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Adjuvant TACE Combined with Tislelizumab and Donafenib for High-Risk Hepatocellular Carcinoma After Curative Resection (TIDE): A Phase II Study

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Abstract

Hepatocellular carcinoma (HCC) frequently recurs after curative resection, particularly in patients with large tumors and microvascular invasion (MVI). An effective adjuvant therapy for patients with these features remains uncertain. Combining transarterial chemoembolization (TACE) with systemic therapy has shown activity in unresectable HCC, but its role after resection is unclear. Here we report a prospective, single-center, single-arm phase II study (TIDE; ChiCTR2200063003, registered on 27 August 2022.) of one postoperative TACE session followed by one year of tislelizumab and donafenib in patients with a solitary HCC larger than 5 cm and pathologically confirmed MVI. Among 30 patients, the estimated 3-year recurrence-free survival rate, the primary endpoint, was 56.7% (95% confidence interval, 37.3–72.1%) after a median follow-up of 38.7 months. The estimated 3-year overall survival rate was 93.3% (95% confidence interval, 75.9–98.3%). Grade 3 or higher treatment-related adverse events occurred in eight patients (26.7%), and there were no treatment-related deaths. This study show that adjuvant TACE combined with tislelizumab and donafenib is a feasible treatment option for HCC patients with high-risk recurrence after resection, warranting confirmation in largescale randomized clinical trials.

Introduction

Early-stage hepatocellular carcinoma (HCC) remains associated with a substantial risk of recurrence even after curative-intent resection or local ablation[1]. The principal aim of adjuvant therapy is to eradicate microscopic residual disease that is not detectable by

imaging, thereby reducing recurrence and improving long-term survival. However, despite years of investigation, the efficacy of adjuvant therapy for HCC remains uncertain. The STORM, IMbrave050, and KEYNOTE-937 trials failed to demonstrate a significant improvement in recurrence-free survival (RFS) with adjuvant systemic therapy. Further analysis of these trials suggests that their study populations were heterogeneous and predominantly comprised patients with a relatively low risk of recurrence[2–4]. In contrast, an exploratory subgroup analysis of IMbrave050 suggested that patients with a higher tumor burden beyond the up-to-seven subgroup might derive better RFS benefit from adjuvant atezolizumab plus bevacizumab[5]. Similarly, a randomized controlled trial in patients with microvascular invasion (MVI) reported that adjuvant sintilimab significantly prolonged RFS[6]. Collectively, these findings suggest that baseline recurrence risk may be an important determinant of the benefit derived from adjuvant therapy. Similar controversy has also arisen regarding local adjuvant therapy. Previous randomized studies have shown that adjuvant transarterial chemoembolization (TACE) can improve recurrence-free and overall survival in patients with intermediate- or high-risk HCC[7]. In addition, a phase III randomized trial in patients with MVI-positive HCC demonstrated that adjuvant FOLFOX-based hepatic arterial infusion chemotherapy (HAIC) significantly prolonged disease-free survival (DFS)[8]. By contrast, a recent study by Liang et al. enrolled patients with a relatively low risk of early recurrence and found no clear survival benefit from adjuvant TACE[9]. These findings further suggest that the efficacy of local adjuvant therapy may depend on patients' baseline risk of recurrence.

In recent years, the treatment paradigm for unresectable HCC has gradually shifted from TACE alone toward the combination of TACE and systemic therapy. The EMERALD-1, LEAP-012, and LAUNCH trials have provided evidence of clinical benefit from combining local and systemic treatments[10–12]. Mechanistic studies further suggest that this combination may exert synergistic or complementary effects by enhancing local tumor control, suppressing tumor angiogenesis, and modulating the tumor immune microenvironment[13,14]. In our previous study, a triple regimen comprising TACE, a tyrosine kinase inhibitor (TKI), and a programmed cell death protein 1 (PD-1) inhibitor showed promising efficacy and an acceptable safety profile as conversion therapy for unresectable HCC[15,16]. Therefore, the present phase II study was designed to investigate the feasibility of this triple regimen to reduce recurrence in patients with HCC at high risk of recurrence after curative-intent treatment.

Results

Patient characteristics

Between January 2023 and December 2024, a total of 85 patients were screened, of whom 32 met the eligibility criteria. 2 patients withdrew informed consent during the study period. Therefore, 30 patients were included in the final efficacy and safety analyses (Fig. 1).

The median age of the enrolled patients was 59.0 years (IQR, 53.3–65.8 years), and the majority were male (86.7%). HBV infection was present in 63.3% of patients. The median tumor size was 7.5 cm (range, 5.2–14.5 cm). Baseline demographic and clinical

characteristics are summarized in Table 1.

Efficacy

As of January 20, 2025, the last enrolled patient had completed the prespecified 1-year treatment period. Among the 30 patients included in the efficacy analysis, three patients discontinued study treatment due to disease recurrence, and one patient discontinued treatment due to death from cerebral hemorrhage following an accidental fall.

At the data cutoff date of September 1, 2026, the median follow-up duration was 38.7 months (95% CI, 34.9–39.8 months). The study met its prespecified primary endpoint. The estimated RFS rates at 1, 2 and 3 years were 86.7% (95% CI, 68.3–94.8%), 60.0% (95% CI, 40.5–75.0%), and 56.7% (95% CI, 37.3–72.1%), respectively (Fig. 2A). The median RFS was not reached (95% CI, 21.0–not evaluable [NE]).

During follow-up, 13 patients (43.3%) experienced RFS events, including disease recurrence or death. Among the 12 patients who developed recurrence, intrahepatic and extrahepatic recurrence accounted for 58.3% and 41.7% of cases, respectively. A total of three deaths occurred during follow-up, and the median OS was not reached. The estimated OS rates at 1, 2 and 3 years were 96.7% (95% CI, 78.6–99.5%), 93.3% (95% CI, 75.9–98.3%), and 93.3% (95% CI, 75.9–98.3%), respectively (Fig. 2B).

Safety

A total of 28 patients (93.3%) experienced TRAEs. Grade 3 or higher TRAEs were observed in 8 patients (26.7%). The most common TRAEs (>50%) were rash (76.7%), hand-foot skin reaction (76.7%), and hypothyroidism (60.0%) (Table 2). One patient

developed grade 4 immune-related pneumonitis, which was downgraded to grade 2 or lower following a delay in tislelizumab administration. No treatment-related deaths occurred during the entire study treatment period (Table 2).

Discussion

In this single-arm phase II trial, we evaluated the efficacy and safety of adjuvant TACE combined with tislelizumab and donafenib in patients with HCC who had solitary tumors larger than 5 cm and pathological evidence of MVI following curative resection. Our findings demonstrated a 3-year RFS rate of 54.5%, meeting the predefined efficacy threshold. These results suggest that TACE combined with tislelizumab and donafenib may represent a promising adjuvant therapy for patients with HCC harboring high-risk recurrence features.

MVI is widely recognized as an important risk factor for recurrence, and its incidence is substantially increased among patients with larger solitary tumors[17,18]. Adjuvant TACE may help eradicate residual microscopic disease and reduce the risk of recurrence. In addition, TACE may enhance antitumor immunity by inducing immunogenic cell death (ICD) and promoting tumor antigen-specific immune responses through the release of tumor-associated antigens[13,19]. However, TACE-induced hypoxia may activate hypoxia-inducible factor-1α (HIF-1α), resulting in increased expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and potentially contributing to vascular remodeling and tumor regrowth[20,21]. Moreover, VEGF signaling can suppress effector T-cell proliferation and cytotoxic

activity, thereby promoting an immunosuppressive tumor microenvironment (TME)[22]. Therefore, combining TACE with VEGF inhibition may counteract TACE-induced angiogenic responses and enhance treatment efficacy. Meanwhile, PD-1/programmed death ligand 1 (PD-L1) inhibitors has been shown to promote tumor vascular normalization and partially reverse tumor-induced immune suppression[23]. Collectively, these findings provide a biological rationale for the potential synergistic effects of combining TACE with VEGF inhibitors and PD-1/PD-L1 inhibitors. This may partially explain the favorable clinical outcomes observed with this triple combination strategy.

The central challenge of adjuvant therapy for HCC is to identify patients at high risk of recurrence who are most likely to benefit. The negative findings reported in several previous studies of adjuvant therapy may be partly attributable to the limited representation of patients at high risk of tumor recurrence among the enrolled participants. [2–4]. These findings should therefore not be interpreted as evidence against all adjuvant therapies. By contrast, some recent studies have focused on patients with clearly aggressive tumor features, including MVI, portal or hepatic vein tumor thrombus, tumors larger than 5 cm, and multifocal disease, and have reported encouraging signals of potential benefit[6,7,8,28,29]. Accordingly, adjuvant therapy should be considered primarily for selected patients at high risk of early recurrence rather than being applied broadly to all patients after surgery. Beyond conventional clinicopathological features, such as tumor size, tumor number, and vascular invasion, molecular residual disease (MRD) detected by postoperative circulating tumor DNA (ctDNA) testing may provide an important complement to postoperative recurrence risk

stratification[26,27]. Persistent postoperative ctDNA positivity is associated with a higher risk of recurrence, and serial ctDNA monitoring may enable the detection of molecular residual disease before radiographic recurrence. In addition, the CARES-009 and TALENTOP studies suggest that, in carefully selected patients at intermediate-to-high risk of recurrence or with locally advanced disease, a sequential adjuvant therapy after surgery may provide greater survival benefit[28,29]. Overall, future research should move beyond the question of whether adjuvant therapy should be administered and instead determine which patients should receive it, when treatment should be initiated, and which regimen is most likely to provide the greatest benefit.

To our knowledge, the present study is the first to evaluate TACE combined with immunotherapy and antiangiogenic therapy as an adjuvant regimen for patients with early-stage HCC at high risk of recurrence. A previous randomized controlled trial evaluated adjuvant TACE following R0 resection in patients with a solitary tumor measuring ≥5 cm and MVI, reporting a 3-year DFS rate of 38.4%[30]. Another study investigated adjuvant sintilimab in patients with resectable HCC and MVI, and among patients with tumors >5 cm, the 2-year RFS rate was approximately 48.3%[6]. Compared with these previous reports, our findings suggest that the combination strategy evaluated in the present study may provide encouraging disease control in this high-risk population, although direct comparisons should be interpreted cautiously due to differences in study design and patient characteristics.

Beyond efficacy, treatment tolerability represents an important consideration for adjuvant therapy, particularly in patients without measurable disease after surgery. In

the present study, no patients experienced TACE-related liver failure, and the observed toxicity profile was generally consistent with previous reports of donafenib and tislelizumab[31,32]. Notably, the initial planned dose of donafenib was 200 mg per dose. However, among the first six enrolled patients, four experienced grade ≥3 TRAEs, all of which were considered by investigators to be associated with donafenib. Following multidisciplinary discussion and consideration of previous clinical evidence and experience, the donafenib dose was reduced to 100 mg per dose[33]. Thereafter, protocol-permitted dose adjustments were implemented according to the occurrence and severity of TRAEs. Similarly, in CARES-009, postoperative TRAEs led to discontinuation of study treatment in 17 patients (12%), while rivoceranib dose reduction was required in 14 patients (10%) during the postoperative phase[28]. These findings suggest that individualized dose reduction of targeted agents should be considered when toxicity emerges to improve treatment continuity and adherence, and support further evaluation of dose-optimized adjuvant therapies in future randomized clinical trials.

This study has several limitations. First, the primary limitation was the single-arm design, which lacked a concurrent control group and therefore limited the ability to determine the comparative efficacy of this treatment strategy. Second, the sample size was relatively small, with only 30 patients included in the final analysis. Consequently, the subgroup analyses were limited by small patient numbers and insufficient statistical power, and these findings should therefore be interpreted cautiously. Third, the OS data remain immature because most patients who

experienced recurrence received subsequent anticancer therapies. Longer follow-up is warranted to obtain more mature OS estimates and further evaluate the long-term survival benefit of this treatment strategy.

In conclusion, postoperative adjuvant TACE combined with donafenib and tislelizumab in the TIDE study demonstrated preliminary efficacy and acceptable safety in patients with HCC harboring high-risk recurrence factors. This strategy provides a promising adjuvant therapy option for patients with HCC at high risk of recurrence. Further validation in phase III randomized controlled trials is warranted.

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Table 1. Patient baseline characteristics

Parameters	Total (n=30)
Age (year), median (range)	59 (21,70)
Sex, n (%)	
Male	26 (86.7%)
Female	4 (13.3)
Etiology, n (%)	
HBV	19 (63.3%)
HCV	1 (3.3%)
Others	10 (33.3%)
White blood cell count ($\times 10^9$/L), mean±SD	6.7±2.0
Red blood cell count ($\times 10^{12}$/L), mean±SD	135.3±6.5
Platelet count ($\times 10^9$/L), mean±SD	248.0±84.8
Prothrombin time (sec), mean±SD	12.9±2.7
Alanine aminotransferase (IU/L), mean±SD	28.3±8.4
Aspartate aminotransferase (IU/L), mean±SD	29.7±5.5
Albumin (g/dL), mean±SD	41.5±3.8
Total bilirubin (μmol/L), mean±SD	10.4±5.6
Peroperative α-Fetoprotein (ng/mL), n(%)	
< 400	23 (76.7%)
⩾400	7 (23.3%)
Cirrhosis, n (%)	
With	13 (43.3%)
Without	17 (56.7%)
Tumor size, n (%)	
> 5cm	23 (76.7%)
≥10cm	7 (23.3%)
MVI grade, n (%)	
Hight-risk	3 (10%)
Low-risk	27 (90%)
Satellite nodules	
With	4 (13.3%)
Without	26 (86.7%)
Edmondson-Steiner grade, n (%)	
I-II	26 (86.7%)
III-IV	4 (13.3)

Table 2 | Treatment-related adverse events (TREAs) occurring in ≥10% of patients.

	Total (n=30)	
	Any grade	Grade≥3
All TREAs	28(93.3)	8(26.7)
Rash	23(76.7)	2(6.7)
Hand-food syndrome	23(76.7)	2(6.7)
Hypothyroidism	18(60.0)	0(0)
Platelet count decrease	13(43.3)	0(0)
Proteinuria	11(36.7)	0(0)
Diarrhea	11(36.7)	0(0)
Hypertension	10(33.3)	0(0)
Alanine aminotransferase increased	9(30.0)	1(3.3)
Aspartate aminotransferase increased	8(26.7)	2(6.7)
Hematuria	7(23.3)	0(0)
Urinary tract infection	4(13.3)	0(0)
Alopecia	4(13.3)	0(0)
Weight loss	4(13.3)	0(0)

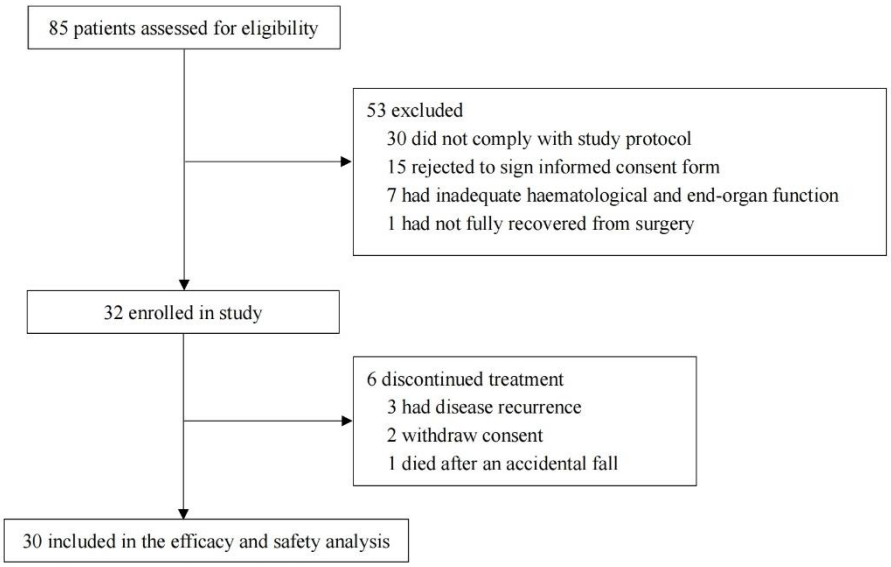


Fig. 1 | Trial profile.

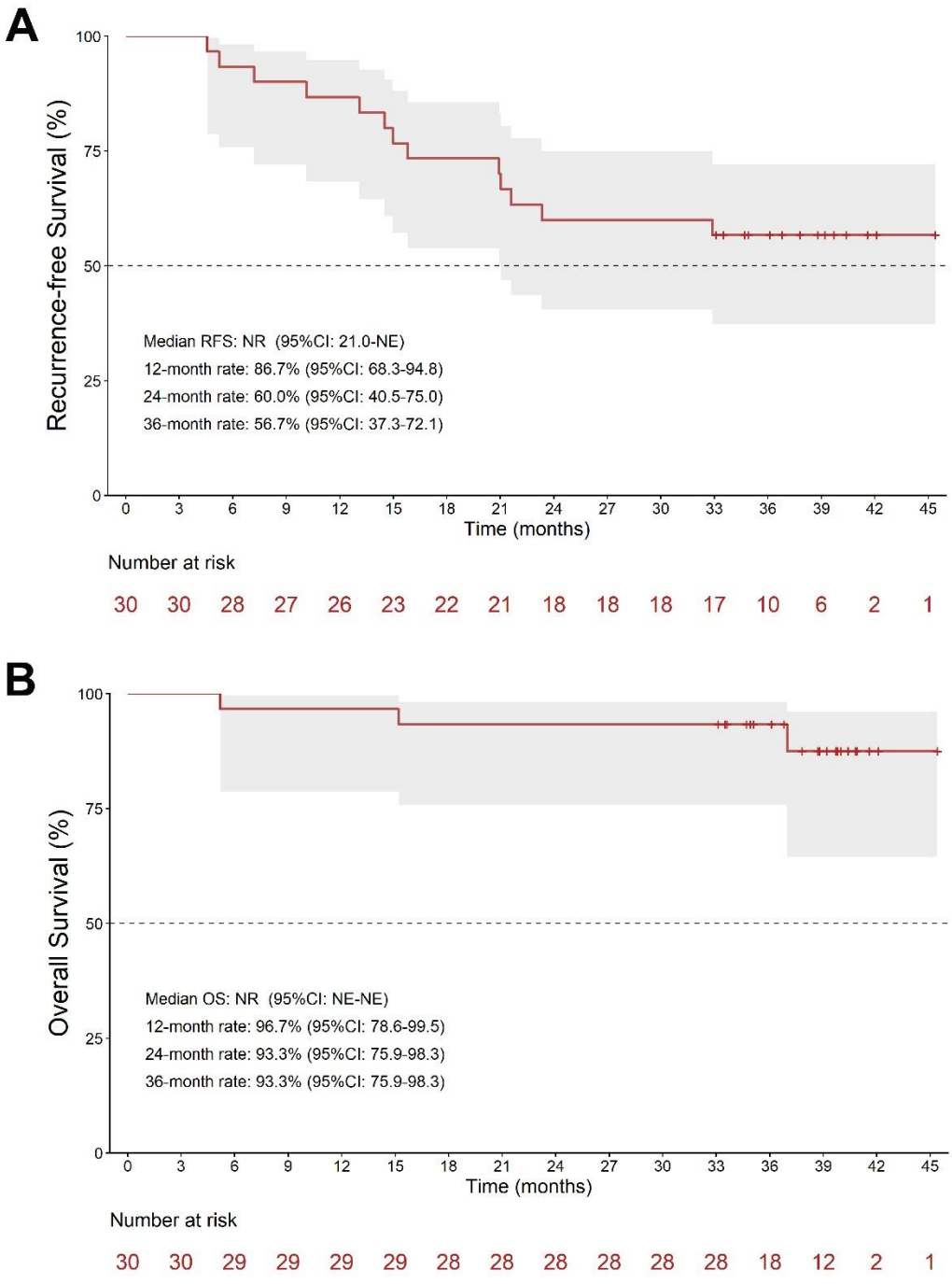


Fig. 2 | Survival outcomes. Kaplan-Meier analysis of recurrence-free survival (A) and overall survival (B).

NR not reached, CI confidence interval, NE not evaluable.

Methods

Study design and patients

This study was designed as a single-center, single-arm, prospective phase II clinical trial conducted in China. The trial was prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2200063003) on 27 August 2022.

Eligible patients were 18–75 years of age and had a solitary HCC measuring >5 cm in diameter, with MVI confirmed by postoperative pathological examination. The presence of satellite nodules was permitted. All patients had undergone curative-intent resection with R0 margins, defined as macroscopically and microscopically negative surgical margins, and had achieved adequate postoperative recovery. Radiological evaluation performed 1 month after surgery was required to show no evidence of residual disease or recurrence. Patients were excluded if they had previously undergone liver transplantation or were listed for liver transplantation; had received any prior anticancer therapy, including locoregional and systemic therapy; had any macrovascular invasion involving the portal vein, hepatic vein, or inferior vena cava; or had histological diagnoses of fibrolamellar HCC, sarcomatoid HCC, or combined hepatocellular–cholangiocarcinoma.

A complete list of inclusion and exclusion criteria is provided in Supplementary Method 1.

Procedures

Eligible patients received one session of TACE 1 month after surgery. All TACE procedures were performed by experienced interventional physicians using a standardized treatment protocol[34]. Using the Seldinger technique, a microcatheter was advanced into the proper hepatic artery via the femoral arterial approach, followed by hepatic arterial angiography. Epirubicin (40 mg) and 5-fluorouracil (800–1000 mg), mixed with lipiodol (3–5 mL), were subsequently administered through the microcatheter. Two weeks after TACE, patients received tislelizumab (200 mg intravenously every 3 weeks) combined with donafenib (100 mg orally twice daily). This treatment regimen was administered for 1 year unless disease recurrence or unacceptable toxicity occurred. Dose modifications of donafenib were permitted according to the occurrence and severity of treatment-related adverse events (TRAEs). For a detailed experimental procedure, see Supplementary Method 2 and Supplementary Figure 1.

Endpoints and assessments

The primary endpoint was the 3-year RFS rate. RFS was defined as the time from enrollment to disease recurrence, or death from any cause, whichever occurred first. Intrahepatic and extrahepatic recurrence were defined according to European Association for the Study of the Liver criteria and Response Evaluation Criteria in Solid Tumours version 1.1, respectively[35,36]. Disease recurrence was evaluated with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) at

baseline, every 12 weeks (±7 days) from the date of enrollment for the first year, and every 24 weeks thereafter (±10 days), until confirmation of disease recurrence. Following disease recurrence, subsequent treatment was determined by a multidisciplinary team (MDT). Thereafter, patients were followed approximately every 12 weeks until death or the end of the study, whichever occurred first, to collect information on subsequent anticancer therapy and survival status.

The key secondary endpoint was overall survival (OS), defined as the time from enrollment to death from any cause. Other secondary endpoints included the incidence and characteristics of adverse events (AEs), including the number, severity, duration, and outcomes of AEs occurring during treatment and follow-up. AEs were assessed throughout the treatment period and up to 30 days after the last administration of study treatment (90 days for serious AEs) or until initiation of subsequent anticancer therapy, whichever occurred first. AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. During follow-up, survival status was assessed every 8 weeks until death, withdrawal of consent, study termination, or completion of the maximum follow-up period of 3 years, whichever occurred first.

Sample size assumption and statistical analysis

Based on a previous study investigating the impact of MVI on postoperative recurrence and prognosis among 1,517 patients with HCC undergoing curative resection, the 3-year RFS rate was reported to be less than 30%[37]. We hypothesized that adjuvant

therapy would improve the 3-year RFS rate to 50%. Assuming a two-sided α level of 0.05 and a statistical power of 80%, a total sample size of 29 patients was required. Considering a potential 10% dropout rate, the planned enrollment target was set at 32 patients.

Demographic characteristics, clinical characteristics, and safety outcomes were summarized using descriptive statistics. The Kaplan–Meier method was used to estimate median RFS and OS, along with corresponding two-sided 95% confidence intervals (CIs). For the RFS analysis, patients who remained alive without disease recurrence at the last follow-up assessment were censored. For the OS analysis, patients who were alive at the last follow-up were censored. Data were recorded and managed using Microsoft Excel (version 2019). Statistical analyses were performed using SPSS software (version 26.0) and R software (version 4.5.2). A two-sided P value <0.05 was considered statistically significant.

Ethics statement

This study was approved by the Biomedical Research Ethics Committee of West China Hospital, Sichuan University (No. 2022691). This clinical study complied with all local laws and regulations and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Before the study, all patients provided written informed consent.

Data availability

The study protocol is available in the Supplementary Information. The datasets of the

clinical trial may be requested 12 months after the publication of this article. Researchers who wish to request access to raw and analyzed data should send an email to the corresponding authors (W.P.), and a response can be expected within 14 days. Individual deidentified data of the participants are available for approved eligible applications and investigators after signing a data access agreement. Source data are provided with this paper.

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Author contributions

Concept and design: W.P.; Acquisition, analysis, or interpretation of data: D.K., Y.-F.P., Y.Z., C.L., X.-L.Y.,J.-Y.S, X.-L.Y., F.X., and Y.-G.W.; Drafting of the manuscript: D.K., Y.-F.P., and Y.Z.; Critical review of the manuscript for important intellectual content: W.P., T.-F.W., and Z.-Y.C.; Statistical analysis: D.K., Y.-F.P., Y.-J.Z., M,-H,Y and Y.Z.; Obtained funding: W.P.; Supervision: W.P., T.-F.W., and Z.-Y.C.

Competing interests

The authors declare no competing interests.

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