TISLELIZUMAB VERSUS SORAFENIB IN FIRST-LINE TREATMENT OF UNRESECTABLE HEPATOCELLULAR CARCINOMA: IMPACT ON HEALTH-RELATED QUALITY OF LIFE IN RATIONALE-301 POPULATION

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Conclusions

The RATIONALE-301 study met its primary endpoint and key secondary endpoints of ORR and safety. Tislelizumab monotherapy as a first-line treatment for patients with uHCC was associated with more favorable HRQoL outcomes than sorafenib. Compared to patients receiving sorafenib, patients receiving tislelizumab had less worsening in general health status, physical functioning, fatigue, and HCC symptom index. These results, along with effects on overall survival, response rate, and a favorable safety profile, support the benefit of tislelizumab as a potential first-line treatment option for uHCC.

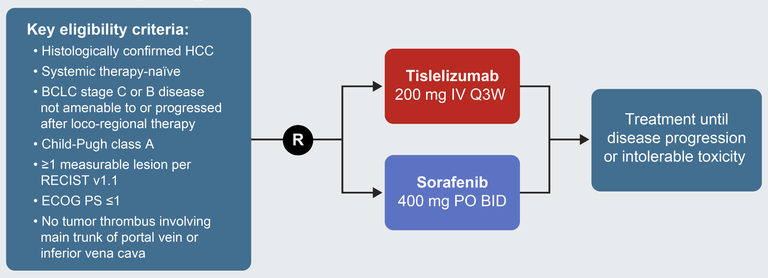
Introduction

- Hepatocellular carcinoma (HCC) is a substantial global health challenge that accounts for 75% to 85% of all reported cases of liver cancer and is one of the most common causes of cancer-related death[1]
- The diagnosis and treatment of HCC profoundly impacts the health-related quality of life (HRQoL) of patients, spanning physical, psychological, social, and spiritual QoL domains[2]
- RATIONALE-301 (NCT03412773), a global phase 3 study, comparing tislelizumab to sorafenib as first-line treatment in adult patients with unresectable HCC (uHCC), met its primary endpoint of overall survival (OS) non-inferiority
  - OS benefit was non-inferior to sorafenib for patients treated with tislelizumab (median OS: 15.9 months vs 14.1 months, respectively; stratified hazard ratio [HR]: 0.85 [95% CI: 0.712, 1.019]; *P*=0.0398)
  - Tislelizumab was also associated with a higher objective response rate (ORR: 14.3% vs 5.4%) and longer median duration of responses (mDoR: 36.1 vs 11.0 months) compared to sorafenib
  - Median progression-free survival (mPFS) was 2.1 vs 3.4 months with tislelizumab vs sorafenib, respectively
- The objective of this analysis was to evaluate the impact of tislelizumab monotherapy on patients' HRQoL and HCC-related symptoms

Methods

- Randomized, open-label, multicenter, multiregional phase 3 study
- The study population consisted of adult patients (aged ≥18 years) with histologically confirmed uHCC who had not received systemic therapy
- Eligible patients were randomized (1:1) to receive tislelizumab (200 mg intravenously every 3 weeks, n=342) or sorafenib (400 mg orally twice daily, n=332) (**Figure 1**)
- HRQoL was a secondary endpoint and was assessed using patient-reported outcomes (PROs) via three validated PRO instruments:
  - The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30)
  - The EORTC Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions (QLQ-HCC18)
  - The EuroQoL Five-Dimensions Five-Levels (EQ-5D-5L) Visual Analogue Scale (VAS)

Figure 1. RATIONALE-301 Study Design



BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; ECOG PS, European Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IV, intravenous; PO, oral; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

HRQoL Assessments and Endpoints

- The PRO measures were collected at baseline, and at every cycle through Cycle 12, then every four cycles thereafter, and at the end of treatment visit
- The following key pre-specified PRO endpoints were selected based on their relevance to HCC and treatment side effects, as well as their use in previous studies:
  - EORTC QLQ-C30: the global health status/quality of life (GHS/QoL), physical functioning, and fatigue scales, with higher scores representing better outcomes on the GHS/QoL scale and physical functioning scale but the worse outcome on the fatigue scale
  - QLQ-HCC18: the index, fatigue, and pain scores where higher scores on these scales indicated worse outcomes
  - The EQ-5D-5L's VAS score recorded the patient's self-rated health with higher scores reflecting better perceived health

Statistical Analyses

- All analyses were conducted using the data cutoff of 11 July 2022
- Completion rate was defined as the number of patients that completed the questionnaire from the total number of patients in the relevant treatment arm
- Adjusted completion rate was defined as the proportion of patients that completed the questionnaire from the total number of patients that participated at that visit
- Change from baseline in each key PRO endpoint to Cycle 4 and Cycle 6 was analyzed using a mixed effect model analysis for measuring changes post-baseline; differences in the change from baseline to Cycle 4 and Cycle 6 between the arms were assessed using mixed models which included baseline score, stratification factors, treatment arm, visit, and treatment arm by visit interaction as fixed effects and visit as a repeated measure
- Time to deterioration was defined as time to first onset of a ≥10-point change in the direction of worsening from baseline with confirmation by a subsequent decrease from baseline; the Kaplan-Meier method was used to estimate the deterioration curve in each group
  - The log-rank test and hazard are provided to show the magnitude of treatment effect and only used for descriptive purposes

Results

Patient Demographics and Clinical Characteristics

- A total of 674 patients were randomly assigned to either the tislelizumab arm (n=342) or the sorafenib arm (n=332)
- The demographics and clinical characteristics were generally balanced across the two treatment arms and were representative of the target patient population (**Table 1**)

Table 1. Patients Demographics and Patient Characteristics

		Tislelizumab (n=342)	Sorafenib (n=332)
Median age, years (range)		62.0 (25.0-86.0)	60.0 (23.0-86.0)
Male sex, n (%)		289 (84.5)	281 (84.6)
Geographic region, n (%)	Asia (excluding Japan)	215 (62.9)	210 (63.3)
	Japan	38 (11.1)	39 (11.7)
	Rest of world[a]	89 (26.0)	83 (25.0)
ECOG PS, n (%)	0	183 (53.5)	181 (54.5)
	1	159 (46.5)	151 (45.5)
BCLC staging at study entry, n (%)	B	70 (20.5)	80 (24.1)
	C	272 (79.5)	252 (75.9)
HCC etiology, n (%)	HBV	203 (59.4)	206 (62.0)
	HCV	46 (13.5)	39 (11.7)
	HBV and HCV co-infection	11 (3.2)	7 (2.1)
	Uninfected	82 (24.0)	80 (24.1)
Extrahepatic spread, n (%)		219 (64.0)	198 (59.6)
Macrovascular invasion, n (%)		51 (14.9)	49 (14.8)
Local regional therapy, n (%)		265 (77.5)	250 (75.3)
AFP ≥400 ng/ml, n (%)		135 (39.5)	116 (34.9)
Child-Pugh score, n (%)	5	263 (76.9)	248 (74.7)
	6	77 (22.5)	84 (25.3)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, European Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus. [a] Rest of world includes EU and US.

Completion Rates

- For the QLQ-C30, QLQ-HCC18, and the EQ-5D-5L the completion rate at baseline was over 95% (**Table 2**)
- The adjusted completion rates for all three PRO measures remained >92% for both arms at Cycle 4 and Cycle 6

Table 2. Completion Rates for HRQoL Assessments

	QLQ-C30		QLQ-HCC18		EQ-5D-5L	
	Tislelizumab	Sorafenib	Tislelizumab	Sorafenib	Tislelizumab	Sorafenib
Baseline						
Patients in study at visit, n	342	332	342	332	342	332
Patients complete questionnaire, n	328	321	326	320	327	321
Completion rate[a] (%)	95.9	96.7	95.3	96.4	95.6	96.7
Adjusted completion rate[b] (%)	95.9	96.7	95.3	96.4	95.6	96.7
Cycle 4						
Patients in study at visit, n	235	181	235	181	235	181
Patients complete questionnaire, n	220	176	220	176	220	176
Completion rate[a] (%)	64.3	53.0	64.3	53.0	64.3	53.0
Adjusted completion rate[b] (%)	93.6	97.2	93.6	97.2	93.6	97.2
Cycle 6						
Patients in study at visit, n	180	145	180	145	180	145
Patients complete questionnaire, n	166	137	166	138	166	137
Completion rate[a] (%)	48.5	41.3	48.5	41.6	48.5	41.3
Adjusted completion rate[b] (%)	92.2	94.5	92.2	95.2	92.2	94.5

HRQoL, health-related quality of life; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions.
[a]Completion rate = number of patients completed questionnaire / total number of patients in relevant treatment arm.
[b]Adjusted completion rate = number of patients completed questionnaire / total number of patients in study at relevant visits in relevant treatment arm.

Change from Baseline for EORTC QLQ-C30

- GHS/QoL, physical functioning, and fatigue maintained in patients treated with tislelizumab while worsening in patients treated with sorafenib at both cycles (**Figure 2**)

Change From Baseline for EORTC QLQ-HCC18

- At Cycle 4, the HCC18 index, fatigue, and pain symptoms were maintained in patients receiving tislelizumab while patients receiving sorafenib experienced worsening (**Figure 3**)
- At Cycle 6, the HCC18 index score worsened in both arms but the change from baseline was greater in the sorafenib arm
  - Fatigue maintained in the tislelizumab arm while worsening in the sorafenib arm; pain in both arms worsened

Change From Baseline for EQ-5D-5L VAS

- Maintenance in the VAS score at cycles 4 and 6 were observed for the tislelizumab arm while scores worsened in the sorafenib arm (**Table 3**)

Table 3. Change From Baseline for EQ-5D-5L VAS Scores at Cycle 4 and Cycle 6

	Tislelizumab (n=342)		Sorafenib (n=332)	
	Observed score, mean (SD), n	Change from baseline, mean (SD)	Observed score, mean (SD), n	Change from baseline, mean (SD)
Baseline	80.8 (16.16), 327	--	82.8 (14.37), 321	--
Cycle 4	81.8 (14.82), 213	−0.4 (14.52)	79.4 (15.10), 171	−4.3 (12.92)
Cycle 6	82.8 (15.42), 160	−0.2 (17.03)	78.7 (15.35), 133	−5.4 (13.09)

EQ-5D-5L, EuroQoL Five-Dimensions Five-Levels; SD, standard deviation; VAS, visual analogue scale.

Time to Deterioration

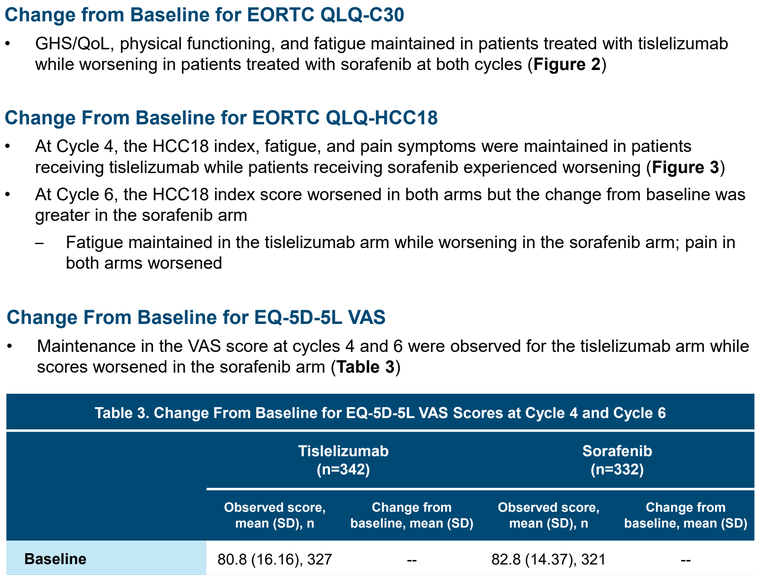
- For the QLQ-C30, patients receiving tislelizumab had a lower risk for deterioration of GHS/QoL, physical functioning, and fatigue
- Patients receiving tislelizumab also had a lower risk for deterioration in the HCC18 index score and the fatigue score of the QLQ-HCC18; both arms had a similar risk for deterioration in pain

Table 4. Time to Deterioration for EORTC QLQ-C30 and QLQ-HCC18

		Tislelizumab (n=342)	Sorafenib (n=332)
QLQ-C30			
GHS/QoL scale	Patients with event, n (%)	68 (19.9)	85 (25.6)
	Stratified[a] HR (95% CI)	0.68 (0.49, 0.94)	
Physical functioning scale	Patients with event, n (%)	57 (16.67)	94 (28.3)
	Stratified[a] HR (95% CI)	0.46 (0.33, 0.64)	
Fatigue	Patients with event, n (%)	96 (28.1)	150 (45.2)
	Stratified[a] HR (95% CI)	0.48 (0.37, 0.63)	
QLQ-HCC18			
Index score	Patients with event, n (%)	41 (12.0)	53 (16.0)
	Stratified[a] HR (95% CI)	0.53 (0.34, 0.81)	
Pain	Patients with event, n (%)	70 (20.5)	75 (22.6)
	Stratified[a] HR (95% CI)	0.78 (0.56, 1.09)	
Fatigue	Patients with event, n (%)	91 (26.6)	121 (36.4)
	Stratified[a] HR (95% CI)	0.60 (0.46, 0.80)	

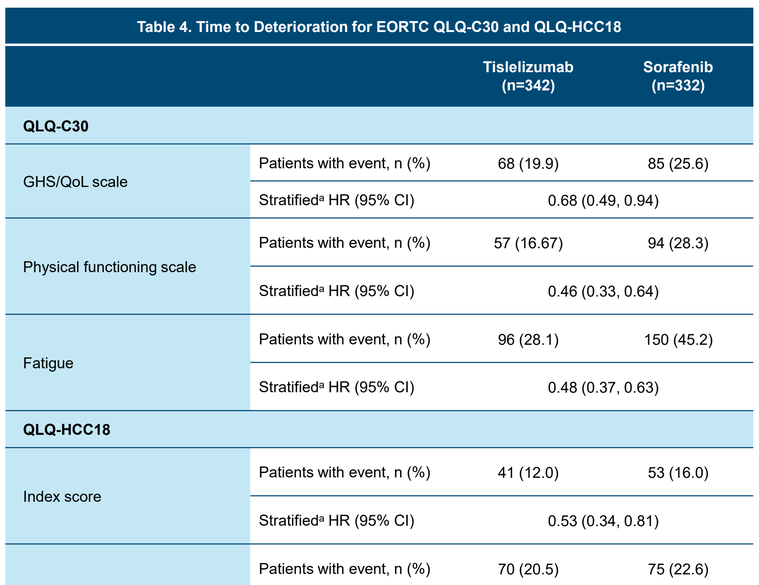
CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; QoL, quality of life. [a]Stratification factors included ECOG PS (0 versus 1) and investigator-chosen chemotherapy option (paclitaxel versus docetaxel versus irinotecan cells).

Figure 2. Change from Baseline for EORTC QLQ-C30



n = patients with baseline and at least 1 post-baseline measurement. Reported p-values are nominal.
EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LS, least square; QLQ-C30, Quality of Life Questionnaire Core 30 items; QoL, quality of life; SOR, sorafenib; TIS, tislelizumab.

Figure 3. Change From Baseline for EORTC QLQ-HCC18 at Cycle 4 and Cycle 6



n = patients with baseline and at least 1 post-baseline measurement. Reported p-values are nominal.
EORTC, European Organisation for Research and Treatment of Cancer; LS, least square; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions.

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