ASCO® Gastrointestinal Cancers Symposium

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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Introduction

- 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 of HCC and its treatments profoundly impact the 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 uHCC, met its primary endpoint of OS non-inferiority (mOS: 15.9 months vs 14.1 months; stratified HR 0.85 [95% CI 0.712, 1.019; P=0.0398)
- The objective of this analysis was to evaluate the impact of tislelizumab monotherapy on patients' HRQoL and HCC-related symptoms

HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; OS, overall survival; uHCC, unresectable hepatocellular carcinoma.

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians.* 2021;71(3):209-249. 2. Norman EML, Weil J, Philip J. Hepatocellular Carcinoma and its Impact on Quality of Life: A Review of the Qualitative Literature. *European Journal of Cancer Care.* 2022:e13672.

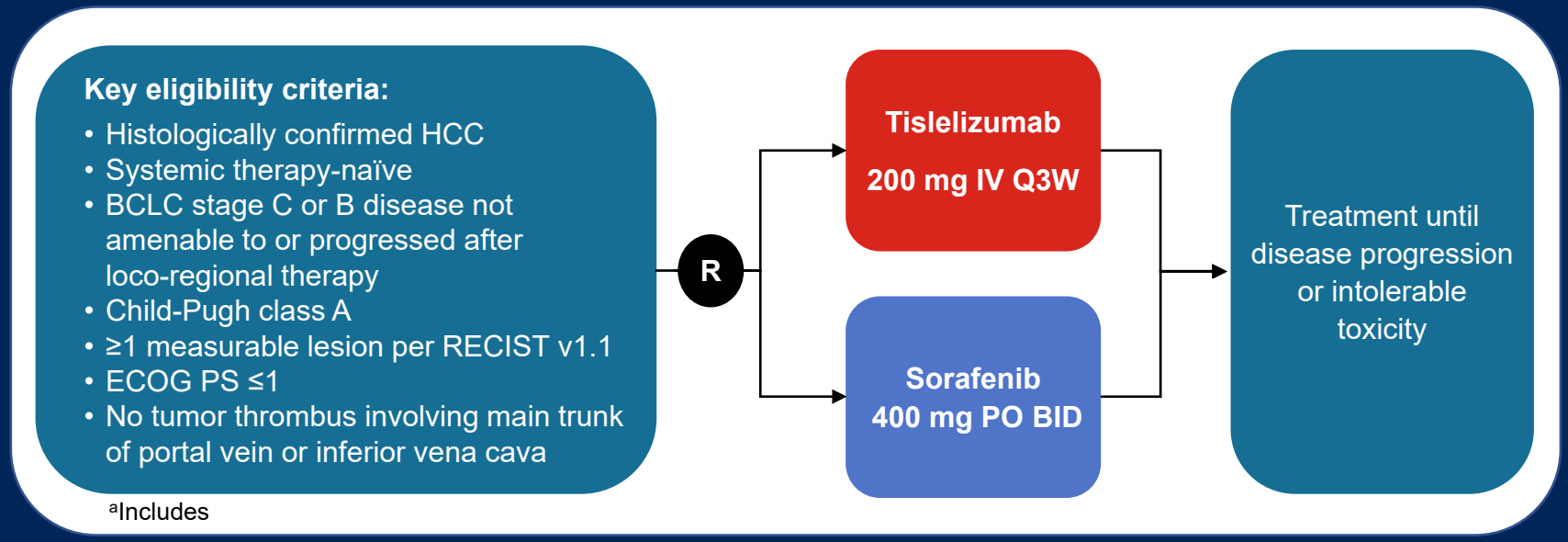
Methods

PRO endpoints to compare health-related quality of life (HRQoL) between tislelizumab and sorafenib

- The EORTC QLQ-C30: GHS/QoL, physical functioning, and fatigue
- The EORTC QLQ-HCC18: index, fatigue, and pain scores

For descriptive purposes the EQ-5D-5L's VAS score was included

RATIONALE-301 Study Design



- **Primary endpoint:** OS in the ITT population
- **Key secondary endpoints:** ORR, PFS, and DoR by BIRC per RECIST v1.1, and safety
- **Stratification factors:** Macrovascular invasion (present vs absent), extrahepatic spread (present vs absent), ECOG PS (0 vs 1), etiology (HCV vs other[a]), geography (Asia [excluding Japan], vs Japan vs rest of world)

BCLC, Barcelona Clinic Liver Cancer; BID, Twice daily; ECOG PS, European Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQoL Five-Dimensions Five-Levels; GHS/QoL, global health status/quality of life; HBV, Hepatitis B Virus; HCC, Hepatocellular Carcinoma; IV, Intravenous; PO, Oral; PRO, patient-reported outcome; Q3W, Once every 3 weeks; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; R, randomized; VAS, Visual analog scale; RECIST, Response Evaluation Criteria In Solid Tumors.

Methods

- The key clinical cycles were cycle 4 and cycle 6, and were selected to measure short-term change (cycle 4) and long-term change (cycle 6)
- Differences in change from baseline to cycle 4 and cycle 6 in each key PRO endpoint was analyzed using a mixed effect model analysis for measuring changes post-baseline
- TTD analysis was performed to compare key quality of life scores between the two treatment groups
  - TTD is defined as the time from randomization to the first occurrence of a worsening by ≥10 points (HCC18 index score and GHS/QoL of the QLQ-C30)

GHS/QoL, global health status/quality of life; HCC18, Hepatocellular Carcinoma 18 Questions; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30 items; TTD, time to deterioration.

Patient Demographics and Patient Characteristics

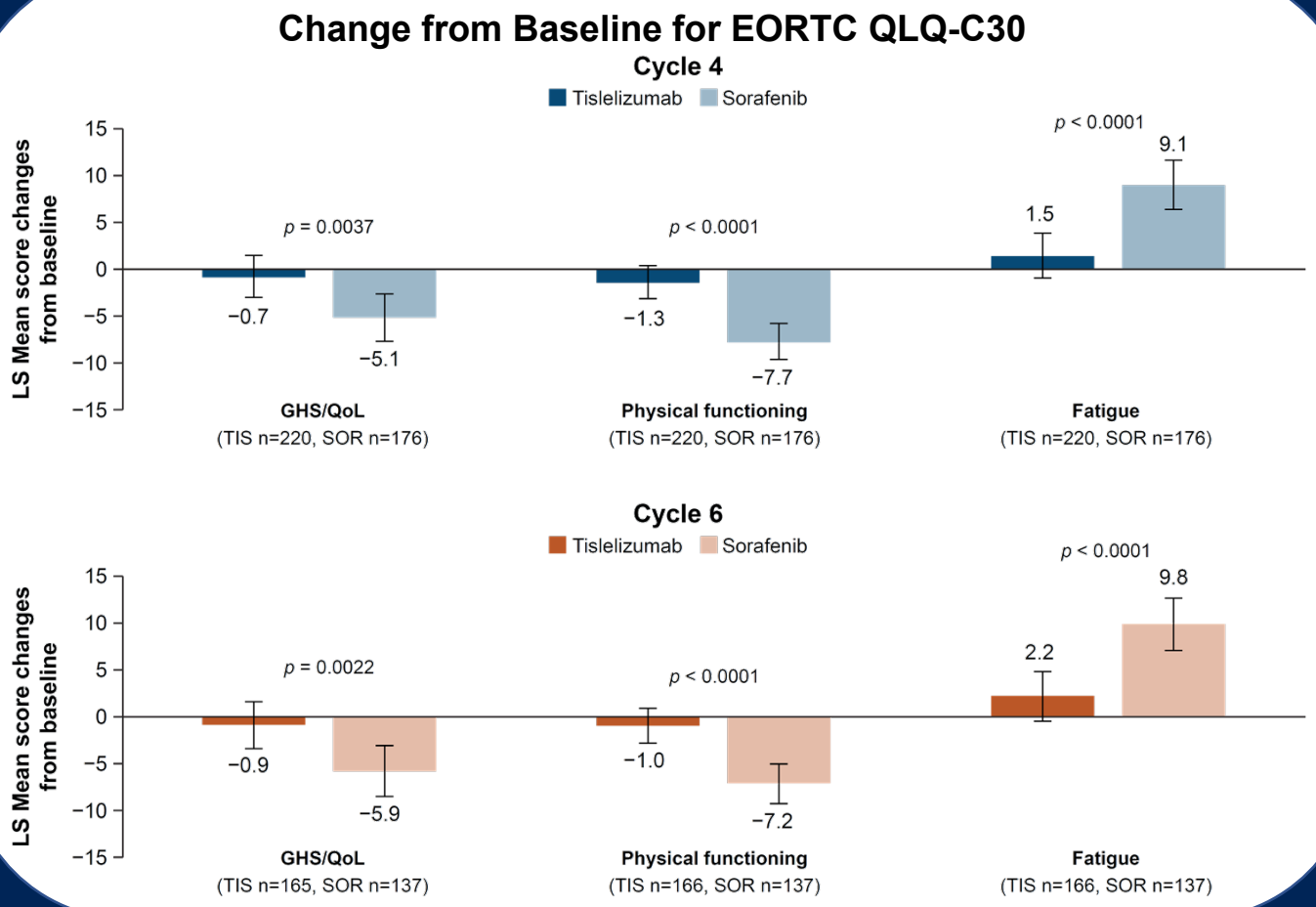
- A total of 674 patients were randomly assigned to either the tislelizumab arm (n = 342) or the sorafenib arm (n = 332)
- The demographics and clinical characteristics were generally balanced across the two treatment arms and were representative of the target patient population
- For the QLQ-C30, QLQ-HCC18, and the EQ-5D-5L the completion rate at baseline was over 95%
  - The adjusted completion rates for all three PRO measures remained > 92% for both arms at cycle 4 and cycle 6

		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)

[a] Rest of world includes EU and US.

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, European Cooperative Oncology Group performance status; EU, European Union; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; US, United States.

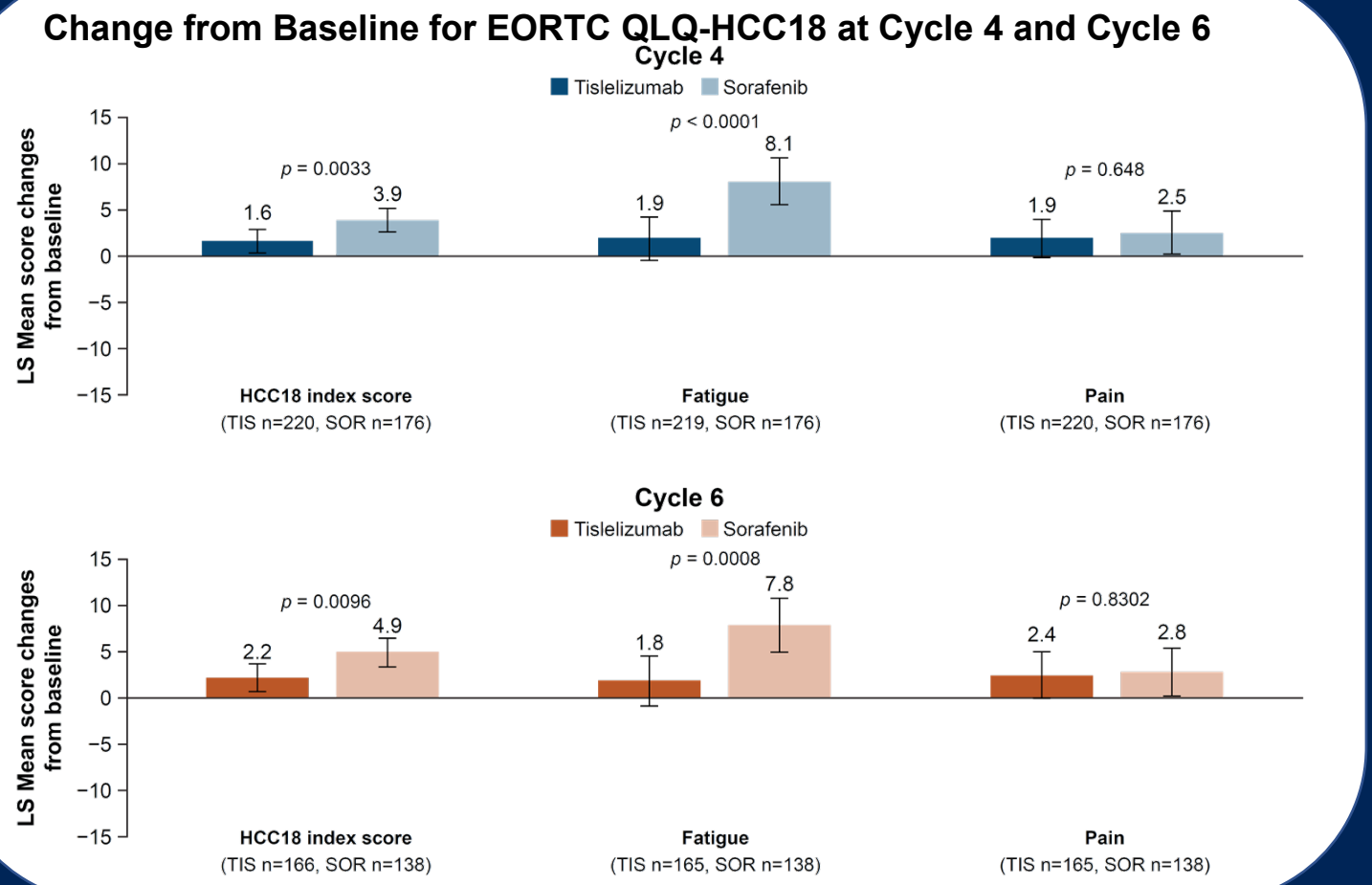
QLQ-C30 Scales Maintained in Tislelizumab Treated Patients



GHS/QoL, physical functioning, and fatigue maintained in patients treated with tislelizumab while worsened in patients treated with sorafenib at both cycles

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

HCC Symptoms Maintained in Tislelizumab Treated Patients



- At cycle 4, tislelizumab patients maintained on the HCC18 index score as well as the fatigue and pain symptoms scores while the sorafenib patients experienced worsening of fatigue
- 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 and for pain both arms worsened

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

Maintenance in the VAS Score at Cycles 4 and 6 was Observed for the Tislelizumab arm While Scores Worsened in the Sorafenib arm

Change from Baseline for EQ-5D-5L VAS Scores at Cycle 4 and Cycle 6

	Tislelizumab (N = 342)		Sorafenib (N = 332)	
	Observed Mean (SD), n	Change from Baseline Mean (SD)	Observed 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.

Tislelizumab had a Lower Risk for Deterioration of GHS/QoL, Physical Functioning, and Fatigue [9]

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)	

[a] Stratification factors included Eastern Cooperative Oncology Group performance status (0 versus 1) and investigator-chosen chemotherapy option (paclitaxel versus docetaxel versus irinotecan cells).

EORTC, European Organisation for Research and Treatment of Cancer; CI, confidence interval; GHS/QoL, global health status/quality of life; HR, hazard ratio; QLC-C30, Quality of Life Questionnaire Core 30 items; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions.

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, tislelizumab patients 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

HCC, hepatocellular carcinoma; HRQoL, health-related quality of life; uHCC, unresectable hepatocellular carcinoma.

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