Tislelizumab versus Sorafenib in First-Line Treatment of Unresectable Hepatocellular Carcinoma: Impact on Health-Related Quality of Life in RATIONALE-301 Study

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Abstract

Introduction: RATIONALE-301 (NCT03412773) was a global, phase 3 study comparing the efficacy and safety of tislelizumab with sorafenib as first-line (1L) treatment in adult patients with unresectable hepatocellular carcinoma (HCC) that met its primary endpoint of noninferiority in overall survival (OS). This analysis compared health-related quality-of-life (HRQOL) outcomes between the arms. ***Methods:*** Systemic therapy-naive adults with HCC were randomized 1:1 to receive tislelizumab (*n* = 342) or sorafenib (*n* = 332). HRQOL was assessed using EORTC QLQ-C30, QLQ-HCC18, and EQ-5D-5L. At cycles 4 and 6, a mixed model for repeated measures was performed using key-prespecified patient-reported outcome (PRO) endpoints of the QLQ-C30 and the QLQ-HCC18. Time to deterioration was analyzed with the Kaplan-Meier method using the PRO endpoints. ***Results:*** At cycles 4 and 6, patients in the tislelizumab arm had better HRQOL outcomes than the patients in the sorafenib arm per mean-change difference in GHS/QOL, QLQ-C30 physical functioning and fatigue, and QLQ-HCC18 symptom index; however, no differences for pain were observed. Patients in the tislelizumab arm had lower risk of deterioration in GHS/QOL (HR: 0.68; 95% CI: 0.49–0.94), QLQ-C30 physical functioning (HR: 0.45; 95% CI: 0.32–0.63) and fatigue (HR: 0.47; 95% CI: 0.36–0.61), QLQ-HCC18 symptom index (HR: 0.52; 95% CI: 0.34–0.81), and HCC-specific fatigue (HR: 0.59; 95% CI: 0.45–0.79). For pain, both arms had similar risk of deterioration (HR: 0.78; 95% CI:

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0.56–1.09). At cycles 4 and 6, patients in the tislelizumab arm maintained in EQ-5D-5L visual analog scale, whereas scores decreased for the patients in the sorafenib arm. ***Conclusion:*** Patients with 1L HCC treated with tislelizumab had favorable HRQOL outcomes compared with patients treated with sorafenib, particularly in fatigue and physical functioning. These results, along with favorable safety profile, better response rate, and OS noninferiority, support tislelizumab as a potential 1L treatment option for unresectable HCC.

Introduction

Hepatocellular carcinoma (HCC) is a global health challenge that accounts for 75–85% of all reported cases of liver cancer and is one of the most common causes of cancer-related death [1]. The natural progression of HCC, as well as the side effects associated with some treatments, has a substantial negative impact on patients' health-related quality of life (HRQOL) [2, 3]. In fact, patients with HCC often have significantly worse HRQOL than patients with other chronic liver diseases [4]. Moreover, HRQOL has been found to be a meaningful prognostic factor for overall survival (OS), with better HRQOL associated with longer survival [5–7].

For the treatment of HCC, atezolizumab plus bevacizumab is the standard treatment for first-line HCC; no single-agent checkpoint inhibitor has been approved in this setting [8, 9]. Atezolizumab and other immunotherapeutic agents (e.g., tislelizumab, nivolumab, sintilimab), used in combination with bevacizumab or as monotherapy, have been shown to stabilize and in some cases improve HRQOL as they reduce some of the HCC-related symptoms [10–13]. While a combination therapy is clinically effective, there are patients who would benefit from single-agent tyrosine kinase inhibitor (TKI), such as sorafenib, or immunotherapy including those with bevacizumab contraindication who cannot tolerate doublet therapy.

Tislelizumab is a humanized immunoglobulin G4 variant monoclonal antibody against programmed cell death protein-1 (PD-1). Tislelizumab was specifically engineered to minimize binding to Fcγ receptors on macrophages in order to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. In other indications, such as advanced squamous or nonsquamous non-small cell lung cancer and esophageal squamous cell carcinoma, in which tislelizumab demonstrated clinical benefits [14–16], patients experience maintenance or improvement in HRQOL as well as reduced cancer-specific symptoms compared with patients receiving chemotherapy [17–19].

RATIONALE-301 (NCT03412773), a multi-country, phase 3 study comparing tislelizumab with sorafenib as first-line treatment in adult patients with unresectable HCC, met its primary endpoint of OS noninferiority [20]. The trial demonstrated noninferiority of tislelizumab compared to sorafenib with respect to OS (median OS, 15.9 months vs. 14.1 months, respectively; stratified HR: 0.85; 95% CI: 0.712–1.019; p = 0.0398). Tislelizumab was also associated with a higher objective response rate (14.3% vs. 5.4%) and more durable responses versus sorafenib (median duration of response, 36.1 vs. 11.0 months); median progression-free survival was 2.1 versus 3.4 months with tislelizumab versus sorafenib, respectively.

The secondary endpoints in RATIONALE-301 included HRQOL using patient-reported outcome (PRO) measures. The objective of the current analysis was to determine the differences in HRQOL and assess the time to deterioration (TTD) in patients with unresectable HCC treated with tislelizumab versus sorafenib in the first-line setting.

Methods

Study Design and Population
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). Eligible patients were systemic therapy-naive adults (≥18 years of age) with histologically confirmed HCC, Barcelona Clinic Liver Cancer stage C or B disease not amenable to or having progressed after locoregional therapy, and Child-Pugh class A. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, at least one measurable/evaluable lesion by Response Evaluation Criteria in Solid Tumors version 1.1, and adequate hematological, hepatic, renal, and coagulation functions. In addition, patients were required to have no tumor thrombus involving the main trunk of the portal vein or inferior vena cava. The study was carried out in accordance with the International Conference for Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations. All patients provided written informed consent before participating. This study protocol was reviewed and approved by Ethics Committees at each of the participating sites. This full list of participating sites and Ethics Committees can be found in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000537966).

PRO Endpoints
The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30), EORTC-Hepatocellular Carcinoma 18 Questions (QLQ-HCC18), and EuroQol Five-Dimensions Five-Levels (EQ-5D-5L) were used to assess HRQOL and symptoms associated with HCC. Key PRO endpoints were selected based on the most relevant disease- and treatment-related symptoms [2, 3] and included the global health status/quality of life (GHS/QOL), physical

Table 1. Patient demographics and characteristics

	Tislelizumab (n = 342)	Sorafenib (n = 332)
Median age (range), years	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 infection	203 (59.4)	206 (62.0)
HCV infection	46 (13.5)	39 (11.7)
HBV and HCV coinfection	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)
Locoregional 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, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus. [a]Rest of world includes the European Union and the USA.

functioning, and fatigue scales of the EORTC QLQ-C30 and the index, fatigue, and pain scores of the QLQ-HCC18. Higher scores in GHS/QOL and physical functioning and lower scores in symptom scales indicated better HRQOL outcomes. The prespecified key clinical cycles were cycle 4 and cycle 6, which were selected to measure short-term change (cycle 4) and long-term change (cycle 6). Additionally, the EQ-5D-5L's visual analog scale (VAS) score recorded the patient's self-rated health, with higher scores reflecting better perceived health.

Statistical Analyses

The PRO analyses included all randomized patients who completed baseline, received at least one dose of study drug, and completed at least one post-baseline HRQOL assessment. Completion rates were defined as the number of patients who completed the PRO questionnaires at that cycle divided by the total number of patients in each treatment arm. Adjusted completion rates were defined as the number of patients who completed the PRO questionnaires divided by the total number of patients remaining in the study at cycle 4 or 6 in the treatment arms.

Descriptive analyses for all the scales of the PRO questionnaires were performed. Within-arm and between-arm differences in the change from baseline at 95% CI to cycle 4 and cycle 6 were assessed using a mixed model for repeated measures. The model included baseline scores, stratification factors, treatment arms, visits, and treatment arm by visit interaction as fixed effects and visit as a repeated measure with an unstructured covariance matrix based on the missing at random assumption. The compound symmetry covariance matrix was used if there was a convergence issue for the unstructured covariance matrix.

TTD was performed to compare key PRO endpoints between treatment arms. The deterioration threshold was defined as the time from randomization to the first occurrence of a ≥10 point increase in scores in a worsening direction [21–23]. A deterioration was not counted as an event if an improvement subsequently occurred. If a patient did not have an event (death or ≥10% deterioration), they were censored at the last clinic visit at which HRQOL was measured. A nonparametric Kaplan-Meier method was used to estimate the deterioration curve in each group. A Cox regression model was estimated that included

Table 2. Completion rates for HRQOL assessments

	Tislelizumab (n = 342)	Sorafenib (n = 332)
QLQ-C30		
Baseline		
Completion rate	95.9	96.7
Adjusted completion rate	95.9	96.7
Cycle 4		
Completion rate	64.3	53.0
Adjusted completion rate	93.6	97.2
Cycle 6		
Completion rate	48.5	41.3
Adjusted completion rate	92.2	94.5
QLQ-HCC18		
Baseline		
Completion rate	95.3	96.4
Adjusted completion rate	95.3	96.4
Cycle 4		
Completion rate	64.3	53.0
Adjusted completion rate	93.6	97.2
Cycle 6		
Completion rate	48.5	41.6
Adjusted completion rate	92.2	95.2
EQ-5D-5L		
Baseline		
Completion rate	95.6	96.7
Adjusted completion rate	95.6	96.7
Cycle 4		
Completion rate	64.3	53.0
Adjusted completion rate	93.6	97.2
Cycle 6		
Completion rate	48.5	41.3
Adjusted completion rate	92.2	94.5

EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol Five-Dimensions Five-Levels; HRQOL, health-related quality of life; QLC-C30, Quality of Life Questionnaire Core 30 items; QLC-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions.

treatment as covariate, geography (Asia [including Japan] vs. EU/US), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. other), and ECOG (0 vs. 1) as stratification factor. The log-rank test and hazard ratio were provided to show the magnitude of treatment effects, and p values were calculated for descriptive purposes.

Results

A total of 674 patients were randomly assigned to either the tislelizumab arm (n = 342) or the sorafenib arm (n = 332). Demographics and clinical characteristics were generally balanced between the two treatment arms and were representative of the target patient population (Table 1). The data cutoff date for the current analysis was August 1, 2022.

Adjusted Completion Rates
Adjusted completion rates were similar for all three PRO assessments and between the arms, with ≥95% completion at baseline, ≥94% at cycle 4, and ≥92% at cycle 6 (Table 2).

Descriptive Analysis
Observed means and mean change from baseline for each of the QLQ-C30 and QLQ-HCC18 scales are provided in online supplementary Tables 2 and 3. Overall, changes in
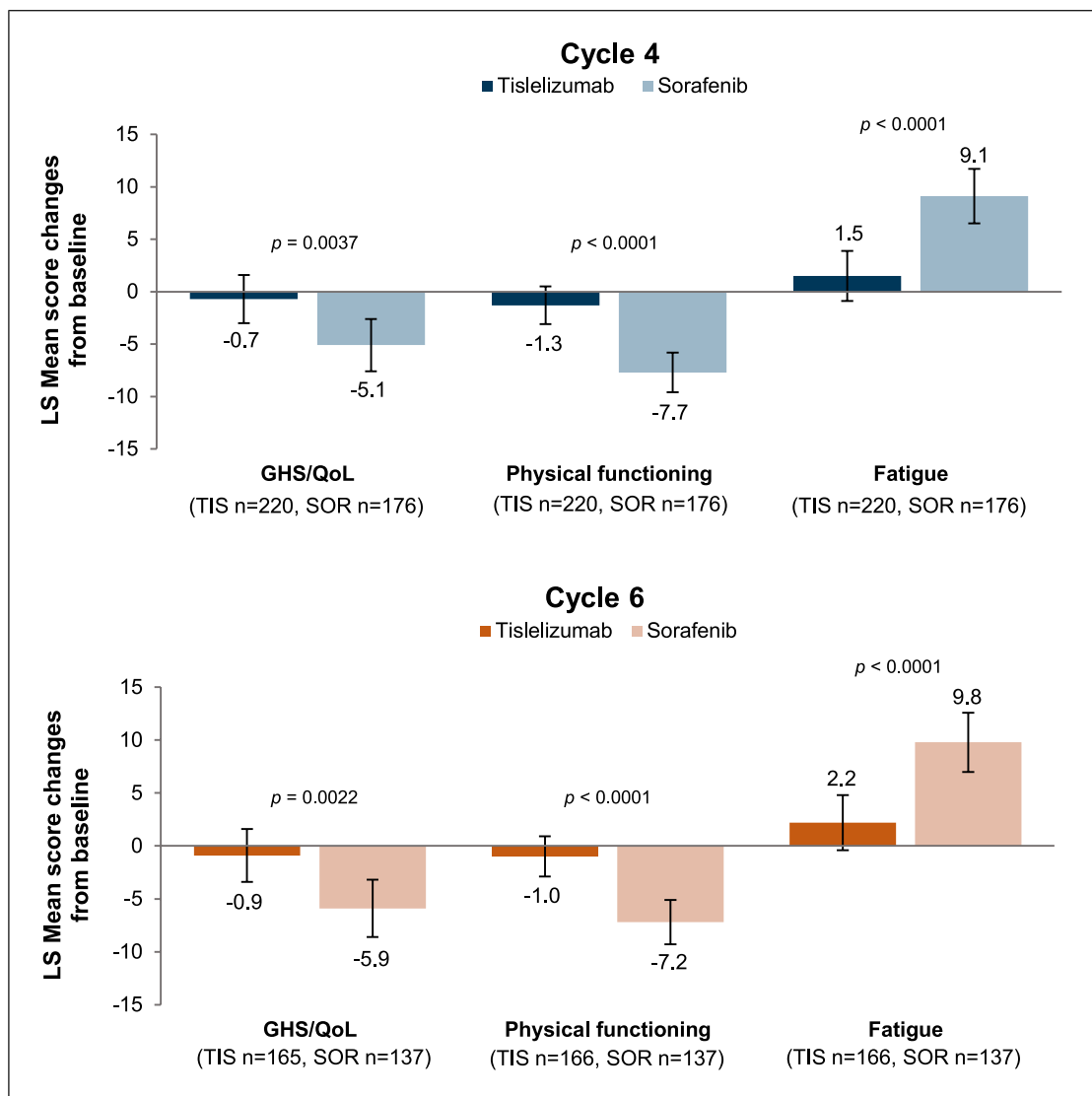
Fig. 1. Changes from baseline for EORTC QLQ-C30 at cycle 4 and cycle 6. Reported *p* values are nominal. EORTC, European Organisation for Research and Treatment of Cancer; GHS/QOL, global health status/quality of life; LS, least squares; *n*, patients with one baseline and at least one post-baseline measurement; QLQ-C30, Quality of Life Questionnaire Core 30; SOR, sorafenib; TIS, tislelizumab.
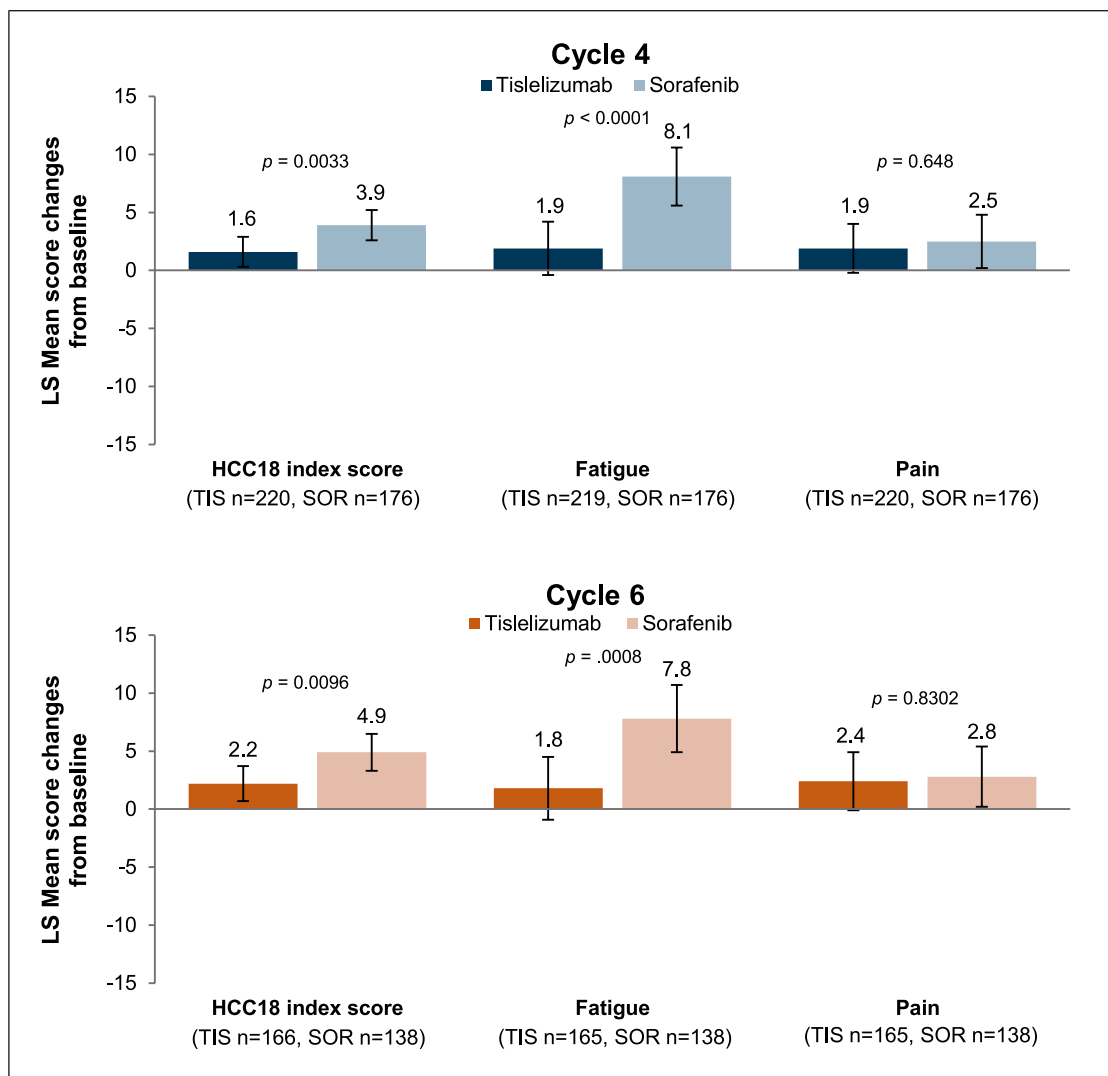
scores from baseline to cycle 4 and cycle 6 indicated better outcomes for the patients in the tislelizumab arm versus patients in the sorafenib arm, especially for GHS/QOL, physical functioning, and fatigue measured by QLQ-C30 (online suppl. Table 2) and by the index and fatigue scores measured by QLQ-HCC18 at cycle 6 (online suppl. Table 3).

Mixed Model for Repeated Measures Analysis Results

Least-squares mean differences at 95% CI demonstrated (Fig. 1) that the GHS/QOL score was maintained for patients in the tislelizumab arm and declined for patients in the sorafenib arm at both cycle 4 (tislelizumab, −0.7 [95% CI: −3.0 to 1.6]; sorafenib, −5.1 [95% CI: −7.6 to −2.6]) and cycle 6 (tislelizumab, −0.9 [95% CI: −3.4 to 1.6]; sorafenib, −5.9 [95% CI: −8.6 to −3.2]). The worsening of GHS/QOL from baseline was greater for patients in the sorafenib arm than the change for patients in the tislelizumab arm at both cycle 4 (4.4 [95% CI: 1.4–7.3]) and cycle 6 (5.0 [95% CI: 1.8–8.2]).

At both cycles, the physical functioning score was maintained for patients in the tislelizumab arm (cycle 4, −1.3 [95% CI: −3.1 to 0.5]; cycle 6, −1.0 [95% CI: −3.0 to 0.9]) while it worsened for patents in the sorafenib arm

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Fig. 2. Changes from baseline for EORTC QLQ-HCC18 at cycle 4 and cycle 6. Reported *p* values are nominal. EORTC, European Organisation for Research and Treatment of Cancer; LS, least squares; *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.

(cycle 4, −7.7 [95% CI: −9.6 to −5.8]; cycle 6, −7.2 [95% CI: −9.3 to −5.1]). The worsening in physical functioning experienced by patients in the sorafenib arm was greater than the change experienced by patients in the tislelizumab arm at cycle 4 (6.4 [95% CI: 4.2–8.6]) and cycle 6 (6.2 [95% CI: 3.7–8.6]). Fatigue, measured by QLQ-C30, was maintained for patients in the tislelizumab arm at cycle 4 (1.5 [95% CI: −0.9–3.9]) and worsened in cycle 6 (2.2 [95% CI: −0.4–4.8]) while worsening for patients in the sorafenib arm at both cycles (cycle 4, 9.1 [95% CI: 6.5–11.7]; cycle 6, 9.8 [95% CI: 7.0–12.6]). Patients in the sorafenib arm experienced greater worsening than the change for patients in the tislelizumab

arm at both cycle 4 (−7.6 [95% CI: −10.6 to −4.7]) and cycle 6 (−7.6 [95% CI: −10.8 to −4.3]).

The QLQ-HCC18 index score (Fig. 2), indicating the general HCC symptomology, was maintained for patients in the tislelizumab arm at cycle 4 (1.6 [95% CI: 0.4–2.9]) and worsened for patients in the sorafenib arm (3.9 [95% CI: 2.6–5.2]). At cycle 6, patients in the tislelizumab arm (2.2 [95% CI: 0.6–3.7]) experienced less worsening compared to patients in the sorafenib arm (4.9 [95% CI: 3.2–6.5]). Worsening of HCC symptomology was greater for patients in the sorafenib arm compared to patients in the tislelizumab arm at

Table 3. Changes from baseline for EQ-5D-5L VAS scores at cycle 4 and cycle 6

	Tislelizumab (n = 342)		Sorafenib (n = 332)	
	Observed	Change from baseline	Observed	Change from baseline
Baseline				
Mean (SD)	80.8 (16.16)	–	82.8 (14.37)	–
n	327		321	
Cycle 4				
Mean (SD)	81.8 (14.82)	−0.4 (14.52)	79.4 (15.10)	−4.3 (12.92)
n	220	213	175	170
Cycle 6				
Mean (SD)	82.8 (15.42)	−0.2 (17.03)	78.7 (15.35)	−5.4 (13.09)
n	165	161	136	132

EQ-5D-5L, EuroQol Five-Dimensions Five-Levels; VAS, visual analog scale; SD, standard deviation.
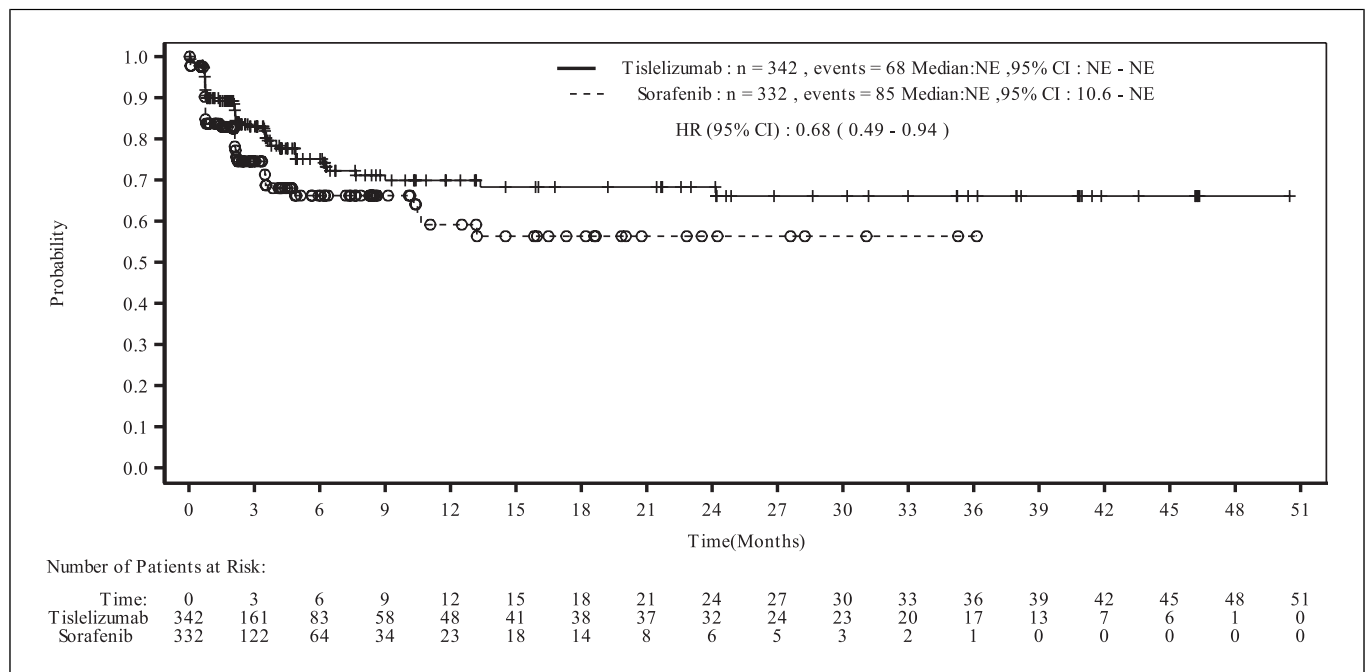
Fig. 3. TTD for EORTC QLQ-C30: GHS/QOL. EORTC, European Organisation for Research and Treatment of Cancer; GHS/QOL, global health status/quality of life; NE, not evaluable; QLQ-C30, Quality of Life Questionnaire Core 30; TTD, time to deterioration.

both cycle 4 (−2.3 [95% CI: −3.8 to −0.8]) and cycle 6 (−2.7 [95% CI: −4.7 to −0.7]).

At both cycles, the fatigue score was maintained in the tislelizumab arm (cycle 4, 1.9 [95% CI: −0.4–4.2]; cycle 6, 1.8 [95% CI: −0.9–4.5]) while worsened in the sorafenib arm (cycle 4, 8.1 [95% CI: 5.6–10.6]; cycle 6, 7.8 [95% CI: 4.9–10.7]). The worsening of fatigue for

patients in the sorafenib arm was greater than the change for patients in the tislelizumab arm at cycle 4 (−6.2 [95% CI: −9.0 to −3.4]) and cycle 6 (−6.0 [95% CI: −9.4 to −2.5]).

Pain was maintained in the tislelizumab arm at cycle 4 (1.9 [95% CI: −0.3–4.0]) and slightly worsened in the sorafenib arm (2.5 [95% CI: 0.2–4.8]) and worsened in

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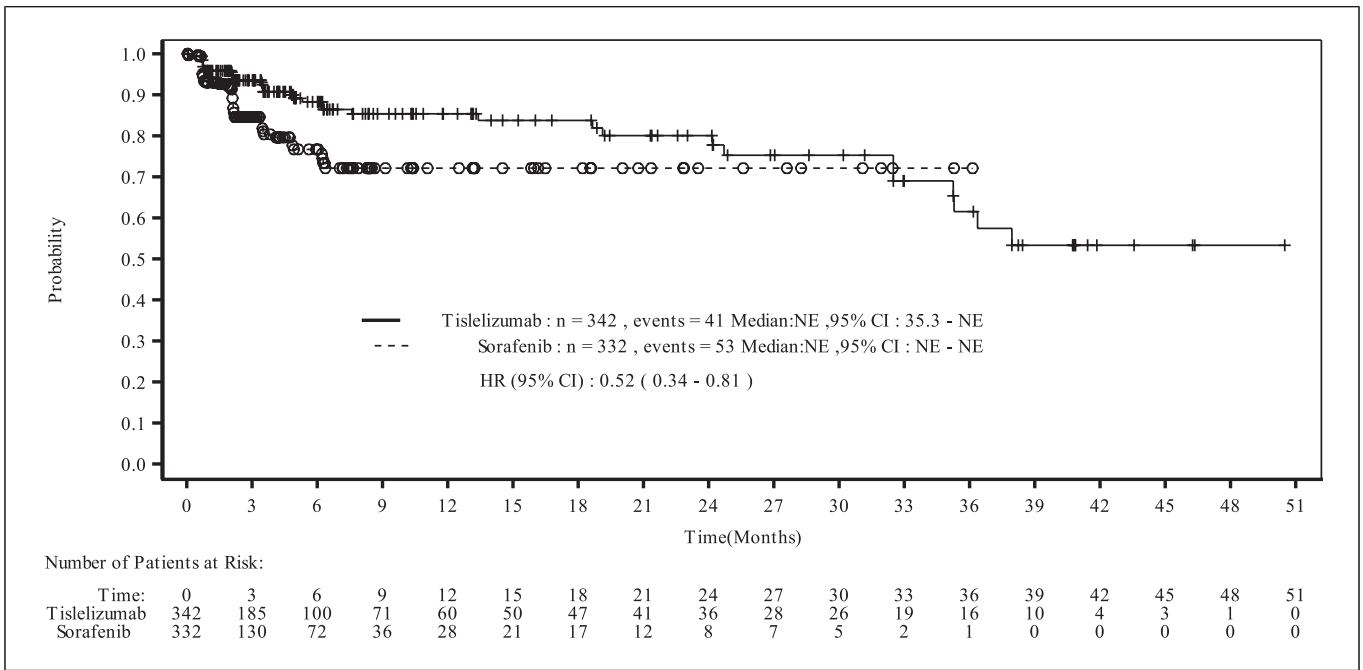Abdrashitov/Chen/Li/Zhu/Qin/Vogel
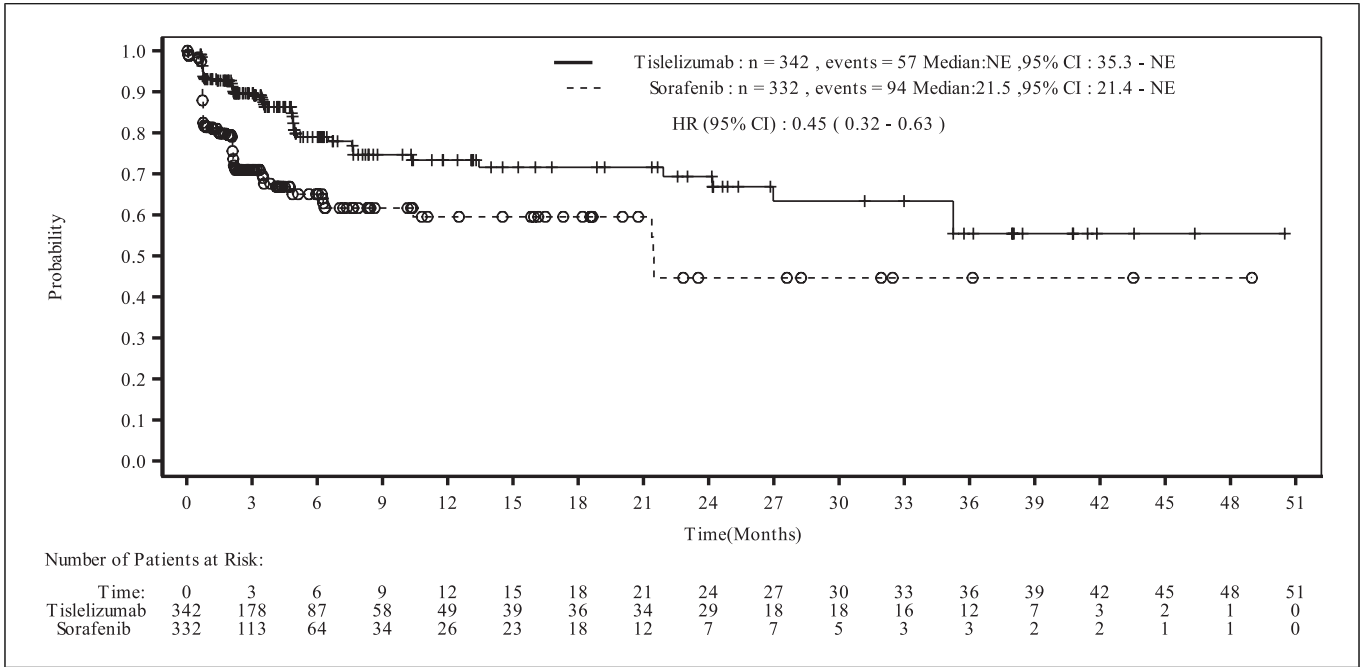
Fig. 4. TTD for EORTC QLQ-C30: Physical Functioning. EORTC, European Organisation for Research and Treatment of Cancer; NE, not evaluable; QLQ-C30, Quality of Life Questionnaire Core 30; TTD, time to deterioration.
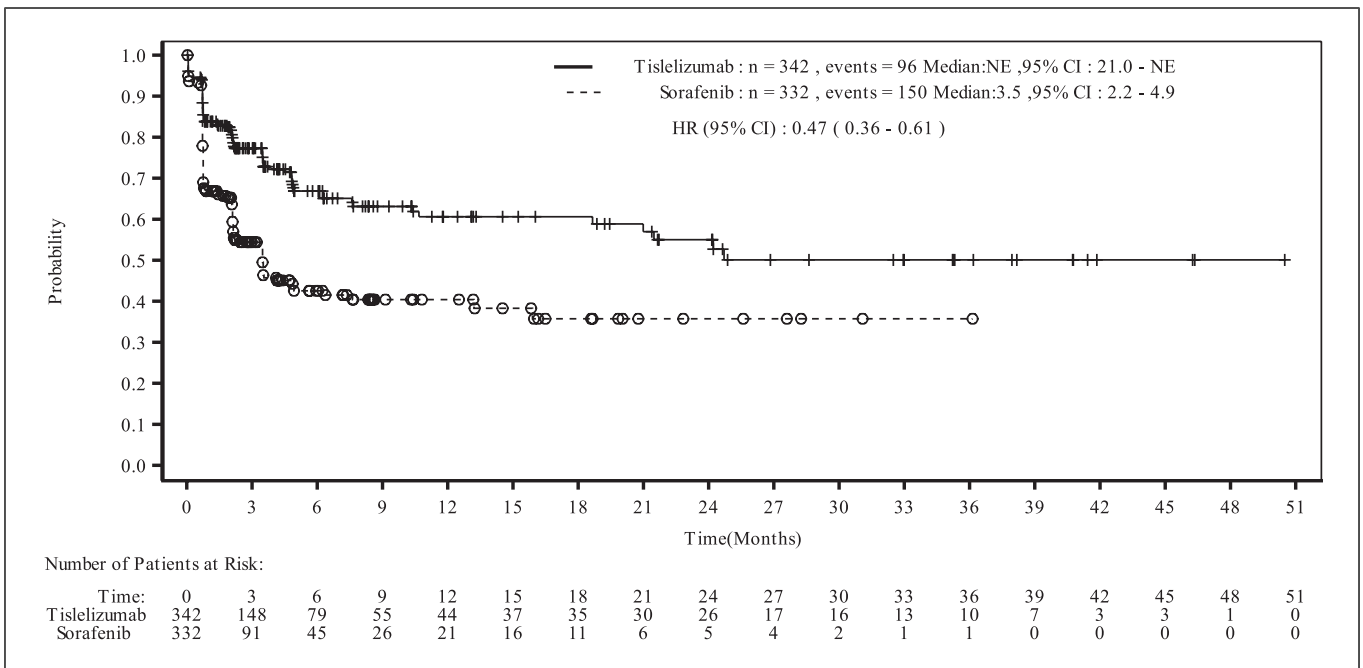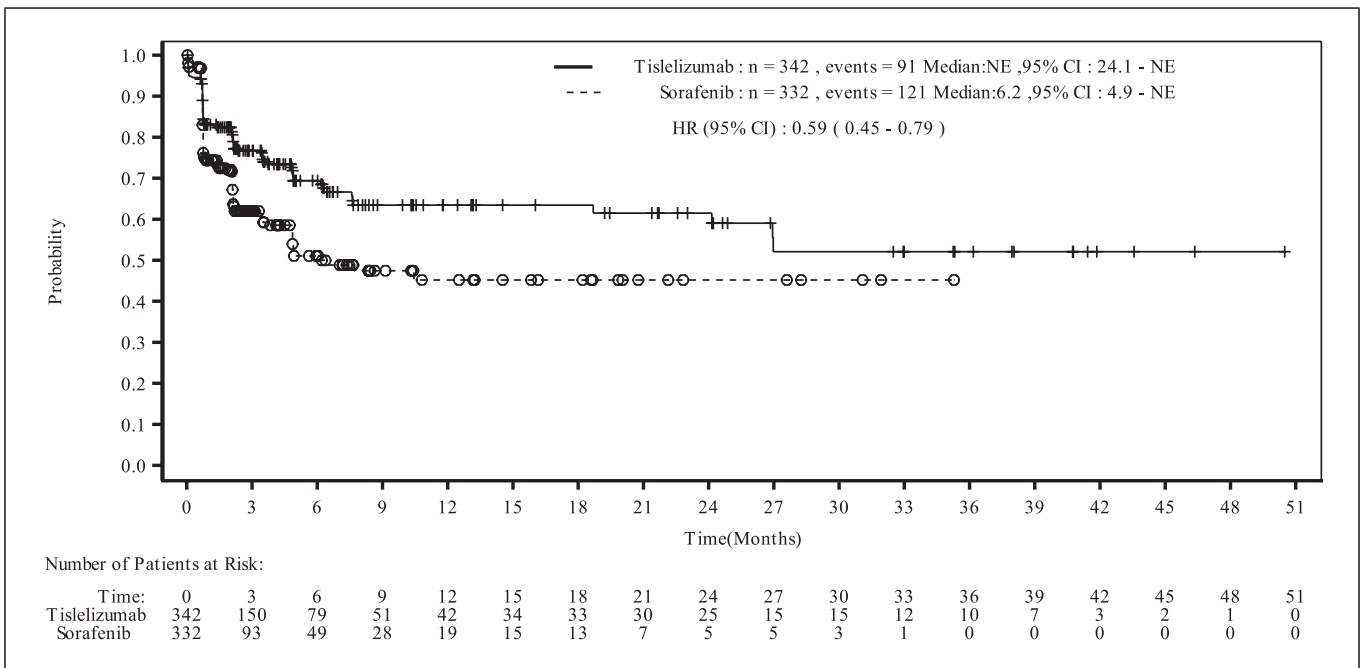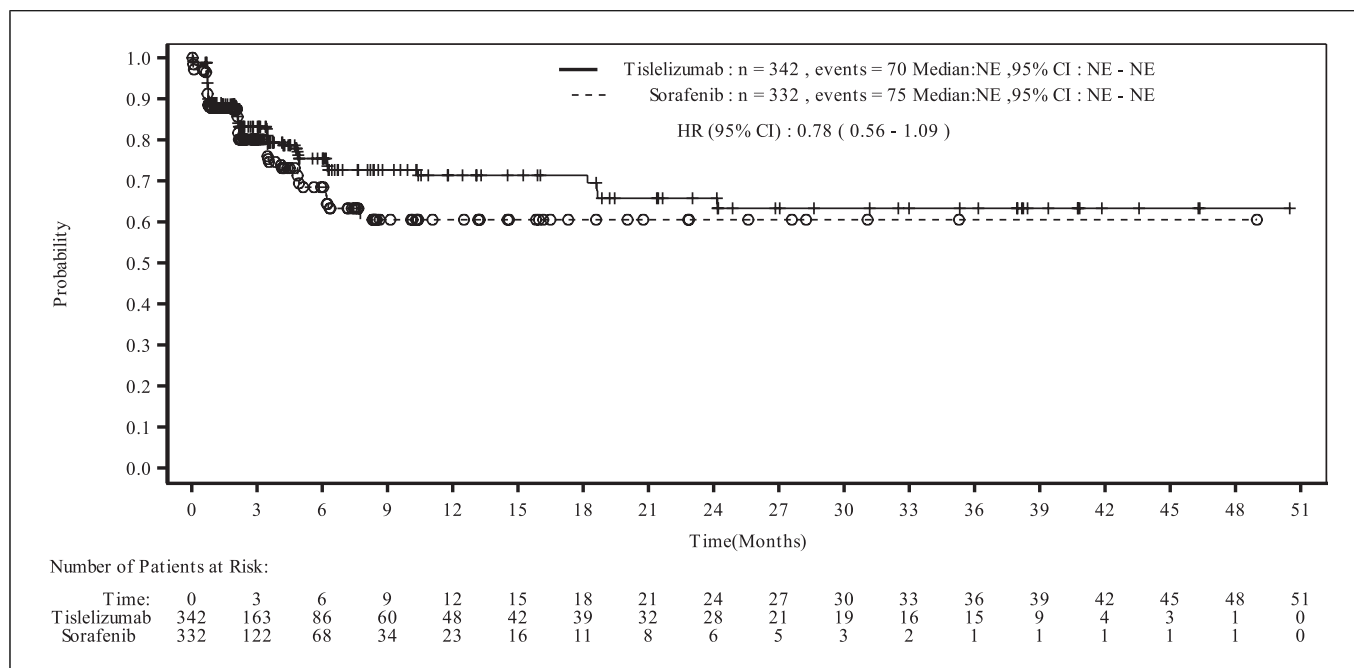

Fig. 5. TTD for EORTC QLQ-C30: Fatigue. EORTC, European Organisation for Research and Treatment of Cancer; NE, not evaluable; QLQ-C30, Quality of Life Questionnaire Core 30; TTD, time to deterioration.

Fig. 6. TTD for EORTC QLQ-HCC18: Index Score. EORTC, European Organisation for Research and Treatment of Cancer; NE, not evaluable; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; TTD, time to deterioration.

Fig. 7. TTD for EORTC QLQ-HCC18: Fatigue. EORTC, European Organisation for Research and Treatment of Cancer; NE, not evaluable; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; TTD, time to deterioration.

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Fig. 8. TTD for EORTC QLQ-HCC18: Pain. EORTC, European Organisation for Research and Treatment of Cancer; NE, not evaluable; QLQ-HCC18, Quality of Life Questionnaire Hepatocellular Carcinoma 18 Questions; TTD, time to deterioration.

both arms at cycle 6 (tislelizumab, 2.4 [95% CI: −0.1–4.9]; sorafenib, 2.8 [95% CI: 0.1–5.4]). There were no differences in change between the arms at cycle 4 (−0.6 [95% CI: −3.3 to 2.1]) or cycle 6 (−0.4 [95% CI: −3.6 to 2.9]).

EQ-5D-5L

The mean VAS score (indicating health status) was maintained for patients in the tislelizumab arm at both cycle 4 {−0.4 (standard deviation [SD]: 14.52)} and cycle 6 (−0.2 [SD: 17.03]); however, scores worsened for patients in the sorafenib arm at both cycle 4 (−4.3 [SD: 12.92]) and cycle 6 (−5.4 [SD: 13.09]) (Table 3).

Time to Deterioration

Patients receiving tislelizumab had a lower risk of deterioration; scores were favorable compared to sorafenib in GHS/QOL (HR: 0.68; 95% CI: 0.49–0.94; Fig. 3), physical functioning (HR: 0.45; 95% CI: 0.32–0.63; Fig. 4), and fatigue (HR: 0.47; 95% CI: 0.36–0.61; Fig. 5). Patients receiving tislelizumab also had a lower risk of deterioration in the QLQ-HCC18 index score (HR: 0.52; 95% CI: 0.34–0.81; Fig. 6) and fatigue (HR: 0.59; 95% CI: 0.45–0.79; Fig. 7). Both

treatment arms had a similar risk for deterioration in the QLQ-HCC18 pain score (HR: 0.78; 95% CI: 0.56–1.09; Fig. 8).

Discussion

In the RATIONALE-301 clinical trial, patients with unresectable HCC treated with tislelizumab monotherapy as a first-line therapy experienced more-favorable HRQOL outcomes than patients treated with sorafenib. Specifically, changes from baseline to cycles 4 and 6 in the GHS/QOL score were different between the arms, with patients treated with tislelizumab maintaining general health and QOL and patients treated with sorafenib experiencing a decline. Similarly, the physical functioning and fatigue of patients treated with tislelizumab remained similar to baseline, whereas the same outcomes declined in patients treated with sorafenib. Patients treated with tislelizumab maintained overall HCC symptoms, while symptoms worsened for the patients receiving sorafenib. Analysis further indicated that through the course of treatment, patients in the tislelizumab arm were at lower risk of reaching the threshold for worsening in GHS/QOL, physical functioning, overall HCC symptoms, and fatigue.

The findings of the current study add to the growing body of clinical trials examining the benefit of anti-PD-(L)1 monotherapy on HRQOL and other PROs in patients with HCC. For instance, the CheckMate 459 trial reported that patients with advanced HCC treated with nivolumab showed benefits on some subscales of HRQOL, whereas no subscales favored sorafenib [13]. This study also found that TTD was delayed with nivolumab for some subscales. In KEYNOTE-240, changes from baseline to week 12 in GHS/QOL score were stable and similar between pembrolizumab and placebo patients, and TTD was similar between the arms in the EORTC QLQ-HCC18 domains of abdominal swelling, fatigue, and pain [24]. The findings also suggest that anti-PD-(L)1 therapy may have a more favorable impact on HRQOL than TKIs, which are currently the default approach for patients not receiving anti-PD-L1 + anti-VEGF treatment in the front line. The REFLECT trial, comparing lenvatinib with sorafenib in patients with unresectable HCC, did not find any clinically meaningful or nominally statistically significant differences in GHS/QOL, the functioning scores of the QLQ-C30, or the symptom scores of the QLQ-HCC18 [25]. The REFLECT investigators did, however, report that patients treated with lenvatinib experienced delayed deterioration on the QLQ-C30 fatigue and diarrhea scales [25].

While the results of the current study are encouraging, they should be considered alongside the following limitations. First, RATIONALE-301 used an open-label design; therefore, the patients were aware of the study treatment received, which may have influenced responses to the PRO assessments. Second, 63.1% of patients recruited into the study were from Asia (excluding Japan), which is in line with the global distribution of HCC, with the highest prevalence reported in Eastern Asia [26]. Third, the PRO data and analysis should be interpreted with caution in this early progress disease setting. Fourth, given the patient attrition at cycles 4 and 6, results might not be completely reflective of actual patients who dropped from the study. However, more patients in the sorafenib arm dropped out of the study (cycle 4: 31% tislelizumab arm vs. 56% sorafenib arm), and the results could be biased against tislelizumab. Despite this limitation, the tislelizumab arm still demonstrated better HRQOL outcomes. Future analysis may use joint modeling to include clinical adverse events along with PROs and further sensitivity analysis to account for missing at random and missing at non-random. Finally, the TTD analysis with a large number of early censoring may limit the interpretation of HR estimation as this reflects many patients without an event who were considered lost to follow-up, reducing the number of at-risk patients over time.

Conclusions

The RATIONALE-301 study met its primary endpoint of OS noninferiority and key secondary endpoints of objective response rate and safety. Tislelizumab monotherapy as a first-line treatment for patients with unresectable HCC was associated with better HRQOL outcomes than sorafenib. Compared with patients receiving sorafenib, patients on tislelizumab had less worsening in general health status, physical functioning, the HCC symptom index, and fatigue, which are considered the most important symptoms associated with HCC and its treatment. These results, along with its effects on OS, response rate, and a favorable safety profile, support tislelizumab as a potential first-line treatment option for unresectable HCC, particularly for patients who are unable to receive a TKI or anti-angiogenic agents.

Statement of Ethics

The study was carried out in accordance with the International Conference for Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki, and local laws and regulations and was approved by the relevant Institutional Review Board or Independent Ethics Committee for each study site. All patients provided written informed consent before participating. Additional information about the study design can be found elsewhere [21].

Conflict of Interest Statement

R.F. has served as a consultant for AstraZeneca, BMS, Bayer, CStone, Hengrui, Eisai, Eli Lilly, Exelixis, Merck, Pfizer, and Roche/Genentech. M.K. has served as a lecturer for Eli Lilly, Bayer, Eisai, Chugai, Takeda, and MSD and has received grants from Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, AbbVie, Eisai, and GE Healthcare. T.M. has served as a consultant for Eisai, BMS, Adaptimmune, Ipsen, Roche, AstraZeneca, MSD, and BeiGene and has received

Author Contributions

Finn, Kudo, Boisserie, Abdrashitov, Chen, Vogel Meyer, Li, Qin, Barnes, and Zhu were responsible for study design and data collection. All authors were responsible for data interpretation and reviewing and approving drafts of the manuscript. Li and Barnes were responsible for data analysis.

Data Availability Statement

On request, and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted with medicines for (1) indications that have been approved or (2) programs that have been terminated. Data requests may be submitted to Data-Disclosure@beigene.com.

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