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Research Article

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A Prospective, Single-Arm, Phase 2 Study of Modified Transarterial Chemoembolization Using Low-Dose Chemotherapy with Blank Microspheres Plus Low-Dose Lenvatinib and Microwave Ablation in Patients with Large (≥7 cm) Unresectable Hepatocellular Carcinoma: The TALEM Trial

Zhi-Mei Huang[a] Xue Han[a] Jian Wang[b] Ling Gu[a] Lu Tang[a] Shao-Yong Wu[b] Tian Di[a] Ying-Wen Hou[a, c] Wan Yee Lau[d] Yi-Quan Jiang[a] Jin-Hua Huang[a]

[a]Department of Minimally Invasive Interventional Therapy, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, PR China; [b]Department of Anesthesiology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, PR China; [c]Department of Interventional Radiology, Harbin Medical University Cancer Hospital, Harbin, PR China; [d]Faculty of Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong, China

Keywords
Blank microsphere transarterial chemoembolization · Large unresectable hepatocellular carcinoma · Levatinib

Abstract
Introduction: For patients with large unresectable hepatocellular carcinoma (HCC), the effectiveness of conventional transarterial chemoembolization (cTACE) remains suboptimal. This study investigated the efficacy and safety of modified TACE using low-dose chemotherapy with blank microspheres (BMS-TACE) plus low-dose lenvatinib (LD-LEN) and microwave ablation (MWA) in patients with large unresectable HCC. ***Methods:*** In this prospective, single-arm, phase 2 study, patients with unresectable HCC exceeding the up-to-seven criteria, with maximum tumor diameter ≥7 cm, and without macrovascular invasion or extrahepatic metastases, received initial BMS-TACE (lipiodol, low-dose doxorubicin, and lobaplatin up to 30 mg each, and blank microspheres; subsequently modified and repeated in most patients) plus LD-LEN (4–8 mg/day) and MWA. The primary endpoint was downstaging rate (DSR); secondary endpoints were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events. ***Results:*** From November 2019 to March 2022, 43 patients were enrolled. Median follow-up was 21.2 months. Median largest tumor diameter was 11.2 cm (interquartile range [IQR],

Zhi-Mei Huang, Xue Han, and Jian Wang contributed equally to this work.

karger@karger.com
www.karger.com/lic

Correspondence to:
Yi-Quan Jiang, jiangyq@sysucc.org.cn
Jin-Hua Huang, huangjh@sysucc.org.cn

7–25). Following BMS-TACE and LD-LEN, downstaging occurred in 37 (86.0%) patients, 32 of whom received MWA, and 8 of whom had a complete response (CR) without MWA. ORR was 93.0% (CR in 32 [74.4%] and partial response in 8 [18.6%] patients). The 1-, 2-, and 3-year PFS rates were 57.5%, 25.9%, and 18.1%, respectively (median PFS, 14.7 months [95% CI: 8.1–19.5]). The 1-, 2-, and 3-year OS rates were 85.8%, 67.7%, and 61.6%, respectively (median OS, 36.4 months [95% CI: 26.8-not reached]). After BMS-TACE, a significant decline in CD11b+/CD33+/HLA-DR- myeloid-derived suppressor cells and early elevation in CXCR5+/CD8+ and CXCR5+/CD4+ T cells were observed (both $p < 0.05$). ***Conclusion:*** BMS-TACE plus LD-LEN and MWA resulted in promising efficacy and tolerable toxicity in patients with large unresectable HCC exceeding the up-to-seven criteria with a maximum tumor diameter ≥7 cm and without macrovascular invasion or extrahepatic metastases.

Introduction

Primary liver cancer, of which hepatocellular carcinoma (HCC) is the most common subtype, ranks as the sixth most prevalent cancer and the third leading cause of cancer-related death globally [1]. Despite advances in cancer screening methodologies, a substantial proportion of patients with HCC are diagnosed at intermediate or advanced stages, at which point the disease is often unresectable [2]. The Barcelona Clinic Liver Cancer (BCLC) guidelines advocate the use of transarterial chemoembolization (TACE) as a therapeutic strategy for patients with unresectable HCC [3]. However, the effectiveness of TACE is often suboptimal, particularly in patients with large HCC [4, 5]. This raises the question of how the use of TACE might be refined to improve outcomes.

In one modification to optimize the treatment of large HCC, patients have received systemic tyrosine kinase inhibitors (TKIs) in addition to TACE, a combination that has proven to be effective in the treatment of HCC, though typically not curative [6–9]. Also, the addition of blank microspheres to TACE has been shown to improve efficacy and survival [10, 11]. Another modification has involved the downstaging of HCC with TACE or systemic therapy, followed by treatment with curative intent involving tumor ablation or surgical resection [12–15].

Building upon these strategies and other recent studies, we considered additional modifications that might lead to better outcomes while limiting adverse effects in patients with large HCC. Utilizing blank microspheres and reducing the dose of chemotherapy administered during TACE could be used to reduce liver damage and chemotherapy-related side effects [10, 16, 17]. Preclinical study and a phase IB trial demonstrated low-dose TKI's potential in reshaping TME and improving treatment efficacy in advanced NSCLC patients [18]. In addition, the recently published CARES-310 study using low-dose TKIs showed the longest median survival time among 5 phase 3 clinical trials of patients with advanced-stage HCC [19–23].

We hypothesized that a treatment protocol incorporating some of these modifications could result in promising efficacy without compromising safety in the treatment of large unresectable HCC. Herein, we report the results of a phase 2, single-arm study to investigate the efficacy and safety of a treatment protocol using TACE with low-dose chemotherapy and blank microspheres, plus a low-dose TKI (lenvatinib) and followed by microwave ablation (MWA), in a group of patients with large unresectable HCC that exceeded up-to-seven staging criteria, had a maximum tumor diameter ≥7 cm, and demonstrated no evidence of macrovascular tumor invasion or extrahepatic metastases. This report is intended to offer a preliminary assessment of the efficacy and safety of this modified treatment protocol, aiming to lay the groundwork for future clinical trials and potentially wide clinical adoption.

Patients and Methods

Study Design and Participants

This was a single-arm, single-center, phase 2 trial investigating the efficacy and safety of a combination treatment strategy involving TACE, done initially with chemotherapeutic drugs and blank microspheres, later shifting toward mainly blank microspheres with reduced or no chemotherapy (BMS-TACE), low-dose lenvatinib (LD-LEN), and MWA (in those who were successfully downstaged) in patients with HCC that was unresectable and exceeded up-to-seven criteria and had a maximum tumor diameter ≥7 cm without evidence of macrovascular tumor invasion or extrahepatic metastases (Fig. 1) (Clinicaltrials.gov: NCT05555316).

The study was conducted at Sun Yet-sen University Cancer Center (Guangzhou City, Guangdong Province, China) and was approved by the Research Ethics Board of Sun Yet-sen University Cancer Center (Institutional Review Board approval number: B2019-166-X01). The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before undergoing any study-specific procedures.

Key inclusion criteria were ages 18–75 years; histologically or cytologically confirmed HCC or clinically confirmed HCC

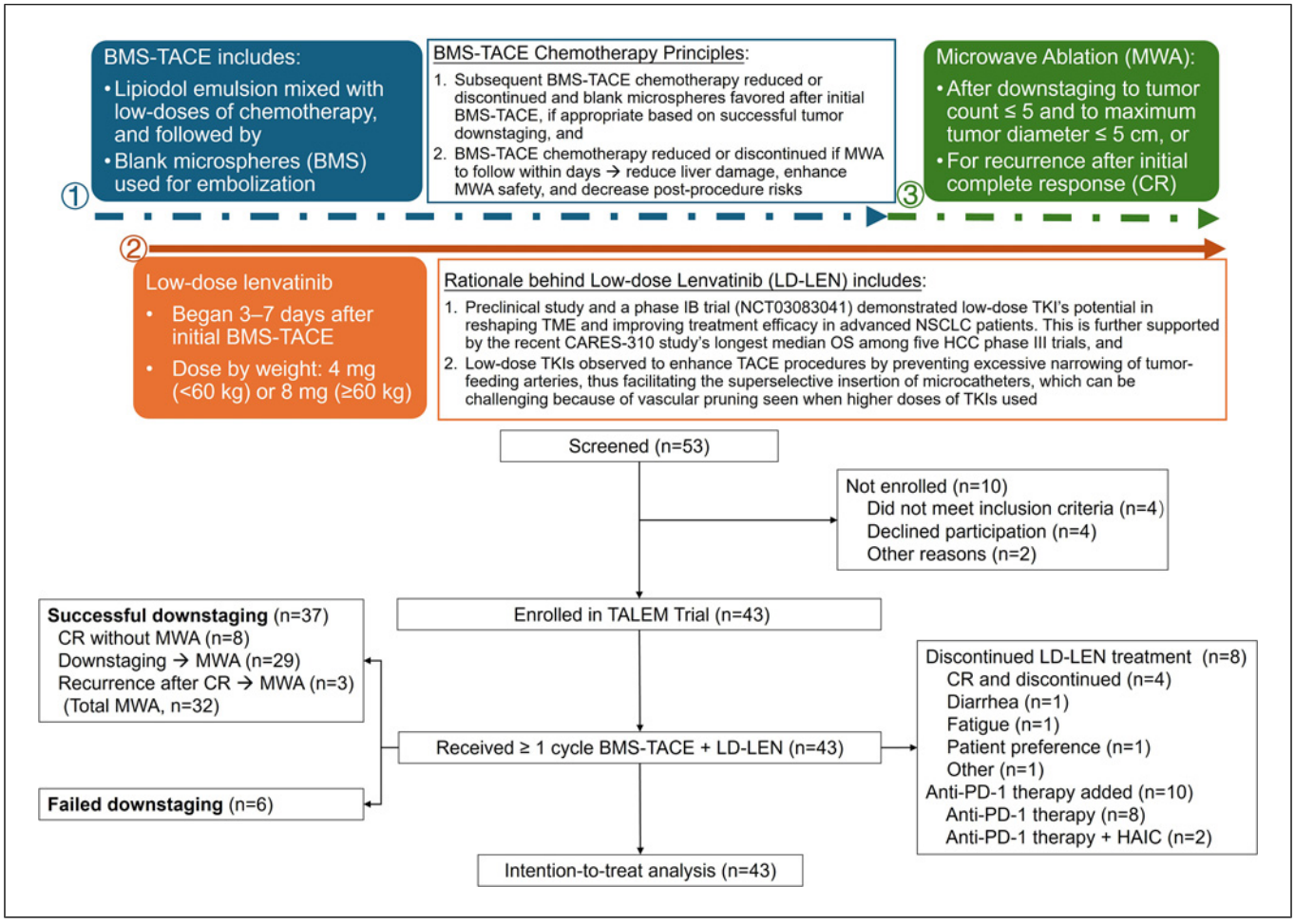

Fig. 1. Schematic representations of treatment protocol and patient disposition in the TALEM Trial.

according to the American Association for the Study of Liver Diseases criteria; large unresectable HCC exceeding up-to-seven criteria with a maximum tumor diameter ≥7 cm; one or more measurable target lesions according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [24, 25] per investigator assessment; Child-Pugh class A or B liver function; and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Patients were excluded if they had fibrolamellar carcinoma, sarcomatoid HCC, or mixed hepatocellular cholangiocarcinoma; bile duct invasion (patients were clinically classified as having cholestatic HCC when initial manifestations included obstructive jaundice due to tumor thrombosis, compression, and/or diffuse infiltration of the biliary tract); and any evidence of macrovascular invasion or extrahepatic metastases. Additionally, patients were excluded who had received previous treatment for HCC.

Each patient included in this study underwent an assessment by surgical experts and was determined to have HCC that was unresectable. Surgical resection was not feasible in patients with excessively large or unfavorably located tumors, impaired liver function, or residual liver volume that was insufficient to avoid the risk of liver failure post-surgery. Additionally, some patients were deemed to be unsuitable for hepatic resection because of comorbid conditions like heart disease and renal insufficiency, which significantly increase intraoperative and postoperative risks, or because of advanced age and frailty, which increase the likelihood of poor postoperative recovery.

Treatment Strategies

In our treatment design, the use of BMS-TACE combined with LD-LEN was intended to serve as both a palliative treatment and a therapeutic bridging strategy, with the main objectives being to reduce the tumor burden and to downstage the HCC (Fig. 1). Patients received ongoing LD-LEN and one or more BMS-TACE procedures, until the HCC was downstaged so that there were ≤5 tumors and each tumor was ≤5 cm in size. Once these criteria were met, MWA was undertaken with curative intent, aiming for the complete eradication of all tumors. Our treatment protocol differs from LEN-TACE sequential therapy as described by Kudo [15] in his 2021 editorial, in that we modified cTACE by using a low dose of chemotherapy drugs and relying in some cases on blank

microspheres, we employed lenvatinib at a low dose, and we intended BMS-TACE combined with LD-LEN to achieve downstaging and to be followed by MWA as potentially curative therapy.

Initial BMS-TACE

Just prior to BMS-TACE, visceral angiography of the abdominal vessels, including the superior mesenteric artery, diaphragmatic artery, and common hepatic vessels, was performed to assess tumor arterial blood supply. Then, a 2.8 F microcatheter (Renegade™ HI-FLO™ kit, Boston Scientific Corporation, Marlborough, USA) was placed super-selectively into the tumor-feeding arteries using the coaxial technique. To begin BMS-TACE, an emulsion of low-dose chemotherapy, consisting of 10–30 mg of doxorubicin and 10–30 mg of lobaplatin, in 5–10 mL of lipiodol (ethiodized poppyseed oil, Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, Jiangsu Province, China), was injected slowly into each targeted artery to achieve ultraterminal embolization.

Next, blank microspheres (Embosphere®, Merit Medical, South Jordan, UT, USA) of different particle diameters were infused. First, small microspheres (40–120 μm or 100–300 μm), mixed with 5–10 mL of contrast agent solution, were delivered to embolize tumor arterial terminals. Large microspheres (300–500 μm or 500–700 μm) were then delivered to embolize tumor arterial branches. The endpoint of embolization was considered to be when there was significant stasis of blood flow, typically indicated by clearance of the contrast column within 3–5 heartbeats and confirmed by postprocedural angiography 5–10 min after that.

Subsequent BMS-TACE

After the initial BMS-TACE, some patients had tumor that was completely necrotic on enhanced computed tomography (CT) or magnetic resonance imaging (MRI), while most demonstrated a decrease in tumor size or diminished tumor viability consistent with necrosis. In the latter cases, if the patient had maintained good liver function (Child-Pugh grade A or B) and good performance status (ECOG score of 2 or lower), additional BMS-TACE treatments were undertaken, and this approach continued until the criteria to proceed with ablation therapy (i.e., ≤5 tumors and each tumor ≤5 cm in size) were met, at which point MWA therapy was performed. For patients with stable or progressive tumors after the initial BMS-TACE, if there was still no evidence of extrahepatic metastases, liver function was good (Child-Pugh grade A or B), and performance status was good (ECOG score of 2 or below), additional BMS-TACE treatments were performed.

However, if target lesions continued to remain stable or were progressing after 3 or more BMS-TACE treatments within a 6-month span, second-line treatment strategies were pursued. These next options included: (1) adding immune checkpoint inhibitors, such as PD-L1 or PD-1 monoclonal antibodies; (2) using transarterial infusion chemotherapy; and/or (3) switching to a TKI other than lenvatinib, such as rigorafenib or dorafenib.

The doses of chemotherapy and quantities of blank microspheres given as part of subsequent BMS-TACE procedures varied. In patients whose tumors exceeded 10 cm in diameter or exhibited a significantly rich blood supply on angiography, the higher end of the chemotherapy dose range (i.e., 30 mg of doxorubicin and lobaplatin) was typically used.

On the other hand, in some patients whose HCC exhibited downstaging after BMS-TACE, the chemotherapy doses given during subsequent BMS-TACE procedures were reduced or no chemotherapy was administered, and instead the focus of the procedure was on administering blank microspheres for super-selective embolization of tumor-feeding arteries. Also, if MWA was to follow within days of BMS-TACE, chemotherapy drug doses were reduced or no chemotherapy was administered in some patients, in an effort to reduce the risk of liver damage and enhance the overall safety of MWA.

Low-Dose Lenvatinib

Lenvatinib (LENVIMA®, Eisai Europe Ltd., Tokyo, Japan) was started 3–7 days after the initial BMS-TACE in order to minimize the potential for exacerbating adverse events related to BMS-TACE. Patients received oral LD-LEN 4 mg (if body weight was <60 kg) or 8 mg (if body weight was ≥60 kg) once daily, and this was continued until disease progression, unacceptable toxicity, or withdrawal of patient consent. During the perioperative periods surrounding BMS-TACE or MWA procedures, LD-LEN was discontinued on the day of the procedure, and it was typically restarted 3–5 days after the procedure, as long as the Child-Pugh score for liver function was within the range of 5–8.

Imaging and Laboratory Assessment after BMS-TACE

Three-phase intravenous contrast-enhanced CT or MRI and liver function tests were performed 4–6 weeks after each BMS-TACE procedure, and then at various intervals after that depending upon subsequent treatments and responses.

Criteria for MWA

MWA was performed after patients achieved successful HCC downstaging with BMS-TACE and LD-LEN. Successful downstaging was defined as a viable tumor count of ≤5 and a maximum individual tumor diameter ≤5 cm, with Child-Pugh grade A or B liver function and no evidence of macrovascular tumor invasion. MWA was also performed in patients who had a recurrence after a complete response, provided that the recurrence still met the above-mentioned criteria to proceed with MWA.

Of note, after patients achieved the criteria for ablation, BMS-TACE therapy was not always discontinued, so at times BMS-TACE was given concurrently with MWA. In some cases, patients had met the criteria for MWA but still had multiple residual viable tumors, so they were given MWA while still undergoing additional BMS-TACE treatments as well.

MWA Procedure

After confirmation of successful tumor downstaging and review of the case by a multidisciplinary team, MWA was performed by interventional radiologists under CT guidance. A commercially available ablation system (Water-cooled™ Microwave Ablation Probe, Vison-China Medical Devices R&D Center, Nanjing, China) was used with the manufacturer's recommended standard power settings and ablation times. The goal of MWA was complete ablation (i.e., a complete response [CR] according to mRECIST [24]), and an ablated tumor margin of ≥5 mm was achieved in all patients. If residual viable tumor was evident on immediate follow-up imaging, additional MWA was performed at that time.

Table 1. Baseline demographics and clinical characteristics of the patients

Characteristic	*N* (%)
Age, years	
Median (IQR)	58 (50–65)
Sex	
Male	39 (90.7)
Female	4 (9.3)
ECOG performance status	
0	42 (97.7)
1	1 (2.3)
BCLC stage	
A	27 (62.8)
B	16 (37.2)
Up-to-seven criteria	
Exceeded	43 (100)
Child-Pugh class	
A	41 (95.5)
B	2 (4.5)
ALBI grade	
1	27 (62.8)
2	14 (32.6)
3	2 (4.5)
Etiology of HCC	
HBV	40 (93.0)
Other	3 (7.0)
AFP[a]	
≤400 ng/mL	25 (58.1)
>400 ng/mL	17 (39.5)
DCP	
≤1,000 mAU/mL	23 (53.5)
>1,000 mAU/mL	20 (46.5)
Maximum tumor diameter	
<100 mm	22 (51.1)
100–150 mm	18 (41.9)
>150 mm	3 (7.0)
Tumor number	
1	27 (62.8)
2–3	16 (37.2)
TBIL, μmol/L	
Median (IQR)	12.1 (9.1–18.4)
ALB, g/L	
Median (IQR)	40.4 (36.9–43.0)
Platelets, 10^9/L	
Median (IQR)	197 (140–248)

HCC, hepatocellular carcinoma; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin; HBV, hepatitis B virus; AFP, alpha-fetoprotein; DCP, Des-γ-carboxy-prothrombin (also referred to as protein induced by vitamin K absence-II [PIVKA-II]); TBIL, total bilirubin; ALB, albumin. [a]AFP data missing for 1 patient.

Follow-Up after MWA

Chest radiography and multiphasic enhanced abdominal CT or MRI were performed 1 month after treatment, then every 3 months during the first 2 years, and then every 6 months thereafter. In the event of a CR, the starting interval for imaging was extended to every 9 weeks. Imaging was evaluated by 2 independent radiologists, and in the case of differing opinions, a third radiologist would render an opinion to achieve consensus. Chest CT, brain MRI, and whole-body bone scintigraphy were also performed if extrahepatic recurrence was suspected based on clinical symptoms.

Blood biomarkers including alpha-fetoprotein (AFP), protein induced by vitamin K absence-II (PIVKA-II, also called des-gamma-carboxy-prothrombin or DCP), and the albumin-bilirubin score were measured at baseline (i.e., before any BMS-TACE), before initiation of LD-LEN, and before MWA, as well as every 3–4 weeks during the first 6 months after initial BMS-TACE, and then every 6–8 weeks thereafter.

Outcomes

The primary endpoint was downstaging rate (DSR). Secondary endpoints included objective response rate (ORR) according to mRECIST [24, 25], progression-free survival (PFS), and overall survival (OS), as well as complications and adverse events (AEs). Treatment responses were based on investigator assessments using mRECIST. All responses were confirmed by a second assessment by a different investigator 4 weeks later.

MWA- and BMS-TACE-related complications were defined as those AEs that occurred during or after these procedures and negatively impacted the health or recovery process of patients. Major complications were defined as those requiring escalation of care, prolongation of hospital stay, or hospital readmission for treatment, or those that resulted in permanent adverse sequelae. All other complications were considered minor.

LD-LEN-related AEs were defined as harmful or unintended consequences resulting from the administration of LD-LEN. These AEs were determined based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, as well as laboratory evaluations, vital signs, electrocardiograms, and echocardiograms or multigated acquisition scans. The frequency, duration, and severity of AEs were recorded. All observations pertinent to study medication safety were recorded on case report forms and included in the final reports.

Systemic Immune Response Assessment

In order to assess systemic immune markers during the process of treatment, blood (10 mL in EDTA vials) was collected from patients immediately prior to initiating treatment, then from 18 patients 24 h after the initial BMS-TACE, and from 13 patients 1 month after the initial BMS-TACE. We were unable to successfully collect blood samples from all patients because of a lack of cooperation from some patients. Peripheral blood mononuclear cells (PBMCs) were isolated and cryopreserved at −80°C. After thawing, cells were incubated with specific surface antibodies, and flow cytometry was performed using a BD Cytometer (BD Biosciences, San Diego, CA, USA). Details of the antibodies and phenotypes as well as the gating strategies used for lymphoid and myeloid cells are presented in online supplementary Figures 1 and 2 (for all online suppl. material, see https://doi.org/10.1159/000536518).

Statistical Analysis

This study used Simon's two-stage design. We set the expected downstaging rate of our treatment protocol at 50% and the downstaging failure rate at 30%; past research indicated that the TACE downstaging rate from United Network for Organ Sharing (UNOS) stage T3 to T2 was just over 30% [26]. Assuming a significance level (α) of 0.05 and a power of 80%, the optimal two-stage design sample sizes were 5/15 and 18/46. This meant that in the first stage, 15 patients needed to be treated, and if the number of downstaged patients did not exceed 5, the trial would be terminated. This also meant that otherwise the trial would proceed to the second stage until a total of 46 patients were included, and that if the total number of downstaged patients in both stages exceeded 18, the new treatment method would be considered effective. In the first stage of our trial, all 15 (100%) patients achieved successful downstaging, leading us to proceed to the second stage.

Categorical variables were compared using either the χ^2 test, Fisher's exact test, or Yate's continuity correction, while continuous variables were compared using the Student's *t* test for normal distributions or the Mann-Whitney U test for non-parametric distributions. The Kaplan-Meier method was used to estimate median PFS and OS rates. The Clopper-Pearson method was used to calculate the associated 95% confidence intervals (CI). The duration of follow-up was calculated using the reverse Kaplan-Meier estimate of OS and PFS rates. All statistical analyses were performed using SPSS, v. 25.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient Characteristics

A schematic representation of the treatment protocol and patient disposition is shown in Figure 1. Of 53 patients screened between November 2019 and March 2022, 43 were enrolled in the study. At the point of data cut-off in June 2023, the median follow-up was 21.2 (IQR: 17.0–27.2) months, and all patients had a minimum follow-up of 8 months.

Patient demographics and baseline characteristics are summarized in Table 1. The tumors of all patients exceeded the up-to-seven criteria. The median (IQR) age of patients was 58 (50–65) years. Of the 43 patients, 42 (97.7%) patients had an ECOG performance status of 0, 1 (2.3%) patient had an ECOG performance status of 1, 41 (95.4%) patients had Child-Pugh class A, 2 (4.6%) patients had Child-Pugh class B, 16 (37.2%) patients had ALBI grades of 2 or 3, and 20 (46.5%) patients had DCP >1,000 mAU/mL. AFP data were missing for 1 patient, and of 42 patients, 17 (39.5%) patients had AFP >400 ng/mL. The etiology of HCC was hepatitis B in 40 (93.0%) patients. The median (IQR) tumor size was 11.2 (7.8–14.5) cm, and the maximum tumor diameter was >10 cm in 21 (48.9%) patients and >15 cm in 3 (7.0%) patients.

Efficacy

Details of the number of BMS-TACE procedures, BMS-TACE drug doses, and MWA procedures for each patient are summarized in online supplementary Table 1. A summary of the clinical course of each patient, showing clinical characteristics, treatments received, responses to treatment, duration of treatment, and follow-up, is provided in Figure 2. All patients received chemotherapy as part of their initial BMS-TACE, but 12 patients did not receive chemotherapy as part of their subsequent BMS-TACE sessions.

Of the 43 patients, 37 were downstaged, yielding a DSR of 86.0% (Table 2). Using mRECIST for all 43 patients, 40 patients had an objective response (an ORR of 93.0%), with 32 (74.4%) patients achieving a best overall response of CR and 8 (18.6%) patients having a CR without undergoing MWA.

In an analysis based on mRECIST of all 43 patients at the interim timepoint after receiving BMS-TACE and LD-LEN but before having MWA, the ORR was 88.4%, yet the CR rate was 18.6% (Table 2). Of all 43 patients, only 32 (74.4%) received MWA, either after downstaging (n = 29) or after a recurrence following a CR (n = 3) (Fig. 1). Focusing on only those 32 patients who had MWA, the CR rate based on mRECIST was 9.4% before MWA and 84.4% after MWA (Table 2).

The 1-, 2-, and 3-year OS rates (based on mRECIST) were 85.8%, 67.7%, and 61.6%, respectively (median OS, 36.4 months [95% CI: 26.8–not reached) (Fig. 3). The 1-, 2-, and 3-year PFS rates (based on mRECIST) were 57.5%, 25.9%, and 18.1%, respectively (median PFS, 14.7 months [95% CI: 8.1–19.5]).

Patients with AFP ≤400 ng/mL had a significantly higher CR rate than those with AFP >400 ng/mL (88.0% vs. 52.9%; p = 0.03) (online suppl. Table 2). This suggests that AFP ≤400 ng/mL was a positive prognostic factor for achieving CR in these patients.

OS and PFS rates of patients were stratified by AFP level and tumor size, with results shown in online supplementary Figure 3. OS rates of patients were also stratified by whether they had successful HCC downstaging after BMS-TACE and LEN and by whether they subsequently received MWA, and this demonstrated that those who were successfully downstaged or received MWA had significantly better OS (online suppl. Fig. 4). Univariate analyses of the relationship between patient characteristics and both OS and PFS were performed, with results depicted in online supplementary Figures 5 and 6, respectively.

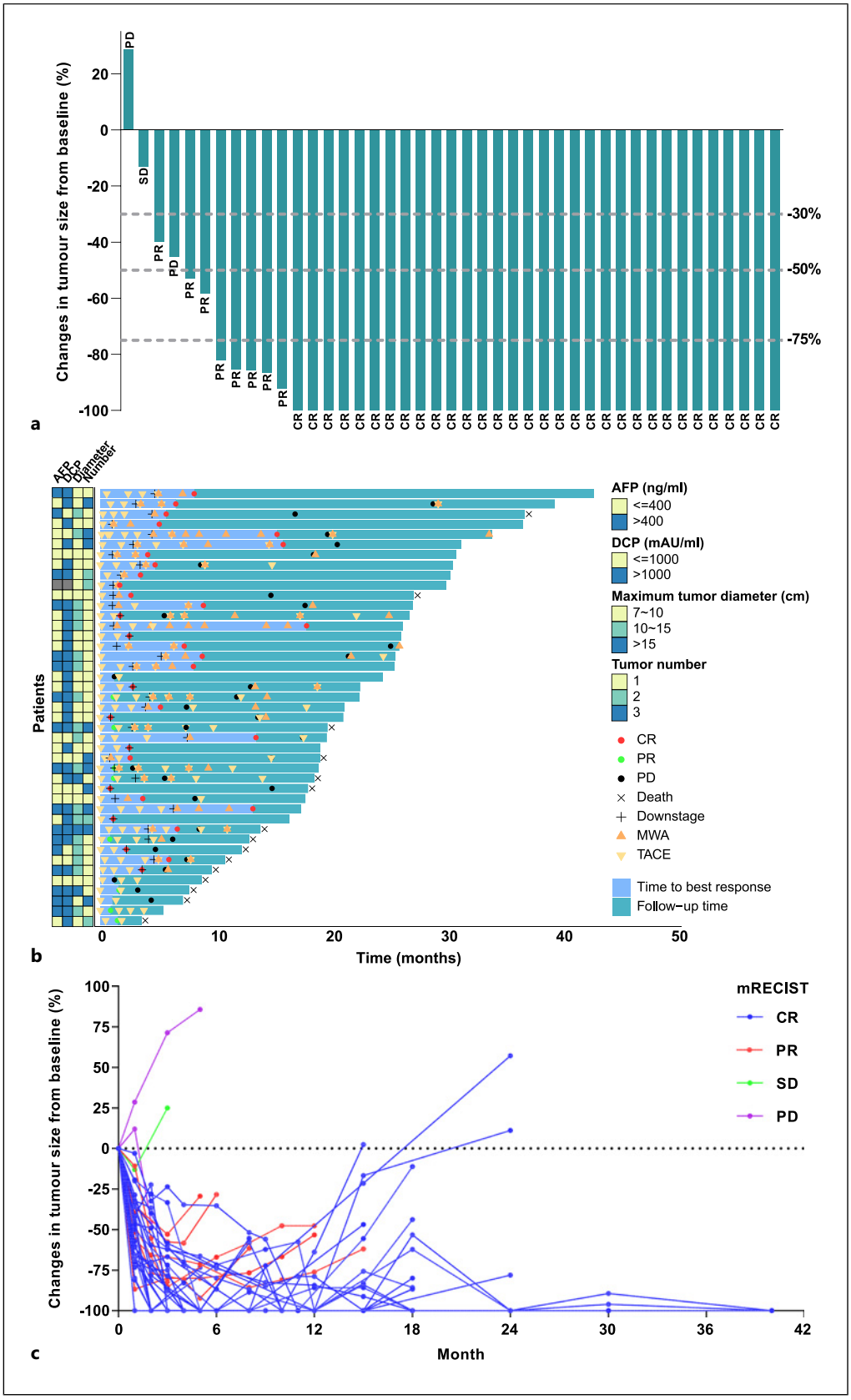

Fig. 2. Treatment responses and changes in tumor sizes, based on mRECIST, after treatment with the TALEM protocol, of 43 patients with HCC. **a** Bar graph of changes from baseline of sums of diameters of target tumors of patients, shown by individual patient response (i.e., CR, PR, SD, or PD). **b** Swimmer's Plot showing clinical course tracking of each patient, demonstrating clinical characteristics, treatments received, timing of TACE and MWA treatments, responses to treatment, and overall durations of treatment and follow-up. **c** Scatter plot of changes from baseline of sums of diameters of target tumors of all patients over the duration of the study and by type of patient response (i.e., CR, PR, SD, or PD).

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Table 2. Outcomes in 43 patients with HCC who were enrolled in the TALEM Trial

Parameter	Response criteria	
	mRECIST	RECIST v. 1.1
ORR, *n* (%)	40 (93.0)	9 (20.9)
DCR, *n* (%)	41 (95.4)	41 (95.4)
Best overall response, *n* (%)		
CR	32 (74.4)	0 (0)
PR	8 (18.6)	9 (20.9)
SD	1 (2.3)	32 (74.4)
PD	2 (4.7)	2 (4.7)
DSR, *n* (%)	37 (86.0)	
OS[a]		
Median, months	36.4 (95% CI: 26.8–NR)	
1-year, %	85.8	
2-year, %	67.7	
3-year, %	61.6	
PFS[a]		
Median, months	14.7 (95% CI: 8.1–19.5)	
1-year, %	57.5	
2-year, %	25.9	
3-year, %	18.1	
After BMS-TACE + LD-LEN, before MWA (*N* = 43)[b], *n* (%)		
ORR	38 (88.4)	
DCR	41 (95.3)	
CR	8 (18.6)	
PR	30 (69.8)	
SD	3 (6.9)	
PD	2 (4.7)	

	Patients who received MWA (*N* = 32)[b]		
	before MWA, *n* (%)	after MWA, *n* (%)	*p* value
CR	3 (9.4)	27 (84.4)	<0.001
PR	27 (84.4)	5 (15.6)	
SD	2 (6.2)	0 (0)	

HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; DSR, downstaging rate; OS, overall survival; NR, not reached; PFS, progression-free survival; TACE, transarterial chemoembolization; LD-LEN, low-dose lenvatinib; MWA, microwave ablation. [a]Kaplan-Meier method used to estimate OS and PFS rates. [b]Responses based on mRECIST.

Safety

Table 3 summarizes the LD-LEN-related AEs and BMS-TACE and MWA procedural complications. The overall incidence of LD-LEN-related AEs was 48.8%. The most common LD-LEN-related AEs of any grade were fatigue (34.9%), proteinuria (32.6%), anorexia (21.0%), abdominal pain (14.0%), and hypertension (14.0%). LD-LEN-related grade 3 or 4 AEs occurred in 10 (23.3%) patients and mostly included fatigue, abdominal pain, and diarrhea. The most frequent procedural complications were abdominal pain (81.4%), fever (11.6%), and dyspepsia (11.6%). Grade 3 or 4 abdominal pain occurred in 30.2% of patients, and the only other severe complication was pulmonary embolism in a single patient.

Dynamics of Systemic Immunity after Initial BMS-TACE

The peripheral blood mononuclear cells (PBMCs) from blood samples of patients were tested for a combination of population markers (e.g., myeloid cells, myeloid-derived suppressor cells [MDSCs], CD8+ T cells, and CD4+ T cells) and phenotypic markers (e.g., PD-L1, CCR2, CXCR3, CXCR5, CD69, and HLA-DR) (Fig. 4). In the 18 patients tested at 2 points in time, the percentage of MDSCs decreased significantly from Day 0 before to Day 1 after initial BMS-TACE, while CD4+ T cells and CD8+ T cells expressing the activation marker CXCR5 increased significantly ($p < 0.05$) (Fig. 4c). The subgroup of patients in which mononuclear-MDSCs (M-MDSCs) decreased exhibited a significant overall survival advantage over the subgroup in which it increased ($p = 0.02$) (Fig. 4e). On the other hand, in the 13 patients who were tested at 3 points in time, there were no statistically significant variations in peripheral T-cell or myeloid cell subgroups between Day 0 before and Day 1 after or between Day 1 after and Month 1 after initial BMS-TACE (online suppl. Fig. 7).

Discussion

In our treatment design, BMS-TACE combined with LD-LEN served as a palliative treatment approach. The main objectives were to downstage the HCC and reduce the tumor burden, positioning the approach as a bridging therapeutic strategy. Once the HCC was downstaged, the performance of MWA was viewed by us as a curative method aimed at the complete eradication of all tumors.

We formulated the TALEM regimen in response to suboptimal outcomes in patients with large HCC who have received other treatment approaches [4, 5]. We chose the components of the TALEM regimen based on the recent evolution of TACE treatment theory and on the demonstrated benefits offered by the addition of TKIs in this patient population [6–9].

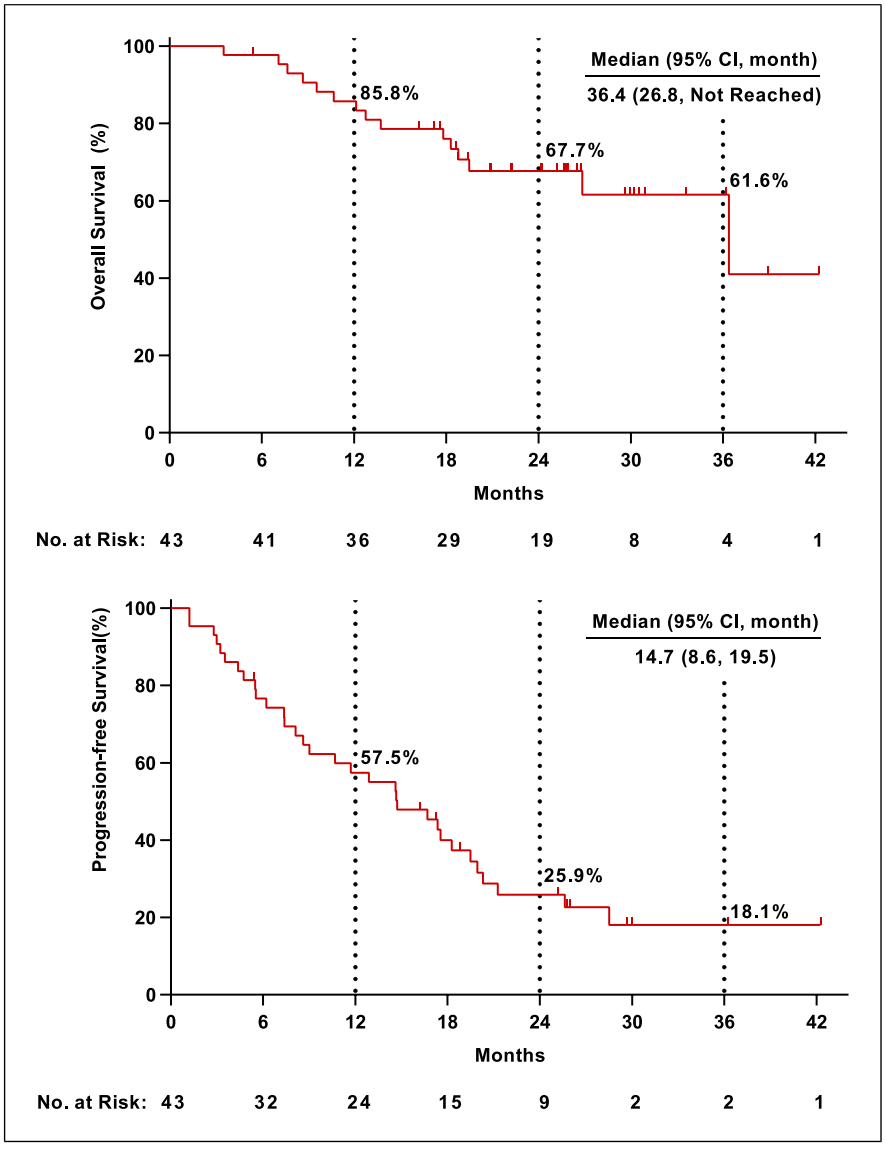

Fig. 3. Kaplan-Meier estimates of OS and PFS rates, based on mRECIST, of 43 patients with HCC who were enrolled in the TALEM Trial from November 2019 through March 2022.

Conventional TACE (cTACE) for large HCC necessitates patients receiving substantial volumes of lipiodol and chemotherapy drugs, thereby increasing the risks of liver failure and other chemotherapy-related complications [27, 28]. In our protocol, we sought to modify TACE, favoring a strategy that involved using blank microspheres as the principal agent, complemented by lower volumes of lipiodol emulsion and low or zero doses of the chemotherapy drugs doxorubicin and lobaplatin.

We were encouraged to use chemotherapy in low doses for BMS-TACE by a comprehensive meta-analysis that demonstrated equivalent efficacy between low- and standard-dose systemic chemotherapy in patients being treated for a variety of cancers [29]. The overall goal of reducing the doses of or discontinuing chemotherapy drugs during BMS-TACE was to see if we could obtain satisfactory therapeutic outcomes while reducing liver damage and chemotherapy-related toxicities. By reducing complications and adverse events, patients might experience an enhanced quality of life and an improved ability to maintain the physical stamina necessary for them to complete the arduous treatment regimens required for advanced HCC.

Though the addition of TKIs has been helpful for patients with HCC [6–9], there is also a rationale for the administration of these agents at lower doses. First, Fred R. Hirsch's study demonstrated that administering low-dose TKI enhances immunotherapy responsiveness in lung cancer models by optimizing the immunosuppressive

Table 3. LD-LEN-related adverse events and BMS-TACE and MWA procedural complications

	Any grade, *n* (%)	Grade 1–2, *n* (%)	Grade 3–4, *n* (%)
LD-LEN-related adverse events			
Fatigue	15 (34.9)	10 (23.3)	5 (11.6)
Proteinuria	14 (32.6)	14 (32.6)	0 (0)
Anorexia	9 (20.9)	8 (18.6)	1 (2.3)
Abdominal pain	6 (14.0)	5 (11.6)	1 (2.3)
Hypertension	6 (14.0)	6 (14.0)	0 (0)
Diarrhea	2 (4.7)	1 (2.3)	1 (2.3)
Oral hemorrhage	2 (4.7)	1 (2.3)	1 (2.3)
Fever	1 (2.3)	1 (2.3)	0 (0)
Hand-foot skin reaction	1 (2.3)	0 (0)	1 (2.3)
Hoarseness	1 (2.3)	1 (2.3)	0 (0)
Muscle weakness	1 (2.3)	1 (2.3)	0 (0)
Procedural complications			
Abdominal pain	35 (81.4)	22 (51.2)	13 (30.2)
Fever	5 (11.6)	5 (11.6)	0 (0)
Dyspepsia	5 (11.6)	5 (11.6)	0 (0)
Pleural effusion	2 (4.7)	2 (4.7)	0 (0)
Hypotension	2 (4.7)	2 (4.7)	0 (0)
Abdominal distension	2 (4.7)	2 (4.7)	0 (0)
Cough	2 (4.7)	2 (4.7)	0 (0)
Hemorrhage	2 (4.7)	2 (4.7)	0 (0)
Non-cardiac chest pain	1 (2.3)	1 (2.3)	0 (0)
Pulmonary embolism	1 (2.3)	0 (0)	1 (2.3)
Pneumothorax	1 (2.3)	1 (2.3)	0 (0)

LD-LEN, low-dose lenvatinib; BMS-TACE, blank microsphere transarterial chemoembolization; MWA, microwave ablation; CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma.

TME, a finding corroborated by a phase IB clinical trial (NCT03083041) results [18]. Second, patients in the recently published CARES-310 study had a better median OS than patients in several other phase III clinical trials involving standard-dose TKIs [19–23]. Third, based on our accumulated experience with TACE, low-dose TKIs appear to enhance TACE by preventing the excessive narrowing of tumor-feeding arteries. This facilitates the super-selective insertion of micro-catheters, which can otherwise be challenging because of the vascular pruning effects observed with higher TKI doses. Finally, lower TKI doses are likely to result in fewer adverse events and better patient tolerance, potentially improving the likelihood that patients will accept long-term therapy. In line with this, we encouraged patients in our study not to abruptly discontinue LD-LEN treatment upon achieving a CR. However, we acknowledge that the criteria for when to discontinue TKI in this setting still require further investigation.

Given the unique strategy used in our TALEM protocol, there are no previous clinical studies that are directly comparable. As an alternative, in order to provide context for the efficacy and adverse event results in our trial, we searched for studies in the literature that involved patients with similar HCC tumor burdens, and the results of those studies are summarized in online supplementary Tables 3 and 4. Of note, Si et al. [30] conducted a study of TACE plus MWA, but without a TKI, for patients with BCLC stage A-B (>5 cm) HCC. They included patients with HCC >5 cm, whereas our study was limited to patients with larger HCC ≥7 cm. They reported an ORR of 93.9%, which was similar to the ORR of 93.0% achieved in our study. However, the CR rate in our study was 74.4%, substantially higher than the CR rate of 42.4% that they reported. An additional meta-analysis of studies of TACE plus MWA (also without a TKI) found that patients with BCLC stage A-B, including stage A >5 cm HCC, had CR, PR, SD, and PD rates that ranged from 4.5% to 58.7%, 13.0–59.7%, 0.0–30.2%, and 2.7–63.6%, respectively [31]. In our patients, these rates were 74.4%, 18.6%, 2.3%, and 4.7%, respectively. This suggests that the TALEM protocol could potentially be superior to cTACE with MWA, particularly with regards to achieving a complete tumor response.

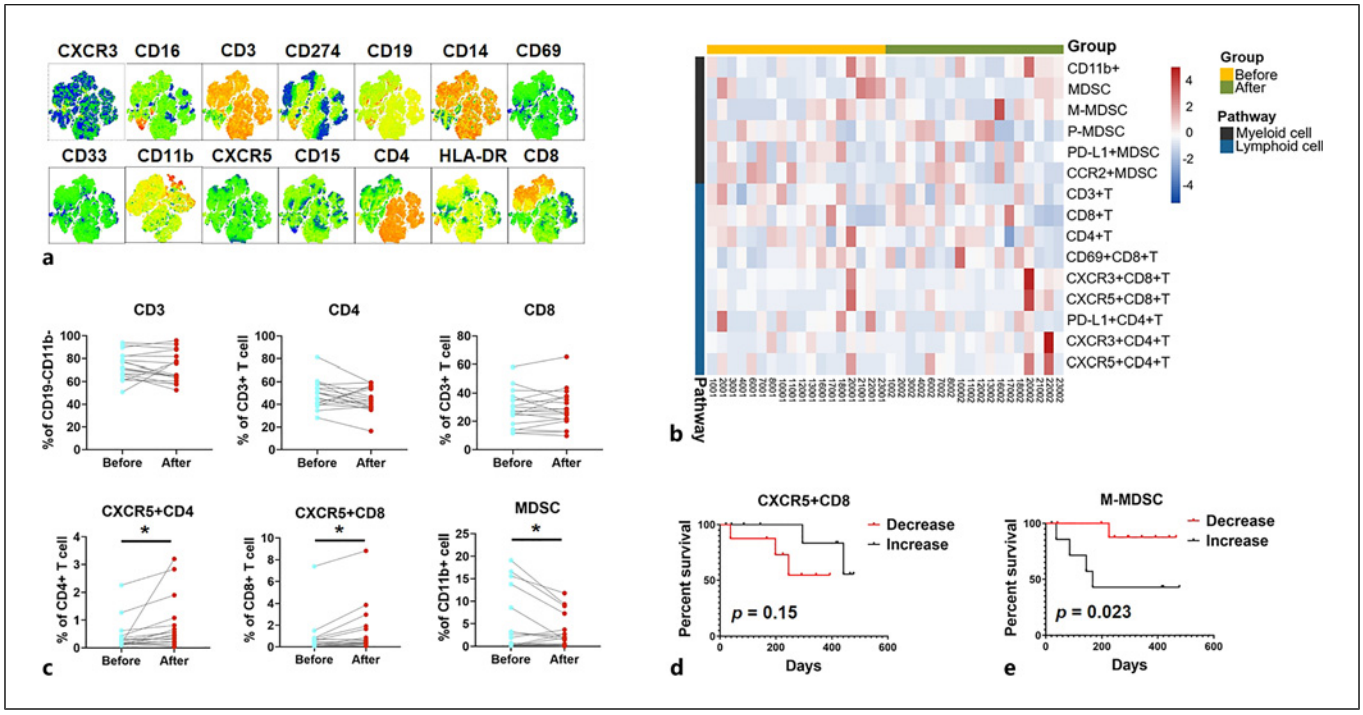

Fig. 4. Variations in systemic immunity in 18 patients with HCC after initial BMS-TACE treatment as part of the TALEM Trial. **a** Phenotypic marker expression patterns are shown in tSNE plots of PBMCs. **b** Heat map of the changes in peripheral T-cell subsets and myeloid cell subsets in patients before and after BMS-TACE. **c** Proportions of T-cell and myeloid cell subgroups on Day 0 before and Day 1 after BMS-TACE, compared using one-way ANOVA analysis with Bonferroni post hoc test, with $p < 0.05$ designated by asterisk (*). **d** Kaplan-Meier overall survival curves comparing the patient subgroup in which CXCR5+CD8 increased with the subgroup in which it decreased, demonstrating a non-significant ($p = 0.15$) survival advantage in the subgroup in which CXCR5+CD8 increased. **e** Kaplan-Meier overall survival curves comparing the patient subgroup in which M-MDSCs increased with the subgroup in which they decreased, demonstrating a significant ($p = 0.02$) survival advantage in the subgroup in which M-MDSCs decreased.

A stratified analysis of our study population was conducted to investigate whether there was an association between any particular clinical characteristics and the likelihood of achieving a CR. Patients presenting with AFP levels ≤400 ng/mL demonstrated significantly higher CR rates than those with higher AFP levels. This suggests that the TALEM strategy may be most beneficial for patients with low AFP levels and that a more aggressive treatment strategy, such as the use of an immune checkpoint inhibitor or higher doses of chemotherapy during TACE, may be warranted for those with high AFP levels [32].

Another stratified analysis was carried out only in the 32 patients who subsequently underwent MWA, comparing tumor responses in these patients before and after MWA. For this group, the likelihood of a CR was significantly higher after MWA than before MWA. This underscored the importance of these patients receiving MWA after BMS-TACE and LD-LEN, and it reinforced the concept that BMS-TACE plus LD-LEN are adequate for downstaging and a reduction in tumor burden, but that MWA is crucial in achieving a complete response and eventually a possible cure.

Our analysis of peripheral blood immune cells in patients prior to and following initial BMS-TACE was helpful in understanding anti-tumor immune activity in response to this part of treatment. We observed that patients who experienced a reduction in M-MDSCs following the first BMS-TACE treatment had significantly better OS. MDSCs are immunosuppressive cells that can negatively impact the prognosis of HCC patients [33], but the exact role of circulating MDSCs after BMS-TACE therapy remains unexplored. We also observed that CD8+ T cells and CD4+ T cells, both of which express the activation marker CXCR5, and either trigger the immune response or directly attack and destroy tumor cells, increased on the first day after BMS-TACE. These findings lend support to the proposition that BMS-TACE therapy not only may destroy tumor cells but also may induce a systemic anti-tumor response.

This study has some limitations. First, as a single-center study, it was constrained by factors such as limited sample size and patients from a single, unique setting. Thus, generalizing the results to other settings should be done with caution, and the efficacy and safety of treatment with the TALEM protocol necessitate further verification through multicenter studies with larger sample sizes before the approach has a clear role in clinical practice. Second, given that over 90% of our study cohort had chronic hepatitis B infections as the cause of their HCC, the findings of this study may not be directly applicable to populations of patients with HCC who have different or more diverse HCC etiologies. Third, we regret that we were able to collect blood from only 13 patients to evaluate the immune responses a month after initial BMS-TACE. Furthermore, because all but 1 of these 13 patients demonstrated an objective response to treatment, we were unable to perform a meaningful analysis of the correlation between variations in peripheral blood immune cells and treatment efficacy at the 1-month timepoint, a matter of additional regret.

Conclusions

In this Phase 2 study, the combination of BMS-TACE, LD-LEN, and MWA demonstrated promising efficacy and safety for patients with unresectable HCC that exceeded up-to-seven criteria, had a maximum tumor diameter ≥7 cm, and had no evidence of macrovascular invasion or extrahepatic metastases. This TALEM treatment protocol also appeared to enhance the adaptive anti-tumor immune response. This combination strategy could potentially serve as a new first-line treatment option for patients with large unresectable HCC, though it first requires confirmation in a multicenter, randomized, controlled phase 3 clinical trial.

Statement of Ethics

The study was conducted at Sun Yet-sen University Cancer Center (Guangzhou City, Guangdong Province, China) and was approved by the Research Ethics Board of Sun Yet-sen University Cancer Center (Institutional Review Board approval number: B2019-166-X01). The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before undergoing any study-specific procedures.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Zhi-Mei Huang, Xue Han, Yi-Quan Jiang, and Jin-Hua Huang: substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the work or reviewing it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Jian Wang: substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; drafting the work or reviewing it critically for important intellectual content. Lu Tang, Shao-Yong Wu, Tian Di, Ling Gu, and Ying-Wen Hou: contributions to the acquisition, analysis, or interpretation of data for the work. Wan-Yee Lau: contributions to drafting the work or reviewing it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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