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Editorial

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Immune Checkpoint Inhibitors plus Anti-VEGF/ Tyrosine Kinase Inhibitors Combined with TACE (Triple Therapy) in Unresectable Hepatocellular Carcinoma

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Introduction

The results of the Phase 3 EMERALD-1 study were presented at the January 2024 ASCO-GI plenary session [1]. This study is a prospective, randomized, controlled trial comparing durvalumab (Durva) plus bevacizumab (Bev) plus transarterial chemoembolization (TACE) with TACE alone. The primary endpoint was progression-free survival (PFS) based on RECIST v1.1. The results showed that Durva plus Bev plus TACE was associated with a statistically significant improvement in PFS compared with TACE alone, indicating that the study results were positive.

To date, six trials have evaluated the efficacy of combining drugs (tyrosine kinase inhibitors [TKIs]) with TACE in intermediate-stage HCC [2–8]. The TACTICS study had only positive results [7, 8]. The endpoint of the TACTICS study was TACE-specific PFS, which defines PFS as the time to UnTACEable progression or death [9, 10]. The results of the TACTICS study demonstrated that overall survival (OS) was better in the TACE plus sorafenib group than in the TACE alone group, with a median OS benefit of 5.4 months [8, 11]. These results validate the consensus statements of the Asia-Pacific Primary Liver Cancer Expert Association and the Japan Society of Hepatology [12, 13].

However, the EMERALD-1 trial is the first phase 3 trial to extend the primary endpoint of PFS with the combination of immunotherapy with an anti-VEGF agent and TACE. It can be considered a historical success and a practice-changing result. Many other clinical trials of combination immunotherapy plus TACE are ongoing in intermediate-stage HCC [14].

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Table 1. Ongoing phase 3 clinical trials testing the efficacy and safety of combination immunotherapy with TACE

Study	Phase/N	Patients	Stratification factor	Drugs/method	Timing of systemic therapy	Type of TACE	On-demand TACE	Primary endpoint	Country
EMERALD-1 [1]	Randomized PIII (*N* = 724)	Intermediate (including Vp1-2)	• TACE modality (DEB-TACE vs. cTACE) • Geographic region • Portal vein invasion (Vp1 or Vp2±Vp1 vs. none)	3 arms A) TACE + Dur + Bev B) TACE + Dur C) TACE	Post-TACE	cTACE DEB-TACE	No	PFS (RECIST 1.1) Arm A vs. C	17 countries
LEAP-012 [2]	Randomized PIII (*N* = 450)	Intermediate (without portal vein invasion)	• Study site • AFP level (≤400 vs. >400) • ECOG PS (0 vs. 1) • ALBI grade (1 vs. 2 or 3) • Tumor burden (>6, 6–12, >12)	2 arms A) Pembro + LEN + TACE B) TACE	Peri-TACE (2–4 weeks before 1st TACE)	cTACE DEB-TACE	Yes	PFS (RECIST 1.1) OS	24 countries
EMARALD-3 [3]	Randomized PIII (*N* = 725)	Intermediate (including Vp1-2)	• Geographic region • History of locoregional therapy • Tumor burden (UT7 in or out)	3 arms A) Dur+Tre+LEN + TACE B) Dur+Tre + TACE C) TACE	Peri-TACE (>7 days before 1st TACE)	cTACE DEB-TACE	No	PFS (RECIST 1.1) Arm A vs. C	23 countries
TALENTACE [4]	Randomized PIII (*N* = 342)	Intermediate (including Vp1-2)	• AFP level at baseline • History of locoregional therapy • Vp 1/2 (+ or -)	2 arms A) TACE + Atezo + Bev B) TACE	Post-TACE	cTACE DEB-TACE	Yes	TACE PFS (RECICL) OS	China Japan
IMPACT [5]	Randomized PIII (*N* = 600)	Intermediate + Advanced (excluding Vp3/4)	• MVI and/or EHS (yes or no) • Child-Pugh score (5vs. 6) • Tumor shrinkage rate (0 ~ −29% vs. 1~ +19%)	2 arms A) Atezo + Bev + TACE B) Atezo+Bev	Peri-TACE (6–12 weeks before 1st TACE)	cTACE DEB-TACE LEN-TACE	Yes	OS (randomized cohort)	Japan

AFP, alpha-fetoprotein. [1] ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04712643. [2] ClinicalTrials.gov https://clinicaltrials.gov/study/NCT05301842. [3] ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT04246177. [4] ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT03778957. [5] Japan Registry of Clinical Trials https://jrct.niph.go.jp/latest-detail/jRCTs051230037.

Table 2. EMERALD-1 trial: efficacy results

	D+B+TACE	D+TACE	TACE
Median **PFS** (95% CI), months (RECIST 1.1)	**15.0** (11.1–18.9)	**10.0** (9.0–12.7)	**8.2** (6.9–11.1)
HR (95% CI)	**0.77** (0.61–0.98)	**0.94** (0.75–1.19)	Ref.
p value	**0.032**	0.638	
Total events	**136**	**144**	**149**
Median **TTP** (95% CI), months (RECIST 1.1)	**22.0** (16.6–24.9)	**11.5** (9.2–13.9)	**10.0** (7.1–13.6)
HR (95% CI)	**0.63** (0.48–0.82)	0.89 (0.69–1.15)	Ref.
Total events	**99**	**120**	**132**

Bold and underlined values are for emphasis. D, durvalumab; B, bevacizumab; PFS, progression-free survival; TTP, time to progression; HR, hazard ratio; TACE, transarterial chemoembolization.

Clinical trials in intermediate-stage HCC can be divided into two categories with PFS as the primary endpoint in both (1) immune checkpoint inhibitor (ICI) plus anti-VEGF/TKI plus TACE compared with TACE alone and (2) ICI plus anti-VEGF/TKI without TACE compared with TACE alone. The former includes the EMERALD-3, LEAP-012, TALENTACE, and IMPACT studies in addition to the EMERALD-1 study. The latter includes the ABC-HCC and REPLACE studies [14]. This Editorial reviews the results of the EMERALD-1 study and the trial designs of other major combination immunotherapy plus TACE studies.

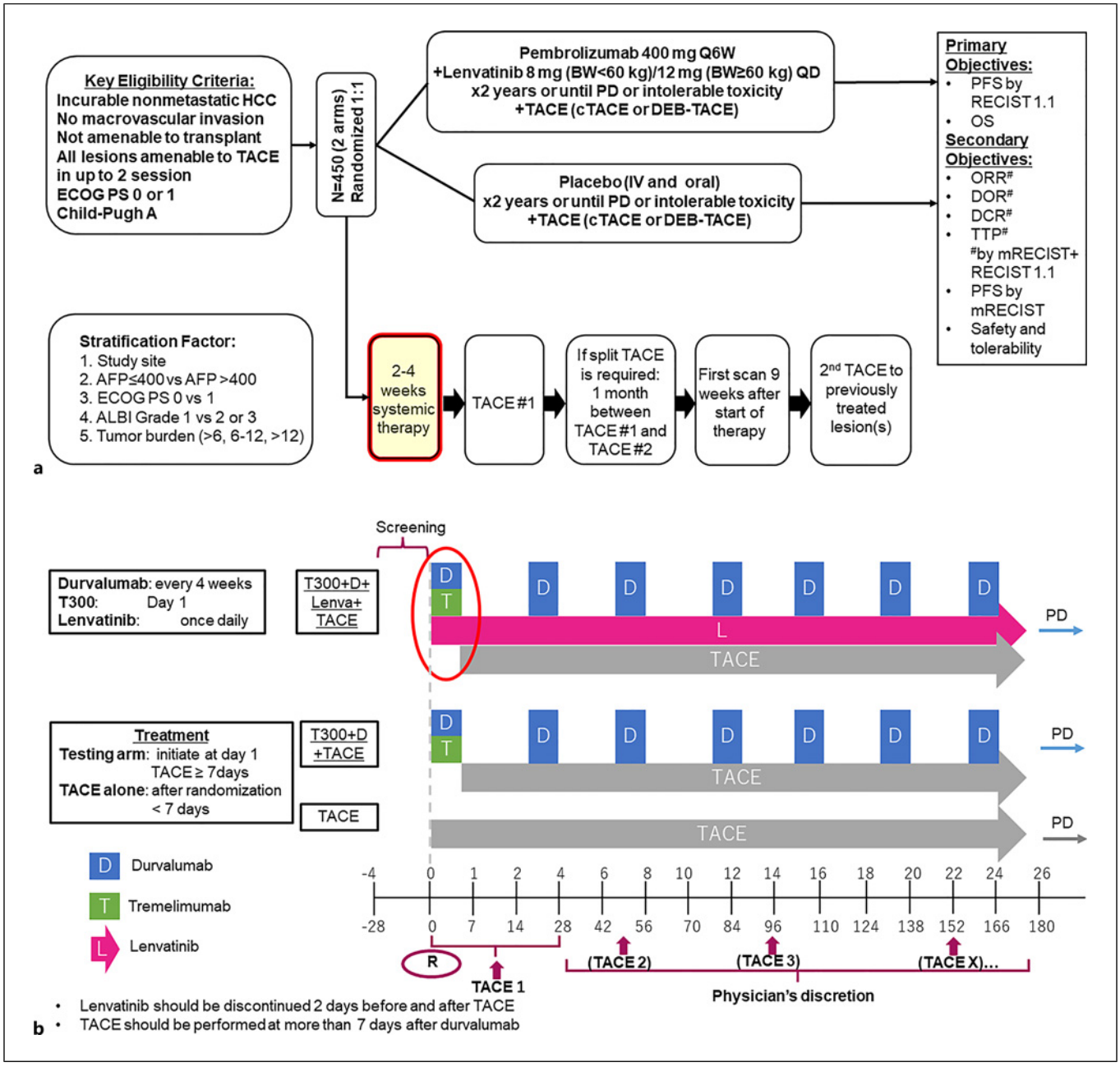
Results of the Phase 3 EMERALD-1 Study

The EMERALD-1 study analyzed patients who were not eligible for resection, ablation, or transplantation, had no macrovascular invasion (MVI) or extrahepatic spread (EHS), and had Child-Pugh A or B7 liver function [1]. Stratification factors included TACE modality (DEB-TACE vs. cTACE), geographic region, and portal vein invasion (Table 1). This population was assigned at a ratio of 1:1:1 to arms A, B, and C. Arm A (n = 204) received Durva + Bev + TACE, arm B (n = 207) received Durva + TACE, and arm C (n = 205) received TACE alone. The primary endpoint was the superiority of PFS in arm A over that in arm C. The results showed a statistically significant improvement in PFS for Durva + Bev + TACE over TACE alone (15.0 months vs. 8.2 months; hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.61–0.98; p = 0.032) (Table 2). In terms of time to progression (TTP), the TTP for the Durva + Bev + TACE arm was 22.0 months (95% CI, 16.6–24.9), whereas the TTP for the TACE alone arm was 10.0 months (95% CI, 7.1–13.6). The HR was 0.63 (95% CI, 0.48–0.82) [1] (Table 2). This is a positive study because the primary endpoint was met, and follow-up is planned until the final OS results are obtained. The results of the OS follow-up are eagerly awaited.

One concern in this study is the number of death events: 136 PFS events in the Durva + Bev + TACE arm versus 149 PFS events in the TACE alone arm. However, the number of TTP events was 99 in the Durva + Bev + TACE group compared with 132 in the TACE alone arm. The PFS events include disease progression + death, whereas the TTP events consist of disease progression only. Therefore, the death events in the Durva + Bev + TACE arm can be calculated as follows: 136 (death + disease progression) minus 99 (disease progression) = 37 death events, whereas the death events in the TACE alone group can be defined as 149 (death + disease progression) minus 132 (disease progression) = 17 death events. The results that TTP HR was better than PFS HR and median TTP (22.0 months) was longer than median PFS (15.0 months) in the Durva + Bev + TACE group also indicate that early death is more frequent in the Durva + Bev + TACE arm. However, actual number of death events is unknown since there should be some cases who died after disease progression. As the Kaplan-Meier curve of OS was not presented, we do not imagine the exact data of OS.

In addition, the difference in death events is expected to be reduced by the tail plateau effect unique to immunotherapy. Conversely, the OS curve in the TACE alone arm will be lowered, eventually leading to a favorable Kaplan-Meyer curve for OS.

The second concern is that only approximately 75% of patients in Groups A, B, and C were able to receive combination therapy. This suggests that 25% of the



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patients could not receive combination therapy probably because liver function may have been impaired by the up to four TACE cycles received during the TACE phase. Further analysis is expected to explore why 25% of patients could not receive combination therapy at the time of routine clinical use after the regulatory authorities approved it. No new safety concerns were reported in the Durva + Bev + TACE arm.

LEAP-012 Trial Design

LEAP-012 is a phase 3 randomized controlled trial designed to evaluate the PFS superiority of lenvatinib (LEN) + pembrolizumab (PEM) + TACE versus TACE alone in patients with intermediate-stage HCC without EHS or MVI and with Child-Pugh A liver function and performance stats (PS) of 0 or 1 [15]. Study site, alpha fetoprotein, ECOG PS, albumin bilirubin (ALBI) grade,

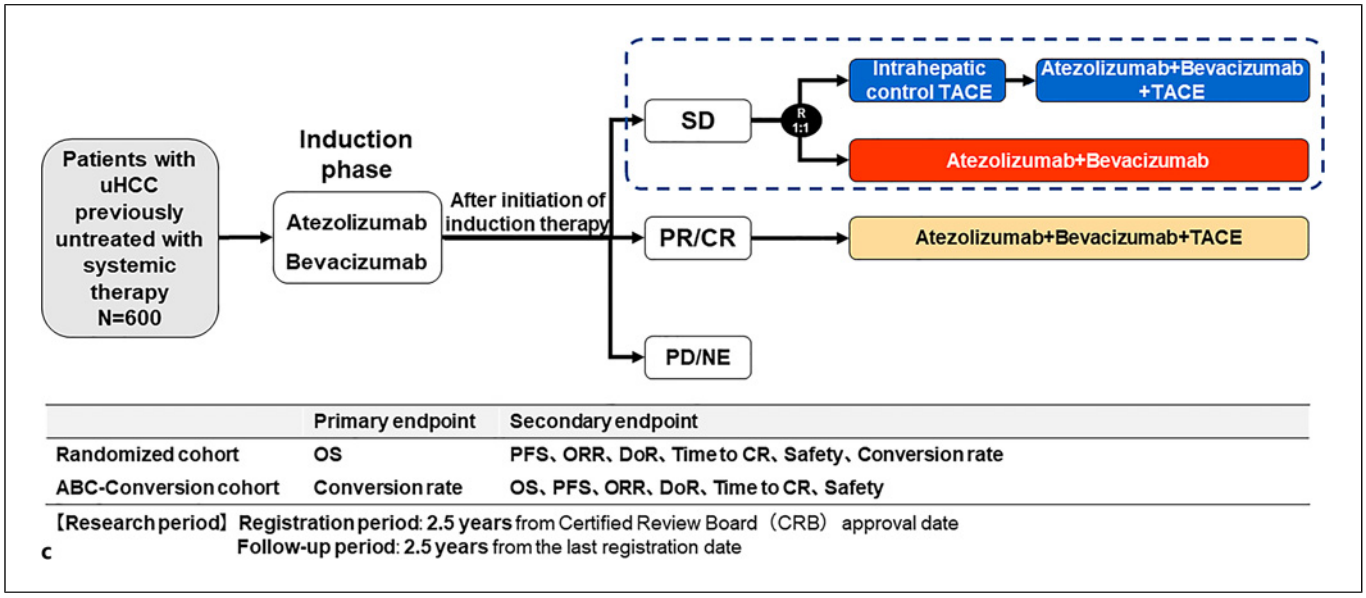

Fig. 1. a LEAP-012 trial design. **b** EMERALD-3 trial design. **c** IMPACT trial design.

and tumor burden were used as stratification factors (Table 1; Fig. 1a).

The strength of this trial design is that LEN + PEM was administered immediately after randomization and 2–4 weeks before the first TACE. In particular, LEN [16] was administered 2–4 weeks before the first TACE. LEN + PEM were continued after the first TACE until progressive disease or unacceptable toxicity.

Another strength of this trial is the inclusion of ALBI grade, a precise measure of liver function [17], as a stratification factor. LEN is well tolerated, and dose intensity can remain high in patients with ALBI grade 1; however, in those with ALBI grade 2 or higher, LEN is poorly tolerated, requiring dose reduction, which leads to unfavorable results [18]. Therefore, the use of ALBI grade as a stratification factor for combination immunotherapy with ICI plus LEN and TACE is critical to ensure that LEN is well tolerated in the combination arm [18], which may lead to prolonged PFS and OS without an imbalance between the two arms. Liver function is a strong prognostic factor, and because OS differs between ALBI grades 1 and 2 or 3, it is an excellent stratification factor to demonstrate the superior OS trend in the LEN + PEM + TACE arm. Another strong prognostic factor is alpha fetoprotein, which was also used as a stratification factor in this trial. Tumor burden is also an essential stratification factor. Tumor burden, which can be divided into very low, moderate, and high, is a strong prognostic factor in intermediate-stage HCC, which is the target population of TACE. In the LEAP-012 study, patients were divided into groups using tumor burden as a stratification factor as follows: <6, 6–12, and >12. The design of the LEAP-012 study will not result in an imbalance in tumor burden between the LEN + PEM + TACE arm and the TACE alone arm. Thus, the LEAP-012 study was designed to minimize the imbalance of various prognostic factors between the two arms to accurately evaluate the efficacy of LEN + PEM + TACE for improving PFS and OS compared with TACE alone.

The TACTICS [7] and TACTICS-L [19] trials also showed that prior administration of sorafenib or LEN, which has anti-VEGF effects, results in excellent outcomes. Prior administration of sorafenib or LEN may enhance the efficacy of TACE by normalizing the tumor vasculature, reducing interstitial pressure, normalizing vascular permeability, and improving drug delivery [7, 19–24]. These findings may have influenced the design of the LEAP-012 study. The TACTICS trial showed a statistically significant increase in PFS in the TACE plus sorafenib arm and a clinically meaningful 5.4-month OS improvement. However, the difference in OS was not statistically significant. The TACTICS-L trial also demonstrated a high complete response (CR) rate (68% CR rate per mRECIST) and a significantly longer duration of response (>1 year in >50% of patients) associated with LEN administration before TACE [19], although it was a single arm study. In addition, LEN pre-treatment plus

TACE achieved CR rates of >50% not only within the up-to-seven criteria, but also in patients exceeding the up-to-seven criteria.

EMERALD-3 Trial Design

The EMERALD-3 study is a phase 3 prospective randomized trial. This trial compares PFS between two arms: the STRIDE regimen (tremelimumab [Treme] + Durva), which showed OS prolongation over sorafenib in the Phase 3 HIMALAYA trial in advanced HCC [25], plus LEN plus TACE arm and the TACE alone arm (Fig. 1b). This trial also has an excellent design in that LEN is administered in addition to Treme +Durva and precedes the first TACE by at least 7 days (Table 1). As noted above, administration of LEN >7 days prior to TACE increases the efficacy of TACE. Furthermore, the simultaneous activation of CD8-positive T cells and the release of activated CD8-positive T cells into the bloodstream by the anti-CTLA4 antibody Treme, the release of tumor antigens by TACE, and the promotion of CD8-positive T cell infiltration into the tumor by LEN synergistically exert antitumor effects and increase the efficacy of the initial TACE. This mechanism of action of Treme + Durva + LEN + TACE should result in a longer PFS than that achieved with TACE alone.

Stratification factors in this study included geographic region, history of locoregional therapy, and tumor burden, as shown in Table 1. In particular, the EMERALD-3 trial design used tumor burden up-to-seven in or out as the stratification factor. As mentioned above, OS and PFS differ according to the tumor burden at baseline, as demonstrated in the TACTICS [7] and TACTICS-L [19] trials. Another excellent feature of the EMERALD-3 trial design is that the administration of LEN for at least 7 days prior to initial TACE is essential to improve the efficacy of TACE and to improve PFS and OS.

TALENTACE Trial Design

TALENTACE is a phase 3 trial currently being conducted in Japan and China comparing atezolizumab (Atezo) + Bev + on-demand TACE with TACE alone [26]. The primary endpoints are PFS and OS. In this trial, PFS refers to TACE-specific PFS, which was defined as UnTACEable progression or death in the TACTICS [7] and TACTICS-L [19] trials. In TACE, progression, according to RECIST v1.1, does not necessarily mean treatment failure by TACE. In cases in which new lesions appear, tumor control can be achieved by performing additional sessions of selective TACE. The TALENTACE study with this design may demonstrate the efficacy of Atezo + Bev + on-demand TACE in prolonging PFS and the co-primary endpoint of OS.

IMPACT Trial Design

The IMPACT study is an ongoing phase 3 randomized controlled clinical trial in Japan [27]. Patients with intermediate-stage and advanced-stage HCC (excluding Vp3/4) with stable disease (SD) after four cycles of Atezo + Bev are the subject population. Patients were randomized into two groups at a 1:1 ratio: one group received Atezo + Bev plus immune boost TACE for 1–3 intrahepatic lesions to preserve liver function in an on-demand fashion, and the other group continued to receive standard of care with Atezo + Bev. Stratification factors were MVI and/or EHS (presence vs. absence), Child-Pugh score (5 vs. 6 points), and tumor shrinkage rate (0 to −29% vs. 1– +19%) within the SD range (Table 1; Fig. 1c). The results to date show a significant difference in OS between the tumor shrinkage group and the non-tumor shrinkage group, even within the SD range [28]. Because the primary endpoint is OS, the success of this trial may lead to a significant change in the treatment strategy for SD patients treated with combination immunotherapy. In addition, this trial was designed with the aim of curative conversion (ABC conversion) by curative TACE, ablation, and resection in patients who achieved CR or PR with Atezo + Bev [29, 30].

Conclusion

The clinical trials described are likely to produce positive results, and in that case, the triple therapy consisting of ICIs plus Anti-VEGF/TKIs plus TACE will probably become the standard of care in patients with intermediate-stage and advanced-stage HCC excluding Vp3 and VP4.

Statement of Ethics

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

Conflict of Interest Statement

Lectures: Eli Lilly, Bayer, Eisai, Chugai, Takeda, AstraZeneca. Grants: Taiho, Otsuka, EA Pharma, AbbVie, Eisai, Chugai, GE Healthcare. Chugai, Roche, AstraZeneca, Eisai. Masatoshi Kudo is the Editor-in-Chief of Liver Cancer.

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Author Contributions

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

Data Availability Statement

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

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