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

Shukui Qin, MD, PhD; Masatoshi Kudo, MD, PhD; Tim Meyer, MD, PhD; Yuxian Bai, MD; Yabing Guo, MD, PhD; Zhiqiang Meng, MD, PhD; Taroh Satoh, MD, PhD; Donatella Marino, MD; Eric Assenat, MD, PhD; Songzi Li, PhD; Yaxi Chen, MD; Frederic Boisserie, MSc; Raml Abdrashitov, MD, PhD; Richard S. Finn, MD; Arndt Vogel, MD; Andrew X. Zhu, MD, PhD

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-naïve 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 sorafenibtosylate, 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.

TRIAL REGISTRATION
ClinicalTrials.gov Identifier: NCT03412773

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Shukui Qin, MD, PhD, Nanjing Tianyinshang Hospital of China Pharmaceutical University, No. 3789 Jieyin Rd, Jiangning District, Nanjing, Jiangsu 211102, China (qinsk@csco.org.cn).
Hepatocellular carcinoma (HCC) is the most common type of liver cancer and a leading cause of cancer-related mortality globally. Most patients present with advanced stage unresectable disease, which has a poor prognosis. Median survival time is approximately 1.0 to 1.5 years for symptomatic patients with advanced HCC receiving systemic therapies. Recommended first-line systemic treatments for HCC include the single-agent multitargeted tyrosine kinase inhibitors (TKIs) sorafenib tosylate and lenvatinib. 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.

Other checkpoint inhibitors have also shown promising results in the first-line advanced HCC setting. 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. 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. Durvalumab (anti–PD-L1) demonstrated OS noninferiority as monotherapy and superiority in combination with tremelimumab compared with sorafenib in the phase 3 HIMALAYA trial, leading to recent US Food and Drug Administration and European Medicines Agency 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. Tyrosine kinase inhibitors are recommended for patients with contraindications to atezolizumab or bevacizumab; 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 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. 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 and has shown efficacy and a tolerable safety profile in patients with various solid tumors. Tislelizumab demonstrated durable clinical activity in patients with previously treated advanced HCC in the phase 2 RATIONALE-208 trial, 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 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, 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 4.0.32 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
Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable HCC

vs sorafenib in the ITT analysis set (HR, 0.85 [95% CI, 0.71-1.02]); noninferiority margin upper limit of 0.95.003% CI for HR <1.08). Median OS was 15.9 (95% CI, 13.2-19.7) months in the sorafenib arm (Figure 1A). Superiority of OS for tislelizumab vs sorafenib was not met (1-sided 0.05 level of 95.003% CI for HR, 0.85 [95% CI, 0.71-0.99]) (Figure 1A). Among patients who were censored in the tislelizumab (510 [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
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 (Table 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tislelizumab (n = 342)</td>
</tr>
<tr>
<td>Median age, (range), y</td>
<td>62 (23-86)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>289 (84.5)</td>
</tr>
<tr>
<td>Women</td>
<td>53 (15.5)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
</tr>
<tr>
<td>Asia (excluding Japan)</td>
<td>215 (62.9)</td>
</tr>
<tr>
<td>Japan</td>
<td>38 (11.1)</td>
</tr>
<tr>
<td>Rest of worlda</td>
<td>89 (26.0)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>183 (53.5)</td>
</tr>
<tr>
<td>1</td>
<td>159 (46.5)</td>
</tr>
<tr>
<td>BCLC stage at study entry</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>70 (20.5)</td>
</tr>
<tr>
<td>C</td>
<td>272 (79.5)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma etiology</td>
<td></td>
</tr>
<tr>
<td>HBV only</td>
<td>203 (59.4)</td>
</tr>
<tr>
<td>HCV only</td>
<td>46 (13.5)</td>
</tr>
<tr>
<td>HBV and HCV coinfection</td>
<td>11 (3.2)</td>
</tr>
<tr>
<td>Uninfected</td>
<td>82 (24.0)</td>
</tr>
<tr>
<td>o-Fetoprotein level ≥400 ng/mL</td>
<td>135 (39.5)</td>
</tr>
<tr>
<td>Child–Pugh score at study entryc</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>263 (76.9)</td>
</tr>
<tr>
<td>6</td>
<td>77 (22.5)</td>
</tr>
<tr>
<td>Otherd</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Albumin-bilirubin score at study entryb</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>256 (74.9)</td>
</tr>
<tr>
<td>2</td>
<td>81 (23.7)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Extrahepatic spread</td>
<td>219 (64.0)</td>
</tr>
<tr>
<td>Macrovascular invasion</td>
<td>51 (14.9)</td>
</tr>
<tr>
<td>Locoregional therapy</td>
<td>265 (77.5)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>205 (59.9)</td>
</tr>
<tr>
<td>Location of metastases</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>120 (35.1)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>76 (22.2)</td>
</tr>
<tr>
<td>Bone</td>
<td>32 (9.4)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (9.1)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>20 (5.8)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>15 (4.4)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Skin</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Muscle</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

2 Unless otherwise indicated, data are expressed as number (percentage) of patients.

3 Includes Europe, the UK, and the US.

4 Scores range from 5 to 15; higher scores indicate greater severity of cirrhosis.

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

6 Scores range from 1 to 3; higher scores indicate greater mortality risk.
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.

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) and HIMALAYA (13.8 months) HCC studies. A higher proportion of patients in the 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 IMbrave, 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.
Patients who had progressive disease or died were excluded from this analysis. 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

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 estimable; ORR, objective response rate.

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

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

<table>
<thead>
<tr>
<th>Response</th>
<th>Patient group</th>
<th>Tislelizumab (n = 342)</th>
<th>Sorafenib (n = 332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, No. (%) [95% CI]</td>
<td>49 (14.3) [10.8-18.5]</td>
<td>18 (5.4) [3.2-8.4]</td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>2.755 (1.566-4.846)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ORR difference (95% CI)</td>
<td>8.28 (3.85-12.70)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Best overall response, No. (%)

- Complete response: 10 (2.9) vs 1 (0.3)
- Partial response: 39 (11.4) vs 17 (5.1)
- Stable disease: 94 (27.5) vs 139 (41.9)
- Progressive disease: 169 (49.4) vs 121 (36.4)
- Undetermined*: 22 (6.4) vs 44 (13.3)
- Noncomplete response and nonprogressive disease: 8 (2.3) vs 10 (3.0)

DCR, No. (%) | 151 (44.2) vs 167 (50.3)

CBR, No. (%) | 87 (25.4) vs 81 (24.4)

Patients with treatment response, No. | 49 vs 18

DOR, median (95% CI), mo | 36.1 (16.8 to NE) vs 11.0 (6.2-14.7)

Time to response, median (range), mo | 2.2 (1.8-24.4) vs 4.0 (1.9-13.2)

Patients with ongoing response, No./total No. (%) | 20/28 (71.4) vs 22/28 (78.6)

Table 3. Safety Summary in the Safety Analysis Set

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Tislelizumab (n = 338)</th>
<th>Sorafenib (n = 324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE Any</td>
<td>325 (96.2) vs 324 (100)</td>
<td></td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>163 (48.2) vs 212 (65.4)</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>101 (29.9) vs 91 (28.1)</td>
<td></td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>37 (10.9) vs 60 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Leading to treatment modification Any</td>
<td>105 (31.1) vs 210 (64.8)</td>
<td></td>
</tr>
<tr>
<td>Interrupted or withheld</td>
<td>105 (31.1) vs 177 (54.6)</td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>0 vs 144 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Leading to death</td>
<td>15 (4.4) vs 17 (5.2)</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of TRAEs occurring in ≥ 10% of patients in either arm:

- AST level increased: 78 (23.1) vs 93 (28.7)
- ALT level increased: 56 (16.6) vs 81 (25.0)
- Blood bilirubin level increased: 42 (12.4) vs 67 (20.7)
- Pruritus: 35 (10.4) vs 16 (4.9)
- Rash: 34 (10.1) vs 54 (16.7)
- Platelet count decreased: 24 (7.1) vs 49 (15.1)
- Fatigue: 21 (6.2) vs 34 (10.5)
- Diarrhea: 19 (5.6) vs 127 (39.2)
- Decreased appetite: 17 (5.0) vs 39 (12.0)
- Weight decreased: 11 (3.3) vs 36 (11.1)
- Hypertension: 9 (2.7) vs 80 (24.7)
- Alopecia: 1 (0.3) vs 73 (22.5)
- Palmar-plantar erythrodysesthesia syndrome: 1 (0.3) vs 203 (62.7)

IMAЕ Any | 62 (18.3) vs 0
Grade ≥3 | 28 (8.3) vs 0
Serious | 17 (5.0) vs 0
Leading to treatment discontinuation | 11 (3.3) vs 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 24.037 and ordered based on decreasing incidence in the tislelizumab arm.
due to contraindications or toxic effects. Of note, the OS and ORR outcomes were similar with nivolumab in CheckMate 459 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, and the combination with tremelimumab was approved by the US Food and Drug Administration in 2022 for treatment of adult patients with unresectable HCC. Of interest, median OS was comparable with the combination compared with 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. 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. 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.

Author Contributions: Dr Qin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Qin, Meyer, Meng, Li, Chen, Boissiere, Finn, Zhu. Acquisition, analysis, or interpretation of data: Qin, Kudo, Meyer, Bai, Guo, Satoh, Marino, Assenat, Chen, Boissiere, Abrashitov, Finn, Vogel, Zhu. Drafting of the manuscript: Bai, Assenat, Chen, Abrashitov, Zhu. Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Li, Chen.

Obtained funding: Qin, Guo, Chen, Administrative, technical, or material support: Bai, Guo, Meng, Satoh, Chen, Zhu.

Supervision: Qin, Kudo, Bai, Meng, Chen, Abrashitov, Finn, Vogel, Zhu.

Conflict of Interest Disclosures: Dr Kudo reported receiving speaker fees from AstraZeneca, Bayer AG, Chugai Pharmaceutical Co, Ltd, Eisai Co, Ltd, Eli Lilly and Company, and Takeda Pharmaceutical Company Limited; consulting for F. Hoffmann-La Roche AG, and receiving research grants from AbbVie Inc, EA Pharma, Co, Ltd, Eisai Co, Ltd, Gilead Sciences, Inc, Otsuka Pharmaceutical Co, Ltd, Sumitomo Dainippon Pharma, Taiho Pharmaceutical Co, Ltd, Takeda Pharmaceutical Company Limited, and GE Healthcare outside the submitted work. Dr Meyer reported serving as a member the steering committee for Beigene during the conduct of the study and consulting for Adaptimmune Therapeutics LC, AstraZeneca, Beigene, Inc, Bristol-Myers Squibb, Eisai Co, Ltd, MSD, and F. Hoffmann-La Roche AG and receiving research grants for MSD outside the submitted work. Dr Satoh reported receiving grant funding from Bristol-Myers Squibb, Chugai Pharmaceutical Co, Ltd, HUTCHMED, Ono Pharmaceutical Co, Ltd, Yakult Honsha Co, Ltd, Eli Lilly andCompany, and Beigene, Inc during the conduct of the study and receiving personal fees from Chugai Pharmaceutical Co, Ltd, Daiichi Sankyo Inc, Ono Pharmaceutical Co, Ltd, Bristol-Myers Squibb, and Eli Lilly and Company outside the submitted work. Dr Marino reported receiving advisory board fees from F. Hoffmann-La Roche AG, MSD, and Merck & Co, Inc, and receiving travel expenses from Pierre Fabre and Amgen Inc outside the submitted work. Dr Assenat reported receiving advisory board fees from AstraZeneca, Ipsen, F. Hoffmann-La Roche AG, and Servier Laboratories. Dr Abrashitov reported having stock ownership in AstraZeneca, Beigene, Inc, Mirati Therapeutics, Inc, Syndax Pharmaceuticals Inc, and Takeda Pharmaceutical Company Limited. Dr Finn reported receiving serving on advisory boards for AstraZeneca, Bayer AG, Bristol Myers Squibb, CStone Pharmaceuticals, Eisai Co, Ltd, Eli Lilly and Company, Exelixis, Inc, Jiangsu Hengrui Pharmaceuticals Co, Ltd, Merck & Co, Inc, Pfizer Inc, and Roche-Genentech; receiving grant funding from Adaptimmune Therapeutics LC, Bayer AG, Bristol-Myers Squibb, Eli Lilly and Company, Eisai Co, Ltd, Merck & Co, Inc, Pfizer Inc, and Roche-Genentech; and being a principal investigator for Bristol Myers Squibb, Eisai Co, Ltd, Merck & Co, Inc, Pfizer Inc, and Roche-Genentech outside the submitted work. Dr Vogel reported receiving speaker fees from and serving on advisory boards for Amgen Inc, AstraZeneca, Beigene, Inc, Bristol Myers Squibb, Boehringer Mannheim, BTG Limited, Daichi Sankyo Inc, Eisai Co, Ltd, Incyte Corporation, Ipsen, MSD, Pierre Fabre, F. Hoffmann-La Roche AG, Servier Laboratories, SirTeX SIR Spheres Pty Ltd, Taiho Pharmaceutical Co, Ltd, and Terumo Corporation and receiving speaking fees from GSK, AAA Imaging Solutions, and Jiangsu Hengrui Pharmaceuticals Co, Ltd, outside the submitted work. Dr Zhu reported having advisory roles and consulting for Eisai Co, Ltd, Roche-Genentech, Eli Lilly and Company, Sanofi SA, and Merck & Co, Inc. Dr Zhu reported...
Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable HCC

Original Investigation Research

Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable HCC


