Tislelizumab versus sorafenib in first-line treatment of unresectable hepatocellular carcinoma: Impact on health-related quality of life in RATIONALE-301 population

Richard S. Finn[1], Shukui Qin[2], Masatoshi Kudo[3*], Tim Meyer[4], Frederic Boisserie[5], Songzi Li[5], Yaxi Chen[6], Gisoo Barnes[5], Ramil Abdrashitov[5], Andrew X. Zhu[7,8], Arndt Vogel[9]

[1]Department of Medicine, Division of Hematology/Oncology, University of California Los Angeles, Los Angeles, CA, United States; [2]Cancer Center, Qinhuai Medical District, General Hospital of Eastern Theater of PLA, Nanjing, China; [3]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan; [4]Department of Oncology, Royal Free Hospital NHS Trust and UCL Cancer Institute, London, United Kingdom; [5]BeiGene, USA., United States; [6]BeiGene (Beijing) Co., Ltd., China; [7]I-Mab Biopharma, Shanghai, China; [8]Jiahui International Cancer Center, Shanghai, China; [9]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

*Presenting Author

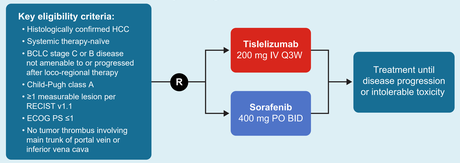
Introduction

- 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 3 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 4 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 Demographic and Clinical Characteristics

- A total of 674 patients was 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

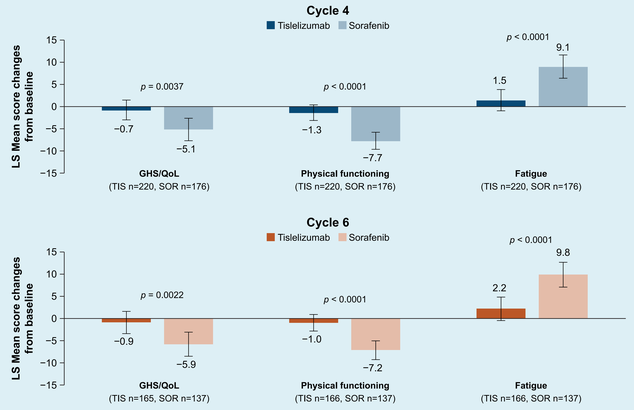
	QLQ-C30		QLQ-HCC18		EQ-5D-5L	
	Tislelizumab	Sorafenib	Tislelizumab	Sorafenib	Tislelizumab	Sorafenib
Baseline						
Patients in study at visit, n	342	332	342	332	342	332
Patients complete questionnaire, n	328	321	326	320	327	321
Completion rate[a] (%)	95.9	96.7	95.3	96.4	95.6	96.7
Adjusted completion 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**)

Figure 2. Change from Baseline for EORTC QLQ-C30

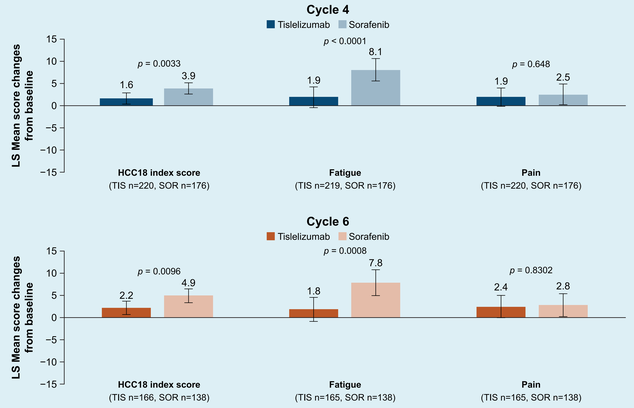


n = patients with baseline and at least 1 post-baseline measurement. Reported p values are nominal.
EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; LS, least square; QLQ-C30, Quality of Life Questionnaire Core 30 items; QoL, quality of life; SOR, sorafenib;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

Change from Baseline for EORTC QLQ-HCC18

- At cycle 4, the HCC18 index, fatigue, and pain symptoms scores 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

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



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

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; VAS, visual analogue scale; SD, standard deviation.

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).

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**

References

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Disclosures

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