Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) Analysis to Assess the Impact of Treatment With Camrelizumab + Rivoceranib (cam+rivo) on Quality of Life vs Sorafenib in Patients With Unresectable Hepatocellular Carcinoma: Study CARES-310

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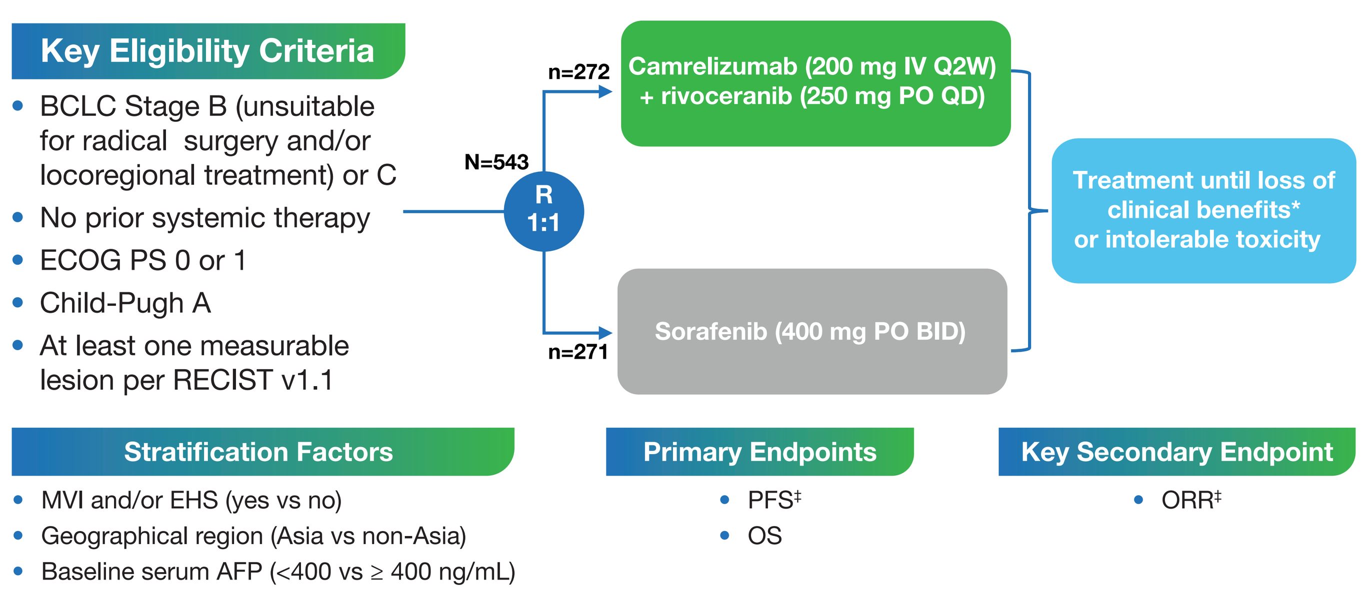
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BACKGROUND

- Study 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 (also known as apatinib) with sorafenib for the treatment of unresectable hepatocellular carcinoma.[1]
- At the protocol-specified final analysis (median follow-up: 22.1 months), camrelizumab plus rivoceranib continued to show significantly improved overall survival (OS) and progression-free survival (PFS) compared with sorafenib (median OS 23.8 months vs 15.2 months; HR 0.64 [95% CI, 0.52-0.79; P<0.0001]; mPFS 5.6 months vs 3.7 months; HR 0.54 [95% CI, 0.44-0.67; P<0.0001]).[2]
- The most common (≥10%) grade ≥3 treatment-related adverse events at the protocol-specified final analysis for camrelizumab plus rivoceranib were hypertension (38.2%), increased aspartate aminotransferase (AST) (17.3%), increased alanine aminotransferase (ALT) (14.0%), palmar-plantar erythrodysesthesia (PPE) syndrome (12.1%), and platelet count decreased (11.8%) vs PPE syndrome (15.6%) and hypertension (14.9%) for sorafenib.[2]
- We performed a Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TWiST) analysis based on safety data from the interim analysis to assess the impact of treatment with camrelizumab plus rivoceranib on quality of life as compared with sorafenib.

METHODS

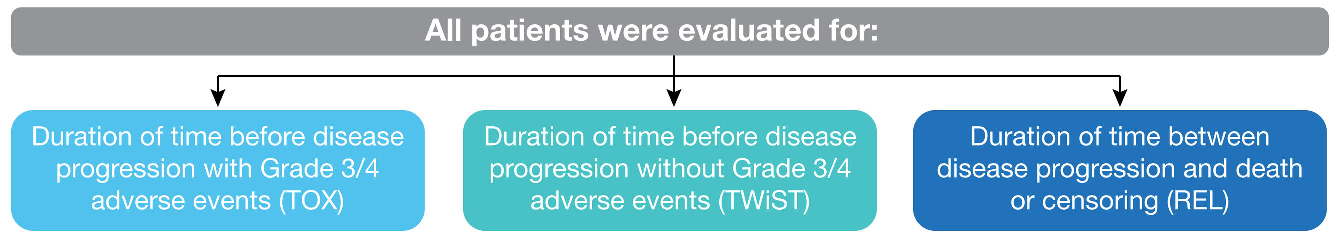
CARES-310 Study Design and Endpoints[1]


Key Eligibility Criteria
BCLC Stage B (unsuitable for radical surgery and/or locoregional treatment) or C
No prior systemic therapy
ECOG PS 0 or 1
Child-Pugh A
At least one measurable lesion per RECIST v1.1
N=543
R 1:1
n=272
Camrelizumab (200 mg IV Q2W) + rivoceranib (250 mg PO QD)
n=271
Sorafenib (400 mg PO BID)
Treatment until loss of clinical benefits* or intolerable toxicity
Stratification Factors
MVI and/or EHS (yes vs no)
Geographical region (Asia vs non-Asia)
Baseline serum AFP (<400 vs ≥ 400 ng/mL)
Primary Endpoints
PFS‡
OS
Key Secondary Endpoint
ORR‡

*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.

Q-TWiST Analysis

- Q-TWiST is a weighted analysis that evaluates how much of a patient's survival time is spent with toxicities, after disease progression or relapse, or time without symptoms of disease or toxicity (TWiST).[3,4]


All patients were evaluated for:
Duration of time before disease progression with Grade 3/4 adverse events (TOX)
Duration of time before disease progression without Grade 3/4 adverse events (TWiST)
Duration of time between disease progression and death or censoring (REL)

- Utility coefficients (u) of 1 for TWiST, and 0.5 for TOX and REL were used to calculate Q-TWiST:

$$\text{Q-TWiST} = (u\text{TOX} * \text{TOX}) + (u\text{TWiST} * \text{TWiST}) + (u\text{REL} * \text{REL})$$

- Mean duration in each state was calculated using the method of Restricted Mean Survival Time (RMST)

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RESULTS

- At the interim analysis for overall survival, the most common grade 3 or 4 treatment-related adverse events were hypertension (102 [38%] of 272 patients in the camrelizumab plus rivoceranib arm vs 40 [15%] of 269 patients in the sorafenib arm), palmar-plantar erythrodysaesthesia syndrome (33 [12%] vs 41 [15%]), increased aspartate aminotransferase (45 [17%] vs 14 [5%]), and increased alanine aminotransferase (35 [13%] vs 8 [3%]) (**Table 1**).

Table 1: TRAEs in The Safety Analysis Set at the Interim Analysis for Overall Survival[1]

	Camrelizumab + rivoceranib (n=272)				Sorafenib (n=269)			
TRAE, n (%)	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any TRAE	45 (17)	193 (71)	26 (10)	1 (<1)	128 (48)	128 (48)	12 (4)	1 (<1)
Hypertension	87 (32)	100 (37)	2 (1)	0	76 (28)	40 (15)	0	0
AST increased	102 (38)	42 (15)	3 (1)	0	85 (32)	14 (5)	0	0
Proteinuria	118 (43)	16 (6)	0	0	67 (25)	5 (2)	0	0
ALT increased	92 (43)	34 (13)	1 (<1)	0	72 (27)	8 (3)	0	0
Platelet count decreased	94 (35)	28 (10)	4 (1)	0	85 (32)	4 (1)	0	0
Blood bilirubin increased	92 (34)	24 (9)	0	0	71 (26)	4 (1)	0	0
Palmar-plantar erythrodysaesthesia syndrome	69 (25)	33 (12)	0	0	122 (45)	41 (15)	0	0
Diarrhea	77 (28)	6 (2)	0	0	91 (34)	14 (5)	0	0
Reactive cutaneous capillary endothelial proliferation	72 (26)	7 (3)	0	0	0	0	0	0
Neutrophil count decreased	57 (21)	14 (5)	2 (1)	0	24 (9)	1 (<1)	2 (1)	0
White blood cell count decreased	66 (24)	7 (3)	0	0	35 (13)	3 (1)	0	0
Gamma-glutamyl transferase increased	39 (14)	25 (9)	2 (1)	0	29 (11)	15 (6)	5 (2)	0
Hypothyroidism	58 (21)	0	0	0	16 (6)	0	0	0
Fatigue	46 (17)	7 (3)	0	0	20 (7)	1 (<1)	0	0
Blood alkaline phosphatase increased	44 (16)	3 (1)	0	0	30 (11)	3 (1)	0	0
Conjugated blood bilirubin increased	34 (13)	10 (4)	2 (1)	0	28 (10)	6 (2)	2 (1)	0
Rash	40 (15)	5 (2)	0	0	47 (17)	3 (1)	0	0
Anemia	41 (15)	4 (1)	0	0	19 (7)	2 (1)	0	0
Decreased appetite	39 (14)	3 (1)	0	0	31 (12)	3 (1)	0	0
Unconjugated blood bilirubin increased	33 (12)	2 (1)	0	0	20 (7)	1 (<1)	0	0
Hypoalbuminemia	34 (13)	0	0	0	21 (8)	0	0	0
Weight decreased	28 (10)	4 (1)	0	0	33 (12)	6 (2)	0	0
Asthenia	29 (11)	3 (1)	0	0	15 (6)	0	0	0
Hematuria	31 (11)	0	0	0	12 (4)	0	0	0
Nausea	31 (11)	0	0	0	14 (5)	0	0	0
Headache	28 (10)	2 (1)	0	0	4 (1)	1 (<1)	0	0
Blood lactate dehydrogenase increased	26 (10)	1 (<1)	0	0	29 (11)	0	0	0
Lymphocyte count decreased	18 (7)	8 (3)	0	0	14 (5)	3 (1)	0	0
Amylase increased	15 (6)	9 (3)	1 (<1)	0	6 (2)	0	1 (<1)	0
Hyponatremia	13 (5)	8 (3)	0	0	8 (3)	1 (<1)	0	0
Lipase increased	7 (3)	7 (3)	6 (2)	0	6 (2)	4 (1)	1 (<1)	0
Hypophosphatemia	17 (6)	2 (1)	0	0	27 (10)	12 (4)	0	0
Upper GI hemorrhage	2 (1)	6 (2)	0	0	0	0	0	0
Alopecia	4 (1)	0	0	0	52 (19)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; TRAE, treatment related adverse event.

Q-TWiST Analysis Results

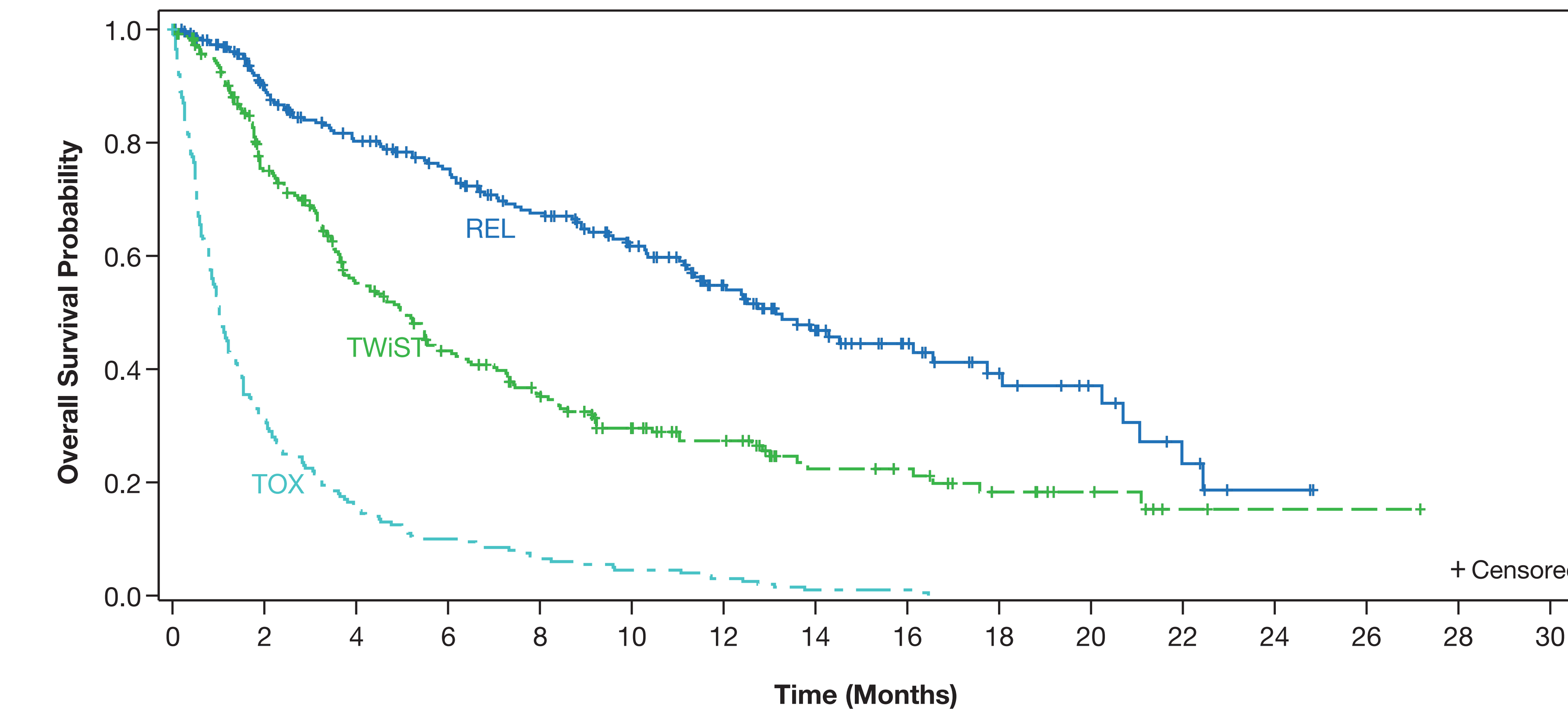
- Duration of TOX and TWiST was longer for patients in the camrelizumab plus rivoceranib arm vs sorafenib arm (**Table 2**).
- Duration of REL was not significantly different between arms (**Table 2**).
- Clinically important relative Q-TWiST gains favored camrelizumab plus rivoceranib vs sorafenib by 10.6% (= difference 1.61/median overall survival of sora 15.2) (**Table 2**, **Figure 1**, and **Figure 2**).

Table 2: Mean Duration of TOX, TWiST, REL, and Q-TWiST

Mean duration, months (SE)	Camrelizumab + rivoceranib (n=272)	Sorafenib (n=271)	Difference, Camrelizumab + rivoceranib vs Sorafenib	P value
TOX	2.18 (0.2)	1.21 (0.14)	0.97 (0.25)	<0.0001
TWiST	8.92 (0.67)	6.01 (0.55)	2.91 (0.87)	0.0008
REL	13.71 (0.67)	12.64 (0.61)	1.07 (0.91)	0.2375
Q-TWiST	10.11 (0.31)	8.51 (0.29)	1.61 (0.42)	0.0002

REL, duration of time between disease progression and death or censoring; SE, standard of error; TOX, duration of time before disease progression with Grade 3/4 adverse events; TWiST, duration of time before disease progression without Grade 3/4 adverse events.

Figure 1: Kaplan-Meier Plot for Partitioned Overall Survival: Camrelizumab + Rivoceranib

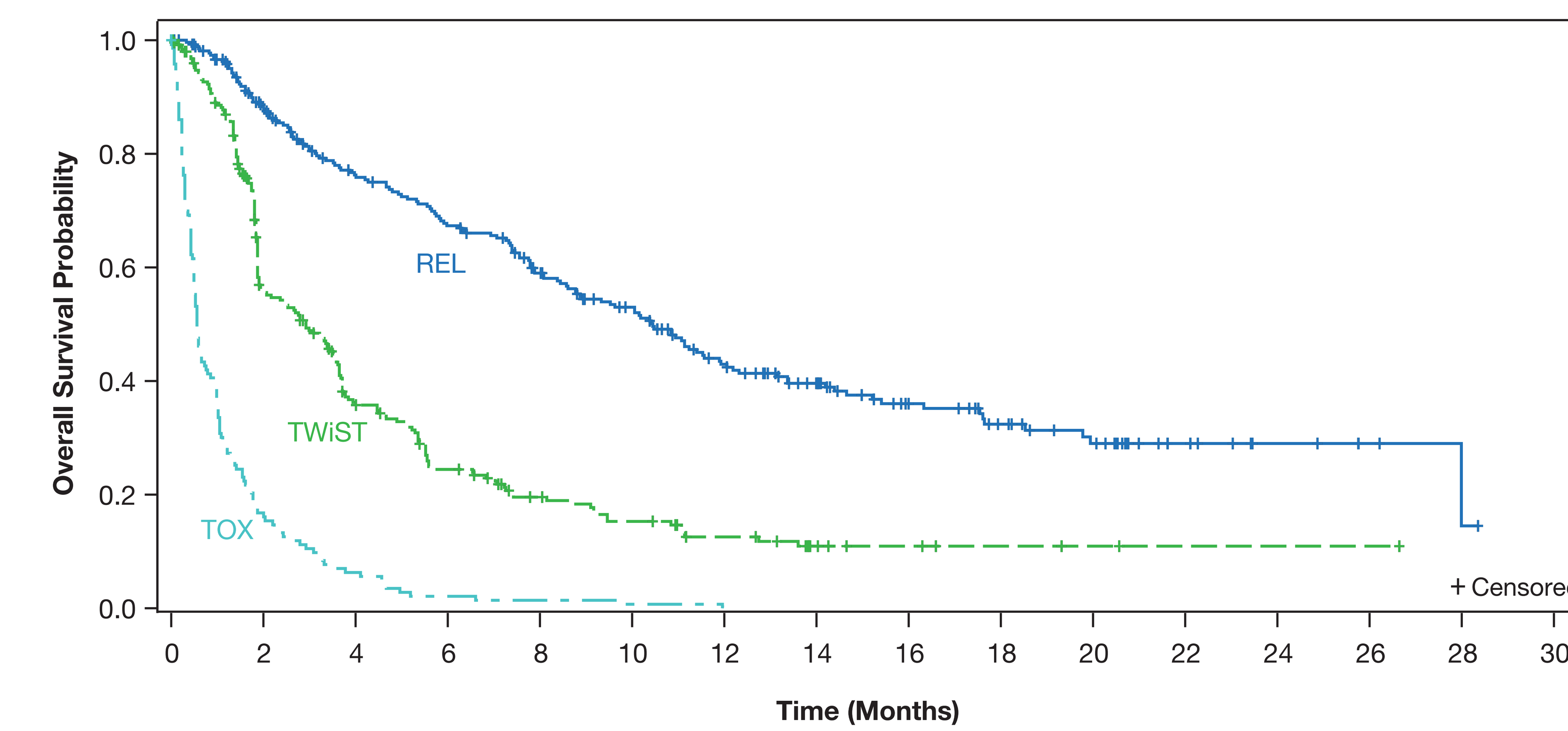

Overall Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
REL
TWiST
TOX
+ Censored
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time (Months)

Number of patients at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
REL	272	207	171	150	126	96	68	46	29	19	12	6	2	0	
TWiST	272	174	118	88	68	47	35	20	18	11	7	2	1	1	0
TOX	272	62	31	20	13	9	6	2	2	0					

REL, time from disease progression until death or the last recorded date on which patients were known to be alive; TOX, toxicity time for grade 3/4 adverse events; TWiST, time without toxicity or disease progression.

Figure 2: Kaplan-Meier Plot for Partitioned Overall Survival: Sorafenib


Overall Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
REL
TWiST
TOX
+ Censored
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time (Months)

Number of patients at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
REL	269	219	180	158	131	110	82	63	44	33	25	12	7	3	1	0
TWiST	269	126	76	49	33	25	17	8	5	3	2	1	1	1	0	
TOX	269	24	9	3	2	1	0									

REL, time from disease progression until death or the last recorded date on which patients were known to be alive; TOX, toxicity time for grade 3/4 adverse events; TWiST, time without toxicity or disease progression.

CONCLUSIONS

- Patients with unresectable hepatocellular carcinoma treated with camrelizumab plus rivoceranib had clinically meaningful quality-adjusted survival benefits compared with patients treated with sorafenib.
- This benefit was driven primarily by time before disease progression without toxicity, supporting that the higher incidence of adverse events in patients treated with camrelizumab + rivoceranib vs sorafenib is likely due to longer treatment duration with camrelizumab