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A Phase 2, Prospective, Multicenter, Single-Arm Trial of Transarterial Chemoembolization Therapy in Combination Strategy with Lenvatinib in Patients with Unresectable Intermediate-Stage Hepatocellular Carcinoma: TACTICS-L Trial

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Abstract
Introduction: Transarterial chemoembolization (TACE) is the standard treatment for unresectable intermediate-stage hepatocellular carcinoma (HCC), but recurrence after TACE is common. The present phase 2, prospective, multicenter, single-arm trial, the TACTICS-L trial, investigated the efficacy and safety of TACE plus lenvatinib (LEN), a drug that more strongly promotes vascular normalization and has a better objective response rate (ORR) than sorafenib (jRCTs031180074). ***Methods:*** Participants were patients with HCC who had not previously received systemic therapy, hepatic arterial infusion chemotherapy, or immunotherapy and who were ineligible for resection or percutaneous ablation therapy. LEN was to be administered 14–21 days before the first TACE, stopped 2 days before TACE, and resumed 3 days after TACE. Key inclusion criteria were unresectable HCC, Child-Pugh A liver function, 0–2 prior TACE sessions, tumor size ≤10 cm, number of tumors ≤10, and ECOG performance status 0–1. Key exclusion criteria were vascular invasion and extrahepatic spread. The primary endpoint was progression-free survival (PFS) by RECICL, and secondary endpoints were time to untreatable progression, ORR, overall survival (OS), and safety. ***Results:*** A total of 62 HCC patients were enrolled in this trial. The median age was 72 years, 77.4% of patients were men, and 95.2% had PS 0. The primary endpoint of median PFS was 28.0 months (90% confidence interval [CI] 25.1–31.0) after a minimum 24 months of follow-up. The secondary endpoint of median OS was not reached (90% CI 35.5 months–NR). LEN-TACE achieved a high response rate and high complete response (CR) rate (4 weeks after the first TACE: ORR 79.0%, CR rate 53.2%; best response: ORR 88.7%, CR rate 67.7%) by RECICL. Exploratory subgroup analyses showed that the characteristics of responders/nonresponders (ORR and CR rate) were similar and that LEN-TACE would be effective in all subgroups, including the population in whom TACE alone would be less likely to be curative (e.g., patients with the non-simple nodular type or a high tumor burden). The relative dose intensity of LEN before the first TACE was important for achieving higher CR rate/ORR by LEN-TACE. No new safety concerns were observed. ***Conclusion:*** The results of this trial provide encouraging evidence, supporting the efficacy and favorable safety profile of LEN-TACE in patients who are ineligible for locoregional therapy.

Introduction

Transarterial chemoembolization (TACE) is considered the standard treatment for unresectable intermediate-stage hepatocellular carcinoma (HCC). However, as a large percentage of patients experience recurrence after TACE, many clinical practice guidelines for HCC characterize TACE as a palliative rather than curative treatment [1–3]. Therefore, it is increasingly important to not only improve TACE techniques but also add systemic therapy to further improve the effectiveness of TACE.

Six clinical trials have been conducted to develop treatments that combine TACE with molecular-targeted agents [1–6], but only the TACTICS trial has been successful [6–8]. In that trial, TACE plus sorafenib significantly improved progression-free survival (PFS) compared with TACE alone. The median PFS was 25.2 months for TACE plus sorafenib versus 13.5 months for TACE alone (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.41–0.87; $p = 0.006$) [6]. Sorafenib and other such drugs with anti-vascular endothelial growth factor (VEGF) activity normalize the tumor vasculature and improve drug delivery by normalizing microvascular density, interstitial density, and vascular permeability [9–13]. Consequently, upfront sorafenib 2–3 weeks before the first TACE may have improved the efficacy of the first TACE; it may also have reduced the recurrence rate and tumor growth by attenuating the increase in HIF-1α-induced cytokines (e.g., VEGF) that is observed with TACE-induced hypoxia [14].

However, the TACTICS trial showed no survival benefit in terms of the coprimary endpoint median overall survival (OS), which was 36.2 months for TACE plus sorafenib versus 30.8 months for TACE alone (HR: 0.861; 95% CI: 0.607–1.223; $p = 0.40$) [7]. One reason why the OS benefit did not differ between TACE plus sorafenib and TACE alone could be that postprogression survival was extended by the considerable amount of subsequent treatment in the TACE alone group [8]. In summary, the TACTICS trial showed that TACE plus sorafenib significantly extends PFS and provides a certain degree of OS benefit, although the objective response rate (ORR) did not differ significantly between TACE plus sorafenib and TACE alone (71.3 vs. 61.8%, $p = 0.23$). In addition, the complete response (CR) rate did not differ significantly between TACE plus sorafenib and TACE alone (28.8 vs. 27.6%, $p = 0.77$).

The molecular-targeted drug lenvatinib (LEN) is an orally administered multikinase inhibitor that targets VEGF receptors 1–3, fibroblast factor receptors 1–4,

platelet-derived growth factor receptor alpha, and RET. LEN is a more potent VEGF receptor inhibitor than sorafenib, and its effects are observed faster after treatment initiation. In addition, LEN promotes vascular normalization and reduces intratumoral interstitial pressure more rapidly and to a greater extent than sorafenib, and its effects are already detectable by the fourth day of treatment [15]. In this study, vascular normalization (i.e., reduction of microvascular density, increase in vessels covered by pericytes, and increase in perfused vessels) was more pronounced in mice treated with LEN for 4 days than that in controls and even compared with the effect of sorafenib. The tumor microenvironment was also more favorable in LEN-treated mice than that in control mice or sorafenib-treated mice, showing less hypoxic conditions and lower intratumor interstitial pressure [15]. Additionally, the immune microenvironment was also changed by LEN that decreased in tumor-associated macrophages and increased activated cytotoxic T cells [16–19].

The REFLECT trial showed that LEN has shown noninferiority to sorafenib for OS with statistically significant and clinically meaningful improvements in PFS and ORR [16]. LEN has a considerably higher response rate than sorafenib (40.6 vs. 12.4% per mRECIST) [20], and the findings that LEN yields faster and greater vascular normalization and a better tumor microenvironment than sorafenib strongly suggest that LEN will be very effective when combined with TACE. A multicenter proof-of-concept trial investigating TACE plus LEN in intermediate-stage HCC with a high tumor burden (exceeding up-to-seven criteria) showed that TACE plus upfront LEN results in better ORR (73.3 vs. 33.3%), median PFS (16.0 months vs. 3.0 months), and median OS (37.9 months vs. 21.3 months) and preserves liver function better than TACE alone [21]. The results of this proof-of-concept trial were presented as evidence for establishing the concept of TACE ineligibility and for recommending upfront LEN followed by locoregional therapy in the APPLE Consensus [22] and JSH Consensus [23]. Since then, LEN-TACE sequential therapy has been investigated in several follow-up studies, and its efficacy has been confirmed in real-world practice [24–28].

We designed and conducted the present trial as a phase 2, multicenter, prospective, single-arm trial to evaluate the efficacy and safety of combination/sequential LEN plus TACE therapy using a design similar to that of the TACTICS trial. Specifically, we examined the benefit of LEN plus TACE using the same inclusion and exclusion criteria and the same TACE-specific PFS endpoint as the TACTICS trial.

Patients and Methods

Trial Design

The prospective, multicenter, single-arm trial of TACE therapy in combination strategy with LEN in patients with unresectable intermediate-stage HCC (TACTICS-L Trial) was a phase 2 trial conducted at 21 sites in Japan that included patients enrolled between February 2019 and April 2020 (jRCTs031180074). Patients with HCC who had not previously received systemic therapy, hepatic arterial infusion chemotherapy, or immunotherapy and who were ineligible for resection or percutaneous ablation therapy were included in the trial. LEN was to be administered 14–21 days before the first TACE, stopped 2 days before TACE, and resumed 3 days after TACE. Treatment with LEN was interrupted when a patient developed any kind of post-TACE syndrome (e.g., fever, elevated aspartate aminotransferase/alanine aminotransferase, or abdominal pain) and was resumed at the investigator's discretion once these symptoms had resolved. LEN could be resumed up to 21 days after the first TACE at the latest. LEN was continued until untreatable progression [6] or appearance of unacceptable toxicity. ORR at 4 weeks after the first TACE and best response over the course of treatment were evaluated separately. LEN was administered orally once daily at a dose of 12 mg for patients weighing ≥60 kg and 8 mg for patients weighing <60 kg. Subsequent TACE sessions were performed on demand as needed. LEN-TACE was continued until a PFS event or serious adverse event (AE) occurred, and the primary analysis was conducted after a minimum of 12 months of follow-up using data collected. An additional analysis after a minimum of 24 months of follow-up was performed with data collected. Tumor response was evaluated by computed tomography or magnetic resonance imaging 4 weeks after the first TACE and every 8 weeks thereafter.

Key Eligibility Criteria

Key inclusion criteria were unresectable HCC that is unapplicable for either surgical resection or percutaneous ablation therapy, Child-Pugh A liver function, 0–2 prior TACE sessions, tumor size ≤10 cm, number of tumors ≤10, and ECOG performance status (PS) 0–1. Key exclusion criteria were vascular invasion and extrahepatic spread.

Sample Size Calculation

A sample size of 60 patients was based on a 90% power with the one-side alpha of 0.05 to detect that median PFS would exceed the threshold of 13.5 months, with an expected median PFS of 25.2 months (based on the TACTICS trial [6]). In addition, the sample size was also determined by an enrollment period of 18 months and a follow-up period of 12 months, using a one-arm nonparametric survival model by Brookmeyer-Crowley.

Evaluation of Treatment Response

Response was evaluated using the Response Evaluation Criteria in Cancer of the Liver (RECICL) as defined by the Liver Cancer Study Group of Japan [29]. In brief, according to RECICL, CR is defined as 100% tumor-necrotizing effect or 100% tumor size reduction; PR as the tumor-necrotizing effect or tumor size reduction between 50% and <100%; SD as effects other than PR and PD; and PD as the tumor growth >25% regardless of the necrotizing effect as compared with baseline nodule tumor burden [29]. Lipiodol retention area in the nodule after more than

Table 1. Baseline demographic and clinical characteristics of patients enrolled in this trial results reported as N (%), unless otherwise indicated

Characteristic	*n* = 62
Age, median (range), years	72.0 (39–90)
Weight, median (range), kg	60.65 (39.9–102.3)
Sex	
Male	48 (77.4)
Female	14 (22.6)
PS	
0	59 (95.2)
1	3 (4.8)
Etiology	
Hepatitis B	8 (12.9)
Hepatitis C	20 (32.3)
Non-B non-C	31 (50.0)
Other	3 (4.8)
Child-Pugh score	
5	51 (82.3)
6	11 (17.7)
AFP	
<200 ng/mL	52 (83.9)
≥200 ng/mL	10 (16.1)
Milan criteria	
Within	28 (45.2)
Outside	34 (54.8)
Up-to-7 criteria	
Within	40 (64.5)
Outside	22 (35.5)
BCLC stage	
A	24 (38.7)
B1**	14 (22.6)
B2**	21 (33.9)
C	3 (4.8)*
Prior TACE	
0	35 (56.5)
1–2	26 (41.9)
3	1 (1.6)
Tumor type	
Simple nodule	30 (48.4)
Non-simple nodule	27 (43.5)
Unknown	5 (8.1)

Data are presented as *n* (%) unless otherwise stated. AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization. *BCLC-C due to PS1 patients, not Vp or extrahepatic metastasis. **BCLC B subclassification according to Kinki criteria/Bolondi criteria.

1 month following TACE was regarded as necrosis [30]. Evaluation using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) was performed at the same time [31].

Primary and Secondary Endpoints

The primary endpoint was PFS by RECICL. The definition of PFS for this trial was time from enrollment to untreatable progression (TTUP) or death, which is the same definition used in the TACTICS trial. TTUP was defined as follows [1]: time to transient liver function deterioration to Child-Pugh C [2], time to intrahepatic tumor progression (>25% compared with the baseline tumor burden) [3], time to vascular invasion [4], time to extrahepatic spread, or [5] time to TACE failure [32, 33]. The secondary endpoints were TTUP, ORR, PFS by mRECIST, OS, and safety. Safety was analyzed in patients who received protocol treatment.

Statistical Analysis

For the primary endpoint of PFS by RECICL, Kaplan-Meier survival curves were plotted, and median PFS and its 90% CI were calculated. For the secondary endpoints of OS and TTUP, Kaplan-Meier survival curves were plotted, and median PFS by mRECIST, median OS, and their 90% CIs were calculated. The cumulative probability of PFS and OS at 24 months was calculated. CR rates and ORR at 4 weeks after first TACE and at best response and 90% CI by the Clopper-Pearson method were calculated. We used logistic regression to compare the difference in CR and ORR between each subgroup.

Results

Baseline Characteristics

A total of 62 HCC patients were enrolled in this trial. Baseline patient characteristics are shown in Table 1. Median age was 72 years, 77.4% of patients were men, and 95.2% had PS 0. The most common HCC etiology was non-B non-C (50.0%), followed by hepatitis C (32.3%) and hepatitis B (12.9%). The percentage of patients with a Child-Pugh score of 5 was 82.3%, and the percentage with alpha-fetoprotein <200 ng/mL was 83.9%. The percentage exceeding the up-to-seven criteria was 54.8%. Barcelona Clinic Liver Cancer (BCLC) stage was A in 38.7%, B1 in 22.6%, and B2 in 33.9% of patients. BCLC B substage classification was based on the Kinki criteria and Bolondi criteria [34–36]. Three patients (4.8%) were staged as BCLC-C, but only because they had ECOG PS 1, which results in classification as stage C according to the BCLC staging rules. None of these 3 patients had vascular invasion or extrahepatic spread. The number of prior TACE sessions was 0 for 56.5% and 1–2 for 41.9% of patients. Tumor type was simple nodular type in 48.4% and non-simple nodular type in 43.5% of patients (Table 1).

Efficacy

The cutoff date for the primary analysis was April 2021 (median follow-up, 17.4 months). The cutoff date for the additional survival follow-up study was April 2022 (median follow-up, 26.4 months). The median duration of LEN administration was 15.0 days (range, 12–29) before

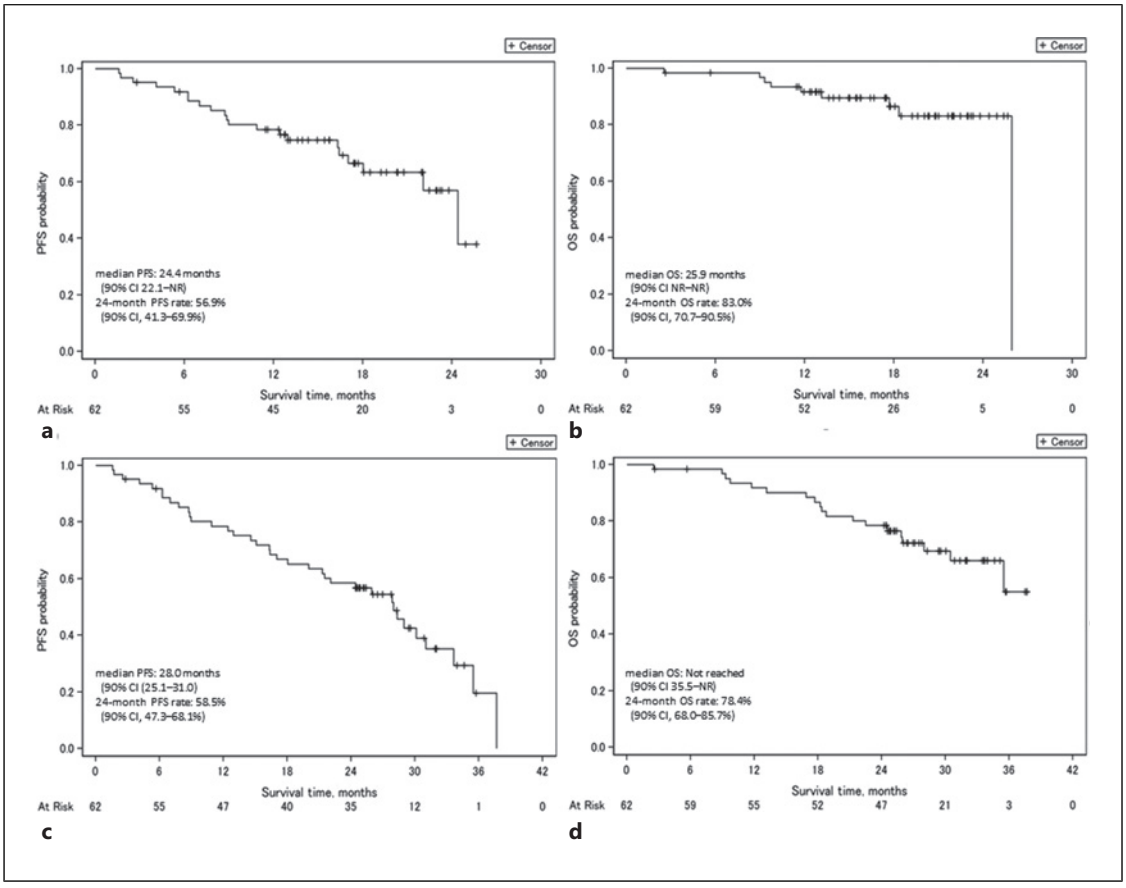

Fig. 1. Kaplan-Meier survival curves. Median PFS according to RECICL (**a**) and median OS for the primary analysis (**b**) (minimum follow-up, 12 months; median, 17.4 months). Median PFS according to RECICL (**c**) and median OS for the additional survival follow-up study (**d**) (minimum follow-up, 24 months; median, 26.4 months). RECICL, Response Evaluation Criteria in Cancer of the Liver; NR, not reached; OS, overall survival; PFS, progression-free survival.

the first TACE and 300.0 days (range, 15–758) after the first TACE (online suppl. Table. 1; for all online suppl. material, see https://doi.org/10.1159/000531377).

The primary endpoint of PFS by RECICL was 24.4 months (90% CI: 22.1–NR [not reached]) in the primary analysis and 28.0 months (90% CI: 25.1–31.0) in the additional analysis. The secondary endpoint of OS was 25.9 months (90% CI: NR–NR) in the primary analysis, whereas it was not reached (90% CI: 35.5 months–NR) in the additional analysis (Fig. 1). 24-month OS rate was 83.0% (90% CI: 70.7–90.5%) in the primary analysis, and 36-month OS rate was 55.0% (90% CI: 34.4–71.5%) in the additional analysis. Median PFS by mRECIST was 24.4 months (90% CI: 22.2–25.9) (online suppl. Fig. 1). When tumor response was evaluated by RECICL, the CR rate and ORR were 53.2% and 79%, respectively, 4 weeks after the first TACE. For the best response, the CR rate was 67.7%, and ORR was 88.7%. When tumor response was evaluated by mRECIST, the CR rate and ORR were 51.6% and 75.8%, respectively, 4 weeks after the first TACE. For the best response according to mRECIST, the CR rate was 67.7%, and the ORR was 88.7% (Table 2). Waterfall plots of response evaluated by mRECIST showed that many patients achieved PR or CR (online suppl. Fig. 2).

Safety

The median duration of LEN treatment was 11.0 months (range; 1–26 months). LEN's dose interruption and reduction rates during the study period were 79.0% (49 of 62 patients) and 80.2% (50 of 62 patients), and the median number of TACE procedures was 1.0 (range; 0–6). Median relative dose intensity (RDI) for LEN was 100.0% (range, 43.3–100.0%) before the first

Table 2. Tumor responses at 4 weeks after first TACE and best response results reported as *n* (%)

	4 weeks after the first TACE		Best response	
	RECICL	mRECIST	RECICL	mRECIST
Tumor response				
CR	33 (53.2)	32 (51.6)	42 (67.7)	41 (66.1)
PR	16 (25.8)	15 (24.2)	13 (21.0)	12 (19.4)
SD	4 (6.5)	7 (11.3)	1 (1.6)	4 (6.5)
PD	2 (3.2)	1 (1.6)	2 (3.2)	1 (1.6)
NE	7 (11.3)	7 (11.3)	4 (6.4)	4 (6.4)
ORR	49 (79.0)	47 (75.8)	55 (88.7)	53 (85.5)
90% CI	68.7–87.1%	65.2–84.5%	79.8–94.6%	76.0–92.2%

RECICL, Response Evaluation Criteria in the Cancer of Liver; mRECIST, modified Response Evaluation Criteria in Solid Tumor; ORR, objective response rate (CR+PR); CI, confidence interval; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

TACE and 47.1% (range, 7.3–100.0%) after the first TACE. Median RDIs at 2 and 6 months were 69.8 and 56.9%, respectively (online suppl. Table 1). In the safety analysis (n = 60) for LEN-TACE sequential therapy, the most common all-grade AEs were hypothyroidism, hypertension, decreased appetite, fatigue, proteinuria, and palmar-plantar erythrodysesthesia syndrome, in that order. AEs of grade 3 or higher included hypertension, decreased appetite, proteinuria, increased aspartate aminotransferase/alanine aminotransferase, and diarrhea. Overall, no new safety concerns were identified (Table 3).

Post hoc Analysis

Swimmer plots of the 42 patients who achieved CR (Fig. 2) and of all patients (online suppl. Fig. 3) showed that many patients achieved CR after their first TACE following upfront LEN treatment. Median duration of CR (at 4 weeks after the first TACE) was 13.8 months (range, 10.1–16.5 months). However, some patients who did not achieve CR after the first TACE achieved it later with continued LEN treatment after TACE or with on-demand TACE. TACE plus LEN did not worsen hepatic functional reserve (i.e., cause deterioration of the albumin-bilirubin [ALBI] score), which in fact improved slightly (Fig. 3).

Subgroup Analysis of CR Rate and ORR

This analysis investigated key predictors of CR at 4 weeks after the first TACE, CR rate among best responses, and ORR. Alpha-fetoprotein, etiology, BCLC stage, and up-to-seven criteria had no significant effects on the CR rate at 4 weeks after the first TACE, the CR rate among best responses, or ORR. However, baseline hepatic function had an effect: a significant difference was observed between patients with Child-Pugh A5 and Child-Pugh A6, indicating that better liver function is associated with a higher CR rate (odds ratio: 0.26; 90% CI: 0.008–0.88) and ORR (odds ratio: 0.05; 90% CI: 0.01–0.23) (Table 4).

By contrast, analysis according to tumor factors showed no clear differences in CR rate or ORR between gross pathological tumor types (simple nodular type vs. other types) (Table 4). Detailed results on CR rate and ORR according to gross pathological tumor type are shown in Figure 4. Similarly, neither CR rate nor ORR clearly differed between patients with different tumor sizes (<5 cm vs. ≥5 cm) or numbers (<5 vs. ≥5) (Table 4).

One treatment-related factor was identified: the CR rate was significantly higher for patients whose RDI of LEN before the first TACE was 100% versus less than 100% (odds ratio: 0.24; 90% CI: 0.07–0.80). Duration of LEN administration before the first TACE (≤14 days vs. >14 days) and RDI after the first TACE (<median RDI vs. ≥median RDI) had no effect on CR rate. Similar trends were observed for CR among best responses and ORR (Table 4).

Discussion

Anti-VEGF agents improve drug delivery by normalizing tumor vasculature, which is achieved through the normalization of interstitial pressure, microvascular density, or vascular permeability [9–11, 15]. This has been known for some time and has prompted trials of combination therapy with TACE and molecular-targeted agents with anti-VEGF activity for intermediate-stage HCC. Six prospective controlled trials have been conducted to date [1–7], although the only trial with positive results was the TACTICS trial. The TACTICS trial was conducted in intermediate-stage HCC and had two coprimary endpoints, PFS and OS. In the primary analysis, TACE plus sorafenib significantly extended PFS compared with TACE alone [6]. Although the difference in OS between TACE plus sorafenib and TACE alone (36.2 months vs. 30.8 months) was not statistically significant, the fact that TACE plus sorafenib extended OS by 5.4 months is clinically relevant [7]. These results offer valuable insights and clearly demonstrate the clinical benefit of combining an anti-VEGF agent with TACE. It is particularly noteworthy that the HRs for PFS and OS were better in patients exceeding the up-to-seven criteria than in those within the up-to-seven criteria, which indicates that the

Table 3. Treatment-emergent AEs (selected all-grade AEs with frequency ≥20%)

	Safety analysis set (n = 60)				
	all grade	grade 1	grade 2	grade 3	grade 4
Hypothyroidism	36 (60.0)	14 (23.3)	22 (36.7)	0 (0.0)	0 (0.0)
Hypertension	32 (53.3)	1 (1.7)	15 (25.0)	16 (26.7)	0 (0.0)
Decreased appetite	31 (51.7)	14 (23.3)	11 (18.3)	6 (10.0)	0 (0.0)
Fatigue	30 (50.0)	14 (23.3)	16 (26.7)	0 (0.0)	0 (0.0)
Proteinuria	26 (43.3)	4 (6.7)	15 (25.0)	7 (11.7)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	22 (36.7)	13 (21.7)	7 (11.7)	2 (3.3)	0 (0.0)
Pyrexia	21 (35.0)	12 (20.0)	9 (15.0)	0 (0.0)	0 (0.0)
Hypoalbuminemia	20 (33.3)	10 (16.7)	9 (15.0)	1 (1.7)	0 (0.0)
Aspartate aminotransferase increased	19 (31.7)	7 (11.7)	3 (5.0)	8 (13.3)	1 (1.7)
Alanine aminotransferase increased	19 (31.7)	10 (16.7)	2 (3.3)	7 (11.7)	0 (0.0)
Dysphonia	18 (30.0)	17 (28.3)	1 (1.7)	0 (0.0)	0 (0.0)
Platelet count decreased	18 (30.0)	3 (5.0)	10 (16.7)	5 (8.3)	0 (0.0)
Diarrhea	16 (26.7)	7 (11.7)	3 (5.0)	6 (10.0)	0 (0.0)
Blood bilirubin increased	16 (26.7)	5 (8.3)	8 (13.3)	3 (5.0)	0 (0.0)
Weight decreased	16 (26.7)	3 (5.0)	12 (20.0)	1 (1.7)	0 (0.0)
Constipation	14 (23.3)	9 (15.0)	5 (8.3)	0 (0.0)	0 (0.0)
Anemia	12 (20.0)	7 (11.7)	4 (6.7)	1 (1.7)	0 (0.0)

Data are presented as n (%). AE, adverse event.

clinical benefit is greater for patients with a high tumor burden [7]. The results support the recommendations in the APPLE Consensus [22] and JSH Consensus [23], stating that addition of an anti-VEGF agent to TACE provides a survival benefit for patients exceeding the up-to-seven criteria who would otherwise be considered poor candidates for TACE. Furthermore, the combination of an anti-VEGF agent with TACE appears to be beneficial for all patients with intermediate-stage HCC as even patients within the up-to-seven criteria experienced some clinical benefit from this combination.

However, the TACTICS trial showed that although TACE plus sorafenib extended PFS, ORR was not significantly different (71.3% for TACE plus sorafenib vs. 61.8% for TACE alone, $p = 0.23$). The CR rate was also not significantly different (23.8 vs. 27.6%, $p = 0.77$). This may be because the response rate for sorafenib was not as high as described in previous reports [23, 37, 38]. By contrast, in a proof-of-concept study published in 2019, LEN-TACE sequential therapy had a very favorable PFS HR and ORR compared with TACE alone [21]. Hepatic functional reserve decreased significantly in patients who received TACE alone, whereas the ALBI score did not deteriorate in those who received upfront LEN. Consequently, OS was also far better for LEN-TACE, at 37.9 months versus just 21.3 months for TACE alone (HR: 0.48; 95% CI: 0.16–0.79; $p < 0.01$), thus demonstrating the superior efficacy of LEN-TACE combination therapy to TACE alone [21].

The TACTICS-L trial essentially adhered to the TACTICS trial design but investigated LEN instead of sorafenib. This was a phase 2, prospective, multicenter, single-arm trial conducted to evaluate the efficacy and safety of LEN in combination with TACE. In this trial, median PFS was a favorable 28.0 months at the additional follow-up (minimum 24 months), and median OS was not reached. For best responses, the CR rate and ORR were 67.7% and 88.7%, respectively, which are excellent results. These ORR and CR rates were significantly higher than those for TACE plus sorafenib in the TACTICS trial. The positive results of the TACTICS-L trial support the results for LEN-TACE sequential therapy in the proof-of-concept trial and reaffirm the excellent efficacy of the combination of LEN and TACE. In the safety analysis, no new safety concerns were identified with respect to all-grade AEs with an incidence of 20% or higher. The tolerability of LEN after TACE is acceptable; the median RDI of LEN at 2 months after TACE was 69.8%, which is consistent with RDI (67–83%) of several real-world retrospective studies on LEN-TACE [39–43]. The median RDI of LEN after TACE for the whole treatment course is relatively low (47.1%). However, this low RDI is attributed to the long treatment duration and prolonged PFS. It is also attributed to the fact that the investigators intentionally

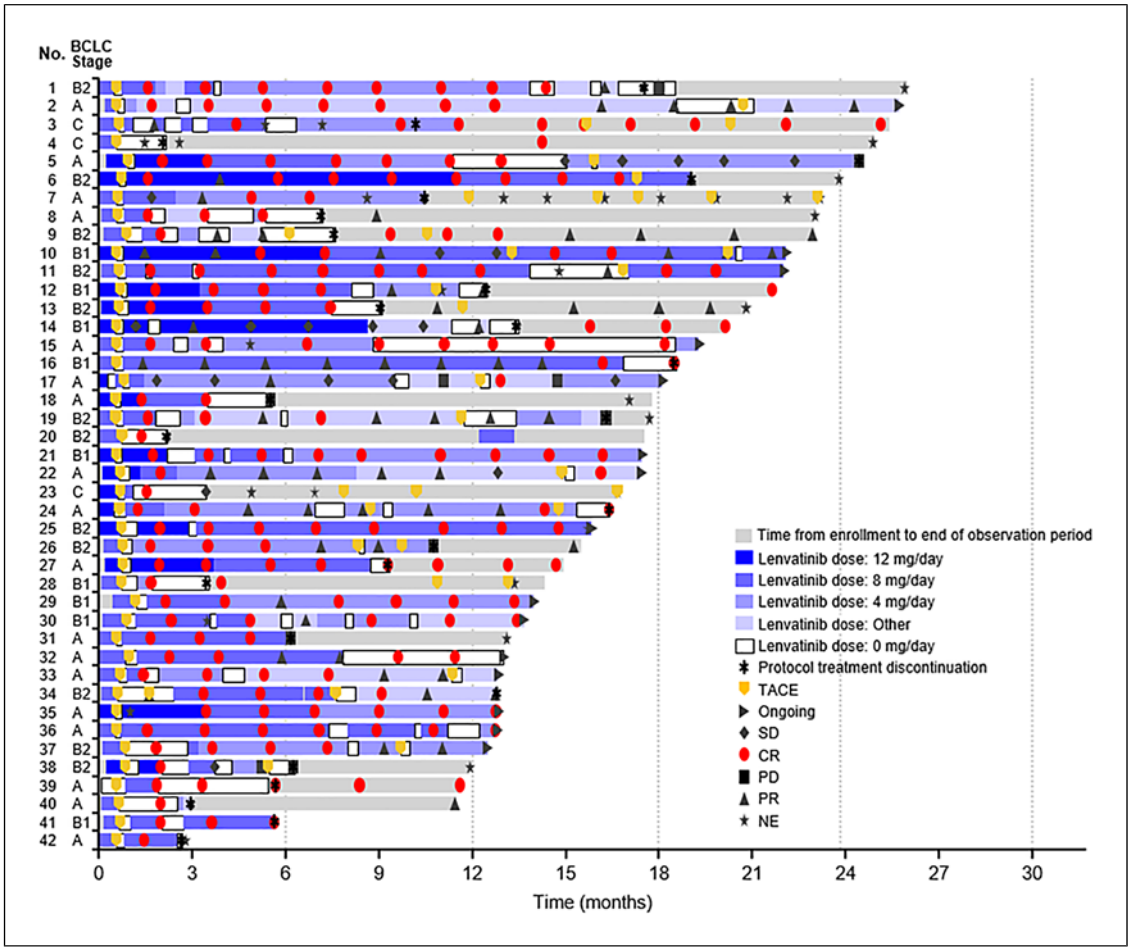

Fig. 2. Swimmer plot: CR cases only. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TACE, transarterial chemoembolization.

reduced the LEN dose after patients achieved CR to keep a good quality of life, not because of the AEs. Exploratory subgroup analysis of factors associated with CR rate and ORR showed that tumor factors, such as number of tumors, tumor size, gross pathological tumor type, and tumor burden, had no significant effect. This demonstrates that LEN-TACE sequential therapy with upfront LEN is effective in HCC patients considered unsuitable for TACE because of factors such as a high tumor burden or a tumor type other than the simple nodular type (e.g., confluent multinodular type, simple nodular type with extranodular growth, or diffuse type). The only factor associated with a significant difference in CR rate or ORR was liver function: better hepatic functional reserve was associated with a higher CR rate and ORR.

Analysis of treatment-related factors associated with CR rate and ORR showed a clear significant difference in CR rate and ORR between patients who received 100% RDI and those who received less than 100% RDI of LEN before the first TACE. Receiving LEN within 14 days before the first TACE versus more than 14 days before the first TACE had no effect on CR rate or ORR, and patients who received any dose of LEN after TACE, even at a low RDI, achieved a good CR rate and ORR. This suggests that receiving a sufficient dose of LEN before TACE, even for a short period of time, is important for achieving CR and OR, whereas the RDI after TACE can be lower.

A swimmer plot of 42 patients with a sustained CR revealed various patterns. Some patients achieved a continuous CR after just the first TACE following upfront LEN, whereas others did not achieve a CR after the first TACE but later achieved and maintained a CR with continued LEN treatment after the first TACE. This explains the 14.5% improvement between

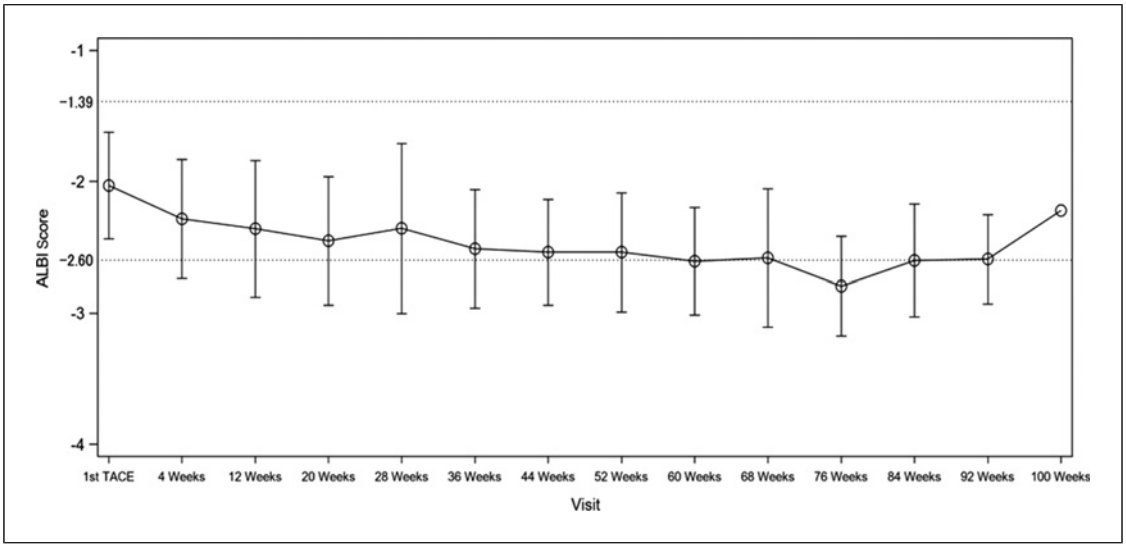

Fig. 3. Change in albumin-bilirubin (ALBI) scores over time.

the CR rate at 4 weeks after TACE (53.2%) and the best response CR rate (67.7%). In other words, this indicates that for sustaining a high-quality CR, it is important not only to maintain a high RDI of upfront LEN but also to continue LEN after TACE at some dose level, even if it is low. In fact, the median duration of the first CR was extremely long at 13.8 months. Furthermore, the ALBI score did not deteriorate during LEN-TACE, indicating a minimal effect on hepatic functional reserve. This could be largely explained by the fact that patients with better hepatic functional reserve experience fewer AEs, allowing them to maintain RDI [44].

The fact that LEN-TACE showed good efficacy and safety in tumors that would not respond to TACE alone makes the TACTICS-L trial extremely significant. The results presented are the first from a prospective trial to clearly support the previously established concept [45, 46] that LEN prior to TACE enhances the efficacy of TACE by improving drug delivery through vascular normalization and the reduction of interstitial pressure, and LEN after TACE prevents the recurrence through the elimination of residual tumor and improvement of hypoxic condition, resulting in the inhibition of releasing hypoxia-inducible cytokines such as VEGF [15]. In the past, TACE was considered ineffective for certain types of HCC, including the simple nodular type with extranodular growth, the confluent multinodular type, and the infiltrative type (Fig. 4). The fact that LEN-TACE sequential therapy produced ORR and CR rate comparable to those obtained for the simple nodular type, which responds well to TACE with or without additional therapy, clearly indicates that LEN-TACE is an effective treatment for patients who would otherwise be considered unsuitable for TACE.

The LAUNCH trial [28], a phase 3 prospective randomized controlled trial, clearly showed that both PFS and OS were improved in the LEN-TACE therapy as compared with LEN alone in advanced-stage HCC. Similarly, in a retrospective comparative study of LEN-TACE versus TACE alone, LEN-TACE showed better efficacy in terms of PFS and OS in intermediate- and advanced-stage HCC [26]. Both reports showed that the combination of LEN and TACE had well-acceptable toxicity and tolerability, similar to the TACTICS-L trial. The present trial had some limitations, including a short follow-up period, high rate of censoring, and a small sample size. In addition, baseline characteristics are not balanced in the subgroup analysis of CR rate and ORR. Further increases in PFS and OS should be observed during an extended follow-up period. Another limitation is that this was a single-arm trial rather than a controlled trial, and the extent of PFS and OS benefit provided by LEN-TACE compared with TACE alone thus remains unclear. This issue may be resolved in the future by the results of ongoing LEAP 012 trial of LEN + pembrolizumab + TACE as compared with TACE alone [47].

In summary, an additional follow-up study (median 26.4 months) of the TACTICS-L trial showed that the median PFS with LEN-TACE was 28.0 (90% CI: 25.1–31.0) months, and the median OS was not reached (90% CI: 35.5 months–NR). LEN-TACE also achieved a

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Table 4. Results of subgroup analyses

Subgroup	Category	*n*	CR rate (4 weeks after the first TACE)					CR rate (best response)					ORR (best response)				
			CR rate	(90% CI)	odds ratio*	(90% CI)*	*p* value*	CR rate	(90% CI)	odds ratio*	(90% CI)*	*p* value*	ORR	(90% CI)	odds ratio*	(90% CI)*	*p* value*
AFP, ng/mL	<200	52	53.8%	(41.6%–65.8%)	-	-	-	71.2%	(59.1%–81.3%)	-	-	-	92.3%	(83.3%–97.3%)	-	-	-
	≥200	10	50.0%	(22.2%–77.8%)	0.86	(0.28, 2.67)	0.823	50.0%	(22.2%–77.8%)	0.41	(0.13, 1.29)	0.199	70.0%	(39.3%–91.3%)	0.19	(0.05, 0.81)	0.058
Etiology	Hepatitis B	8	62.5%	(28.9%–88.9%)	-	-	-	75.0%	(40.0%–95.4%)	-	-	-	87.5%	(52.9%–99.4%)	-	-	-
	Hepatitis C	20	45.0%	(25.9%–65.3%)	0.49	(0.12, 2.01)	0.407	65.0%	(44.2%–82.3%)	0.62	(0.13, 2.91)	0.611	85.0%	(65.6%–95.8%)	0.81	(0.11, 6.21)	0.865
	Non-B non-C	31	51.6%	(35.7%–67.3%)	0.64	(0.17, 2.44)	0.583	64.5%	(48.2%–78.7%)	0.61	(0.14, 2.66)	0.578	90.3%	(76.8%–97.3%)	1.33	(0.18, 10.08)	0.815
BCLC stage	A	24	62.5%	(43.7%–78.8%)	-	-	-	75.0%	(56.5%–88.5%)	-	-	-	83.3%	(65.8%–94.1%)	-	-	-
	B1	14	42.9%	(20.6%–67.5%)	0.45	(0.15, 1.39)	0.244	64.3%	(39.0%–84.7%)	0.60	(0.18, 1.99)	0.484	92.9%	(70.3%–99.6%)	2.60	(0.38, 17.91)	0.415
	B2	21	52.4%	(32.8%–71.4%)	0.66	(0.24, 1.79)	0.494	57.1%	(37.2%–75.5%)	0.44	(0.15, 1.29)	0.209	90.5%	(72.9%–98.3%)	1.90	(0.42, 8.68)	0.487
Up-to-7	Within	40	55.0%	(40.9%–68.5%)	-	-	-	72.5%	(58.6%–83.7%)	-	-	-	87.5%	(75.5%–94.9%)	-	-	-
	Outside	22	50.0%	(31.1%–68.9%)	0.82	(0.34, 1.96)	0.706	59.1%	(39.5%–76.7%)	0.55	(0.22, 1.38)	0.282	90.9%	(74.1%–98.4%)	1.43	(0.33, 6.10)	0.686
Milan Criteria	Within	28	64.3%	(47.0%–79.2%)	-	-	-	78.6%	(62.0%–90.2%)	-	-	-	89.3%	(74.6%–97.0%)	-	-	-
	Outside	34	44.1%	(29.5%–59.5%)	0.44	(0.19, 1.04)	0.116	58.8%	(43.3%–73.1%)	0.39	(0.15, 1.01)	0.103	88.2%	(75.1%–95.9%)	0.90	(0.24, 3.41)	0.897
Child-Pugh score	5	51	58.8%	(46.3%–70.5%)	-	-	-	76.5%	(64.7%–85.8%)	-	-	-	96.1%	(88.2%–99.3%)	-	-	-
	6	11	27.3%	(7.9%–56.4%)	0.26	(0.08, 0.88)	0.069	27.3%	(7.9%–56.4%)	0.12	(0.03, 0.40)	0.004	54.5%	(27.1%–80.0%)	0.05	(0.01, 0.23)	0.001
Prior TACE	0	35	54.3%	(39.2%–68.8%)	-	-	-	71.4%	(56.4%–83.6%)	-	-	-	88.6%	(75.7%–96.0%)	-	-	-
	1–2	26	53.8%	(36.2%–70.8%)	0.98	(0.42, 2.31)	0.973	65.4%	(47.4%–80.6%)	0.76	(0.30, 1.89)	0.615	88.5%	(72.8%–96.8%)	0.99	(0.26, 3.76)	0.989
Tumor type	Simple nodule	30	50.0%	(33.9%–66.1%)	-	-	-	70.0%	(53.5%–83.4%)	-	-	-	90.0%	(76.1%–97.2%)	-	-	-
	Other	27	55.6%	(38.2%–72.0%)	1.25	(0.52, 3.00)	0.675	63.0%	(45.3%–78.3%)	0.73	(0.29, 1.84)	0.574	88.9%	(73.7%–96.9%)	0.89	(0.21, 3.68)	0.891

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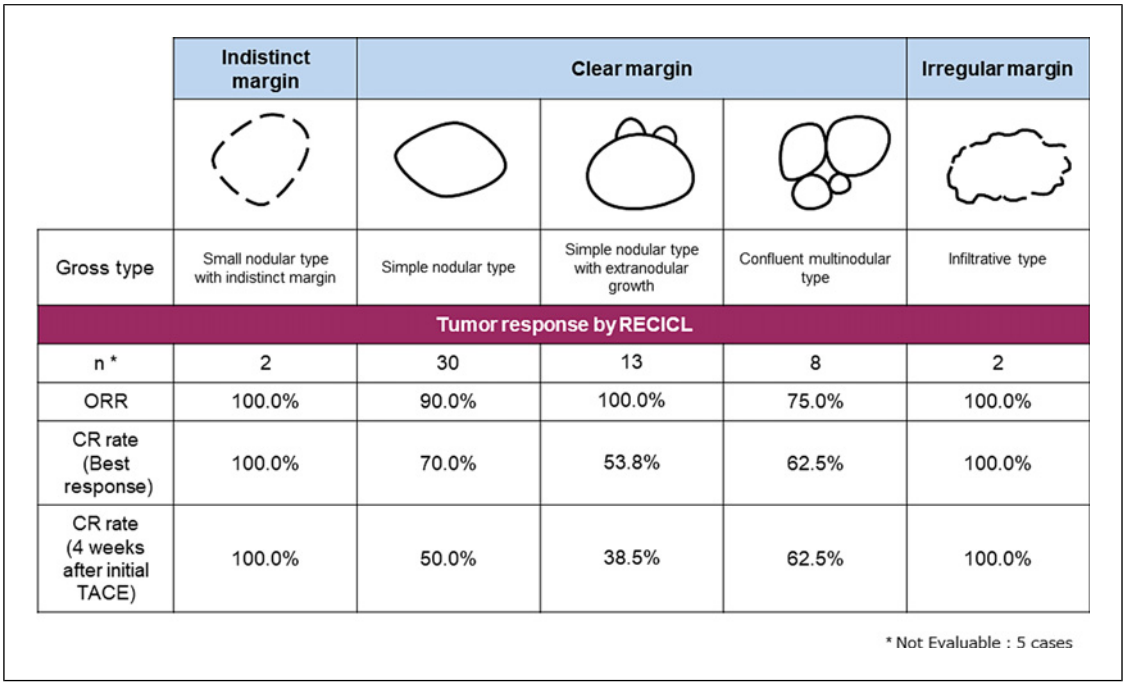
Table 4 (continued)

Subgroup	Category	*n*	CR rate (4 weeks after the first TACE)					CR rate (best response)					ORR (best response)				
			CR rate	(90% CI)	odds ratio*	(90% CI)*	*p* value*	CR rate	(90% CI)	odds ratio*	(90% CI)*	*p* value*	ORR	(90% CI)	odds ratio*	(90% CI)*	*p* value*
Maximum tumor size at baseline	<5 cm	53	54.7%	(42.6%–66.5%)	-	-	-	67.9%	(55.9%–78.4%)	-	-	-	88.7%	(78.9%–95.0%)	-	-	-
	≥5 cm	9	44.4%	(16.9%–74.9%)	0.66	(0.20, 2.18)	0.570	66.7%	(34.5%–90.2%)	0.94	(0.27, 3.33)	0.940	88.9%	(57.1%–99.4%)	1.02	(0.16, 6.72)	0.985
Number of tumors at baseline	<5	45	55.6%	(42.3%–68.3%)	-	-	-	66.7%	(53.4%–78.2%)	-	-	-	86.7%	(75.4%–94.0%)	-	-	-
	≥5	17	47.1%	(26.0%–68.9%)	0.71	(0.28, 1.82)	0.551	70.6%	(47.8%–87.6%)	1.20	(0.43, 3.32)	0.768	94.1%	(75.0%–99.7%)	2.46	(0.39, 15.54)	0.421
Body weight	<60 kg	31	58.1%	(41.8%–73.1%)	-	-	-	74.2%	(58.2%–86.5%)	-	-	-	83.9%	(69.0%–93.4%)	-	-	-
	≥60 kg	31	48.4%	(32.7%–64.3%)	0.68	(0.29, 1.57)	0.446	61.3%	(45.0%–75.9%)	0.55	(0.22, 1.36)	0.280	93.5%	(81.1%–98.8%)	2.79	(0.66, 11.84)	0.243
LEN duration: before the first TACE	≤14 days	26	57.7%	(39.8%–74.2%)	-	-	-	76.9%	(59.5%–89.4%)	-	-	-	88.5%	(72.8%–96.8%)	-	-	-
	>14 days	34	52.9%	(37.7%–67.8%)	0.83	(0.35, 1.96)	0.714	64.7%	(49.2%–78.2%)	0.55	(0.21, 1.45)	0.309	94.1%	(82.6%–98.9%)	2.09	(0.44, 10.01)	0.440
LEN RDI: before the first TACE	100%	49	61.2%	(48.5%–72.9%)	-	-	-	77.6%	(65.6%–86.9%)	-	-	-	95.9%	(87.7%–99.3%)	-	-	-
	<100%	11	27.3%	(7.9%–56.4%)	0.24	(0.07, 0.80)	0.051	36.4%	(13.5%–65.0%)	0.17	(0.05, 0.54)	0.012	72.7%	(43.6%–92.1%)	0.11	(0.02, 0.58)	0.028
LEN RDI: after the first TACE	<median	29	58.6%	(41.7%–74.1%)	-	-	-	62.1%	(45.1%–77.1%)	-	-	-	86.2%	(71.2%–95.1%)	-	-	-
	≥median	29	55.2%	(38.4%–71.1%)	0.87	(0.36, 2.08)	0.791	79.3%	(63.2%–90.6%)	2.34	(0.88, 6.26)	0.154	100.0%	(90.2%–100.0%)	144898.53	(0.00, 2.5014E131)	0.946

*Odds ratio (90% CI) and its *p* value were presented as a referential purpose.



	Indistinct margin	Clear margin			Irregular margin
Gross type	Small nodular type with indistinct margin	Simple nodular type	Simple nodular type with extranodular growth	Confluent multinodular type	Infiltrative type
Tumor response by RECICL					
n *	2	30	13	8	2
ORR	100.0%	90.0%	100.0%	75.0%	100.0%
CR rate (Best response)	100.0%	70.0%	53.8%	62.5%	100.0%
CR rate (4 weeks after initial TACE)	100.0%	50.0%	38.5%	62.5%	100.0%

* Not Evaluable : 5 cases

Fig. 4. Efficacy according to gross pathological tumor type. CR, complete response; ORR, objective response rate; TACE, transarterial chemoembolization.

very durable high CR rate and ORR (4 weeks after the first TACE: ORR 79.0%, CR rate 53.2%; best response: ORR 88.7%, CR rate 67.7%). Subgroup analysis demonstrated that LEN-TACE can achieve a very good CR rate and ORR while preserving hepatic functional reserve, which contributes to extending OS. This is applicable even to patients with a high tumor burden who are typically not expected to respond well to TACE alone, such as those exceeding the up-to-seven criteria or those with a tumor type other than the simple nodular type. This prospective trial showed that maintaining the RDI of upfront LEN is important to achieve this good CR rate and ORR, even when LEN is administered for only a short time before the first TACE (≤2 weeks), and that continuing LEN after TACE, even at a low RDI, is important for maintaining a durable CR.

In conclusion, the results of the TACTICS-L trial provide encouraging evidence supporting the positive efficacy and manageable safety profile of LEN-TACE for patients who are not suitable candidates for TACE. The results also provide clinical support for the rationale that LEN enhances the efficacy of TACE by improving vascular normalization, interstitial pressure, and drug delivery [9–11, 15].

Statement of Ethics

This trial was approved by the Ethics Review Boards of all participating institutions and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. This study protocol was reviewed and approved by Certified Review Board in Hattori Clinic, approved number Hattori Clinic 3-A.

Conflict of Interest Statement

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Data Availability Statement

The datasets generated and analyzed in the present study are available from the corresponding author on reasonable request. Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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