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CLINICAL TRIAL REPORT

Sorafenib Combined with Tislelizumab and Transarterial Chemoembolization for Advanced-Stage Hepatocellular Carcinoma: A Phase II Study

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Purpose: To evaluate the efficacy and safety of sorafenib combined with tislelizumab (a programmed death-1 inhibitor) and transarterial chemoembolization (TACE) in patients with advanced-stage hepatocellular carcinoma (HCC).

Patients and Methods: This was a single-center, single-arm phase II trial. Patients with HCC at Barcelona Clinic Liver Cancer stage C were recruited. Treatment with sorafenib (400 mg orally twice daily) and tislelizumab (200 mg intravenously every 3 weeks) was initiated 3–7 days after the first TACE procedure. Repeated TACE was performed on-demand. The primary endpoint of this study was overall survival (OS).

Results: Thirty patients were enrolled. The median OS for the patients was 18.3 (95% CI = 14.6–22.0) months, with 12-, 18-, and 24-month OS rates of 90.0%, 54.0%, and 28.3%, respectively. The objective response rate was 53.3% per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and 20.0% per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The disease control rate was 86.7% per mRECIST/RECIST 1.1. The median progression-free survival was 6.8 (95% CI = 4.5–9.0) months per mRECIST/RECIST 1.1. The median duration of response was 7.1 (95% CI = 6.1–8.1) months per mRECIST (n = 16) and 4.4 (95% CI = 0.9–7.9) months per RECIST 1.1 (n = 6). Treatment-related adverse events (TRAEs) occurred in 28 patients (93.3%), and grade 3 TRAEs were observed in 11 patients (36.7%). There were no grade 4/5 TRAEs.

Conclusion: Sorafenib combined with tislelizumab and TACE showed promising antitumor activities with a manageable safety profile in patients with advanced-stage HCC. These preliminary findings warrant further evaluation in Phase III randomized trials.

Keywords: hepatocellular carcinoma, sorafenib, tislelizumab, transarterial chemoembolization, combination therapy

Introduction

Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related deaths worldwide.[1] Although early-stage HCC is potentially curative through surgical resection, liver transplantation or ablation, the majority of patients present with advanced disease at initial diagnosis, rendering them ineligible for these approaches and resulting in a dismal prognosis.[2,3]

Sorafenib, a tyrosine-kinase inhibitor (TKI), has been recommended as a first-line treatment option for advanced HCC based on evidence from the SHARP and Asia-Pacific trials.[4–7] However, the efficacy of sorafenib monotherapy is

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limited, extending overall survival (OS) by only about 3 months compared to placebo.[4,5] In this setting, numerous combination strategies have been proposed to improve clinical benefits for patients with advanced disease.[8–12]

In recent years, immune checkpoint inhibitors, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, have revolutionized the therapeutic landscape for HCC.[13] Studies exploring the combination of PD-1/PD-L1 inhibitors and antiangiogenic agents have shown promising results.[2,14–17] In the phase III IMbrave150 and ORIENT-32 trials, atezolizumab (a PD-L1 inhibitor) combined with bevacizumab and sintilimab (a PD-1 inhibitor) combined with bevacizumab, respectively, demonstrated prolonged OS compared to sorafenib in unresectable HCC.[2,14] Similarly, the phase III CARES-310 trial reported improved efficacy with camrelizumab (a PD-1 inhibitor) plus rivoceranib (a TKI) over sorafenib.[15] These findings revealed that the combination of PD-1/PD-L1 inhibitors and antiangiogenic agents is more effective in the treatment of advanced HCC. Antiangiogenic agents are capable of modulating the immune microenvironment of HCC and may enhance the antitumor efficacy of PD-1/PD-L1 inhibitors, thus providing a compelling rationale for this combination therapy.[17,18]

Additionally, locoregional therapies, such as transarterial chemoembolization (TACE), which can reduce intrahepatic tumor burden and achieve favorable disease control, are frequently integrated with systemic therapies to enhance therapeutic outcomes in unresectable HCC.[10–12] Recent retrospective and real-world studies showed that combining TKIs with PD-1/PD-L1 inhibitors and TACE provided better tumor responses and survival in patients with advanced HCC, suggesting potential synergistic antitumor effects through antiangiogenic activity, PD-1/PD-L1 inhibition, and ischemia-induced tumor necrosis.[11,19,20] Therefore, this triple combination may serve as a more effective treatment strategy for advanced HCC.

Yet, to our knowledge, data from prospective trials regarding the combination of sorafenib, PD-1 inhibitors, and TACE for advanced HCC remain scarce. Herein, we present the results of a phase II trial evaluating sorafenib combined with tislelizumab (a PD-1 inhibitor) and TACE (Sor+Tis+TACE) for the first-line treatment of advanced-stage HCC.

Materials and Methods

Study Design and Patients

This was an open-label, single-arm, phase II study conducted at the Second Affiliated Hospital, Guangzhou Medical University. The trial protocol and statistical analysis plan were finalized on 20 July 2020 and approved by the institutional ethics committee on 7 August 2020 (approval number, 2020-ks-13). Study activities commenced on 1 October 2020, with the first patient enrolled on 9 October 2020. Due to institutional requirements for administrative review prior to public registration, the trial was submitted to ClinicalTrials.gov on 19 October 2020 (NCT04599777), resulting in a delay of 10 days relative to the first patient enrollment. The single patient enrolled before registration underwent baseline assessments and received the study treatment per protocol. No outcome data (tumor response or survival) were collected or analyzed during this interval. All procedures were rigorously adhered to the pre-specified protocol and statistical analysis plan. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent prior to enrollment.

Eligible patients were aged 18 years or older, with histologically or clinically confirmed HCC[7,21] at Barcelona Clinic Liver Cancer (BCLC) stage C, disease amenable to TACE,[7] at least one measurable lesion based on modified Response Evaluation Criteria in Solid Tumors (mRECIST) and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), Eastern Cooperative Oncology Group performance status of 0–1, Child-Pugh score of 5–7, and life expectancy of ≥3 months. Laboratory tests were required to meet the following criteria: white blood cell count $\geq 3.0\times10^9$/L, neutrophil count $\geq 1.5\times10^9$/L, platelet count $\geq 50\times10^9$/L, hemoglobin ≥90 g/L, alanine aminotransferase and aspartate aminotransferase <5 times upper limit of normal, total bilirubin <34 μmol/L, albumin ≥28 g/L, prothrombin time prolongation <4 seconds, creatinine ≤1.5 times upper limit of normal. The key exclusion criteria included tumor thrombus involving bilateral portal vein branches, main portal vein or vena cava; extrahepatic metastasis involving major blood vessels or airways; symptomatic, untreated or progressing central nervous system metastasis; previous treatment with systemic therapy, hepatic arterial infusion chemotherapy, transarterial embolization, TACE or radiotherapy; uncontrolled ascites,

hydrothorax or pericardial effusion; history of hepatic encephalopathy; variceal bleeding within 6 months prior to treatment initiation; history of organ or cell transplantation; and history of malignancy other than HCC.

Treatment

After being fully informed, the patients underwent either drug-eluting bead (DEB) TACE (DEB-TACE) or conventional TACE (cTACE) according to the recommendation provided by the interventional team following thorough discussion. Both TACE procedures were performed using a super-selective approach.[3,22] For DEB-TACE, the DEBs (DC Bead; Biocompatibles, Farnham, Surrey, UK) loaded with pirarubicin (Hisun Pfizer Pharmaceuticals, Fuyang, China) were mixed with nonionic contrast medium and injected into the tumor-feeding arteries. If tumor blush was still observed following administration of a vial of DEBs (loaded with 60 mg pirarubicin), regular microspheres (8Spheres; Hengrui Medical, Suzhou, China) with diameters of 100–700 μm were used for further embolization. For cTACE, an emulsion of 20–60 mg pirarubicin in 5–20 mL Lipiodol (Guerbet, Paris, France) was injected, followed by particle embolization with 90–500 μm polyvinyl alcohol (Cook, Bloomington, Indiana, USA). The endpoint of embolization was obliteration of the tumor feeding vessels. In patients with huge or bilobar multiple lesions, the embolization endpoint was not achieved in a single treatment but in the second or third procedure.[23] Given that performing TACE at fixed intervals regardless of the initial treatment outcomes may cause severe hepatic impairment,[7,21] repeated TACE was conducted "on-demand" upon confirmation of viable tumors by follow-up imaging and in the absence of contraindications. Each patient was required to receive the same TACE procedure (ie DEB-TACE or cTACE) throughout the study period.

Sorafenib (Bayer Pharma, Leverkusen, Germany) and tislelizumab (BeiGene, Shanghai, China) were initiated 3–7 days after the first TACE. This timing was designed to 1) mitigate overlapping toxicities, as the initial TACE often involves extensive embolization that may induce post-embolization syndrome and transient liver dysfunction,[7,21] and 2) potentiate the synergistic antitumor effects by counteracting post-TACE angiogenesis and leveraging TACE-induced immunogenic necrosis within a therapeutically responsive window.[21,24–28]

Both agents were maintained without interruption throughout subsequent TACE procedures and continued until intolerable toxicity, disease progression, or withdrawal of consent. Sorafenib was administered orally at an initial dose of 400 mg twice daily. Tislelizumab was administered intravenously at 200 mg every three weeks for up to two years. These doses were adopted based on published data[29,30] and our preliminary experience, both of which indicated manageable safety profiles for the combination therapies involving TKIs and PD-1 inhibitors at their respective standard doses. Treatment interruption and discontinuation due to toxicities were determined by the physicians according to the drug package inserts. Dose modifications of sorafenib (eg, reduction to 400 mg once daily, then to 400 mg every other day) were permitted for toxicity management. The patients were allowed to continue sorafenib or tislelizumab as a single treatment and were still considered on study when the other drug caused intolerable toxicity in the absence of disease progression.

Assessments and Endpoints

Tumor response was assessed according to mRECIST and RECIST 1.1 by two independent radiologists, each with more than 5 years of experience in HCC imaging. In case of discordant readings, a third senior radiologist (with more than 10 years of experience) made the final adjudication. The mRECIST was applied to assist in treatment decision-making. Safety was evaluated by monitoring adverse events (AEs) according to Common Terminology Criteria for Adverse Events version 5.0.

The primary endpoint of this study was OS, which was defined as the time from the initiation of treatment until death from any cause. The secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DOR) and AEs. ORR was defined as the proportion of patients achieving complete response (CR) or partial response (PR) to treatment. DCR was defined as the proportion of patients achieving CR, PR or stable disease (SD). PFS was defined as the time from treatment initiation until disease progression or death, whichever occurred first. DOR was assessed in the patients who achieved an objective response (ie CR or PR). It was defined as the time from the first documented objective response until disease progression or death, whichever occurred first.

Follow-Up

Scheduled visits, hematologic and biochemical tests, fecal occult blood test and urinalysis were performed every 3 weeks. Contrast-enhanced abdominal CT/MRI and chest CT were performed at baseline, three weeks after each TACE and every 6 weeks thereafter. The follow-up ended in October 2022.

Statistical Analyses

Sample size was calculated using PASS 14 (NCSS, Kaysville, Utah, USA). It has been reported that the median OS of Chinese patients with advanced-stage HCC who received sorafenib was 6.0–8.0 months.[31–34] With the triple therapy of Sor+Tis+TACE, the median OS was expected to increase from 8.0 months to 15.0 months. Assuming a one-sided α level of 5%, a power of 80%, a recruitment of 12 months, a follow-up of 12 months and a dropout rate of 10%, a total of 30 patients were required to be enrolled for this trial.

Continuous variables were expressed as mean ± standard deviation or median (range), as appropriate. Categorical variables were expressed as frequency (percentage). 95% confidence intervals (CIs) for ORR and DCR were calculated using the Clopper-Pearson method. PFS, DOR and OS were estimated by the Kaplan-Meier method. All statistical analyses were conducted with SPSS Statistics 26 (IBM, Armonk, New York, USA).

Results

Patients and Treatment

From 1 October 2020 to 3 August 2021, 35 patients were screened for eligibility, of whom 30 were enrolled (Figure 1). The baseline characteristics of the patients are shown in Table 1. Eight patients (26.7%) exhibited tumor recurrence following prior surgical resection or thermal ablation. The mean largest tumor diameter was 11.4±3.9 (range, 4.2–20.3) cm, with intrahepatic tumor number >3 observed in 14 patients (46.7%) and bilobar tumor distribution identified in 18 (60.0%). Twenty-seven patients (90.0%) had macrovascular invasion, and 12 patients (40.0%) had extrahepatic metastases.

The duration of treatment and follow-up for each patient is shown in Figure 2A. As of the cut-off date (31 October 2022), one patient was still on treatment. The mean follow-up period for the 30 patients was 16.6±4.2 (range, 5.2–24.7) months. The patients underwent a total of 99 TACE procedures, with a mean number of 3.3±1.2 (range, 1–6) procedures per patient. The mean duration of sorafenib administration was 7.8±4.1 (range, 1.5–15.5) months. The cycles of tislelizumab injection ranged from 2 to 22, with a mean number of 9.8±5.9 cycles per patient.

After the termination of study treatment, 28 patients (93.3%) received post-study treatments. Among them, 4 continued to receive sorafenib and/or tislelizumab, and 24 received other systemic therapies. In addition, 17 patients underwent additional locoregional therapies (Table 2).

Efficacy

Upon data analysis, 17 patients had died. The causes of death included tumor progression in 11 patients (64.7%), variceal bleeding in four (23.5%), hepatic failure in one (5.9%), and sudden death (unknown etiology) in one (5.9%). The median OS was 18.3 (95% CI = 14.6–22.0) months, with 12-, 18-, and 24-month OS rates of 90.0%, 54.0%, and 28.3% (Figure 3A), respectively.

Tumor responses are summarized in Table 3. Two patients (6.7%) achieved CR per mRECIST and none achieved CR per RECIST 1.1. The ORR was 53.3% (95% CI = 34.4–72.3%) per mRECIST and 20.0% (95% CI = 4.8–35.2%) per RECIST 1.1. The DCR was 86.7% (95% CI = 73.8–99.6%) per mRECIST/RECIST 1.1. A ≥30% reduction in target tumor size was observed in 19 patients (63.3%) per mRECIST and 7 patients (23.3%) per RECIST 1.1 (Figure 2B and C).

During the study, 29 patients (96.7%) experienced disease progression per mRECIST. The median PFS was 6.8 (95% CI = 4.5–9.0) months per mRECIST or RECIST 1.1 (Figure 3B and C). The 6- and 12-month PFS rates were 66.7% and 16.7%, respectively, per mRECIST, and 66.7% and 18.3%, respectively, per RECIST 1.1. The median DOR for patients who achieved an objective response was 7.1 (95% CI = 6.1–8.1) months per mRECIST (n = 16) and 4.4 (95% CI = 0.9–7.9) months per RECIST 1.1 (n = 6).

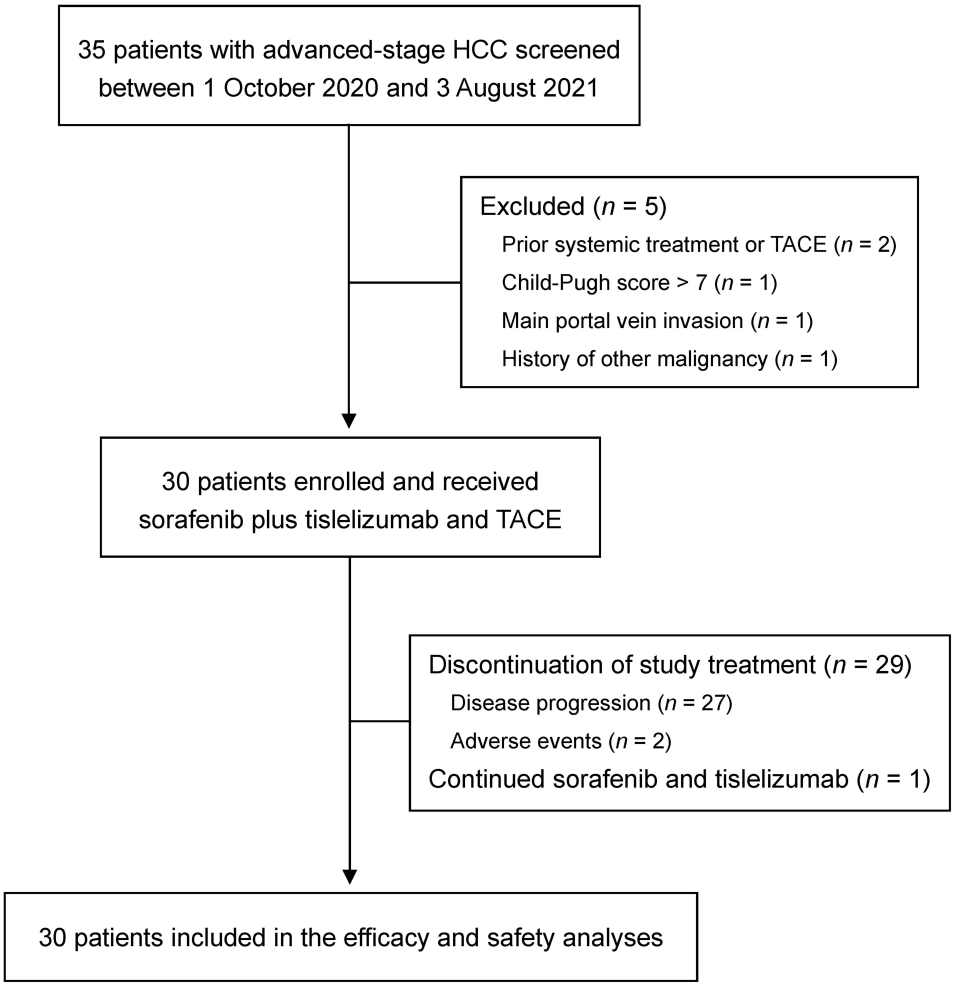

Figure 1 Trial flow diagram.
Abbreviation: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

Safety

Twenty-eight patients (93.3%) experienced at least one TRAE of any grade. Grade 3 TRAEs occurred in 11 patients (36.7%), with no grade 4/5 TRAEs observed (Table 4). All patients developed post-embolization syndrome and/or

Table 1 Baseline Characteristics of the Patients

Characteristic	Value
Age, years	53.8±9.9
≥60/<60	8 (26.7)/22 (73.3)
Sex	
Female/Male	3 (10.0)/27 (90.0)
ECOG PS	
1/0	2 (6.7)/28 (93.3)
Cause of HCC[a]	
Hepatitis B	23 (76.7)
Hepatitis B and alcohol intake	1 (3.3)
Hepatitis C	3 (10.0)
Alcohol intake	2 (6.7)
Unknown	1 (3.3)

(*Continued*)

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Table 1 (Continued).

Characteristic	Value
HBV-DNA[b], IU/mL	
≥1000/<1000	10 (41.7)/14 (58.3)
Recurrent tumor	
Yes/No	8 (26.7)/22 (73.3)
Largest tumor diameter, cm	11.4±3.9
≥10/<10	19 (63.3)/11 (36.7)
Number of intrahepatic tumors	
>3/≤3	14 (46.7)/16 (53.3)
Tumor distribution	
Bilobar/Unilobar	18 (60.0)/12 (40.0)
Macrovascular invasion	27 (90.0)
Extrahepatic metastasis	12 (40.0)
Location of metastases	
Lungs	11 (36.7)
Lymph nodes	5 (16.7)
Bones	1 (3.3)
α-Fetoprotein level, μg/L	203.6 (7.9–2216.0)
≥200/<200	15 (50.0)/15 (50.0)
PIVKA-II, mAU/mL	2201.5 (81.2–15,077.5)
≥400/<400	16 (53.3)/14 (46.7)
Child-Pugh class	
A/B7	29 (96.7)/1 (3.3)
ALBI grade	
1/2	15 (50.0)/15 (50.0)
TACE procedure	
DEB-TACE/cTACE	17 (56.7)/13 (43.3)

Notes: Data are presented as n (%), mean ± standard deviation or median (range). [a]All 24 patients with hepatitis B received antiviral therapy during the study. Three patients with hepatitis C were negative for hepatitis C virus-RNA at enrollment. Three patients had a history of excessive alcohol consumption but had abstained from alcohol prior to enrollment. [b]Six patients without hepatitis B virus infection were excluded.

Abbreviations: ALBI, albumin-bilirubin; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TACE, transarterial chemoembolization.

transient liver enzyme abnormalities following TACE, which were resolved within a short time and were not separately documented. The TACE-related AEs, including ascites, pleural effusion, intrahepatic biliary injury, and inguinal hematoma, were mild and occurred in 4 patients (13.3%). The incidence of AEs related to sorafenib and/or tislelizumab was the same as that of the overall TRAEs.

TRAEs necessitated treatment interruption, dose reduction, and discontinuation of sorafenib in 17 (56.7%), 21 (70.0%), and 3 (10.0%) patients, respectively. For tislelizumab, treatment interruption and discontinuation occurred in 11 (36.7%) and 4 (13.3%) patients, respectively. Discontinuation of both drugs was required in 2 patients (6.7%).

Discussion

The results of this phase II trial indicate that the triple therapy of Sor+Tis+TACE exhibited clinically meaningful antitumor efficacy in patients with advanced HCC. The regimen achieved favorable objective response and survival

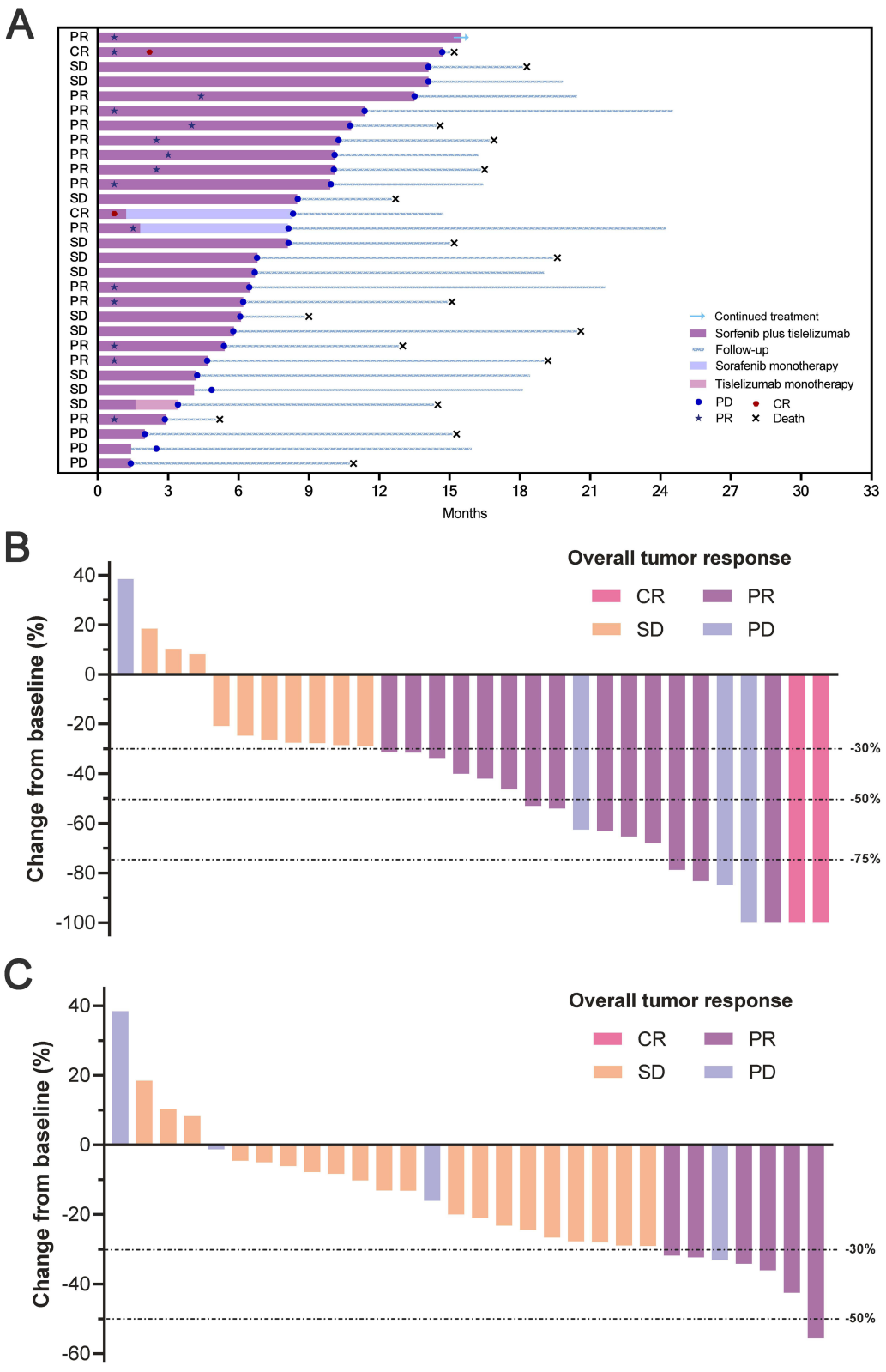

Figure 2 Antitumor activity. Duration of treatment and response assessments by mRECIST (**A**). Best percentage change from baseline in diameters of intrahepatic target lesions per mRECIST (**B**) and RECIST 1.1 (**C**).

Abbreviation: CR, complete response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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Table 2 Post-Study Treatments for the Patients

Post-Study Treatment	Patients (n)
Continued sorafenib and/or tislelizumab	4
Other TKIs	22
Regorafenib	16
Lenvatinib	4
Apatinib	2
Other PD-1 inhibitors	14
Sintilimab	11
Camrelizumab	3
TACE	9
Hepatic arterial infusion chemotherapy	5
Iodine-125 seed brachytherapy	6

Abbreviations: PD-1, programmed death-1; TACE, transarterial chemoembolization; TKI, tyrosine-kinase inhibitor.

outcomes, as well as a manageable and tolerable safety profile, positioning the combination as a viable therapeutic option for advanced-stage disease.

Previous studies have shown that the median OS of sorafenib monotherapy in Chinese patients with advanced-stage HCC ranges from 6.0 to 8.0 months.[31–34] In the present study, the addition of tislelizumab and TACE to sorafenib prolonged the median OS to 18.3 months, despite unfavorable tumor characteristics in the cohort, such as a mean largest tumor diameter of 11.4 cm, intrahepatic tumor number >3 in 46.7% of patients, bilobar involvement in 60.0%, and extrahepatic metastasis in 40.0%. Additionally, the combination therapy achieved an ORR of 53.3% (mRECIST; 20.0% per RECIST 1.1), a DCR of 86.7% (mRECIST/RECIST 1.1), and a median PFS of 6.8 months (mRECIST/RECIST 1.1). These outcomes also surpass those reported for sorafenib in recent trials, which enrolled not only BCLC stage C patients but also a subset with stage A/B disease.[2,14,15,35] All these results indicate that the combination of Sor+Tis+TACE may represent a more intensive and effective treatment strategy for advanced HCC.

Of note, integrating TACE into the combination regimen may contribute to a significant therapeutic enhancement. Previous studies,[8,10,36] including the STAH trial, have demonstrated that sorafenib combined with TACE provides superior tumor control and even survival benefits compared to sorafenib alone in advanced HCC, suggesting that TACE-induced tumor debulking may enhance the efficacy of sorafenib. In our study, treatment with Sor+Tis+TACE led to shrinkage of target lesions in 26 patients (86.7%), such that 16 (53.3%) achieved an overall tumor response per mRECIST, exceeding those of sorafenib monotherapy or sorafenib plus PD-1 inhibitors (ORR per mRECIST: 7.6–22.4%) in previous studies.[2,14,15,35,37] These results reaffirm that adding TACE to systemic therapy may effectively reduce intrahepatic tumor burden, thereby improving disease control in patients with advanced HCC.

Tislelizumab is a PD-1 inhibitor with proven efficacy in HCC, as established by the RATIONALE-208 and RATIONALE-301 trials.[35,38] Its combination therapies have also been preliminarily evaluated in non-randomized trials.[39–41] Interestingly, results from these studies and our own indicate that incorporating tislelizumab into combination therapies may confer benefits exceeding those achievable with the PD-1 inhibitor monotherapy. In the RATIONALE-301 trial,[35] first-line tislelizumab for unresectable HCC demonstrated noninferior OS (median, 15.9 months) compared to sorafenib, yet with an ORR of only 14.3%, a DCR of 44.2%, and a PFS of 2.1 months per RECIST 1.1. Clearly, these outcomes are inferior to those observed with Sor+Tis+TACE in our study. Collectively, these findings further underscore the therapeutic advantage of simultaneously targeting multiple hallmarks of HCC progression through antiangiogenesis, PD-1 blockade, and local tumor debulking, thus achieving enhanced clinical benefits.

There is a sound rationale for combining sorafenib, tislelizumab, and TACE within this therapeutic regimen. Firstly, sorafenib, tislelizumab, and TACE have each been established as effective treatments for HCC.[6,35] Secondly, sorafenib possesses activity in modulating multiple immune cells and the tumor microenvironment, thereby potentially enhancing

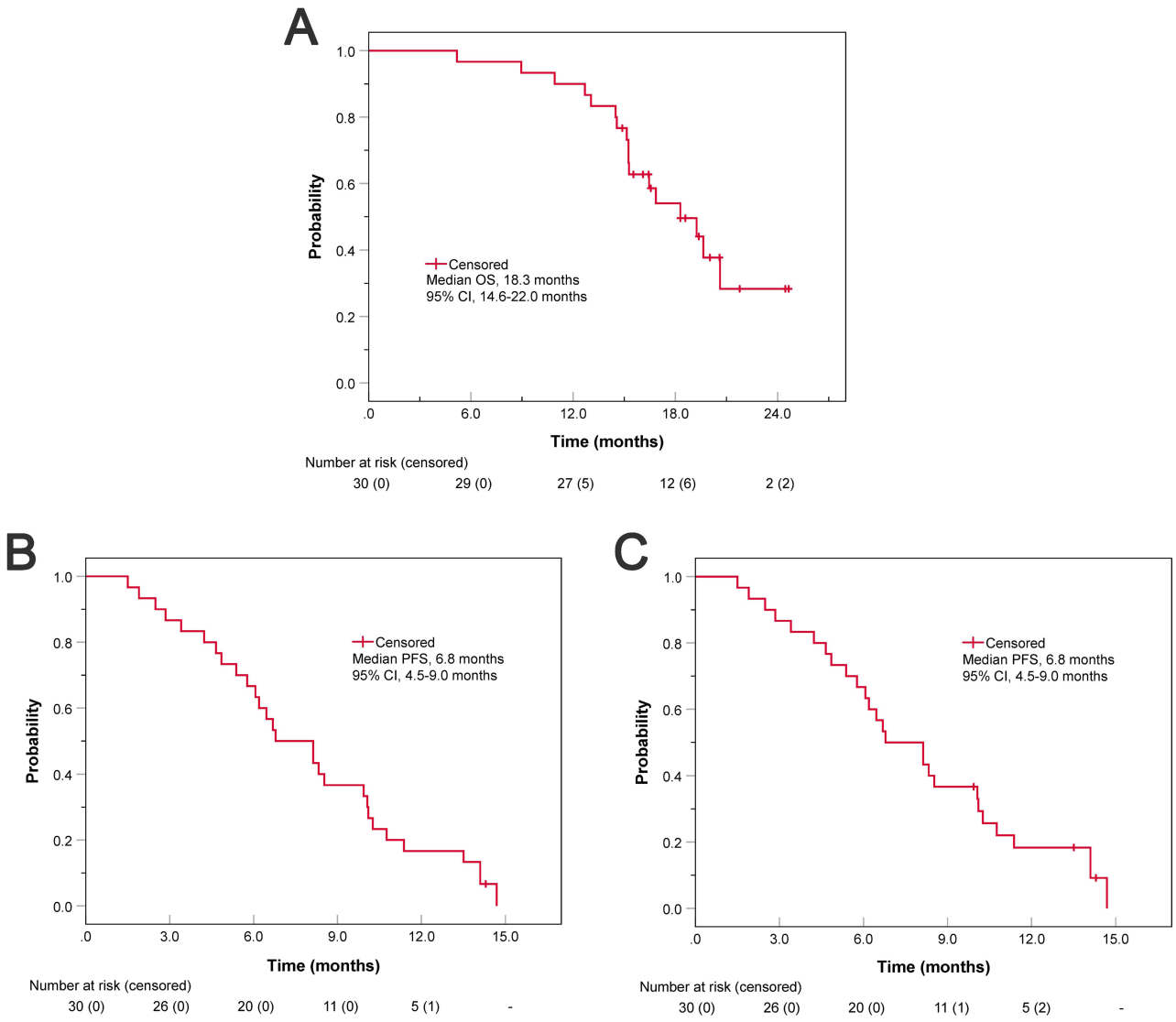

Figure 3 Kaplan-Meier analyses of OS and PFS. Analysis of OS (**A**). Analyses of PFS per mRECIST (**B**) and RECIST 1.1 (**C**).
Abbreviation: CI, confidence interval; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OS, overall survival; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

the antitumor immune response when administered with a PD-1 inhibitor.[17,18] Thirdly, sorafenib, as an antiangiogenic agent, may counteract post-TACE hypoxia-induced tumor angiogenesis, thus impeding tumor revascularization and progression.[10,36] Furthermore, TACE leads to extensive tumor necrosis and may subsequently stimulate a tumor-specific immune response, which may be further boosted by the combination of PD-1 inhibitors.[3,12] Therefore, the combination

Table 3 Tumor Responses for the Patients

Tumor Response	mRECIST	RECIST 1.1
CR, n (%)	2 (6.7)	0
PR, n (%)	14 (46.7)	6 (20.0)
SD, n (%)	10 (33.3)	20 (66.7)

(*Continued*)

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Table 3 (Continued).

Tumor Response	mRECIST	RECIST 1.1
PD, n (%)	4 (13.3)	4 (13.3)
ORR, % (95% CI)	53.3 (34.4–72.3)	20.0 (4.8–35.2)
DCR, % (95% CI)	86.7 (73.8–99.6)	86.7 (73.8–99.6)

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Table 4 Treatment-Related Adverse Events

Adverse Events	Any Grade	Grade 1/2	Grade 3
Total	28 (93.3)	28 (93.3)	11 (36.7)
Related to TACE	4 (13.3)	4 (13.3)	0
Ascites or pleural effusion	2 (6.7)	2 (6.7)	0
Intrahepatic biliary dilatation	2 (6.7)	2 (6.7)	0
Inguinal hematoma	1 (3.3)	1 (3.3)	0
Related to drug[a]	28 (93.3)	28 (93.3)	11 (36.7)
Hand-foot syndrome	15 (50.0)	13 (43.3)	2 (6.7)
Diarrhea	13 (43.3)	11 (36.7)	2 (6.7)
Alopecia	7 (23.3)	7 (23.3)	0
Elevated AST	7 (23.3)	6 (20.0)	1 (3.3)
Hypertension	7 (23.3)	6 (20.0)	1 (3.3)
Rash	6 (20.0)	5 (16.7)	1 (3.3)
Fatigue	6 (20.0)	5 (16.7)	1 (3.3)
Elevated ALT	6 (20.0)	5 (16.7)	1 (3.3)
Decreased leukocyte	5 (16.7)	5 (16.7)	0
Bloating	5 (16.7)	4 (13.3)	1 (3.3)
Elevated GGT	5 (16.7)	4 (13.3)	1 (3.3)
Elevated total bilirubin	5 (16.7)	4 (13.3)	1 (3.3)
Hypothyroidism	4 (13.3)	4 (13.3)	0
Weight loss	4 (13.3)	4 (13.3)	0
Decreased neutrocyte	4 (13.3)	4 (13.3)	0
Constipation	4 (13.3)	4 (13.3)	0
Decreased appetite	4 (13.3)	4 (13.3)	0
Nausea	4 (13.3)	4 (13.3)	0
Abdominal pain	4 (13.3)	4 (13.3)	0
Decreased platelet	4 (13.3)	3 (10.0)	1 (3.3)
Pruritus	3 (10.0)	3 (10.0)	0
Vomiting	2 (6.7)	2 (6.7)	0
Extremity pain	2 (6.7)	2 (6.7)	0
Stomatitis	2 (6.7)	2 (6.7)	0
Proteinuria	1 (3.3)	1 (3.3)	0
Dysphonia	1 (3.3)	1 (3.3)	0
Elevated lipase	1 (3.3)	1 (3.3)	0
Decreased hemoglobin	1 (3.3)	1 (3.3)	0
Infusion reaction[b]	1 (3.3)	1 (3.3)	0

Notes: Data were presented as n (%). [a]Referred to sorafenib and/or tislelizumab. [b]Including fever and/or shiver during infusion of tislelizumab.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; TACE, transarterial chemoembolization.

of Sor+Tis+TACE is likely to exert synergistic effects against HCC, delaying disease progression and improving clinical outcomes in patients with advanced HCC.

Notably, most patients (70.0%) in the present study underwent a reduction in the dose of sorafenib during treatment. Previous studies have shown that giving HCC patients a reduced dose of sorafenib, compared with a full dose, did not compromise the survival.[42,43] Additionally, preclinical evidence indicates that low-dose rather than high-dose sorafenib promotes antitumor immunity.[18] Informed by these findings, we intentionally implemented dose reduction of sorafenib in the patients experiencing significant TRAEs (eg ≥ grade 3 TRAEs or persistent grade 2 TRAEs). Importantly, the combination therapy with dose-adjusted sorafenib did not attenuate tumor control, but provided patients with favorable clinical benefits, as reflected in the tumor response and survival results.

In our study, no unexpected AEs or treatment-related deaths occurred. The TRAEs aligned with the known AE profiles of the single treatments, and no new safety signals were identified.[5,7,35] During the study, 36.7% of patients experienced grade 3 AEs, all attributable to sorafenib and/or tislelizumab. All TRAEs were manageable through appropriate monitoring, treatment interruption, dose reduction (applicable only to sorafenib), and/or treatment discontinuation. There were only two patients (6.7%) who required concurrent discontinuation of both sorafenib and tislelizumab. Additionally, despite some patients having detectable HBV-DNA levels at baseline (≥1000 IU/mL), they all received antiviral therapy during the study treatment and did not suffer from hepatitis flares. These results suggest that the Sor+Tis+TACE triple regimen has an acceptable and tolerable safety profile.

Our study has several limitations. Firstly, this was a single-arm phase II trial lacking a control group for comparative analysis. Secondly, the sample size was small. These may limit the interpretability of the results. Additionally, the open-label design may have introduced bias in the assessments of efficacy and safety. Furthermore, two TACE techniques, DEB-TACE and cTACE, were utilized in patient management. As the superiority of DEB-TACE over cTACE remains contentious,[21] the potential influence of TACE technique on outcomes warrants attention. Moreover, due to constraints in resources and funding, our study did not conduct mechanistic investigations of treatment response involving biomarker analyses, such as genomic profiling or cytokine panels. Thus, our findings should be regarded as preliminary and require validation through large-scale randomized controlled trials.

Conclusion

In conclusion, this phase II trial reveals that Sor+Tis+TACE is a potential therapeutic strategy for patients with advanced-stage HCC. The combination therapy yielded promising clinical benefits, with favorable tumor response, PFS, and OS, as well as an acceptable safety profile. These encouraging results provide a compelling rationale and foundational data for further validation in large-scale, randomized, phase III trials to confirm the clinical benefits of this triple therapy.

Abbreviations

AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; cTACE, conventional transarterial chemoembolization; DCR, disease control rate; DEB, drug-eluting bead; DEB-TACE, drug-eluting bead transarterial chemoembolization; DOR, duration of response; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; Sor+Tis+TACE, sorafenib combined with tislelizumab and transarterial chemoembolization; TACE, transarterial chemoembolization; TKI, tyrosine-kinase inhibitor.

Data Sharing Statement

The data supporting the findings of this study can be made available from the corresponding author (Mingyue Cai) upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital, Guangzhou Medical University (approval number, 2020-ks-13) and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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