Association of alpha-fetoprotein (AFP) and clinical outcomes in patients with unresectable hepatocellular carcinoma (uHCC) treated with camrelizumab + rivoceranib vs sorafenib (CARES-310)

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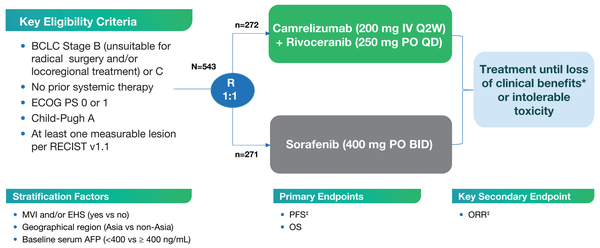
BACKGROUND

- CARES-310 (NCT03764293) compared the combination of the anti-programmed death-1 (PD-1) antibody camrelizumab plus the vascular endothelial growth factor receptor 2 (VEGFR2)-targeted tyrosine kinase inhibitor (TKI) rivoceranib versus sorafenib for the treatment of unresectable hepatocellular carcinoma (uHCC).[1]
- In the CARES-310 study, camrelizumab plus rivoceranib showed significantly improved median overall survival (mOS) and median progression-free survival (mPFS) compared with sorafenib (mOS 23.8 months vs 15.2 months; HR 0.64 [95% CI, 0.52-0.79]; mPFS 5.6 months vs 3.7 months; HR 0.54 [95% CI, 0.44-0.67]).[2]
- The most common ≥5% grade 3-4 treatment-related adverse events for camrelizumab plus rivoceranib were hypertension (38%) and increased aspartate aminotransferase (AST; 17%) vs palmar-plantar erythrodysesthesia syndrome (16%) for sorafenib.[2]
- We performed a post-hoc exploratory analysis of the CARES-310 study evaluating the impact of baseline serum alpha fetoprotein (AFP) levels (<400 ng/mL vs ≥400 ng/mL)[3] on efficacy and safety outcomes.

METHODS

CARES-310 Study Design and Endpoints[1]



*Treatment beyond progression allowed if there was evidence of clinical benefits per investigator. †By BIRC per RECIST v1.1.
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; IV, intravenous; MVI, macrovascular invasion; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; Q2W, every 2 weeks; QD, once daily; RECIST v1.1, Response Evaluation Criteria for Solid Tumors version 1.1.

Post-hoc Analysis

- This post-hoc exploratory analysis assessed post-treatment outcomes by baseline serum AFP levels (<400 ng/mL vs ≥400 ng/mL), where mOS and mPFS were estimated using the Kaplan-Meier method.
- Separate analyses were performed for the intention-to-treat (ITT) population and for the safety population.

RESULTS

- In this post-hoc exploratory analysis, most patients were male, Barcelona Clinic Liver Cancer stage C, Child-Pugh Class A5, and had received previous local therapy (**Table 1**).
- Objective response rate per blinded independent review committee (BIRC) assessment favored the camrelizumab plus rivoceranib arm regardless of baseline AFP level. Disease control rate per BIRC assessment also favored the camrelizumab plus rivoceranib arm regardless of baseline AFP level (**Table 2**).
- Median overall survival was longer with camrelizumab plus rivoceranib compared with sorafenib in patients with baseline AFP <400 ng/mL (**Figure 1**) and ≥400 ng/mL (**Figure 2**).
- Median progression-free survival was longer with camrelizumab plus rivoceranib compared with sorafenib in patients with baseline AFP <400 ng/mL (**Figure 3**) and ≥400 ng/mL (**Figure 4**).
- The most common treatment-related adverse events (TRAEs) were similar for patients who received camrelizumab plus rivoceranib or sorafenib, regardless of baseline serum AFP level (**Tables 3-4**).

RESULTS

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

	AFP <400 ng/mL		AFP ≥400 ng/mL	
	Rivoceranib + Camrelizumab (N=176)	Sorafenib (N=171)	Rivoceranib + Camrelizumab (N=96)	Sorafenib (N=100)
Median age, years (range)	60 (23-83)	57 (28-82)	54 (27-76)	52 (23-82)
Male sex, n (%)	148 (84.1)	148 (86.5)	79 (82.3)	82 (82.0)
Geographic region, n (%)				
Asia	142 (80.7)	139 (81.3)	83 (86.5)	85 (85.0)
Non-Asia	34 (19.3)	32 (18.7)	13 (13.5)	15 (15.0)
Race, n (%)				
Asian	143 (81.3)	139 (81.3)	83 (86.5)	85 (85.0)
Caucasian (non-Asian)	33 (18.8)	32 (18.7)	13 (13.5)	15 (15.0)
ECOG PS, n (%)				
0	80 (45.5)	77 (45.0)	40 (41.7)	39 (39.0)
1	96 (54.5)	94 (55.0)	56 (58.3)	61 (61.0)
BCLC stage, n (%)				
B (middle stage)	27 (15.3)	28 (16.4)	11 (11.5)	12 (12.0)
C (advanced stage)	149 (84.7)	143 (83.6)	85 (88.5)	88 (88.0)
Child-Pugh score, n (%)				
A5	154 (87.5)	144 (84.2)	82 (85.4)	86 (86.0)
A6	22 (12.5)	27 (15.8)	14 (14.6)	14 (14.0)
MVI and/or EHS, n (%)				
Absence	50 (28.4)	49 (28.7)	22 (22.9)	22 (22.0)
Presence	126 (71.6)	122 (71.3)	74 (77.1)	78 (78.0)
EHS, n (%)				
Presence	116 (65.9)	115 (67.3)	59 (61.5)	65 (65.0)
Absence	60 (34.1)	56 (32.7)	37 (38.5)	35 (35.0)
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)
Non-viral	32 (18.2)	31 (18.1)	10 (10.4)	14 (14.0)
BMI, n (%)				
<30 kg/m^2	168 (95.5)	160 (93.6)	92 (95.8)	97 (97.0)
≥30 kg/m^2	8 (4.5)	10 (5.8)	4 (4.2)	3 (3.0)
Missing	0	1 (0.6)	0	0

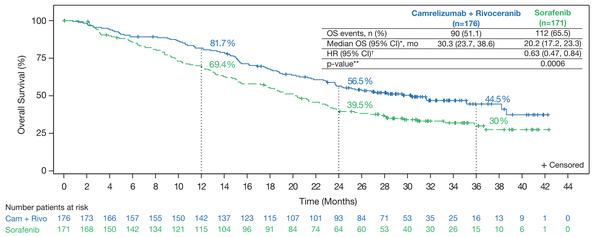
BCLC, Barcelona Clinic Liver Cancer; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; MVI, macrovascular invasion.

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

	AFP <400 ng/mL		AFP ≥400 ng/mL	
	Rivoceranib + Camrelizumab (N=176)	Sorafenib (N=171)	Rivoceranib + Camrelizumab (N=96)	Sorafenib (N=100)
Best overall response, n (%)				
Complete response	5 (2.8)	2 (1.2)	0	0
Partial response	55 (31.3)	11 (6.4)	13 (13.5)	3 (3.0)
Stable disease	84 (47.7)	90 (52.6)	55 (57.3)	39 (39.0)
Progressive disease	26 (14.8)	54 (31.6)	19 (19.8)	46 (46.0)
Not evaluable	6 (3.4)	14 (8.2)	9 (9.4)	12 (12.0)
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]
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 follow-up, months	25	19	16	10
Median time to response, months	2	4	2	2

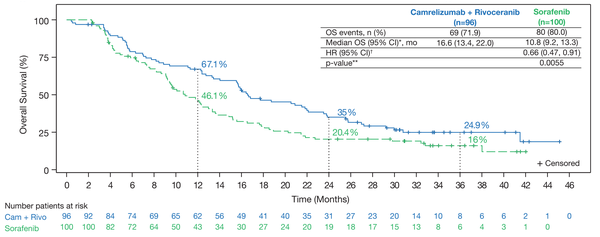
[a]Disease control rate is defined as the percentage of patients with complete response, partial response, or stable disease ≥7 weeks.
BIRC, blinded independent review committee; ITT, intent-to-treat; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Figure 1: Overall Survival for Patients with Baseline AFP < 400 ng/mL



*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: Overall Survival for Patients with Baseline AFP ≥400 ng/mL



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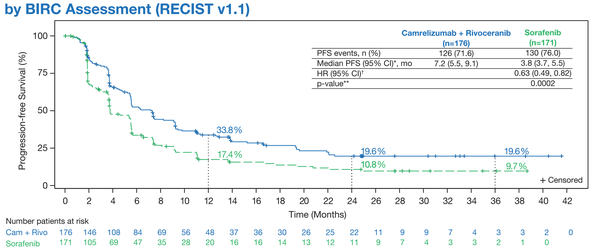
**p-value (one-sided) is calculated based on log-rank test.

Table 3: Most Common (≥20%) Any Grade or Grade 3-4 (≥5%) TRAEs* for Patients with Baseline AFP <400 ng/mL (Safety Population)

TRAE, n (%)	Rivoceranib + Camrelizumab (N=176)		Sorafenib (N=169)	
	Any Grade	Grade 3-4	Any Grade	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)

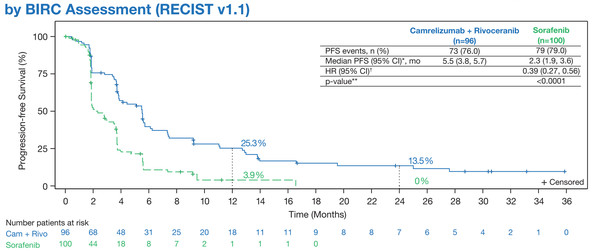
*TRAEs include adverse events related to both rivoceranib + camrelizumab or sorafenib.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TRAE, treatment-related adverse event.

Figure 3: Progression-free Survival for Patients with Baseline AFP < 400 ng/mL by BIRC Assessment (RECIST v1.1)



*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 4: Progression-free Survival for Patients with Baseline AFP ≥400 ng/mL by BIRC Assessment (RECIST v1.1)



*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.

Table 4: Most Common (≥20%) Any Grade or Grade 3-4 (≥5%) TRAEs* for Patients with Baseline AFP ≥400 ng/mL (Safety Population)

TRAE, n (%)	Rivoceranib + Camrelizumab (N=96)		Sorafenib (N=100)	
	Any Grade	Grade 3-4	Any Grade	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)

*TRAEs include adverse events related to both rivoceranib + camrelizumab or sorafenib.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

CONCLUSIONS

- Results of this CARES-310 exploratory post-hoc analysis indicate improved mOS and mPFS in the camrelizumab plus rivoceranib arm with baseline serum AFP levels <400 ng/mL or ≥400 ng/mL.
- Safety results showed that increased AST was the most common treatment-related adverse event, regardless of baseline serum AFP level.
- Independent of uHCC prognosis, camrelizumab plus rivoceranib demonstrated improved OS, PFS, and DCR, and if approved, may be a potential first line treatment option.

REFERENCES

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