
OS events, n (%)	33 (45.8)	39 (61.9)
Median OS,[a] months (95% CI)	19.1 (14.3, 27.2)	12.3 (7.1, 18.5)
Hazard ratio[b] (95% CI)	0.62 (0.4, 1.0)	

Figure 2: Overall Survival by Baseline Child-Pugh Class

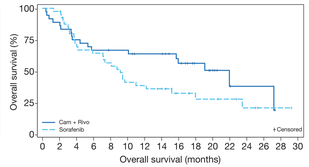
Figure 2A: Child-Pugh Class A5



Child-Pugh Class A5	Cam + Rivo (n=236)	Sorafenib (n=230)
OS events, n (%)	93 (39.4)	123 (53.5)
Median OS,[a] months (95% CI)	23.9 (20.3, NE)	15.6 (13.6, 20.3)
Hazard ratio[b] (95% CI)	0.65 (0.5, 0.85)	

[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 estimated using an unstratified Cox proportional hazard model.
CI, confidence interval; NE, not evaluable; OS, overall survival.

Figure 2B: Child-Pugh Class A6



Child-Pugh Class A6	Cam + Rivo (n=36)	Sorafenib (n=41)
OS events, n (%)	18 (50.0)	28 (68.3)
Median OS,[a] months (95% CI)	22.0 (5.8, NE)	9.2 (4.2, 15.2)
Hazard ratio[b] (95% CI)	0.62 (0.35, 1.13)	

Table 2: Summary of Overall Survival in Subgroup Patients with Post-baseline Grade 3/4 Hepatotoxicity

	Cam + Rivo (n=85)	Sorafenib (n=46)
OS events, n (%)	43 (50.6)	38 (82.6)
Patients censored, n (%)	42 (49.4)	8 (17.4)
Reason for censoring, n (%)		
Withdrawal of consent	1 (1.2)	1 (2.2)
Lost to follow-up	0	0
Alive	41 (48.2)	7 (15.2)
mOS, months (95% CI)	19.1 (15.7, 23.9)	6.3 (3.8, 9.2)

- Of the patients who experienced post-baseline grade 3/4 hepatotoxicity, those in the cam + rivo arm survived for up to 12.8 months longer compared to patients in the sorafenib arm.

Table 3: Summary of Responses by Baseline Liver Function Per BIRC Assessment (mRECIST)

Category	ALBI Grade 1		ALBI Grade 2		Child-Pugh Class A5		Child-Pugh Class A6	
	Cam + Rivo (n=200)	Sorafenib (n=208)	Cam + Rivo (n=72)	Sorafenib (n=63)	Cam + Rivo (n=236)	Sorafenib (n=230)	Cam + Rivo (n=36)	Sorafenib (n=41)
DCR,[a] n (%) [95% CI]	156 (78.0) [71.6, 83.5]	118 (56.7) [49.7, 63.6]	57 (79.2) [68.0, 87.8]	34 (54.0) [40.9, 66.6]	189 (80.1) [74.4, 85.0]	130 (56.5) [49.8, 63.0]	24 (66.7) [49.0, 81.4]	22 (53.7) [37.4, 69.3]
Confirmed ORR,[b] n (%) [95% CI]	71 (35.5) [28.9, 42.6]	19 (9.1) [5.6, 13.9]	19 (26.4) [16.7, 38.1]	8 (12.7) [5.6, 23.5]	78 (33.1) [27.1, 39.4]	24 (10.4) [6.8, 15.1]	12 (33.3) [18.6, 51.0]	3 (7.3) [1.5, 19.9]

[a]DCR=CR+PR+SD, [b]ORR=CR+PR
BIRC, blinded independent review committee; CR, complete response; DCR, disease control rate; mRECIST, Modified Response Evaluation Criteria for Solid Tumors; ORR, overall response rate; PR, partial response; SD, stable disease.

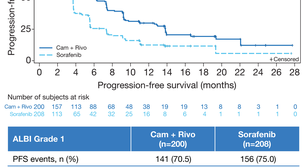
- ORR and DCR favored the cam + rivo arm regardless of baseline ALBI grade or CP class.

Table 4: Summary of Overall Survival by Baseline Liver Function

Category	ALBI Grade 1		ALBI Grade 2		Child-Pugh Class A5		Child-Pugh Class A6		ITT Population	
	Cam + Rivo (n=200)	Sorafenib (n=208)	Cam + Rivo (n=72)	Sorafenib (n=63)	Cam + Rivo (n=236)	Sorafenib (n=230)	Cam + Rivo (n=36)	Sorafenib (n=41)	Cam + Rivo (n=272)	Sorafenib (n=271)
mOS, months (95% CI)	23.9 (20.3, NE)	15.4 (13.3, 21.6)	19.1 (14.3, 27.2)	12.3 (7.1, 18.5)	23.9 (20.3, NE)	15.6 (13.6, 20.3)	22.0 (5.8, NE)	9.2 (4.2, 15.2)	22.1 (19.1, 27.2)	15.2 (13.0, 18.5)
HR (95% CI)	0.62 (0.47, 0.83)		0.62 (0.4, 1.0)		0.65 (0.50, 0.85)		0.62 (0.35, 1.13)		0.62 (0.49, 0.80)	
OS events, n (%)	78 (39.0)	112 (53.8)	33 (45.8)	39 (61.9)	93 (39.4)	123 (53.5)	18 (50.0)	28 (68.3)	111 (40.8)	151 (56.1)

Figure 3: Progression-free Survival by Baseline ALBI Grade Per BIRC Assessment (RECIST v1.1)

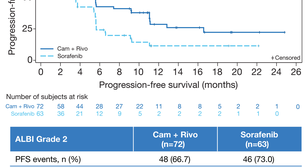
Figure 3A: ALBI Grade 1



ALBI Grade 1	Cam + Rivo (n=200)	Sorafenib (n=208)
PFS events, n (%)	141 (70.5)	156 (75.0)
Median PFS,[a] months (95% CI)	6.1 (5.5, 7.4)	3.7 (3.5, 3.7)
Hazard ratio[b] (95% CI)	0.57 (0.46, 0.73)	

[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 estimated using an unstratified Cox proportional hazard model.
BIRC, blinded independent review committee; CI, confidence interval; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

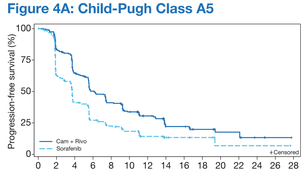
Figure 3B: ALBI Grade 2



ALBI Grade 2	Cam + Rivo (n=72)	Sorafenib (n=63)
PFS events, n (%)	48 (66.7)	46 (73.0)
Median PFS,[a] months (95% CI)	5.6 (4.4, 9.2)	3.1 (2.0, 5.5)
Hazard ratio[b] (95% CI)	0.57 (0.38, 0.86)	

Figure 4: Progression-free Survival by Baseline Child-Pugh Class Per BIRC Assessment (RECIST v1.1)

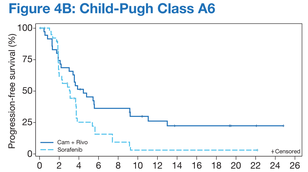
Figure 4A: Child-Pugh Class A5



CP Class A5	Cam + Rivo (n=236)	Sorafenib (n=230)
PFS events, n (%)	163 (69.1)	169 (73.5)
Median PFS,[a] months (95% CI)	6.1 (5.5, 7.4)	3.7 (3.5, 3.8)
Hazard ratio[b] (95% CI)	0.58 (0.47, 0.72)	

[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 estimated using an unstratified Cox proportional hazard model.
BIRC, blinded independent review committee; CI, confidence interval; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

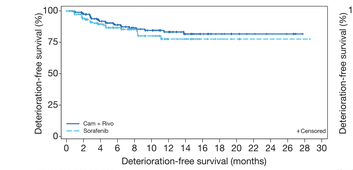
Figure 4B: Child-Pugh Class A6



CP Class A6	Cam + Rivo (n=36)	Sorafenib (n=41)
PFS events, n (%)	26 (72.2)	33 (80.5)
Median PFS,[a] months (95% CI)	4.4 (3.0, 9.2)	3.1 (1.9, 3.7)
Hazard ratio[b] (95% CI)	0.53 (0.32, 0.91)	

Figure 5: Deterioration-free Survival[a] by Baseline ALBI Grade

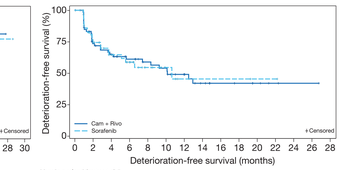
Figure 5A: ALBI Grade 1



ALBI Grade 1	Cam + Rivo (n=200)	Sorafenib (n=206)
DFS[a] events, n (%)	25 (12.5)	25 (12.0)
Median DFS,[b] months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio[c] (95% CI)	0.74 (0.43, 1.29)	

[a]DFS is the time from date of randomization to the date of first Child-Pugh B.
[b]Medians were estimated using the Kaplan-Meier methods with CIs calculated using Brookmeyer and Crowley method.
[c]Hazard ratios and the corresponding 95% CIs were estimated using an unstratified Cox proportional hazard model.
CI, confidence interval; DFS, deterioration-free survival; HR, hazard ratio; NE, not evaluable; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 5B: ALBI Grade 2



ALBI Grade 2	Cam + Rivo (n=72)	Sorafenib (n=63)
DFS[a] events, n (%)	31 (43.1)	22 (34.9)
Median DFS,[b] months (95% CI)	10.1 (4.2, NE)	10.6 (3.7, NE)
Hazard ratio[c] (95% CI)	0.99 (0.57, 1.74)	

Table 5: Safety Summary by Baseline ALBI Grade

Category, n (%)	ALBI Grade 1		ALBI Grade 2	
	Cam + Rivo (n=201)	Sorafenib (n=206)	Cam + Rivo (n=71)	Sorafenib (n=63)
Median treatment duration, months (min, max)	7.7 (0.2, 37.3)	3.9 (0.1, 37.7)	7.4 (0.3, 34.9)	3.7 (0.3, 31.9)
All grade AEs	200 (99.5)	205 (99.5)	71 (100.0)	63 (100.0)
Treatment-related all grade AEs	198 (98.5)	192 (93.2)	67 (94.4)	58 (92.1)
Treatment-related grade 3/4 AEs	165 (82.1)	111 (53.9)	58 (81.7)	34 (54.0)
Serious AEs	80 (39.8)	43 (20.9)	42 (59.2)	14 (22.2)
Treatment-related serious AEs	46 (22.9)	16 (7.8)	23 (32.4)	2 (3.2)
AE leading to withdrawal from any component	54 (26.9)	16 (7.8)	26 (36.6)	8 (12.7)
AE leading to dose interruption of any study treatment	155 (77.1)	90 (43.7)	60 (84.5)	25 (39.7)

AE, adverse event.

- Treatment-related Grade 5 AEs were reported in 1 patient in the cam + rivo arm (multiple organ dysfunction syndrome), and 1 patient in the sorafenib arm (respiratory failure and circulatory collapse)

CONCLUSIONS

- In this post-hoc analysis of the CARES-310 trial, the efficacy of cam + rivo was superior to sorafenib regardless of baseline liver function as measured by both ALBI grade and CP class.
- Despite a higher rate of grade 3/4 AEs, there was no detrimental effect of cam +rivo on liver function and overall survival in patients with both mildly- and moderately-preserved liver function compared to sorafenib.
  - Time to deterioration to CP class B for patients with ALBI grade 2 was similar between treatment arms.
  - In patients with post-baseline grade 3/4 hepatotoxicity, 58.2% of patients treated with cam + rivo vs 14.2% of patients treated with sorafenib were alive at last follow-up, with a mOS of 19.1 months vs 6.3 months.
- These results support cam + rivo as a potential new first-line treatment option for patients with unresectable hepatocecllular carcinoma regardless of baseline liver function (CP class A5 and A6; ALBI grade 1 and grade 2) (i.e., maintaining superior efficacy and similar safety).

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