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Editorial

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Immune Checkpoint Inhibitor plus Anti-VEGF/TKI Combined with Transarterial Chemoembolization in Locally Advanced Nonmetastatic Hepatocellular Carcinoma: Real-World Treatment Strategy Based on Phase 3 Clinical Trial Results

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Introduction

Since the approval of atezolizumab plus bevacizumab (Atezo/Bev) for unresectable hepatocellular carcinoma (HCC) in 2020, Atezo/Bev followed by curative conversion has been developed [1]. After tumor shrinkage with Atezo/Bev, transarterial chemoembolization (TACE) and continued Atezo/Bev treatment can achieve clinical complete response (clinical CR). Furthermore, it was shown that clinical CR can be achieved by Atezo/Bev followed by TACE plus Atezo/Bev, even in patients with stable disease or slow progressive disease (PD) [1]. Clinical CR is defined as (1) imaging CR (based on RECIST 1.1 or mRECIST [2]), (2) AFP, PIVKA -II, and AFP-L3 fractions are all negative for 24 weeks. In addition, if this clinical CR is achieved, CT during hepatic arteriography or contrast enhanced ultrasonography must be performed to confirm complete disappearance of intratumoral blood flow before drug is discontinued. If these three conditions (drug-off criterion) are met, recurrence is extremely rare even after drug-off status [3]. Recently, this drug-off criterion was also confirmed to be accurate [4].

The Editorial of this issue of *Liver Cancer* presents data from two clinical trials of immune checkpoint inhibitor (ICI) plus anti-vascular endothelial growth factor (VEGF)/tyrosine kinase inhibitor (TKI) plus TACE for unresectable, nonmetastatic HCC, EMERALD-1 trial [5], and LEAP-012 trial [6], which were recently demonstrated to be positive in a global phase III randomized controlled

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Table 1. EMERALD-1 trial and LEAP-012 trial: efficacy results

	EMERALD-1 trial		LEAP-012 trial	
	Durva + Bev + TACE (*n* = 204)	TACE (*n* = 205)	LEN + PEM + TACE (*n* = 237)	TACE (*n* = 243)
Media PFS, M	15.0	8.2	14.6	10.0
HR		0.77		0.66
p value		0.032		0.0002
Median TTP, M	22.0	10.0	16.6	10.3
HR		0.63		0.59
p value		NA		<0.0001
PFS events	136	149	132	154
TTP events	99	132	112	146
Death events, *n* (%)	37 (27.2)	17 (11.4)	20 (15.2)	8 (5.2)
Median OS, M	NA	NA	NA	NA
HR		NA		0.80
p value		NA		0.087
OS events	NA	NA	69	82

Durva, durvalumab; Bev, bevacizumab; LEN, lenvatinib; PEM, pembrolizumab; TACE, transarterial chemoembolization; PFS, progression-free survival; TTP, time to progression; HR, hazard ratio; OS, overall survival; NA, not available.

trial, and the future treatment strategy of these triple therapies in locally advanced nonmetastatic HCC in real-world clinical practice setting is discussed.

Results of EMERALD-1 and LEAP-012 Trials

The EMERALD-1 study [5] compared durvalumab plus bevacizumab (Druva/Bev) plus TACE with TACE alone, with the primary endpoint of progression-free survival (PFS) per RECIST v1.1. Time to progression (TTP) was also better with Durva plus Bev plus TACE: 22.0 months versus 10.0 months for TACE alone (hazard ratio [HR] 0.77, *p* value 0.32). However, death events were 27.2% in the Durva plus Bev plus TACE group and 11.4% in the TACE alone group when calculated from PFS and TTP events, indicating that death events were more common in the Durva plus Bev plus TACE group at this first interim analysis [5] (Table 1).

On the other hand, in the LEAP-012 trial [6], lenvatinib (LEN) plus pembrolizumab (PEM) plus TACE was significantly better than TACE alone, with a PFS of 14.6 months in the LEN plus PEM plus TACE group and 10.0 months in the TACE alone group (HR 0.66, *p* value 0.0002). The median TTP was significantly better for LEN plus PEM plus TACE (16.6 months) compared with 10.3 months for TACE alone (HR 0.59, *p* value <0.0001). The death events were 15.2% in the LEN plus PEM plus TACE group and 5.2% in the TACE alone group, again with a slight trend toward more death events in the combination therapy group at this final analysis for PFS. However, the LEAP-012 trial also showed an OS Kaplan-Meier curve, indicating a better OS trend in LEN plus PEM plus TACE over TACE alone (HR 0.80, *p* value 0.087). Obviously, the number of OS events was immature, with 69 events in the LEN plus PEM plus TACE group and 82 events in the TACE alone group [6].

Currently, OS events are being followed in both the EMERALD-1 trial and the LEAP-012 trial. In any case, the positive results of these two global phase 3 trials demonstrate the clinical benefit of ICI plus anti-VEGF/TKI plus TACE.

Recommended Treatment Strategy Based on Clinical Trial Results and Real-World Studies

The data from the trial designs of these two clinical trials were both trial designs in which ICI plus anti-VEGF/TKI was administered until disease progression according to RECIST v1.1, after which the protocol treatment was discontinued, and the patient was switched to receive the subsequent therapy. However, in TACTICS [7] and TACTICS-L [8] trial design and real-world studies [9, 10], which are TACE combination trials conducted so far, if the patient progresses, TACE is administered, and the same systemic therapy is continued

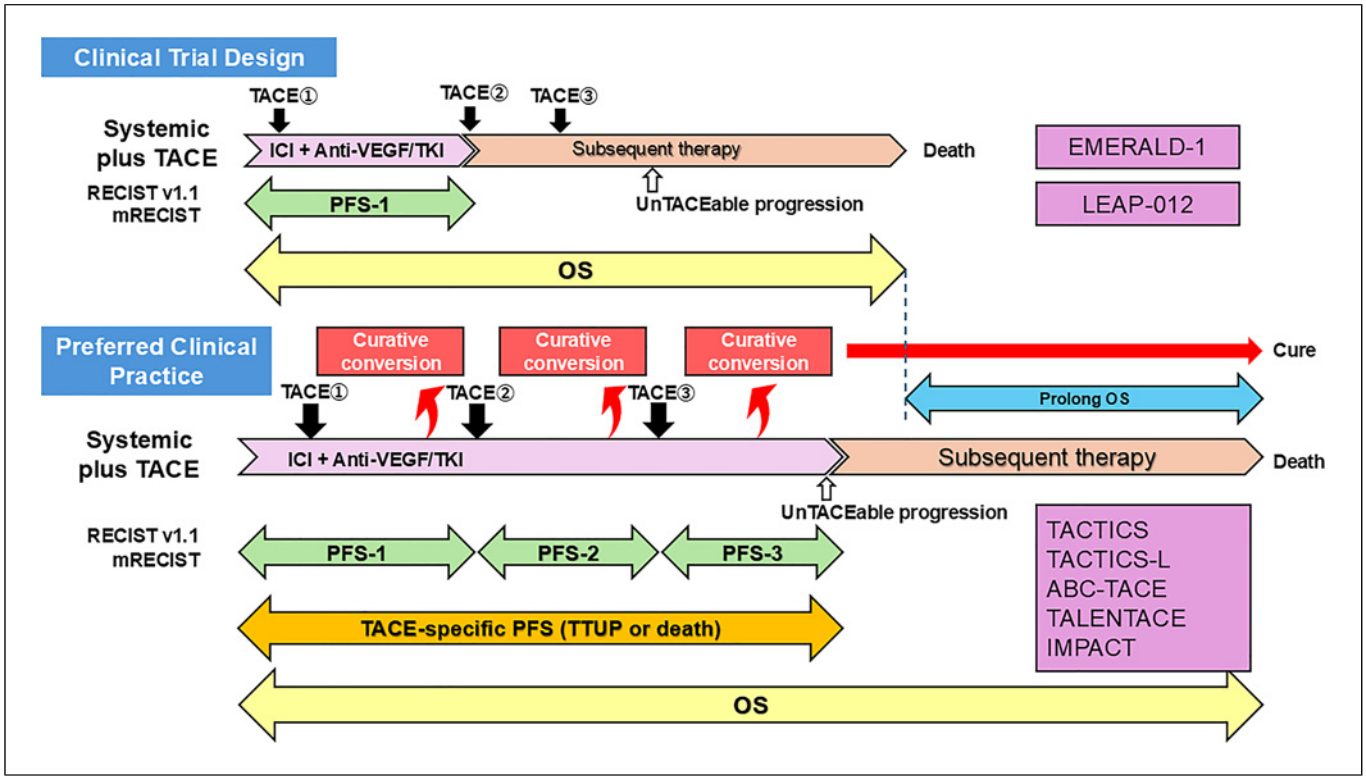

Fig. 1. Clinical trial design. In the clinical trial designs of EMERALD-1 and LEAP-012, ICI plus anti-VEGF/TKI is discontinued at the first progression, after which patients transition to subsequent treatments as per the study protocol. However, in real-world clinical practice, even after the first and second progressions, TACE should be performed as long as it remains feasible, and both TACE and ICI plus anti-VEGF/TKI should be continued until unTACEable progression. UnTACEable progression can be envisioned as the sum of PFS1 + PFS2 + PFS3. This strategy can achieve curative conversion, ultimately leading to pathological CR. Even if curative conversion is not possible, this approach is expected to prolong overall survival (OS). ICI, immune checkpoint inhibitor; VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; TACE, transarterial chemoembolization; PFS, progression-free survival: pCR pathological CR.

until unTACEable progression, as shown in the lower panel of Figure 1. In ABC conversion or ABC-TACE sandwich therapy, curative conversion such as resection, ablation, or curative TACE in cases with tumor shrinkage [1] or in cases of stable disease or slow PD, TACE followed by Atezo/Bev continuation to bring curative conversion. The strategy of continuing ICI plus anti-VEGF/TKI with on-demand TACE, which release the tumor antigen, can be effective to achieve curative conversion in some cases. The number of cases that can be converted to curative conversions is increasing [1]. In that sense, TALENTACE trial and IMPACT trial [11] are similar study designs to ABC-TACE sandwich therapy. In real-world clinical practice, as shown in the lower column of Figure 1, even if the first progression occurs (PFS1), it does not mean treatment failure, so TACE can be performed again and achieved clinical CR after PFS 2 or PFS 3, and several on-demand TACE cycles with the same ICI plus anti-VEGF/TKI can be continued until achieving clinical CR [12–19]. Even if curative conversion cannot be achieved, OS can be extended by this trial design or treatment strategy (Fig. 1). Therefore, such a treatment strategy is recommended in real-world practice.

Curative Conversion after or during ICI plus Anti-VEGF/TKI plus TACE

ABC conversion achieved clinical CR in 35% of TACE-unsuitable intermediate-stage HCC patients and drug-free status (very close to pathological CR [pCR]) in 23% of intermediate-stage HCC population unsuitable for TACE. Similarly, Wu et al. [9] reported that of 241 intermediate-stage and advanced-stage patients treated with PD-1 antibody plus LEN plus TACE, 42 achieved clinical CR (17.4%). They reported that 39 (16%) of the patients who underwent conversion resection had pCR. In addition, Zeng et al. [10] reported that

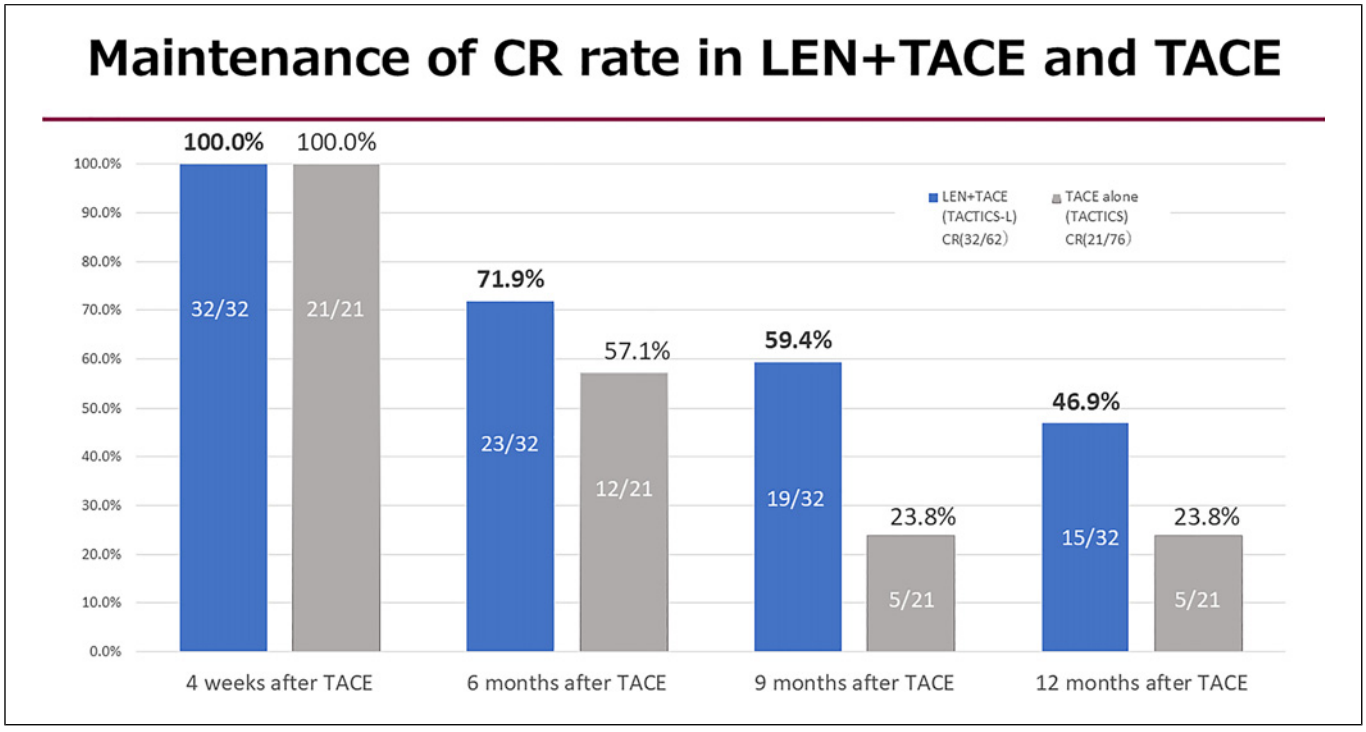

Fig. 2. Sustained high-quality CR rate after TACE: comparison between TACTICS and TACTICS-L. In the TACTICS trial, 21 out of 76 patients in the TACE monotherapy group achieved CR at 4 weeks after the initial TACE. In the TACTICS-L trial, 32 out of 62 patients achieved CR at 4 weeks after the initial TACE. However, as the duration increased to 6 months, 9 months, and 12 months, the CR maintenance rate was clearly better in the LEN plus TACE group compared to TACE monotherapy (modified from ref. #20). CR, complete response.

32.9% of 76 patients, including 69% with advanced-stage HCC, achieved pCR after PD-1 antibody plus LEN plus TACE and 70% achieved major pathological response.

These findings indicate that continuing ICI plus anti-VEGF/TKI combined with TACE can achieve clinical CR or even pCR. Patients achieving pCR or clinical CR had significantly better recurrence-free survival and overall survival (OS) [9, 10, 12–19]. While phase 3 trials typically discontinue treatment upon first progression, ABC conversion study and real-world data suggest that the continued administration of the same IO-based systemic therapy with on-demand TACE is a more effective treatment strategy [9, 10]. Thus, in real-world practice, a treatment strategy similar to that shown in the lower panel of Figure 1 would be desirable.

LEN plus TACE, along with PEM, Improves the Quality of CR

In the TACTICS [7] and TACTICS-L [8] trials, several patients achieved CR. In the TACTICS trial, 21 out of 76 patients achieved CR per mRECIST 4 weeks after the first TACE. On the other hand, in the TACTICS-L trial, 32 out of 62 patients achieved CR per mRECIST 4 weeks after the first TACE with the 2–3 weeks LEN administration before TACE and continued administration of LEN after TACE (Fig. 1).

Comparing the 21 patients who achieved CR with TACE alone and the 32 patients who achieved CR with LEN plus TACE, the CR maintenance rates at 6, 9, and 12 months were 57.1%, 23.8%, and 23.8% in the TACE alone group, showing a gradual decline in the CR rate [20]. In contrast, in the LEN plus TACE group, the CR maintenance rates were 71.9%, 59.4%, and 46.9%, respectively, demonstrating a higher probability of maintaining CR compared to the TACE alone group (Fig. 2) [20]. This phenomenon indicates that the pre-administration of LEN before first TACE and the subsequent administration of LEN are effective in maintaining CR [20, 21]. In other words, LEN plus TACE achieves a sustained high-quality CR more effectively than TACE alone, and likely, some cases have even achieved pCR.

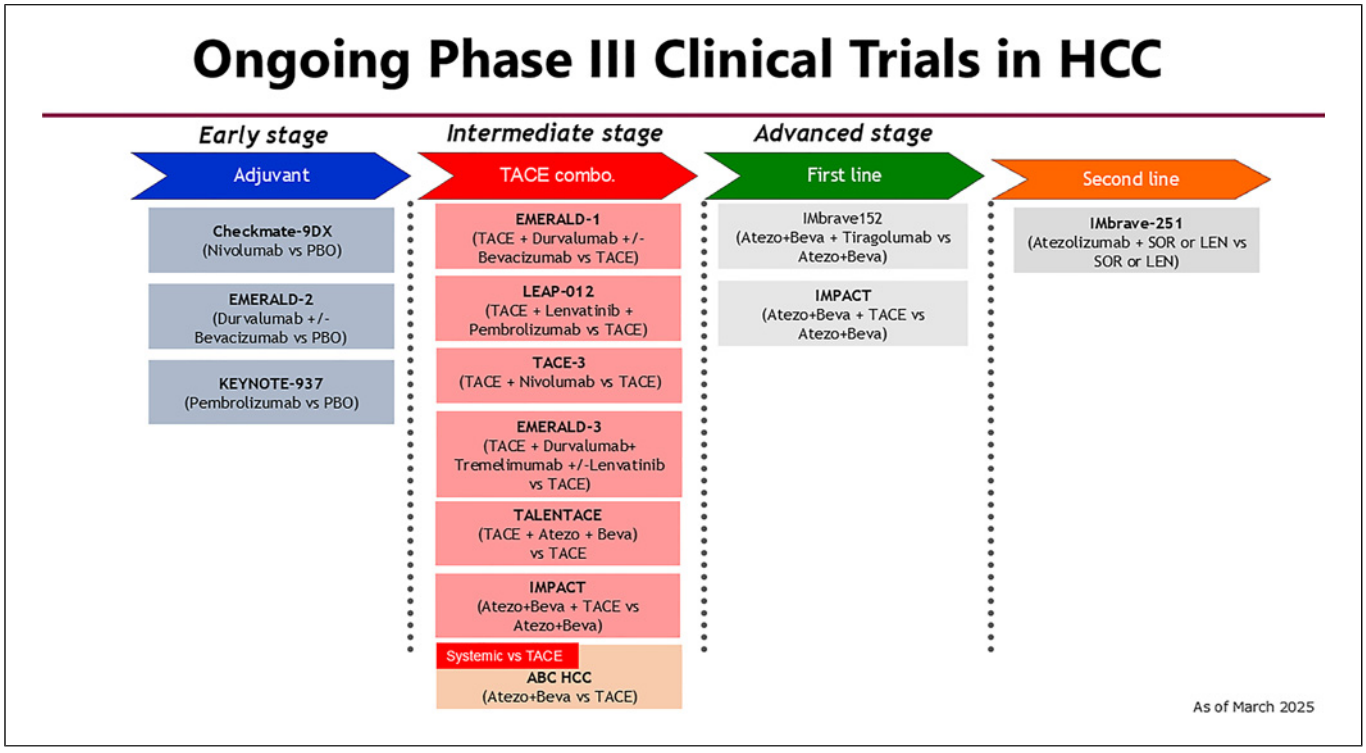

Fig. 3. Ongoing phase III clinical trials in HCC. In the EMERALD-1 and LEAP-012 trials, which are combination trials of TACE and ICI-based systemic therapy for intermediate-stage HCC, the results for OS are currently being followed up after achieving positive PFS. The TACE-3, EMERALD-3, TALENTACE, and IMPACT trials are currently ongoing. Another trial design for intermediate-stage HCC, the ABC HCC trial, is currently in progress, comparing Atezo/Bev with TACE. ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival.

Adding PEM to this LEN-TACE combination therapy is expected to further increase the rate of pCR, as the immune modulation effect of LEN enhances the anti-tumor effect of PEM. Consequently, the rate of achieving sustained high-quality CR is anticipated to increase even further. From this perspective, combining ICI, anti-VEGF/TKI, and TACE is considered an extremely important treatment strategy for achieving high-quality CR.

Ongoing Phase 3 Clinical Trials

Currently ongoing phase 3 clinical trials are shown in Figure 3. In the intermediate-stage, EMERALD-1 [5] and LEAP-012 [6] are currently being followed up for final OS analysis, while EMERALD-3, IMPACT [11], and TALENTACE, a TACE plus ICI plus anti-VEGF/TKI trial, are also ongoing. There are also ongoing comparative trials of TACE plus Atezo/Bev versus TACE (ABC HCC trial). Of these, the TALENTACE trial is a trial design using TACE-specific PFS as shown in the lower panel of Figure 1. The IMPACT trial is also designed to add on-demand immune boost partial TACE to Atezo plus Bev, and the results are highly anticipated. The TALENTACE and IMPACT trials are designed to continue Atezo plus Bev treatment for a long period of time, so the effect of the OS extension is expected to be promising.

Conclusion

While PFS per RECIST v1.1 is usually a primary endpoint in phase 3 trials due to its rapid assessment timeline, OS trends remain crucial for regulatory approval. However, when it is approved in clinical practice, rather than stopping treatment at the first progression, continuing TACE plus ICI plus anti-VEGF/TKI until unTACEable progression may enhance curative conversion opportunities and extend OS. Based on the solid positive results of global phase 3 trials, this triple therapy approach is regarded as a novel treatment strategy for locally advanced, unresectable nonmetastatic 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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