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Editorial

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Lenvatinib plus Pembrolizumab Combined with Transarterial Chemoembolization in Intermediate-Stage Hepatocellular Carcinoma

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Introduction

The results of the LEAP-012 trial were presented at the European Society for Medical Oncology (ESMO) 2024 [1]. The combination of lenvatinib (LEN), pembrolizumab (PEM), and transarterial chemoembolization (TACE) (LEN-PEM-TACE) was found to prolong progression-free survival (PFS) compared with TACE alone in patients with unresectable hepatocellular carcinoma (HCC) without extrahepatic spread or vascular invasion, making the trial a positive study. The design of the LEAP-012 trial was an implementation of the concept of the TACTICS-L trial [2]. LEN-PEM-TACE is expected to be used similarly to LEN-TACE therapy in clinical practice once approved by regulatory authorities.

Trial Design of LEAP-012

The design of the LEAP-012 trial is shown in Figure 1. This phase 3 global randomized controlled trial tested the superiority of LEN-PEM-TACE over TACE alone in patients with unresectable HCC without extrahepatic spread or vascular invasion. Patients were randomized 1:1 to receive LEN-PEM-TACE or dual placebo plus TACE. Beginning 2–4 weeks before the first TACE session, patients in the LEN-PEM-TACE arm were administered LEN 12 mg or 8 mg once daily and PEM 400 mg once every 6 weeks for 2 years after TACE [3], whereas patients in the TACE alone arm received dual placebo plus TACE. Treatments were continued for 2 years or until progressive disease (PD) or unacceptable toxicity. The dual primary endpoints were PFS and overall survival (OS). Stratification factors include study site, alpha-fetoprotein concentration (≤400 ng/mL vs. >400 ng/mL), Eastern Cooperative Oncology Group

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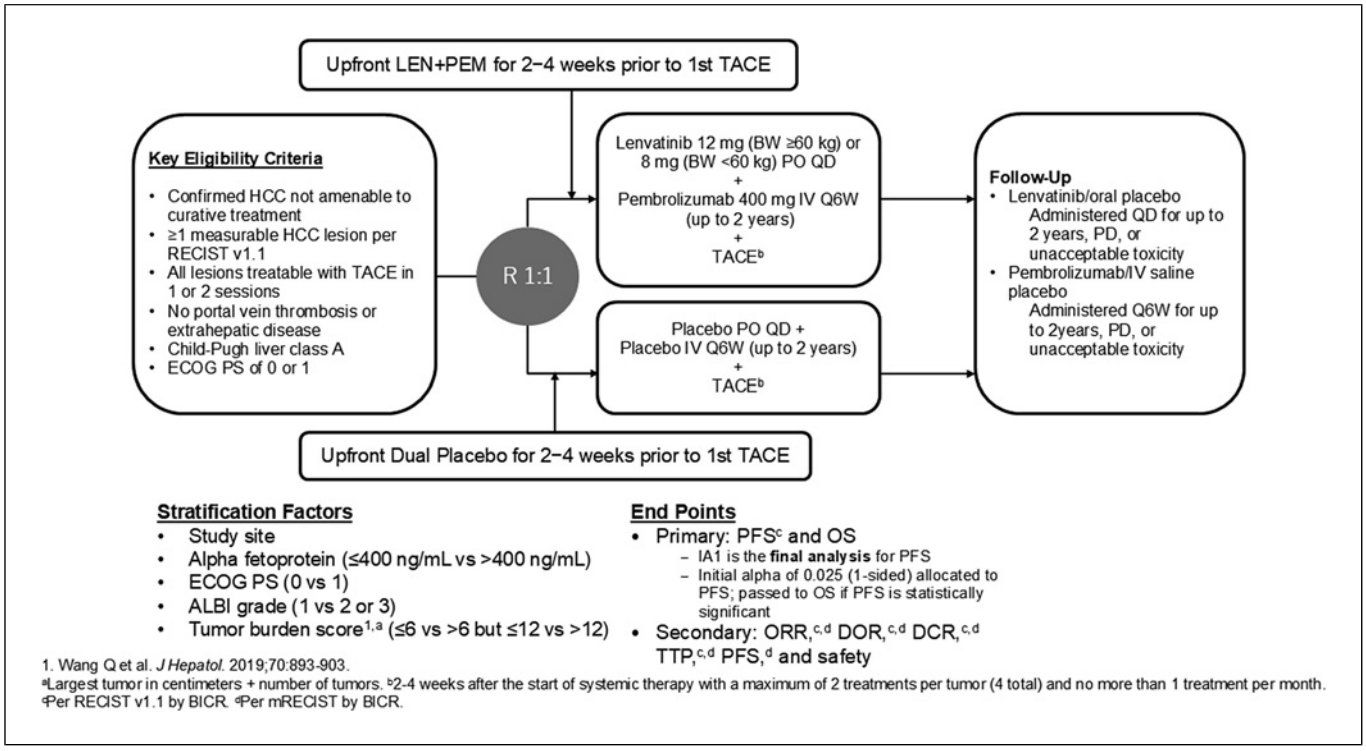

Fig. 1. LEAP-012 study design. First, important point in this trial design: LEN plus PEM was introduced 2–4 weeks before first TACE. Another important point includes ALBI grade and tumor burden score are included in the stratification factors. ALBI grade, albumin-bilirubin grade.

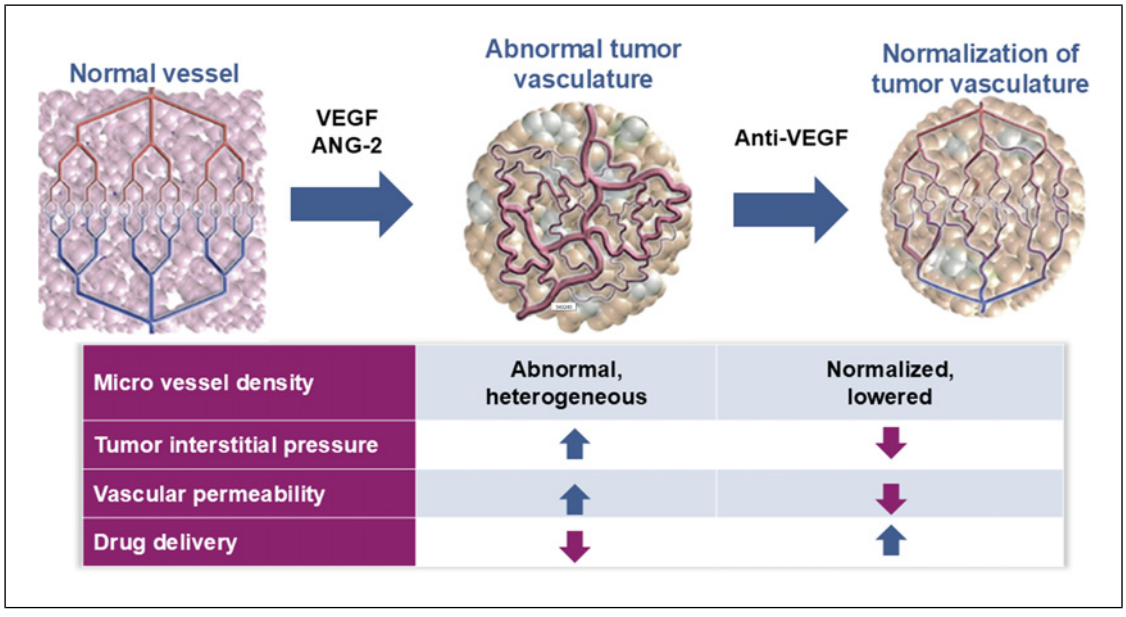

Fig. 2. Effect on tumor vasculature by VEGF inhabitation. Modified by [7]. VEGF, vascular endothelial growth factor.

Table 1. Efficacy results of LEAP-012

	LEN+PEM+TACE	Dual placebo+TACE
PFS		
Events, *n* (%)	132 (55.7)	154 (63.4)
Median (95% CI), months	14.6 (12.6–16.7)	10.0 (8.1–12.2)
HR (95% CI)	0.66 (0.51–0.84)	
p value	$p = 0.0002$	
OS		
Events, *n* (%)	69 (29.1)	82 (33.7)
HR (95% CI)	0.80 (0.57–1.11)	
p value	$p = 0.0867$	
ORR per RECIST 1.1 by BICR		
Best ORR, % (95% CI)	46.8 (40.3–53.4)	33.3 (27.4–39.6)
p value	$p = 0.0005$	
DOR, median (range), months	12.6 (1.3+ to 39.1+)	10.7 (2.0+ to 39.5+)
ORR per mRECIST by BICR		
Best ORR, % (95% CI)	71.3 (65.1–77.0)	49.8 (43.3–56.3)
CR rate, % (95% CI)	56.1 (49.5–62.5)	33.7 (27.8–40.1)
DOR, median (range), months	14.6 (0.0+ to 39.1+)	12.5 (2.1+ to 35.3+)
PFS by tumor burden score		
HR (95% CI)		
≤6	0.68 (0.48–0.96)	
>6 and ≤12	0.59 (0.43–0.83)	
OS by tumor burden score		
≤6	1.02 (0.59–1.75)	
>6 and ≤12	0.61 (0.40–0.92)	

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; HR, hazard ratio; DOR, duration of response; CR, complete response; LEN, lenvatinib; PEM, pembrolizumab; TACE, transarterial chemoembolization.

performance status (ECOG PS; 0 vs. 1), albumin-bilirubin (ALBI) grade (1 vs. 2, 3), and tumor burden score (≤6 vs. ≥6 to ≤12 vs. ≥12). In addition to alpha-fetoprotein and ECOG PS, ALBI grade and tumor burden score are critical prognostic factors not included in previous clinical trials. ALBI grade is particularly important because LEN is very poorly tolerated in patients with ALBI grade ≥2, which can lead to dose reduction or discontinuation [4]. The trial design was similar to the designs of the TACTICS [5, 6] and TACTICS-L [2] trial.

Vascular endothelial growth factor inhibitors such as LEN have been shown to normalize tumor vasculature and microvessel density and to reduce tumor interstitial pressure and vascular permeability, improving drug delivery and the efficacy of TACE [7] (Fig. 2). Because these phenomena occur when LEN is administered only 4 days before TACE [8], treatment with LEN prior to TACE is crucial to increase the efficacy of TACE and prolong PFS [9].

PFS as evaluated by RECIST v1.1 criteria has not been shown to be a surrogate endpoint for OS in patients with intermediate-stage HCC. Thus, LEN-PEM-TACE may be required to show improvements in OS to obtain approval by the US Food and Drug Administration. Liver function has also been found to be an important prognostic factor for OS, with ALBI grade being the most sensitive method of assessing liver function [10, 11]. Furthermore, tumor burden is an important prognostic factor in these patients, with the effect of TACE varying considerably according to tumor burden [12, 13]. Therefore, the inclusion of ALBI grade and tumor burden as stratification factors was crucial for the trial's success in patients with intermediate-stage HCC.

Results of the LEAP-012 Trial

The LEAP-012 trial showed that, compared with TACE alone, LEN-PEM-TACE significantly prolonged PFS in patients with intermediate-stage HCC (14.6 months vs. 10.0 months; hazard ratio 0.66; 95% confidence interval 0.51–0.84; $p = 0.0002$), making this a positive study (Table 1). Of the patients in the LEN-PEM-TACE and TACE alone groups, 29.1% and 33.7%, respectively,

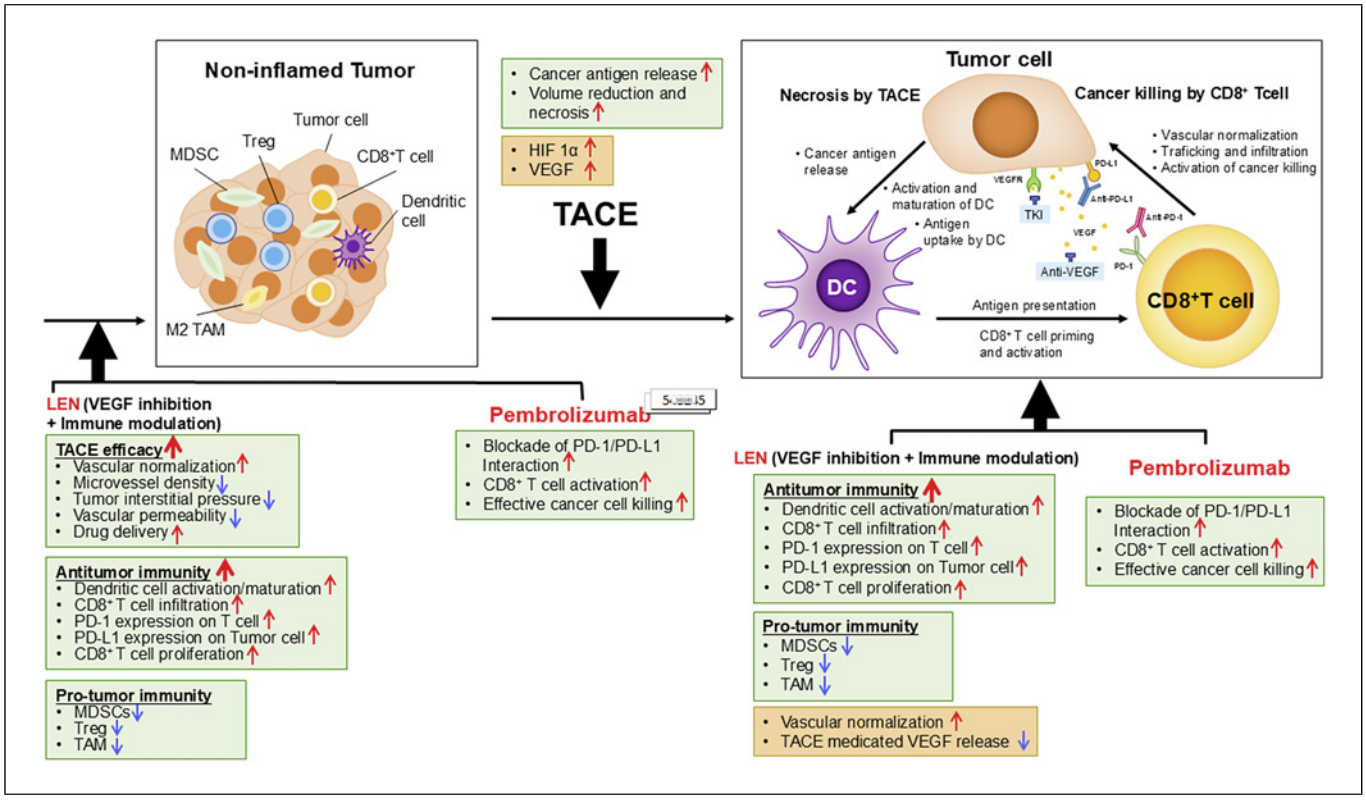

Fig. 3. Scientific rationale of LEN-PEM-TACE therapy upfront lenvatinib (LEN) improves TACE efficacy and increases antitumor immunity and inhibits pro-tumor immunity. TACE increases cancer antigen release and induces volume reduction through tumor necrosis, however, induces HIF-1α and VEGF release. LEN after TACE inhibits TACE mediated VEGF release. TACE, transarterial chemoembolization, HIF-1α, hypoxia inducible factor-1α, VEGF, vascular endothelial growth factor.

experienced OS events. Although these data were quite immature, the hazard ratio of 0.80 (95% confidence interval, 0.57–1.11, $p = 0.0867$) indicated that OS tended to be sufficiently more favorable in the LEN-PEM-TACE arm than in the TACE alone arm. Additional follow-up, however, is required to confirm the better OS trend.

Based on RECIST 1.1, the objective response rates (ORRs), as determined by blinded independent central review, were 46.8% in the LEN-PEM-TACE group and 33.3% in the TACE alone group ($p = 0.0005$), suggesting that LEN-PEM-TACE was significantly more effective in reducing tumor size than TACE alone. ORRs determined by mRECIST were also significantly higher in the LEN-PEM-TACE (71.3%) than in the TACE alone (49.8%). Notably, the complete response (CR) rate in the LEN-PEM-TACE group was 56.1%, similar to the CR rate of patients treated with LEN-TACE [2]. The adverse events of LEN-PEM-TACE were acceptable, and no new safety concerns were observed.

LEN-PEM-TACE: Additive or Synergistic Effect?

LEN-PEN-TACE therapy should theoretically show a synergistic effect. The design of the LEAP-012 trial, however, stipulated that the protocol treatment be terminated at the first progression per RECIST v1.1. Therefore, it was difficult to assess the synergistic effect of LEN-PEM-TACE. The design of the LEAP-012 trial differed somewhat from that observed in a trial testing the combination of atezolizumab plus bevacizumab followed by curative conversion in patients with intermediate-stage HCC (ABC Conversion), in which a synergistic effect was observed [14]. Theoretically, the efficacy of TACE is increased by administering LEN before TACE, and vascular endothelial growth factor inhibition can modulate the immune microenvironment. The release of tumor antigens by subsequent TACE can kill the cancer cells by physical destruction combined with the effects of PEM (Fig. 3). The synergistic effects of LEN+PEM combined with TACE should therefore theoretically

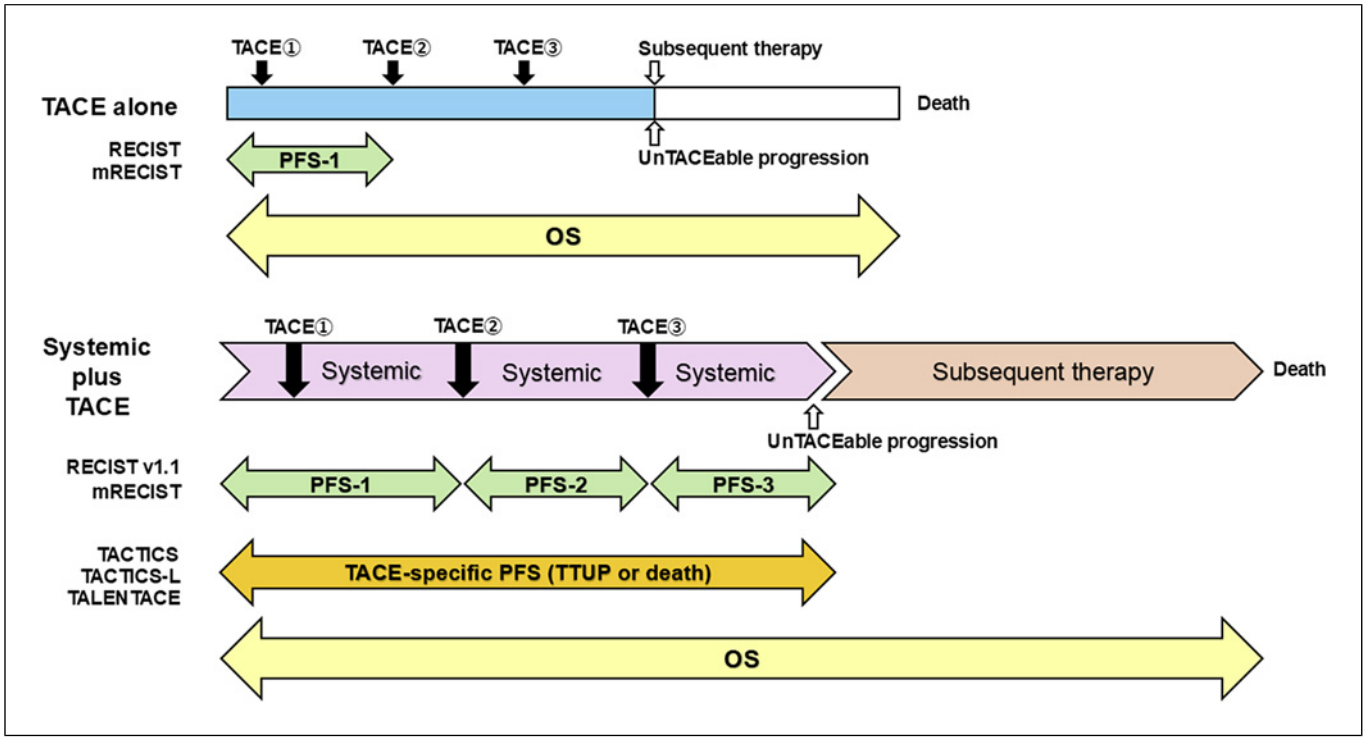

Fig. 4. Relationship between PFS per RECIST v1.1 vs. TACE-specific PFS (UnTACEable progression or death). PFS, progression-free survival; TACE, transarterial chemoembolization.

increase the rate of tumor cell necrosis. Thus, LEN-PEM treatment alone until the first PD after initial TACE would likely be insufficient to induce a synergistic effect. This may explain the relatively unimpressive efficacy results of the LEAP-012 trial.

Performance of a second TACE session to achieve CR in patients with intermediate-stage HCC is technically and oncologically feasible, with the continuation of LEN-PEM further enhancing the synergistic effects of LEN-PEM-TACE. Treatment differs in patients with advanced stage HCC, where PD after the first-line regimen resulting in the switching systemic therapy to the next line of treatment. The design of the LEAP-012 trial, in which LEN-PEN-TACE was discontinued after the first progression, may explain the inability of LEN-PEN-TACE to show a clear synergistic effect. Thus, the possibility that LEN-TACE alone could have produced a similar ORR and CR rate as LEN-PEM-TACE cannot be ruled out [2, 9].

Treatment-related adverse events of grade 3 or higher occurred in 169 (71%) of 237 patients in the LEN-PEM-TACE group and 76 (32%) of 241 patients in the TACE alone group. The most common were hypertension (57 [24%] vs. 18 [7%]) and decreased platelet count (27 [11%] vs. 15 [6%]). There were 4 deaths due to treatment-related adverse events in the LEN-PEM-TACE group (2%) (n = 1, due to hepatic failure, gastrointestinal hemorrhage, myositis, and immune-related hepatitis) and 1 death in the TACE alone group (less than 1%) (due to brainstem hemorrhage).

LEN-PEM-TACE Should Be Continued after Progression until UnTACEable Progression in Clinical Practice: PFS per RECIST v1.1 vs. TACE-Specific PFS

As mentioned earlier, it is difficult to demonstrate that protocol treatment with LEN-PEN-TACE up to the first PD had a synergistic effect. The ESMO presentation of the LEAP-012 trial did not describe the treatments administered to patients following LEN-PEN-TACE or TACE alone. LEN-TACE treatment in patients with intermediate-stage HCC [2, 9], as well as the results of the TACTICS trial [5, 6], found that repeat TACE (re-TACE) was feasible in patients with tumor regrowth at TACE-treated sites or new lesions at non-TACE-treated sites [2]. Because re-TACE can result in CR again, re-growth at TACE-treated sites or new lesions based on

RECIST 1.1 or mRECIST do not indicate TACE failure or the need to switch to the next line of treatment. Therefore, re-TACE and the continuation of the same treatment regimen may have a synergistic effect in achieving a CR [2]. The TACTICS [5, 6] and TACTICS-L [2] trials showed that on-demand TACE, along with continuous administration of sorafenib and LEN, respectively, could prolong OS and the time to untreatable progression (Fig. 4). Thus, even after first progression, OS can be further prolonged by performing on-demand selective TACE for the new lesion or regrowth of the original tumor, followed by LEN+PEM treatment [2].

To explain this more clearly, the continuation of LEN+PEM plus on-demand selective TACE after each PD per RECIST v1.1 may prolong PFS each time. The sum of these prolongations (e.g., PFS 1, PFS 2, and PFS 3) may result in the prolongation of UnTACEable progression (TACE-specific PFS), leading to OS prolongation (Fig. 4). Therefore, in practice, it is essential to continue LEN+PEM after additional selective TACE rather than switching to other drugs at the first PD. TACE-specific PFS has been reported to correlate well with OS (unpublished data), suggesting that TACE-specific PFS might be a surrogate endpoint of OS in the future TACE combination trial. In fact, in the ongoing phase III TALENTACE trial, TACE-specific PFS is set as the primary endpoint (NCT04712643).

Possibility of "LEN-PEM-TACE Followed by Curative Conversion"

Treatment with atezolizumab plus bevacizumab followed by curative conversion (ABC Conversion) has become a common practice in patients with intermediate-stage HCC [14–18]. ABC Conversion has resulted in cancer-free status in 35% of patients with TACE unsuitable intermediate-stage HCC, with 23% of patients achieving drug-free status [14]. Thus, treatment of intermediate-stage HCC patients with LEN+PEM for a certain period of time along with concurrent on-demand TACE for PD lesions may enable curative conversion similar to ABC conversion.

Conclusions

The LEAP-012 trial showed that LEN-PEM-TACE was superior to TACE alone in extending PFS significantly and showing the better trend of OS benefit in patients with intermediate-stage HCC. Regulatory approval of this LEN-PEM-TACE regimen may allow curative conversion, such as ablation, resection or curative TACE, in clinical practice once it is approved. Even in case curative conversion is not possible, LEN-PEM-TACE can prolong OS if this regimen is continued for a more extended period of time after first disease progression. In conclusion, LEN-PEM-TACE is expected to become an excellent treatment option in routine clinical practice in intermediate-stage HCC.

Statement of Ethics

No statement is needed because this study was based exclusively on published data.

Conflict of Interest Statement

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Author Contributions

Masatoshi Kudo conceived, wrote, and approved the final manuscript.

Data Availability Statement

Data availability is not applicable because this is not a research article.

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