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Impact of First-Line Treatment with Tislelizumab on Health-Related Quality of Life in Chinese Patients with Unresectable Hepatocellular Carcinoma

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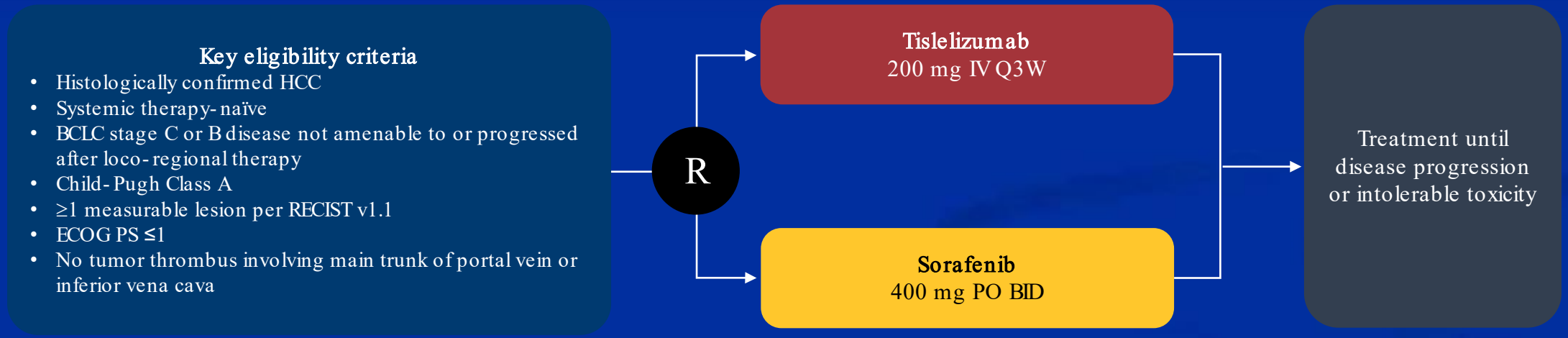
Background

- Liver cancer is the sixth most common cancer globally and the third leading cause of cancer death[1]
- HCC is the predominant subtype of liver cancer, accounting for approximately 80% of cases and occurring most commonly in Africa and Asia[2,3]
- HCC profoundly impacts the HRQoL of patients, spanning physical, psychological, social, and spiritual QoL domains[4-6]
- In the overall population of the phase 3 RATIONALE-301 trial (NCT03412773), tislelizumab demonstrated OS non-inferiority versus sorafenib (HR, 0.85; 95% CI, 0.71-1.02) as a 1L treatment of patients with unresectable HCC; OS superiority versus sorafenib was not met
    - Compared with patients treated with sorafenib, patients with HCC treated with 1L tislelizumab had better HRQoL outcomes, particularly in fatigue and physical functioning
- Given the heavy disease burden of HCC in the Asian population, the current post hoc analysis examined whether tislelizumab could improve HRQoL and reduce symptom burden compared with sorafenib in the Chinese subgroup of patients in RATIONALE-301

1. Sung et al. *CA Cancer J Clin*. 2021;71(3):209-249. 2. Golabi et al. *Medicine*. 2017;96(9):e5904. 3. Vogel et al. *Ann Oncol*. 2021;32(6):801-805. 4. Fan et al. *Clin Gastroenterol Hepatol*. 2010;8(7):559-564.e1-e10. 5. Muzellec et al. *Cancers (Basel)*. 2021;14(1):179. 6. Norman et al. *Eur J Cancer Care (Engl)*. 2022;31(6):e13672.
1L, first-line; HCC; hepatocellular carcinoma; HR, hazard ratio; HRQoL, health-related quality of life; OS, overall survival

Study Design

- 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)



- HRQoL was a secondary endpoint and was assessed using PROs via 3 validated PRO instruments:
  - The EORTC QLQ-C30
  - The EORTC QLQ-HCC18
  - The EQ-5D-5L VAS

BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL 5-dimension 5-level questionnaire; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; IV, intravenous; PO, orally; PROs, patient-reported outcomes; Q3W, once every 3 weeks; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; uHCC, unresectable HCC; VAS, visual analog scale.

Methods

HRQoL Assessments and Endpoints

- The PRO measures were collected at baseline, at every cycle through Cycle 12, then every 4 cycles thereafter, and at the end of the treatment visit
- The following key prespecified 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 GHS/QoL, physical functioning, and fatigue scales, with higher scores representing better outcomes on the GHS/QoL and physical functioning scales but a 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 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 date of July 11, 2022
- The ITT population included all randomized patients; patients were analyzed according to their randomized treatment arm (ie, either tislelizumab or sorafenib)
- 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 the 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 are only used for descriptive purposes

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D-5L, EuroQoL 5-dimension 5-level questionnaire; GHS, global health status; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; ITT, intent-to-treat; PRO, patient-reported outcome; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; QoL, quality of life; VAS, visual analog scale.

Results

- Analysis was conducted in the subgroup of 425 Chinese participants (tislelizumab n=215; sorafenib n=210)

	Chinese Subgroup		ITT Population	
	Tislelizumab (n=215)	Sorafenib (n=210)	Tislelizumab (n=342)	Sorafenib (n=332)
Median age (range), years	55 (25-85)	54 (23-85)	62 (25-86)	60 (23-86)
Male, n (%)	182 (84.7)	180 (85.7)	289 (84.5)	281 (84.6)
Child-Pugh score, n (%)				
5	158 (73.5)	163 (77.6)	263 (76.9)	248 (74.7)
6	57 (26.5)	47 (22.4)	77 (22.5)	84 (25.3)
BCLC staging, n (%)				
Stage B	25 (11.6)	29 (13.8)	70 (20.5)	80 (24.1)
Stage C	190 (88.4)	181 (86.2)	272 (79.5)	252 (75.9)
ECOG Performance Status, n (%)				
0	92 (42.8)	91 (43.3)	183 (53.5)	181 (54.5)
1	123 (57.2)	119 (56.7)	159 (46.5)	151 (45.5)
Extrahepatic spread, n (%)				
Absent	62 (28.8)	64 (30.5)	123 (36.0)	134 (40.4)
Present	153 (71.2)	146 (69.5)	219 (64.0)	198 (59.6)
Macrovascular invasion, n (%)				
Absent	183 (85.1)	177 (84.3)	291 (85.1)	283 (85.2)
Present	32 (14.9)	33 (15.7)	51 (14.9)	49 (14.8)
Median follow-up (range), months	13.8 (0.1-50.8)	13.1 (0.1-49.4)	15.0 (0.1-50.8)	13.5 (0.0-54.5)
Minimum study follow-up, months	34	33	33	33

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat.

Completion Rates for HRQoL Assessments

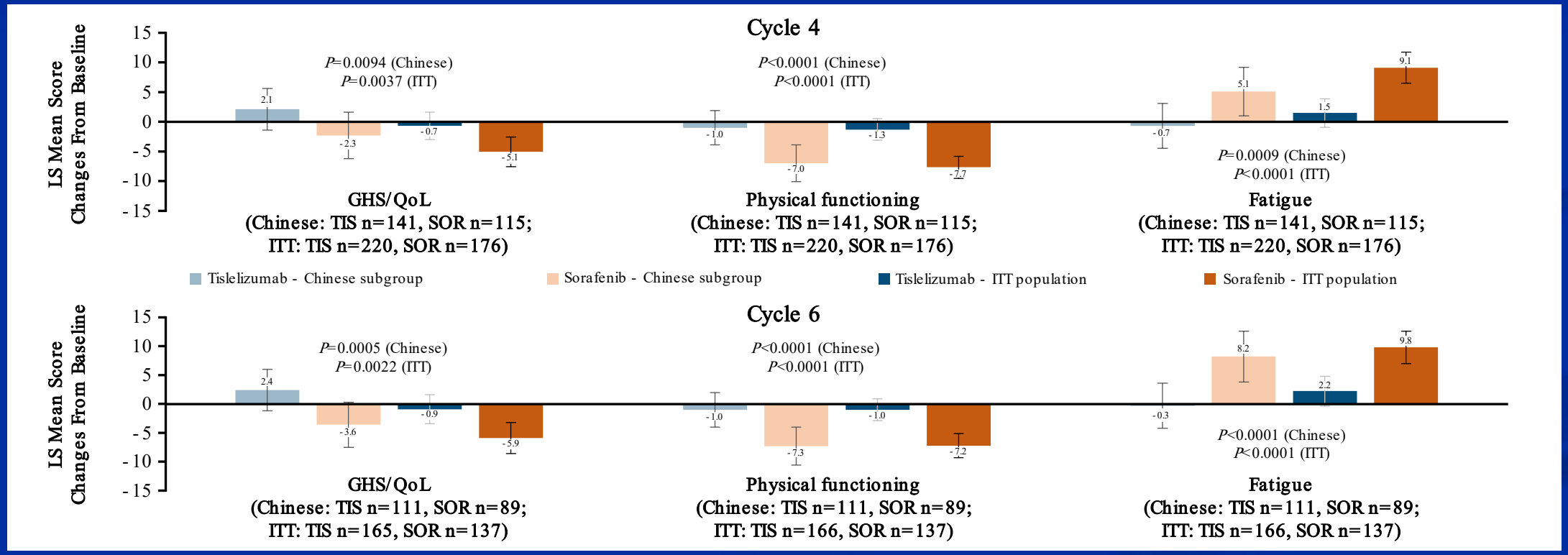
- For the PRO measures, the completion rates and adjusted completion rates for the Chinese subgroup were comparable to those of the ITT population

		Chinese Subgroup		ITT Population	
	n (%)	Tislelizumab (n=215)	Sorafenib (n=210)	Tislelizumab (n=342)	Sorafenib (n=332)
QLQ-C30	**Baseline**				
	Completion rate	99.5	99.5	95.9	96.7
	Adjusted completion rate	99.5	99.5	95.9	96.7
	Cycle 4				
	Completion rate	65.6	54.8	64.3	53.0
	Adjusted completion rate	98.6	100.0	93.6	97.2
	Cycle 6				
	Completion rate	51.6	42.4	48.5	41.3
	Adjusted completion rate	98.2	98.9	92.2	94.5
QLQ-HCC18	**Baseline**				
	Completion rate	99.5	99.5	95.3	96.4
	Adjusted completion rate	99.5	99.5	95.3	96.4
	Cycle 4				
	Completion rate	65.6	54.8	64.3	53.0
	Adjusted completion rate	98.6	100.0	93.6	97.2
	Cycle 6				
	Completion rate	51.6	42.4	48.5	41.6
	Adjusted completion rate	98.2	98.9	92.2	95.2
EQ-5D-5L	**Baseline**				
	Completion rate	99.5	99.5	95.6	96.7
	Adjusted completion rate	99.5	99.5	95.6	96.7
	Cycle 4				
	Completion rate	65.6	54.8	64.3	53.0
	Adjusted completion rate	98.6	100.0	93.6	97.2
	Cycle 6				
	Completion rate	51.6	42.4	48.5	41.3
	Adjusted completion rate	98.2	98.9	92.2	94.5

Completion rate = number of patients completed questionnaire/total number of patients in relevant treatment arm. Adjusted completion rate = number of patients completed questionnaire/total number of patients in study at relevant visits in relevant treatment arm.
EQ-5D-5L, EuroQoL 5-dimension 5-level questionnaire; HRQoL, health-related quality of life; ITT, intent-to-treat; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions.

Change from Baseline for EORTC QLQ-C30

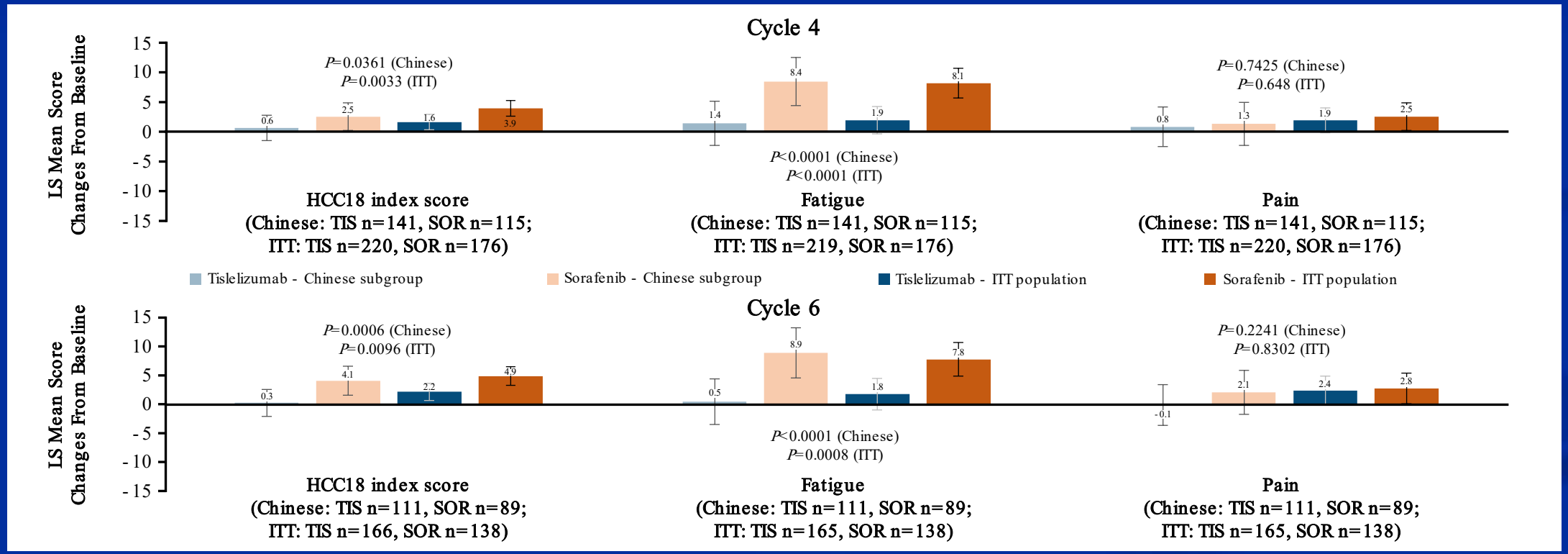
- In the Chinese subgroup, GHS/QoL improved at Cycles 4 and 6 in patients treated with tislelizumab, while it worsened in patients treated with sorafenib. The tislelizumab arm experienced maintenance at both cycles in the ITT population
- Similar to the ITT population, physical functioning and fatigue were maintained in the Chinese subgroup treated with tislelizumab, while they worsened in the Chinese subgroup treated with sorafenib at both cycles



n=patients with baseline and ≥1 post-baseline measurement. Reported *P* values are nominal.
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; GHS, global health status; ITT, intent-to-treat; LS, least squares; QoL, quality of life; SOR, sorafenib; TIS, tislelizumab.

Change from Baseline for EORTC QLQ-HCC18

- Similar to the ITT population at Cycle 4, the index score and fatigue were significantly different in the Chinese subgroup arms, with the tislelizumab arm maintaining and the sorafenib arm worsening
- At Cycle 6, the index score and fatigue were once again significantly different between the arms of the subgroup of Chinese patients with the tislelizumab arm maintaining and the sorafenib arm worsening



n=patients with baseline and ≥1 post-baseline measurement. Reported *P* values are nominal.
EORTC, European Organisation for Research and Treatment of Cancer; ITT, intent-to-treat; LS, least squares; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions.

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

- In the Chinese subgroup, the pattern of change from baseline for the VAS score at Cycles 4 and 6 was similar to what was found in the ITT population
  - The scores in the tislelizumab arm were maintained, while the scores in the sorafenib arm worsened

	Chinese Subgroup				ITT Population			
	Tislelizumab (n=215)		Sorafenib (n=210)		Tislelizumab (n=342)		Sorafenib (n=332)	
	Observed Mean (SD)	Change From Baseline Mean (SD)	Observed Mean (SD)	Change From Baseline Mean (SD)	Observed Mean (SD)	Change From Baseline Mean (SD)	Observed Mean (SD)	Change From Baseline Mean (SD)
Baseline	84.0 (13.29)	-	84.7 (12.78)	-	80.8 (16.16)	-	82.8 (14.37)	-
Cycle 4	84.5 (13.46)	-1.0 (12.26)	81.5 (14.15)	-4.0 (12.60)	81.8 (14.82)	-0.4 (14.52)	79.4 (15.10)	-4.3 (12.92)
Cycle 6	84.9 (13.32)	-0.6 (13.60)	80.0 (14.79)	-5.5 (12.36)	82.8 (15.42)	-0.2 (17.03)	78.7 (15.35)	-5.4 (13.09)

EQ-5D-5L, EuroQoL 5-dimension 5-level questionnaire; ITT, intent-to-treat; SD, standard deviation; VAS, visual analog scale.

Time to Deterioration

- In the Chinese subgroup and ITT population, tislelizumab had a lower risk for deterioration for the QLQ-C30 scales of GHS/QoL, physical functioning, and fatigue
- For the QLQ-HCC18, tislelizumab had a lower risk for deterioration for the index score and fatigue
  - Both arms had a similar risk for deterioration in pain

			Chinese Subgroup		ITT Population	
			Tislelizumab (n=215)	Sorafenib (n=210)	Tislelizumab (n=342)	Sorafenib (n=332)
QLQ-C30	GHS/QoL scale	Patients with event, n (%)	36 (16.7)	56 (26.7)	68 (19.9)	85 (25.6)
		Stratified[a] HR (95%CI)	0.52 (0.34-0.79)		0.68 (0.49-0.94)	
	Physical functioning scale	Patients with event, n (%)	31 (14.4)	59 (28.1)	57 (16.67)	94 (28.3)
		Stratified[a] HR (95%CI)	0.39 (0.25-0.60)		0.46 (0.33-0.64)	
	Fatigue	Patients with event, n (%)	51 (23.7)	93 (44.3)	96 (28.1)	150 (45.2)
		Stratified[a] HR (95%CI)	0.41 (0.29-0.58)		0.48 (0.37-0.63)	
QLQ-HCC18	Index score	Patients with event, n (%)	18 (8.4)	31 (14.8)	41 (12.0)	53 (16.0)
		Stratified[a] HR (95%CI)	0.37 (0.20-0.69)		0.48 (0.37-0.63)	
	Pain	Patients with event, n (%)	43 (20.0)	44. (21.0)	70 (20.5)	75 (22.6)
		Stratified[a] HR (95%CI)	0.83 (0.55-1.27)		0.78 (0.56-1.09)	
	Fatigue	Patients with event, n (%)	52 (24.2)	82 (39.0)	91 (26.6)	121 (36.4)
		Stratified[a] HR (95%CI)	0.49 (0.34-0.69)		0.60 (0.46-0.80)	

[a]Stratification factors included ECOG PS (0 vs 1) and investigator-chosen chemotherapy option (paclitaxel vs docetaxel vs irinotecan cells).
CI, confidence interval; ECOG PS, European Cooperative Oncology Group Performance Status; GHS, global health status; HR, hazard ratio; ITT, intent-to-treat; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; QoL, quality of life.

Conclusions

- Chinese patients with HCC treated with 1L tislelizumab had better HRQoL outcomes compared with patients treated with sorafenib, particularly in terms of GHS/QoL, fatigue, and physical functioning
- These results, coupled with non-inferiority in OS, a numerically higher response rate compared with sorafenib, and a favorable safety profile, highlight the benefit of tislelizumab as a potential 1L treatment option for uHCC

1L, first-line; GHS, global health status; HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; OS, overall survival; QoL, quality of life; uHCC, unresectable HCC.

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