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Camrelizumab plus rivoceranib vs sorafenib as first-line therapy for unresectable hepatocellular carcinoma: final overall survival analysis of the phase 3 CARES-310 study

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Background

- The phase 3 CARES-310 trial is the first to demonstrate significant progression-free survival (PFS) and overall survival (OS) benefits with immunotherapy plus an anti-angiogenic tyrosine kinase inhibitor (TKI) over standard TKI as first-line treatment for unresectable hepatocellular carcinoma (HCC). [1]
- In the primary analysis of PFS (data cut-off [DCO], May. 10, 2021) and interim analysis of OS (DCO, Feb. 8, 2022), significant improvements were observed with camrelizumab (anti-PD-1 antibody) + rivoceranib (VEGFR2-TKI) *vs.* sorafenib. [1]
  - PFS: 5.6 mo *vs.* 3.7 mo; HR 0.52 (95% CI 0.41-0.65); 1-sided p <0.0001
  - OS: 22.1 mo *vs.* 15.2 mo; HR 0.62 (95% CI 0.49-0.80); 1-sided p <0.0001
- Here, we report updated data at the final analysis, after an additional follow-up of ~16 mo.

Methods

- In this international, randomized, open-label, phase 3 trial (NCT03764293), patients with unresectable HCC who had not previously received systemic treatment were randomized 1:1 to receive either camrelizumab + rivoceranib or sorafenib (**Fig. 1**).
- As of Jun.14, 2023, 351 (65%) deaths occurred, and a protocol-specified final analysis was performed.

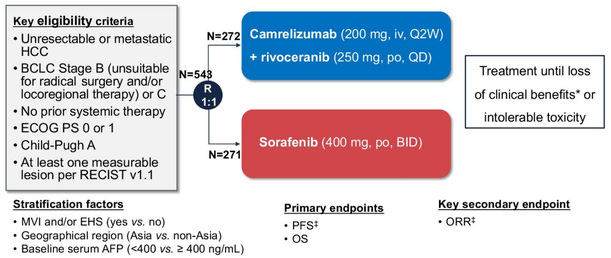

Figure 1. Study design.

*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; BIRC, blinded independent review committee; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; MVI, macrovascular invasion

Results

Patients

- 272 patients were allocated to camrelizumab + rivoceranib and 271 to sorafenib (**Table 1**).
- At DCO of final analysis, median follow-up was 22.1 mo in the camrelizumab + rivoceranib group and 14.9 mo in the sorafenib group.
- After end of study treatment, 43.8% of patients in the camrelizumab + rivoceranib group and and 56.9% in the sorafenib group received subsequent systemic anti-cancer therapy.

Table 1. Baseline characteristics

	Camrelizumab + rivoceranib (N=272)	Sorafenib (N=271)
Age, years	58 (48-66)	56 (47-64)
Male	227 (83.5)	230 (84.9)
Geographical region		
Asia*	225 (82.7)	224 (82.7)
Non-Asia†	47 (17.3)	47 (17.3)
BCLC stage		
B	38 (14.0)	40 (14.8)
C	234 (86.0)	231 (85.2)
Child-Pugh score		
A (5)	236 (86.8)	230 (84.9)
A (6)	36 (13.2)	41 (15.1)
ECOG PS 1	152 (55.9)	155 (57.2)
AFP ≥400 ng/mL	96 (35.3)	100 (36.9)
MVI and/or EHS	200 (73.5)	200 (73.8)
MVI	40 (14.7)	52 (19.2)
EHS	175 (64.3)	180 (66.4)
Etiology‡		
HBV	208 (76.5)	197 (72.7)
HCV	22 (8.1)	29 (10.7)
Non-viral¶	42 (15.4)	45 (16.6)
Previous local therapy	161 (59.2)	149 (55.0)

Data are n (%) or median (IQR). * Include mainland China, Hong Kong, Taiwan and South Korea. †Include Belgium, Italy, Germany, Poland, Russia, Spain, Turkey, Ukraine and USA. ‡ Main underlying cause of HCC per investigator. ¶ Include non-alcoholic fatty liver disease, alcohol cirrhosis, aflatoxin exposure and other non-HBV and HCV causes (known or unknown).

Efficacy

- Median OS was significantly prolonged with camrelizumab + rivoceranib *vs.* sorafenib (23.8 mo *vs.* 15.2 mo; HR 0.64 [95% CI 0.52-0.79]; 1-sided p <0.0001; **Fig. 2**). OS rate with camrelizumab + rivoceranib *vs.* sorafenib was 49.0% *vs.* 36.2% at 24 mo, and 37.7% *vs.* 24.8% at 36 mo.
- OS benefits with camrelizumab + rivoceranib was consistent across most subgroups, regardless of geographical region, race, and aetiology (**Fig. 3**).
- Benefits in PFS (**Fig. 4**), ORR and duration of response (DoR; **Fig. 5**) by BIRC per RECIST v1.1 with camrelizumab + rivoceranib were also sustained after prolonged follow-up.

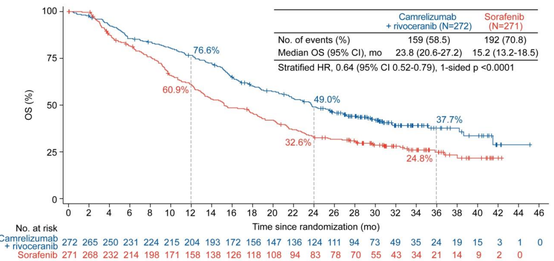

Figure 2. Kaplan-Meier curve of OS.

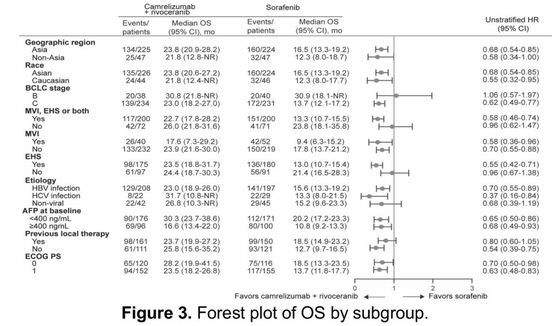

Figure 3. Forest plot of OS by subgroup.

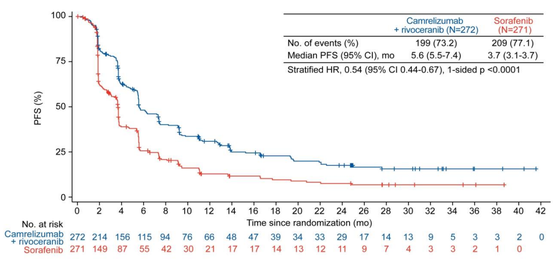

Figure 4. Kaplan-Meier curve of PFS (BIRC per RECIST v1.1).

In Figs. 2 & 4, OS and PFS were analyzed using a stratified one-sided log-rank test; HRs were estimated using a stratified Cox proportional hazards model; the stratification factors were presence of MVI and/or EHS (yes vs no), geographical region (Asia vs non-Asia), and baseline AFP level (<400 vs ≥400 ng/mL). In Fig. 3, HRs were estimated using an unstratified Cox proportional hazards model. NR, not reached.

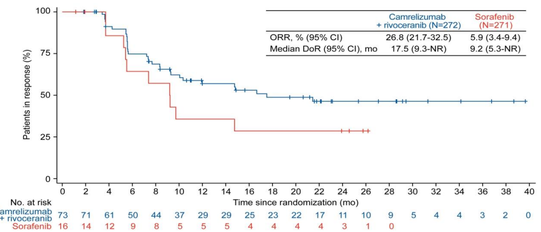

Figure 5. Kaplan-Meier curve of DoR (BIRC per RECIST v1.1).

Safety

- Safety data aligned with the interim OS analysis,[1] with no new signals noted (**Table 2**). TRAE led to discontinuation of camrelizumab in 17.6% of patients and rivoceranib in 16.9% in the combo group; discontinuation rate of both agents was low, at 4.4%. Sorafenib was discontinued in 4.8% due to TRAE.

Table 2. TRAEs

	Camrelizumab + rivoceranib (N=272)		Sorafenib (N=269)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	189 (69.5)	104 (38.2)	117 (43.5)	40 (14.9)
AST increased	149 (54.8)	47 (17.3)	101 (37.5)	14 (5.2)
Proteinuria	135 (49.6)	16 (5.9)	73 (27.1)	5 (1.9)
ALT increased	129 (47.4)	38 (14.0)	81 (30.1)	8 (3.0)
Platelet count decreased	126 (46.3)	32 (11.8)	90 (33.5)	4 (1.5)
Blood bilirubin increased	117 (43.0)	24 (8.8)	75 (27.9)	4 (1.5)
PPE syndrome	102 (37.5)	33 (12.1)	164 (61.0)	42 (15.6)
Diarrhoea	84 (30.9)	6 (2.2)	106 (39.4)	14 (5.2)
RCCEP	82 (30.1)	8 (2.9)	0	0
Neutrophil count decreased	75 (27.6)	16 (5.9)	28 (10.4)	3 (1.1)
White blood cell count decreased	74 (27.2)	7 (2.6)	38 (14.1)	4 (1.5)
GGT increased	65 (23.9)	26 (9.6)	49 (18.2)	19 (7.1)
Hypothyroidism	58 (21.3)	0	17 (6.3)	0
Fatigue	56 (20.6)	8 (2.9)	21 (7.8)	1 (0.4)

Data are n (%). *TRAEs of any grade occurring in ≥20% or of grade ≥3 occurring in ≥5% of patients in either group are listed. AST, aspartate aminotransferase; ALT=alanine aminotransferase; GGT, Gamma-glutamyltransferase; PPE, palmar-plantar erythrodysaesthesia; RCCEP, reactive cutaneous capillary endothelial proliferation

Conclusions

- At the protocol-specified final analysis, camrelizumab + rivoceranib continued to show clinically meaningful survival improvement compared with sorafenib, with manageable safety.
- The extended follow-up further confirmed the favorable benefit-to-risk profile of camrelizumab + rivoceranib, supporting it as a new first-line treatment option for unresectable HCC.

Reference: 1. Lancet. 2023;402(10408):1133-1146.

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