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Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma
A Phase 3 Randomized Clinical Trial

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IMPORTANCE Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality, and additional first-line treatments are needed. The programmed cell death protein 1 inhibitor tislelizumab demonstrated efficacy and a tolerable safety profile as second-line HCC treatment.

OBJECTIVE To investigate efficacy and safety of tislelizumab vs sorafenib tosylate for first-line treatment of unresectable HCC.

DESIGN, SETTING, AND PARTICIPANTS The open-label, global, multiregional phase 3 RATIONALE-301 randomized clinical trial enrolled systemic therapy–naive adults with histologically confirmed HCC, Barcelona Clinic Liver Cancer stage B or C disease, disease progression following (or patient was not amenable to) locoregional therapy, Eastern Cooperative Oncology Group performance status of 1 or less, and Child-Pugh class A, between December 27, 2017, and October 2, 2019. Data cutoff was July 11, 2022.

INTERVENTION Patients were randomized 1:1 to receive tislelizumab, 200 mg intravenously every 3 weeks, or sorafenib tosylate, 400 mg orally twice daily.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival (OS); secondary end points included objective response rate, progression-free survival, duration of response, and safety.

RESULTS A total of 674 patients were included in the analysis (570 men [84.6%]; median age, 61 years [range, 23-86 years]). As of July 11, 2022, minimum study follow-up was 33 months. The primary end point of OS noninferiority of tislelizumab vs sorafenib was met in the intention-to-treat population (n = 674); median overall survival was 15.9 (95% CI, 13.2-19.7) months vs 14.1 (95% CI, 12.6-17.4) months, respectively (hazard ratio [HR], 0.85 [95.003% CI, 0.71-1.02]), and superiority of tislelizumab vs sorafenib was not met. The objective response rate was 14.3% (n = 49) for tislelizumab vs 5.4% (n = 18) for sorafenib, and median duration of response was 36.1 (95% CI, 16.8 to not evaluable) months vs 11.0 (95% CI, 6.2-14.7) months, respectively. Median progression-free survival was 2.1 (95% CI, 2.1-3.5) months vs 3.4 (95% CI, 2.2-4.1) months with tislelizumab vs sorafenib (HR, 1.11 [95% CI, 0.92-1.33]). The incidence of treatment-emergent adverse events (AEs) was 96.2% (325 of 338 patients) for tislelizumab and 100% (n = 324) for sorafenib. Grade 3 or greater treatment-related AEs were reported in 75 patients (22.2%) receiving tislelizumab and 173 (53.4%) receiving sorafenib. There was a lower incidence of treatment-related AEs leading to drug discontinuation (21 [6.2%] vs 33 [10.2%]) and drug modification (68 [20.1%] vs 187 [57.7%]) with tislelizumab vs sorafenib.

CONCLUSIONS AND RELEVANCE In RATIONALE-301, tislelizumab demonstrated OS benefit that was noninferior vs sorafenib, with a higher objective response rate and more durable responses, while median progression-free survival was longer with sorafenib. Tislelizumab demonstrated a favorable safety profile vs sorafenib.

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+ Visual Abstract

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Hepatocellular carcinoma (HCC) is the most common type of liver cancer and a leading cause of cancer-related mortality globally.[1] Most patients present with advanced stage unresectable disease,[2] which has a poor prognosis.[3] Median survival time is approximately 1.0 to 1.5 years for symptomatic patients with advanced HCC receiving systemic therapies.[4] Recommended first-line systemic treatments for HCC include the single-agent multitargeted tyrosine kinase inhibitors (TKIs) sorafenib tosylate and lenvatinib.[5-7] Additionally, the combination of atezolizumab (programmed death ligand 1 [PD-L1] inhibitor) plus bevacizumab (anti-vascular endothelial growth factor antibody) has become the standard of care first-line systemic therapy following evidence from the IMbrave150 trial.[6,8,9]

Other checkpoint inhibitors have also shown promising results in the first-line advanced HCC setting.[10-14] Median overall survival (OS) was numerically longer with nivolumab (programmed cell death protein 1 [PD-1] inhibitor) than with sorafenib in the phase 3 CheckMate 459 study.[13] The combination of sintilimab (PD-1 inhibitor) plus IBI305 (bevacizumab biosimilar) recently received approval in China as a first-line therapy for patients with HCC based on the ORIENT-32 trial.[11,15] Durvalumab (anti-PD-L1) demonstrated OS noninferiority as monotherapy and superiority in combination with tremelimumab compared with sorafenib in the phase 3 HIMALAYA trial,[14] leading to recent US Food and Drug Administration[16] and European Medicines Agency[17] approval of durvalumab plus tremelimumab as a first-line treatment for patients with advanced HCC.

Currently approved first-line HCC therapies have important safety considerations. While atezolizumab plus bevacizumab is associated with a low risk of variceal bleeding in appropriately selected patients, there is a higher risk of bleeding in patients with advanced HCC who have a greater likelihood of portal hypertension.[6] Tyrosine kinase inhibitors are recommended for patients with contraindications to atezolizumab or bevacizumab[6]; however, they are also associated with adverse events (AEs), such as diarrhea and fatigue. Although typically low grade, these AEs may affect patients' quality of life[18] and lead to drug discontinuation. Expert guidance recommends anti-PD-1 monotherapy for patients with contraindications to TKI or anti-vascular endothelial growth factor agents, uncontrolled hypertension, recent cardiovascular conditions, or Child-Pugh B status.[19] However, a single-agent PD-1 or PD-L1 inhibitor has yet to be approved as a first-line systemic treatment option.

Further first-line treatment options are required to improve outcomes and treatment tolerability for patients with unresectable HCC. Tislelizumab is a monoclonal antibody with high affinity and binding specificity for PD-1[20,21] and has shown efficacy and a tolerable safety profile in patients with various solid tumors.[22-26] Tislelizumab demonstrated durable clinical activity in patients with previously treated advanced HCC in the phase 2 RATIONALE-208 trial,[27] warranting investigation of first-line tislelizumab monotherapy. We report results of the final analysis of the phase 3 RATIONALE-301 trial evaluating the efficacy and safety of tislelizumab vs sorafenib as first-line treatment in patients with unresectable HCC.

Key Points

Question How does the efficacy and safety profile of tislelizumab compare with that of sorafenib as first-line treatment among patients with unresectable hepatocellular carcinoma (HCC)?

Findings In this phase 3 randomized clinical trial of 674 patients with HCC, tislelizumab demonstrated overall survival noninferiority compared with sorafenib, with numerically higher and more durable objective responses than sorafenib. Tislelizumab had a favorable safety profile vs sorafenib, with no newly emerging safety signals.

Meaning Tislelizumab may represent a potential first-line treatment option for patients with unresectable HCC.

Methods

Study Design

This open-label, parallel-group, active-controlled, multicenter, phase 3 randomized clinical study was conducted from December 27, 2017, to October 2, 2019, at 117 sites in China, the Czech Republic, France, Germany, Italy, Japan, Poland, Spain, Taiwan, the UK, and the US. Data cutoff was on July 11, 2022. Principal investigators and sites are listed in eTable 1 in Supplement 1. The study design has been described previously[28] and the protocol can be found in Supplement 2. All relevant institutional review boards and independent ethics committees approved the study, which was performed in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline, the principles of the Declaration of Helsinki,[29] and local laws and regulations. All patients provided written informed consent before participation. An independent data monitoring committee assessed safety and efficacy during the study. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Patients were randomized 1:1 to tislelizumab, 200 mg intravenously every 3 weeks, or sorafenib tosylate, 400 mg orally twice daily, until symptomatic deterioration associated with disease progression, unacceptable toxic effects, or study withdrawal (eFigure 1 in Supplement 1). Due to different administrative routes and distinctive safety profiles of the investigational agents, treatment blinding was not considered feasible. Patients in both arms could continue treatment after disease progression providing protocol criteria were met.

Dose modifications were permitted for sorafenib (at the investigator's discretion and consistent with prescribing information); dose interruption or dosing delay was permitted for tislelizumab and sorafenib to manage AEs. The protocol included guidance on how to manage tislelizumab-related toxic effects, including infusion-related reactions and immune-related AEs.

Patients

Eligible patients were adults (aged ≥18 years) who were naive to systemic therapy and had histologically confirmed HCC, either Barcelona Clinic Liver Cancer stage C or stage B disease that was not amenable to locoregional therapy or a curative

treatment approach, or disease that had progressed after locoregional therapy. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, Child-Pugh class A liver function, and at least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[30] Patients were stratified at randomization by macrovascular invasion (present vs absent), extrahepatic spread (EHS; present vs absent), ECOG PS (0 vs 1), etiology (hepatitis C virus vs other [includes hepatitis B virus]), geographic region (Asia [excluding Japan] vs Japan vs the rest of world).

End Points

The primary end point was OS. Secondary efficacy end points included objective response rate (ORR; key secondary end point), progression-free survival (PFS), duration of response (DOR), disease control rate (DCR; the proportion of patients with complete or partial response or stable disease), and clinical benefit rate (the proportion of patients with best overall response of complete or partial response or stable disease for ≥24 weeks). Tumor response end points were assessed by a blinded independent review committee (BIRC) using RECIST, version 1.1.[30] Other secondary end points included health-related quality of life and safety assessments; patient-reported outcomes will be presented elsewhere.

Assessments

Tumor status was evaluated within 28 days prior to the first study treatment and approximately every 9 weeks in year 1 and every 12 weeks from year 2 onward. Assessments included computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis.

Patients were evaluated for any AEs and serious AEs (SAEs) up to 90 days after the last dose of tislelizumab and up to 30 days after the last dose of sorafenib. Suspected drug-related SAEs continued to be recorded after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 24.0,[31] and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[32] Treatment-emergent AEs (TEAEs) were defined as any AE or SAE with a date of onset or date of worsening in severity from baseline occurring on or after the first dose of study drug and up to either 30 days following discontinuation of the study drug or the start of new anticancer therapy.

Statistical Analysis

The Kaplan-Meier method was used to estimate OS, PFS, and DOR. The stratified log-rank test was used to assess OS difference between treatment arms. A stratified Cox proportional hazards regression model with the Efron method of tie handling was used to determine hazard ratios (HRs) and 95% CIs. Actual values of stratification factors for randomization, including region (Asia vs the rest of the world), macrovascular invasion, and/or EHS (present vs absent), etiology (hepatitis C virus vs other), and ECOG PS (0 vs 1), were fitted as strata in the stratified analyses and treatment arms as covariates. The

familywise type I error rate was controlled at .025 in all hypothesis testing of the primary and secondary end points. Statistical power was based on the number of total OS events; with a sample size of 674, the trial had 93.5% power for an OS noninferiority test and 72% power for an OS superiority test. One interim analysis was planned to test OS superiority after approximately 403 events. As of January 15, 2021, there were 404 OS events in the intention-to-treat (ITT) population, which led to a multiplicity-adjusted 1-sided α of .0110, determined based on Hwang-Shih-DeCani spending function with γ parameter of −4. The recommendation of the data monitoring committee was to continue the study as planned. At the final analysis, noninferiority was declared if the upper limit of the 95.003% CI for the HR was less than 1.08. Once OS noninferiority had been demonstrated, OS superiority and ORR and PFS by BIRC were tested sequentially. Superiority of OS between treatment arms was claimed at 1-sided P < .0223. Statistical analyses were done using SAS EG, version 7.15 (SAS Institute Inc).
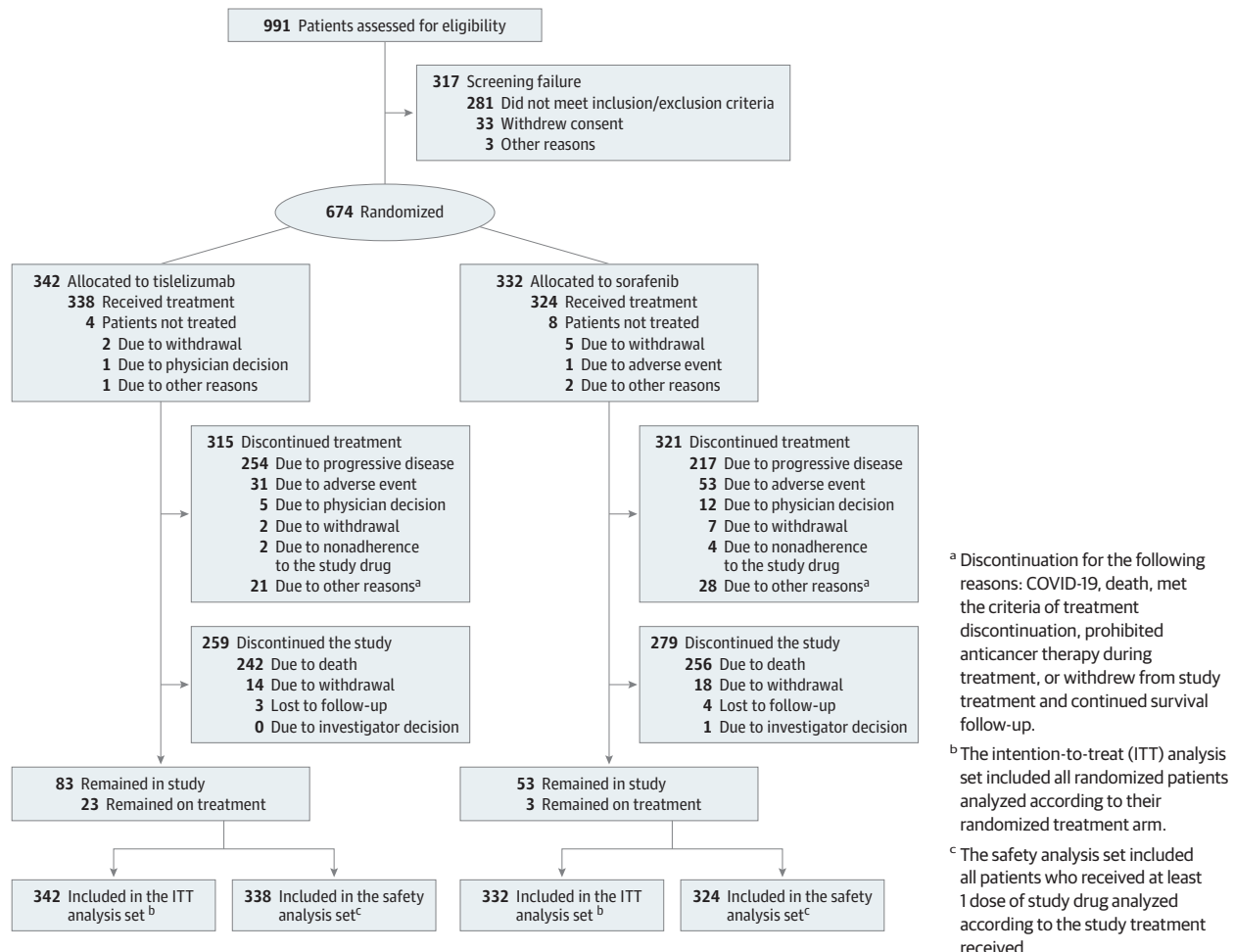
Results

Patients and Treatment

Between December 27, 2017, and October 2, 2019, 674 patients were randomized to treatment and included in the ITT analysis set (342 in the tislelizumab arm and 332 in the sorafenib arm) (**Figure 1**). A total of 570 patients (84.6%) were men, and 104 (15.4%) were women; the median age was 61 years (range, 23-86 years). Patient demographics were generally well balanced between treatment arms; however, there were some numerical differences in baseline disease characteristics, with a higher proportion of patients in the tislelizumab arm having advanced disease and more likely to have risk factors for HCC (**Table 1**). The tislelizumab arm vs the sorafenib arm had more patients with Barcelona Clinic Liver Cancer stage C disease (272 [79.5%] vs 252 [75.9%]), α-fetoprotein level of at least 400 ng/mL (135 [39.5%] vs 116 [34.9%]; to convert to μg/L, multiply by 1), and EHS (219 [64.0%] vs 198 [59.6%]). However, the tislelizumab arm had a higher proportion of patients with an albumin-bilirubin score of 1 (256 [74.9%] vs 226 [68.1%]; scores range from 1 to 3, with higher scores indicating greater mortality risk) (Table 1).

At the time of data cutoff (July 11, 2022), minimum study follow-up time, defined as the time between the date of cutoff to the last patient randomized, was 33 months in both treatment arms. The median durations of treatment were 4.1 (range, 0.6-50.4) months and 2.7 (range, 0.0-49.0) months in the tislelizumab and sorafenib arms, respectively. Poststudy systemic therapies were received by 185 patients (54.1%) in the tislelizumab arm and 199 (59.9%) in the sorafenib arm, including immunotherapy in 33 (9.6%) and 87 (26.2%), respectively (eTable 2 in Supplement 1).

Efficacy

The number of deaths in the tislelizumab and sorafenib arms were 242 (70.8%) and 255 (76.8%), respectively. The study met its primary end point of OS noninferiority with tislelizumab

Figure 1. Patient Flow Diagram

Figure 1. Patient Flow Diagram

a Discontinuation for the following reasons: COVID-19, death, met the criteria of treatment discontinuation, prohibited anticancer therapy during treatment, or withdrew from study treatment and continued survival follow-up.

b The intention-to-treat (ITT) analysis set included all randomized patients analyzed according to their randomized treatment arm.

c The safety analysis set included all patients who received at least 1 dose of study drug analyzed according to the study treatment received.

vs sorafenib in the ITT analysis set (HR, 0.85 [95.003% CI, 0.71-1.02]; noninferiority margin upper limit of 95.003% CI for HR <1.08). Median OS was 15.9 (95% CI, 13.2-19.7) months in the tislelizumab arm vs 14.1 (95% CI, 12.6-17.4) months in the sorafenib arm (Figure 2A). Superiority of OS for tislelizumab vs sorafenib was not met (1-sided P = .04). Among patients who were censored in the tislelizumab (100 [29.2%]) and sorafenib (77 [23.2%]) arms, a greater proportion remained in the study without events in the tislelizumab arm (83 [24.3%]) than in the sorafenib arm (53 [16.0%]). Overall survival rates with tislelizumab (calculated using Kaplan-Meier estimate and Greenwood formula) were similar to those with sorafenib at 12 months and numerically higher than those for sorafenib at both 24 months (39.0% vs 31.8%) and 36 months (29.2% vs 20.3%) (Figure 2A). The OS results observed in the overall population were consistent across all subgroups analyzed (nonprespecified analysis) based on the HR estimates (eFigure 2 in Supplement 1).

Confirmed ORR by BIRC was numerically higher in the tislelizumab arm than in the sorafenib arm (49 [14.3%] vs 18 [5.4%]; ORR difference, 8.28% [95% CI, 3.85%-12.70%]) (Table 2). Tislelizumab was associated with more durable responses compared with sorafenib (median DOR, 36.1 [95% CI,

16.8 to not evaluable] months vs 11.0 [95% CI, 6.2-14.7] months) (eFigure 3 in Supplement 1), and the median time to response was approximately half that with sorafenib (2.2 [range, 1.8-24.4] months vs 4.0 [range, 1.9-13.2] months). The DCR by BIRC was numerically higher in the sorafenib arm vs the tislelizumab arm (167 [50.3%] vs 151 [44.2%]), while clinical benefit rate was similar (81 [24.4%] vs 87 [25.4%]) (Table 2). Median PFS by BIRC was 2.1 (95% CI, 2.1-3.5) months in the tislelizumab arm vs 3.4 (95% CI, 2.2-4.1) months in the sorafenib arm (HR, 1.11 [95% CI, 0.92-1.33]) (Figure 2B). Although the sorafenib arm had a longer median PFS and higher 6-month PFS rate (calculated using Kaplan-Meier estimate and Greenwood formula) than the tislelizumab arm (35.8% vs 28.8%), PFS rates were similar with tislelizumab and sorafenib at 12 months (19.0% vs 18.1%) and higher with tislelizumab at 18 and 24 months (18 months: 16.1% vs 9.5%; 24 months: 13.9% vs 6.1%) (Figure 2B).

Safety and Tolerability

A total of 662 patients were included in the safety analysis set (338 received tislelizumab; 324 received sorafenib). The incidence of TEAEs was similar between treatment arms (Table 3). Grade 3 or greater TEAEs were experienced by 163 patients

(48.2%) in the tislelizumab arm vs 212 (65.4%) in the sorafenib arm. Incidence of treatment-related AEs (TRAEs) was 76.6% (n = 259) with tislelizumab vs 96.0% (n = 311) with sorafenib, while 75 (22.2%) and 173 patients (53.4%), respectively, had grade 3 or greater TRAEs.

The most common TRAEs were increased levels of aspartate aminotransferase (78 [23.1%]), alanine aminotransferase (56 [16.6%]), and blood bilirubin (42 [12.4%]) in patients treated with tislelizumab. Palmar-plantar erythrodysesthesia syndrome (203 [62.7%]), diarrhea (127 [39.2%]), and increased aspartate aminotransferase levels (93 [28.7%]) were the most frequent TRAEs in patients who received sorafenib (Table 3).

Numerically lower proportions of patients discontinued tislelizumab than discontinued sorafenib due to either TEAEs (37 [10.9%] vs 60 [18.5%]) or TRAEs (21 [6.2%] vs 33 [10.2%]), and fewer patients in the tislelizumab arm experienced TEAEs (105 [31.1%] vs 210 [64.8%]) and TRAEs (68 [20.1%] vs 187 [57.7%]) leading to treatment modifications (Table 3). Treatment-emergent AEs and TRAEs leading to death occurred in 15 (4.4%) and 3 (0.9%) patients, respectively, in the tislelizumab arm and in 17 (5.2%) and 2 (0.6%) patients, respectively, in the sorafenib arm (Table 3). In the tislelizumab arm, immune-mediated AEs (IMAEs) occurred in 62 patients (18.3%), grade 3 or greater IMAEs occurred in 28 (8.3%), and IMAEs leading to treatment discontinuation occurred in 11 (3.3%) (Table 3). Systemic corticosteroids were used to treat 47 of the 62 patients with IMAEs in the tislelizumab arm.

Discussion

The phase 3 RATIONALE-301 randomized clinical trial met its primary end point of OS noninferiority with single-agent tislelizumab vs sorafenib as first-line treatment for unresectable HCC. In addition, tislelizumab was associated with higher ORR and more durable responses compared with sorafenib. The Kaplan-Meier analysis demonstrated a 12-month OS delayed effect, with a 29.2% survival rate at 36 months and the plateau in the survival curve. These data suggest long-term survival benefits for patients treated with tislelizumab. Furthermore, the higher proportion of patients in the sorafenib arm who received subsequent immunotherapy (eTable 2 in Supplement 1) and numerical imbalances in baseline disease characteristics favoring the sorafenib arm may have been a confounding factor for OS comparisons. A supplementary OS analysis was performed to adjust for the use of subsequent immunotherapies in the sorafenib arm; the findings were consistent with those of the primary analysis. Subgroup analyses showed consistent OS results for tislelizumab vs sorafenib across all predefined subgroups; OS benefit was less pronounced in the subgroup from Asia (excluding Japan) compared with the subgroups from Japan and the rest of the world, possibly influenced by a slightly greater proportion of patients with advanced disease, presence of EHS, and worse ECOG PS in the subgroup from Asia. The median PFS observed in the tislelizumab arm (2.1 [95% CI, 2.1-3.5] months) was shorter than in the sorafenib arm (3.4 [95% CI, 2.2-4.1] months). The separation of the Kaplan-Meier curves at approximately 13 months

Table 1. Patient Demographic and Baseline Characteristics

Characteristic	Patient group[a]	
	Tislelizumab (n = 342)	Sorafenib (n = 332)
Median age, (range), y	62 (25-86)	60 (23-86)
Gender		
Men	289 (84.5)	281 (84.6)
Women	53 (15.5)	51 (15.4)
Geographic region		
Asia (excluding Japan)	215 (62.9)	210 (63.3)
Japan	38 (11.1)	39 (11.7)
Rest of world[b]	89 (26.0)	83 (25.0)
ECOG performance status		
0	183 (53.5)	181 (54.6)
1	159 (46.5)	151 (45.5)
BCLC stage at study entry		
B	70 (20.5)	80 (24.1)
C	272 (79.5)	252 (75.9)
Hepatocellular carcinoma etiology		
HBV only	203 (59.4)	206 (62.0)
HCV only	46 (13.5)	39 (11.7)
HBV and HCV coinfection	11 (3.2)	7 (2.1)
Uninfected	82 (24.0)	80 (24.1)
α-Fetoprotein level ≥400 ng/mL	135 (39.5)	116 (34.9)
Child-Pugh score at study entry[c]		
5	263 (76.9)	248 (74.7)
6	77 (22.5)	84 (25.3)
Other[d]	2 (0.6)	0
Albumin-bilirubin score at study entry[e]		
1	256 (74.9)	226 (68.1)
2	81 (23.7)	98 (29.5)
3	1 (0.3)	0
Missing	4 (1.2)	8 (2.4)
Extrahepatic spread	219 (64.0)	198 (59.6)
Macrovascular invasion	51 (14.9)	49 (14.8)
Locoregional therapy	265 (77.5)	250 (75.3)
Distant metastasis	205 (59.9)	189 (56.9)
Location of metastases		
Lung	120 (35.1)	106 (31.9)
Lymph node	76 (22.2)	74 (22.3)
Bone	32 (9.4)	40 (12.0)
Other	31 (9.1)	48 (14.5)
Peritoneum	20 (5.8)	23 (6.9)
Adrenal gland	15 (4.4)	15 (4.5)
Soft tissue	7 (2.0)	3 (0.9)
Skin	1 (0.3)	0
Muscle	0	2 (0.6)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus.

SI conversion factor: To convert α-fetoprotein to μg/L, multiply by 1.

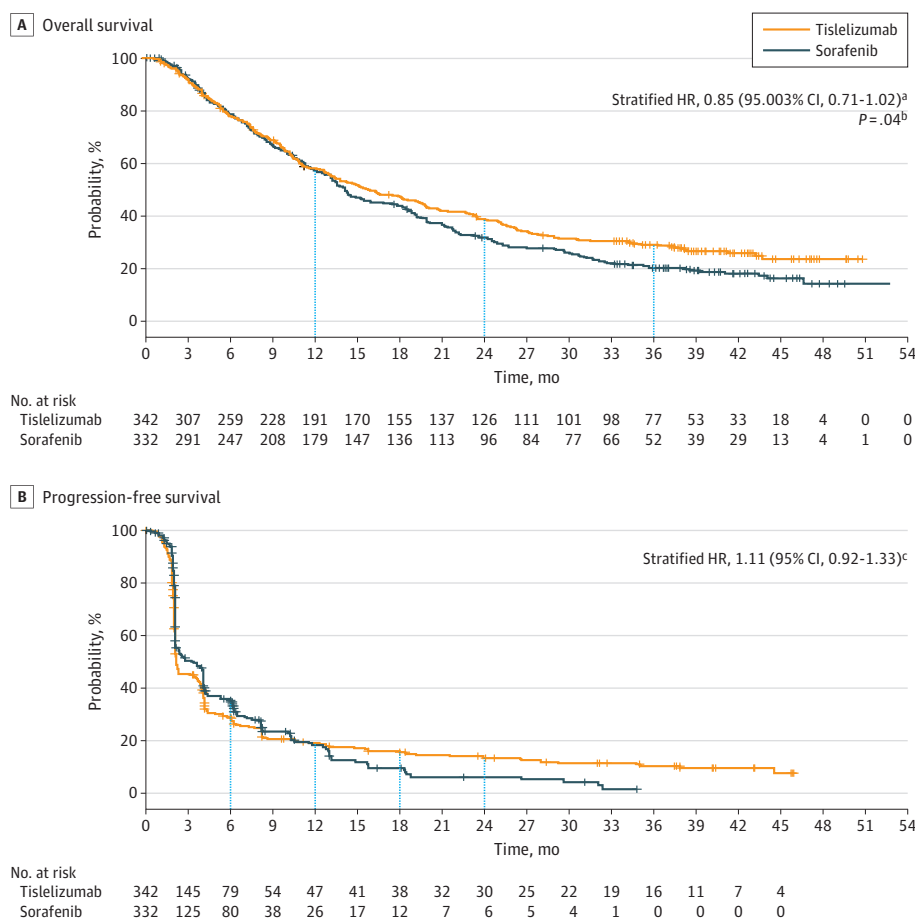[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Includes Europe, the UK, and the US.

[c] Scores range from 5 to 15; higher scores indicate greater severity of cirrhosis.

[d] In the tislelizumab arm, score was missing for 1 patient and was 7 (class B) for 1 patient.

[e] Scores range from 1 to 3; higher scores indicate greater mortality risk.

Figure 2. Survival Analysis by Intention-to-Treat

A | Overall survival

Stratified HR, 0.85 (95.003% CI, 0.71-1.02)[a]
$P = .04$[b]

No. at risk

Tislelizumab	342	307	259	228	191	170	155	137	126	111	101	98	77	53	33	18	4	0	0
Sorafenib	332	291	247	208	179	147	136	113	96	84	77	66	52	39	29	13	4	1	0

B | Progression-free survival

Stratified HR, 1.11 (95% CI, 0.92-1.33)[c]

No. at risk

Tislelizumab	342	145	79	54	47	41	38	32	30	25	22	19	16	11	7	4
Sorafenib	332	125	80	38	26	17	12	7	6	5	4	1	0	0	0	0

Data cutoff was July 11, 2022. A, The prespecified boundary of noninferiority was the upper bound of the 95.003% CI of a stratified hazard ratio (HR) less than 1.08; prespecified boundary of superiority, 1-sided $P < .0223$ (approximate HR <0.8352). A total of 242 events (70.8%) occurred in the tislelizumab group (median overall survival [OS], 15.9 [95% CI, 13.2-19.7] months) and 255 (76.8%) in the sorafenib group (median OS, 14.1 [95% CI, 12.6-17.4] months). B, Data for patients who started to receive new anticancer therapy or were lost to follow-up were censored at the last valid tumor assessment date. A total of 276 events (80.7%) occurred in the tislelizumab group (median progression-free survival [PFS], 2.1 [95% CI, 2.1-3.5] months) and 224 (67.5%) in the sorafenib group (median PFS, 3.4 [95% CI, 2.2-4.1] months).

[a] Based on a Cox proportional hazards regression model including treatment

as a covariate, geographic region (Asia [including Japan] vs rest of world [Europe and the US]), macrovascular invasion (MVI) and/or extrahepatic spread (EHS; present vs absent), etiology (hepatitis C virus [HCV] vs other), and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) as stratification factors.

[b] Calculated using 1-sided stratified log-rank test.

[c] Based on a Cox proportional hazards regression model including treatment as a covariate, geographic region (Asia [including Japan] vs rest of world [Europe and the US]), MVI and/or EHS (present vs absent), etiology (HCV vs other), and ECOG PS (0 vs 1) as stratification factors.

suggests a long-term benefit for some patients. The benefit remained thereafter, with numerically higher 18- and 24-month PFS rates for tislelizumab than for sorafenib. The OS findings were supported by objective tumor responses, with ORR, DOR, and time to response favoring tislelizumab. In contrast, DCR was numerically higher in the sorafenib arm, which may be a consequence of the higher proportion of patients achieving stable disease in the sorafenib arm than in the tislelizumab arm.

Tislelizumab demonstrated favorable safety (fewer patients experienced TRAEs, grade ≥3 TEAEs and TRAEs, and TEAEs and TRAEs leading to discontinuation) compared with sorafenib, indicating its potential suitability for patients who cannot tolerate TKI treatment. The most common

TEAEs were driven by known toxic effects of tislelizumab and sorafenib.[14,27]

Although superiority of tislelizumab vs sorafenib was not demonstrated, tislelizumab showed a numerically longer median OS (15.9 [95% CI, 13.2-19.7] months vs 14.1 [95% CI, 12.6-17.4] months; the median OS with sorafenib was similar in the CheckMate 459 (14.7 months)[13] and HIMALAYA (13.8 months)[14] HCC studies. A higher proportion of patients in RATIONALE-301 were treated with subsequent immunotherapy in the sorafenib arm (26.2%) than in the tislelizumab arm (9.6%); a similar imbalance was also reported in IMbrave150, in which 18.8% of patients in the sorafenib arm were treated with subsequent immunotherapy compared with 1.2% in the atezolizumab plus bevacizumab arm.[8]

Table 2. Summary of Confirmed Response by BIRC in the ITT Analysis Set[a]

Response	Patient group	
	Tislelizumab (n = 342)	Sorafenib (n = 332)
ORR, No. (%) [95% CI][b]	49 (14.3) [10.8-18.5]	18 (5.4) [3.2-8.4]
Odds ratio (95% CI)[c]	2.755 (1.566-4.846)	NA
ORR difference (95% CI)[c]	8.28 (3.85-12.70)[d]	NA
Best overall response, No. (%)		
Complete response	10 (2.9)	1 (0.3)
Partial response	39 (11.4)	17 (5.1)
Stable disease	94 (27.5)	139 (41.9)
Progressive disease	169 (49.4)	121 (36.4)
Undetermined[e]	22 (6.4)	44 (13.3)
Noncomplete response and nonprogressive disease[f]	8 (2.3)	10 (3.0)
DCR, No. (%)	151 (44.2)	167 (50.3)
CBR, No. (%)	87 (25.4)	81 (24.4)
Patients with treatment response, No.	49	18
DOR, median (95% CI), mo[g]	36.1 (16.8 to NE)	11.0 (6.2-14.7)
Time to response, median (range), mo	2.2 (1.8-24.4)	4.0 (1.9-13.2)
Patients with ongoing response, No./total No. (%)[h]	20/28 (71.4)	2/5 (40.0)

Abbreviations: BIRC, blinded independent review committee; CBR, clinical benefit rate (the proportion of patients with best overall response of complete or partial response or stable disease for ≥24 weeks); DCR, disease control rate (the proportion of patients with complete or partial response or stable disease); DOR, duration of response; ITT, intention-to-treat; NA, not applicable; NE, not evaluable; ORR, objective response rate.

[a] Data cutoff was July 11, 2022.

[b] The 95% CI was calculated using Clopper-Pearson method.

[c] The ORR differences and odds ratios between arms were calculated using the exact Cochran-Mantel-Haenszel method.

[d] $P < .001$, by Cochran-Mantel-Haenszel test stratified by geography (Asia [including Japan] vs Europe and the US), macrovascular invasion and/or extrahepatic spread (present vs absent), etiology (hepatitis C virus vs other), and Eastern Cooperative Oncology Group performance status (0 vs 1).

[e] Indicates patients with no postbaseline tumor assessment (not assessable) or a nonevaluable tumor assessment.

[f] Indicates persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

[g] Estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.

[h] Patients who had progressive disease or died were excluded from this analysis.

Table 3. Safety Summary in the Safety Analysis Set

Adverse event	Patient group, No. (%)[a]	
	Tislelizumab (n = 338)	Sorafenib (n = 324)
TEAE		
Any	325 (96.2)	324 (100)
Grade ≥3	163 (48.2)	212 (65.4)
Serious	101 (29.9)	91 (28.1)
Leading to discontinuation	37 (10.9)	60 (18.5)
Leading to treatment modification		
Any	105 (31.1)	210 (64.8)
Interrupted or withheld	105 (31.1)	177 (54.6)
Dose reduction	0	144 (44.4)
Leading to death	15 (4.4)	17 (5.2)
TRAE		
Any	259 (76.6)	311 (96.0)
Grade ≥3	75 (22.2)	173 (53.4)
Serious	40 (11.8)	33 (10.2)
Leading to discontinuation	21 (6.2)	33 (10.2)
Leading to treatment modification		
Any	68 (20.1)	187 (57.7)
Interrupted or withheld	68 (20.1)	152 (46.9)
Dose reduction	0	133 (41.0)
Leading to death	3 (0.9)	2 (0.6)
Incidence of TRAEs occurring in ≥10% of patients in either arm[b]		
AST level increased	78 (23.1)	93 (28.7)
ALT level increased	56 (16.6)	81 (25.0)
Blood bilirubin level increased	42 (12.4)	67 (20.7)
Pruritus	35 (10.4)	16 (4.9)
Rash	34 (10.1)	54 (16.7)
Platelet count decreased	24 (7.1)	49 (15.1)
Fatigue	21 (6.2)	34 (10.5)
Diarrhea	19 (5.6)	127 (39.2)
Decreased appetite	17 (5.0)	39 (12.0)
Weight decreased	11 (3.3)	36 (11.1)
Hypertension	9 (2.7)	80 (24.7)
Alopecia	1 (0.3)	73 (22.5)
Palmar-plantar erythrodysesthesia syndrome	1 (0.3)	203 (62.7)
IMAE		
Any	62 (18.3)	0
Grade ≥3	28 (8.3)	0
Serious	17 (5.0)	0
Leading to treatment discontinuation	11 (3.3)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IMAE, immune-mediated adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a] Data cutoff was July 11, 2022.

[b] Reported by Medical Dictionary for Regulatory Activities, version 24.0[31] and ordered based on decreasing incidence in the tislelizumab arm.

When the RATIONALE-301 protocol was developed, sorafenib represented the global standard of care and was the only treatment available as first-line systemic therapy for patients with unresectable HCC; therefore, it was the most appropriate comparator for use in the trial. Subsequently, atezolizumab with bevacizumab has become the standard of care first-line therapy based on the phase 3 IMbrave150 trial.[6,9] While no anti–PD-1 antibody monotherapy has been approved for first-line treatment of HCC to date, anti–PD-1 antibodies may be offered off label as single-agent first-line treatments for patients who have contraindications for use of

bevacizumab and TKIs.[33] Despite the primary end point of superiority not being met in the CheckMate 459 study,[13] nivolumab is recommended in certain circumstances, for example, in patients who cannot receive antiangiogenics and TKIs

due to contraindications or toxic effects.[33] Of note, the OS and ORR outcomes were similar with nivolumab in CheckMate 459[13] and tislelizumab in RATIONALE-301, although cross-trial comparisons should be interpreted with caution.

Durvalumab as a single agent or in combination with tremelimumab showed promising results in the first-line advanced HCC setting in the HIMALAYA phase 3 trial,[14] and the combination with tremelimumab was approved by the US Food and Drug Administration in 2022 for treatment of adult patients with unresectable HCC.[34] Of interest, median OS for combination treatment and single-agent durvalumab in HIMALAYA were 16.4 and 16.6 months, respectively, and ORRs were 20.1% and 17.0%, respectively. However, the improved efficacy outcomes with the combination compared with single-agent durvalumab were accompanied by increased rates of grade 3 or greater AEs and greater use of high-dose corticosteroids.[14] Consequently, there remains a need for alternative first-line treatment options for HCC.

Limitations

Limitations of RATIONALE-301 include use of open-label treatment, which may increase the risk of bias for PFS and ORR; however, radiological responses were assessed and reported by BIRC to mitigate this bias. In addition, there was potential for confounding of the OS analysis due to the emergence of improved treatments for later lines of therapy to which patients could cross over after disease progression. The sample size of patients enrolled in different regions was somewhat unbalanced, with 63.1% of patients recruited in Asia (excluding Japan); however, this is representative of the global distribution of HCC.[35] This study benefited from inclusion of a diverse patient population in terms of disease status, etiology, and baseline characteristics, which was broadly representative of the patient population with HCC under investigation.

Conclusions

In the RATIONALE-301 trial, tislelizumab monotherapy demonstrated comparable OS, in addition to increased and more durable objective responses, compared with sorafenib, while DCR and median PFS favored sorafenib. Tislelizumab had a favorable safety profile compared with sorafenib, with no new safety signals. These findings demonstrate that tislelizumab represents a potential first-line treatment option for patients with unresectable HCC.

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