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REVIEW

Systemic Therapy Combined with Locoregional Therapy in Intermediate-stage Hepatocellular Carcinoma

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Abstract:
Recent advances in systemic therapy for hepatocellular carcinoma are remarkable. The treatment goal for advanced hepatocellular carcinoma is to prolong survival, while for intermediate-stage hepatocellular carcinoma, it is to achieve a cancer-free and drug-free status. Patients unsuitable for transarterial chemoembolization may benefit from prior systemic therapy with lenvatinib or atezolizumab plus bevacizumab. The TACTICS-L trial, a prospective phase II trial, demonstrated favorable progression-free and overall survival by lenvatinib-transarterial chemoembolization sequential therapy. The REPLACEMENT trial, a multicenter, prospective, single-arm phase II trial, confirmed combination immunotherapy efficacy with atezolizumab plus bevacizumabin a population exceeding up-to-seven criteria. In a proof-of-concept study, atezolizumab plus bevacizumab plus curative therapy showed a 35% complete response rate and 23% drug-free status in intermediate-stage hepatocellular carcinoma patients with a tumor burden exceeding up-to-seven criteria.

Keywords:
systemic therapy, locoregional therapy, hepatocellular carcinoma

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1. Introduction

New systemic therapy agents for unresectable hepatocellular carcinoma (HCC) were recently approved [1-8]. Although these drugs were designed for the treatment of advanced HCC, the REFLECT [2] and IMbrave150 [3] trials demonstrated that these drugs are more effective in intermediate-stage HCC than in advanced-stage HCC. Furthermore, 10%-20% of patients enrolled in these phase III trials have intermediate-stage HCC. Therefore, patients with intermediate-stage HCC who are refractory or not suitable for transarterial chemoembolization (TACE) are frequently treated with systemic therapy. Recently developed drugs with high response rates, such as lenvatinib and atezolizumab plus bevacizumab, are currently being used as sequential/combination therapy with TACE. These agents may be responsible for the recently improved treatment outcomes in Japan [9-11].

This study aims to discuss the current status and prospects of the combination of systemic therapy and TACE.

2. Concept of TACE Refractoriness

Intermediate-stage HCC is defined as multiple HCCs in the guidelines of the 2018 American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver [12, 13], and TACE was the only treatment modality recommended at the time. The 2021 version of the Japan Society of Hepatology clinical practice guidelines for the treatment of HCC includes resection, hepatic arterial infusion chemotherapy, and systemic therapy in addition to TACE for multiple HCCs with four or more tumors and large HCCs >3 cm in size [14]. In 2011, Japan was the first country in the world that proposed the concept of "TACE failure/refractoriness" [15]. In 2014, the concept of "TACE failure/refractoriness" was updated [16], which resulted in its rapid spread worldwide [17, 18]. In Taiwan, sorafenib was initially indicated for advanced HCC. However, the introduction of the concept of TACE refractoriness, as stated in the Japanese "Consensus-based Guidelines for HCC Treatment" [15, 16], led to changes in the insurance system in Taiwan [19, 20].

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Two retrospective clinical studies demonstrated that after the application of the TACE failure/refractoriness criterion, "patients who switched to molecular-targeted agents as soon as TACE became ineffective" had a better survival benefit than "patients who continued to receive ineffective TACE" [21, 22]. Moreover, the OPTIMIS trial [23, 24], a prospective, noninterventional, global study conducted to validate the results of these retrospective clinical studies [23, 24], demonstrated that switching to molecular-targeted agents at the time of TACE failure/refractoriness is associated with longer survival and this concept of "TACE failure and early switching to molecular-targeted therapy at the time of TACE failure" has become a global consensus.

3. Concept of TACE Unsuitability

The concept of "TACE unsuitability" was recently proposed. "TACE unsuitability" refers to three conditions: (1) conditions that are likely to be TACE refractory, (2) conditions that are likely to cause a deterioration in liver function to Child-Pugh B after TACE, and (3) conditions that are inherently resistant to TACE [25]. The Asia-Pacific Primary Liver Cancer Expert Association [25] and the Japan Society of Hepatology [26] published a "Consensus Statement and Recommendations" [25, 26]. These recommendations state that prior administration of lenvatinib (LEN) in patients who are TACE-unsuitable can (1) induce tumor necrosis and achieve downstaging, (2) suppress the release of hypoxia-inducible cytokines (e.g., vascular endothelial growth factor [VEGF]) by TACE and inhibit intrahepatic tumor progression and extrahepatic metastasis, and (3) normalize tumor vasculature through the anti-VEGF effect, thereby increasing the efficacy of TACE [27, 28]. LEN-TACE sequential therapy prolongs OS in patients with tumor burden beyond the up-to-seven criteria than TACE alone [29]. Therefore, LEN-TACE sequential therapy is gradually becoming the preferred approach for TACE-unsuitable HCC patients [30-36]. Lenvatinib is also effective in TACE-resistant tumors such as confluent multinodular type HCCs, simple nodular type HCCs with extranodular growth, diffuse type HCCs, and poorly differentiated HCCs [37-39]. The evidence supporting the use of TACE in intermediate-stage HCC was derived from a meta-analysis of six randomized controlled trials comparing "TACE versus no treatment (or best supportive care)" at the time when there is no effective systemic therapy [40] and there are no comparative trials examining "whether TACE is superior to upfront systemic therapy followed by TACE." In that regard, the treatment strategy of upfront systemic therapy followed by selective TACE (or resection/ablation) addresses an important clinical issue regarding achieving complete response (CR) while preserving liver function in patients not suitable for TACE.

The AASLD Expert Panel's updated AASLD HCC treatment algorithm, which was revised in 2020, recommended systemic therapy as an option in addition to TACE as the initial treatment for patients with a high tumor burden for the first time in 20 years [41]. The ESMO Guideline [42] and the BCLC Guideline, which were updated in 2022 [43], recommend systemic therapy for TACE-unsuitable cases. These recommendations demonstrate that a concept that was initially proposed in Japan is gradually spreading globally.

4. SORA-TACE Sequential Therapy

Administration of molecular-targeted agents with VEGF inhibitory activity prior to TACE can possibly enhance the efficacy of TACE by normalizing tumor vasculature and decreasing microvessel density, intratumoral stromal pressure, and vascular permeability, thereby improving drug delivery [27, 28]. This is the rationale for the combination of TACE and molecular-targeted agents. To date, six combination trials of TACE and molecular-targeted agents have been performed, but have failed to meet their primary endpoint except the TACTICS trial. Although the primary endpoint was progression-free survival (PFS)/time to progression in the post-TACE [44], SPACE [45], TACE-2 [46], and TACTICS [47] trials, only the TACTICS trial was positive, with a PFS hazard ratio (HR) of 0.59 [95% confidence interval (CI), 0.41-0.78] [47].

The PFS of the BRISK-TA and ORIENTAL trials was also significantly better (PFS HR of 0.61 [95% CI, 0.74-0.99] for BRISK-TA and 0.86 [0.74-0.99] for ORIENTAL). However, the BRISK-TA and ORIENTAL trials had negative results because their primary endpoint was OS [48, 49]. The BRISK-TA and ORIENTAL trials, with OS as the primary endpoint, and the SPACE, TACE-2, and post-TACE trials, with OS as the secondary endpoint, found that molecular-targeted agents plus TACE did not show a significant survival benefit over TACE alone.

Similarly, the TACTICS trial found that TACE plus sorafenib did not show a significant survival benefit over TACE alone: the OS of TACE plus sorafenib was 36.2 months (95% CI, 30.5-44.1), whereas that of TACE alone was 30.8 months (95% CI, 23.5-40.8); HR = 0.86 (95% CI, 0.61-1.22; p = 0.40) [50]. Factors contributing to this negative result are as follows: (1) There were only 156 patients included in the phase II trial design, which may have been underpowered to meet the OS endpoint, and (2) post-progression survival was extremely long (17.3 months) in the TACE alone arm because 76.3% of the patients in the TACE alone arm received post-treatment after progression (including 50% of patients treated with sorafenib) [39]. However, the improvement of OS was the longest (5.4 months) reported to date in a prospective trial of the combination of TACE with a molecular-targeted agent. The TACTICS trial demonstrated that the combination of TACE and molecular-targeted agents can prolong PFS and, to some extent, OS as well.

The correlation coefficient (r) of OS HR and PFS HR in the six TACE combination trials performed to date is 0.56. This indicates that although there is a certain correlation between PFS HR and OS HR, it is weaker than that in advanced HCC [39, 50]. This result from TACE combination trials contrasts with the strong correlation coefficient of r =

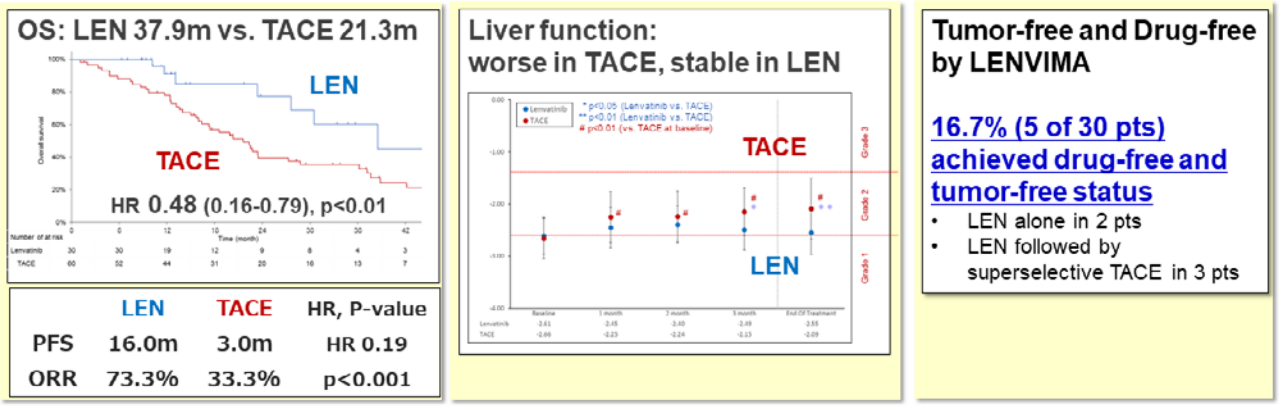

Figure 1. Lenvatinib versus TACE as initial treatment in patients with intermediate-stage HCC beyond the up-to-seven criteria.

0.84 in the plot of the HR of PFS vs. the HR of OS for primary and secondary therapies for advanced HCC published by Llovet et al. [41, 51]. This suggests that post-progression survival owing to post-progression treatment is considerably stronger in combination trials of TACE and molecular-targeted agents in intermediate-stage HCC than in the first- and second-line trials of advanced HCC and the actual impact of PFS on OS was considerably diluted [52, 53].

The TACTICS trial also showed that (1) PFS and OS prolongation is superior in patients with tumor burden exceeding the up-to-seven criteria than in patients with tumor burden within the up-to-seven criteria and (2) clinically meaningful PFS and OS prolongation is observed even in patients with tumor burden within up-to-seven criteria [50]. This indicates that the combination of systemic therapy and TACE is highly relevant for patients not suitable for TACE.

5. LEN-TACE Sequential Therapy

The concept that lenvatinib followed by TACE, which has a high response rate, may be more effective than TACE alone in patients not suitable for TACE has been proposed [53]. In 2019, the results of a multicenter proof-of-concept study showed that patients with tumor burden exceeding the up-to-seven criteria had a better response to lenvatinib followed by additional TACE than to TACE alone (**Fig. 1**) [29]. The results of 37 TACE-naïve patients who received lenvatinib as an initial therapy for intermediate-stage HCC with tumor burden exceeding the up-to-seven criteria were compared with those of 642 patients who received TACE alone for tumor burden exceeding the up-to-seven criteria. A total of 30 patients in the lenvatinib pretreatment group (excluding seven patients whose observation period was less than 6 months) were compared with 60 patients in the TACE group whose baseline characteristics were matched by propensity score matching. The ALBI score indicated that TACE alone caused a greater deterioration of liver function than lenvatinib. The PFS was significantly longer in the lenvatinib group (16.0 months) than in the TACE group (3.0 months) (HR, 0.19; 95% CI, 0.10-0.35; $p < 0.001$). The OS was significantly longer in the upfront lenvatinib group (37.9 months) than in the TACE alone group (21.3 months) (HR, 0.48; 95% CI, 0.16-0.79, $p < 0.01$). Approximately 70% of patients in the upfront lenvatinib group received subsequent TACE (LEN-TACE sequential therapy), and four of them achieved cancer- and drug-free status (including one patient who received lenvatinib alone and achieved drug-free status). Thus, LEN-TACE was extremely effective in patients with tumor burden exceeding the up-to-seven criteria, who were previously extremely difficult to control with TACE alone (**Fig. 1**). Therefore, since lenvatinib has a very high response rate, it should be administered as the first-line treatment for intermediate-stage HCC patients with tumor burden exceeding the up-to-seven criteria. The good OS results observed in the lenvatinib pretreatment group are due to the extremely high response rate compared with TACE alone and the effect of preservation of liver function.

The response rate of lenvatinib was 40.6% and 61.3% in the REFLECT trial and in the Japanese subpopulation with intermediate-stage HCC, respectively [54]. The extremely high response rate of 73.3% observed in this multicenter proof-of-concept study may be attributed to the fact that many TACE-naïve patients have ALBI grade 1 liver function and can tolerate full doses of lenvatinib with few adverse events and a low rate of dose reduction, withdrawal, and discontinuation [55-57]. The high response rate may be due to the following reasons: (1) lenvatinib induces tumor shrinkage and necrosis; (2) selective TACE is often curative when additional TACE is performed later, which preserves liver function; (3) upfront lenvatinib therapy suppresses the release of hypoxia-inducible cytokines such as VEGF and other substances, thereby inhibiting recurrence or metastases; and (4) normalization of tumor vasculature with lenvatinib reduces vascular permeability and intratumoral interstitial pressure, which facilitates the uniform spread of lipiodol containing anticancer drugs throughout the tumor. This increases the efficacy of TACE, which may lead to CR in some patients. Preclinical models have recently shown that vascular normalization and tumor interstitial pressure decrease as early as 4 days after administration of lenvatinib [58]. Therefore, LEN-TACE sequential therapy is a theoretically effective treatment for intermediate-stage HCC with tu-

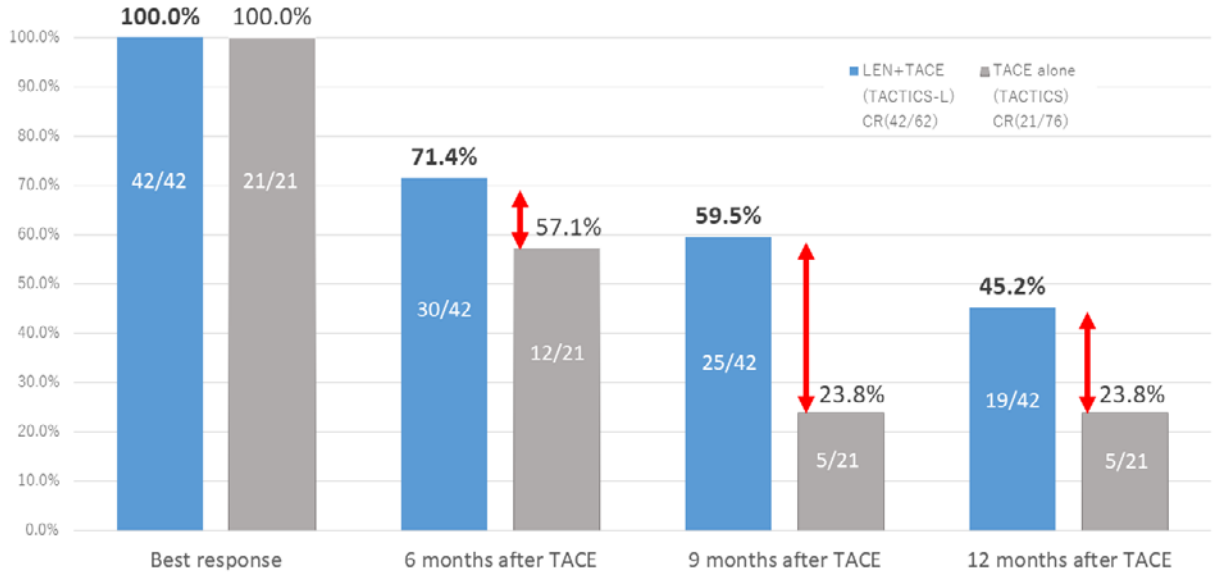

Figure 2. Sustained CR rate with LEN+TACE/TACE alone.

mor burden exceeding the up-to-seven criteria and is gradually becoming the preferred treatment strategy for intermediate-stage HCC with high tumor burden [30-34, 36]. Thus, the treatment paradigm for intermediate-stage HCC is dramatically changing due to the few disadvantages to the administration of lenvatinib prior to TACE in HCC patients with high tumor burden.

The results of TACTICS-L, a prospective study of the efficacy and safety of LEN-TACE, were recently published [59]. TACTICS-L trial, a phase II prospective multicenter single-arm trial, was conducted between 2019 and 2021 in 21 Japanese institutions. The primary endpoint was PFS per response evaluation criteria in cancer of the liver (RECICL) [60]. The baseline characteristics of the patients in the TACTICS-L trial were similar to those of the TACE alone group in the TACTICS trial. In the TACTICS-L trial, lenvatinib was stopped 2 days before TACE and restarted 3 days after TACE based on the study protocol. Specifically, approximately 65% of the patients were up-to-seven criteria in and 35% were out. In this group, the CR rate at 4 weeks after the initial TACE was 53.2% and the best response rate was 67.7%, and the CR rate at 12 months was 57.2%, showing an extremely long-lasting CR. The CR rate at 4 weeks after initial TACE and the CR rate for best response were also >50% regardless of the up-to-seven-in or out criteria. The long-term sustained effect of LEN-TACE on CR rates was also better than that of TACE alone, as evidenced by the CR rates in the LEN-TACE group of TACTICS-L compared with those of the TACE alone group of TACTICS (**Fig. 2**) [61]. Compared with the high CR rate observed in TACTICS-L, the CR rates of 26% in the TACE alone group in the TACTICS trial and 24% in the Japanese population enrolled in the OPTIMIS trial are relatively low, suggesting that TACE with prior administration of lenvatinib is extremely effective and achieves a good CR rate.

The subgroup analysis of the TACTICS-L trial also found that tumor size or the number of tumors had no significant effect on achieving the CR rate and objective response rate (ORR) [62]. In addition, the CR rate and ORR were significantly better in patients with a Child-Pugh score of 5 than in those with a score of 6 and were better in patients who received a higher dose intensity of lenvatinib prior to the initial TACE, whereas the CR rate and ORR were equivalent even if the relative dose intensity of lenvatinib after TACE was lower. A treatment period of less than 14 days with lenvatinib prior to TACE was equivalent to a treatment period of 14 days or longer. This suggests that although administration of lenvatinib for 7-10 days prior to TACE results in a good CR rate and ORR, it is desirable to maintain the dose intensity of lenvatinib prior to initial TACE and that although lenvatinib should be continued after TACE, it does not need to be administered at a high dose and a low dose (e.g., 4 mg) is also acceptable.

LEN-TACE sequential therapy is a rational treatment for TACE-unsuitable patients with tumor burden exceeding the up-to-seven criteria and may become the first-line treatment for intermediate-stage HCC patients not suitable for TACE. In addition, the lenvatinib response rate is high in poorly differentiated HCC [37-39]. Moreover, the CR rates in patients with simple nodular type HCCs with extranodular growth, confluent multinodular type HCCs, and infiltrative type HCCs [62], in which TACE is less effective, also ranged from 54% to 100%; this is comparable with the 70% rate of the simple nodular type, which is expected to show a good response to TACE (**Fig. 3**) [62]. Therefore, LEN-TACE sequential therapy may be an effective treatment strategy for such TACE-resistant tumors [30]. Administration of lenvatinib for 1 week prior to initial TACE may be sufficient. Although lenvatinib can normalize the tumor vessels, arterial blood flow to the tumor also reduces 1/3-1/2 that before administration of lenvatinib [63]. This might make it difficult to identify the tumor stain and its feeders on DSA.

	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

Figure 3. Objective response rate (ORR) and complete response (CR) rate by LEN-TACE sequential therapy according to gross pathological type.

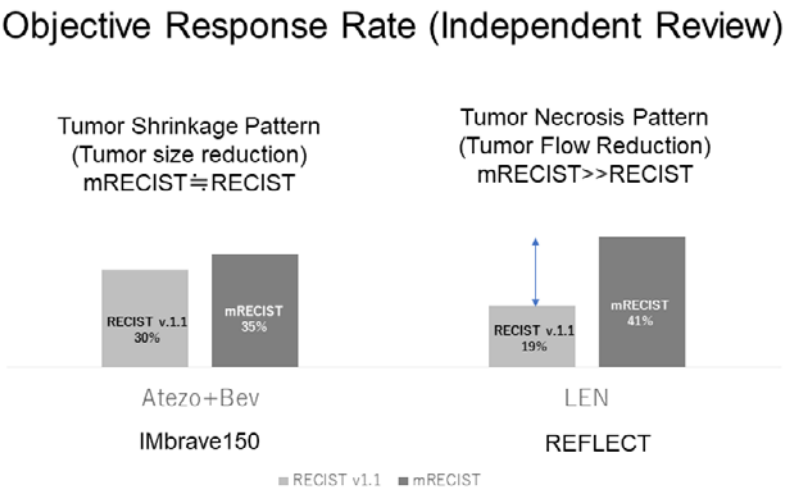

Figure 4. Different response pattern according to different regimens.

The objective of Atezo/Bev treatment is to achieve tumor shrinkage, whereas that of lenvatinib is to achieve tumor necrosis (**Fig. 4**). Drug-off after achieving CR was possible in 4 of 37 patients in the multicenter proof-of-concept study, which suggests that achieving drug-free is possible with LEN-TACE sequential therapy.

6. Atezolizumab plus Bevacizumab Followed by Curative (ABC) Conversion Therapy

In 2020, Atezo/Bev combination therapy was approved based on the positive results of the IMbrave150 trial [3, 64, 65]. An ORR of 44% per response evaluation criteria in solid tumor (RECIST) 1.1 in intermediate-stage HCC was recently reported, indicating an extremely high response rate [64, 66].

In a multicenter study, 110 patients with Child-Pugh grade A liver function received Atezo/Bev combination as the first-line therapy; of these, 38 (35%) patients achieved clinical CR, which was defined as radiological CR with three normalized tumor markers, namely, alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II, and AFP-L3, and 25 (23%) achieved drug-free status [67]. Seven patients underwent resection, 13 underwent radiofrequency or microwave ablation, and 15 underwent curative TACE [67]. Three cases achieved cancer-free status with

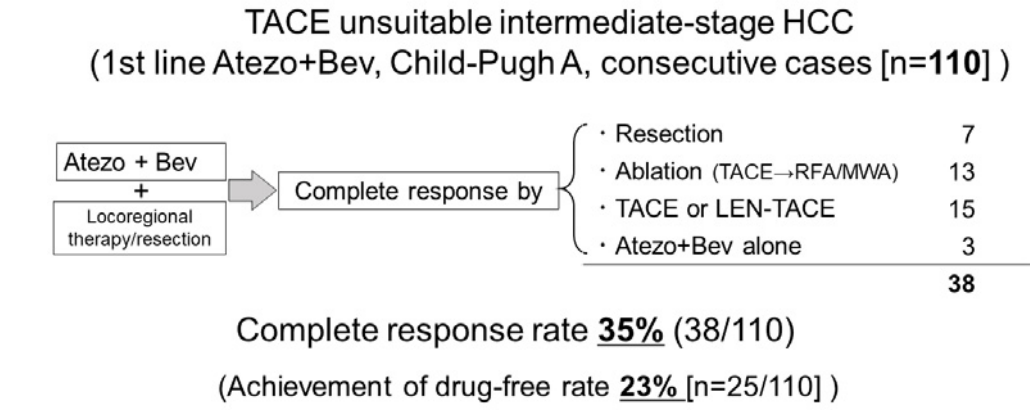

Figure 5. ABC conversion rate in intermediate-stage HCC.

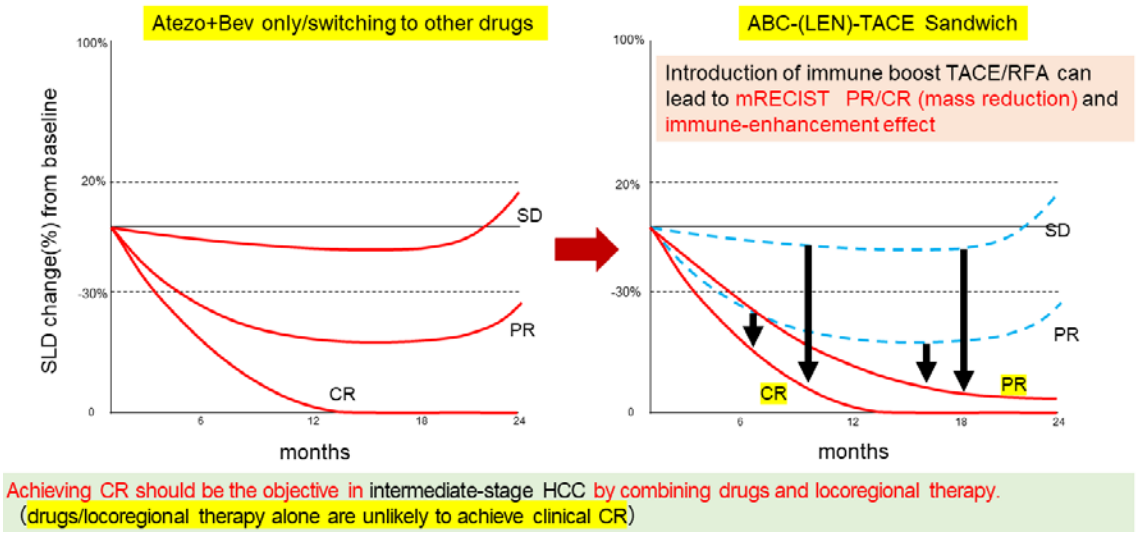

Figure 6. ABC-TACE sandwich therapy in the BCLC-B population (especially SD/slow PD cases).

Atezo/Bev alone, which resulted in an extremely high curative conversion rate of 35% (**Fig. 5**) [67]. This is because Atezo/Bev, unlike molecular-targeted agents, has a marked tumor shrinkage effect even in extremely aggressive PET-positive HCCs, confluent multinodular type HCCs, diffuse type HCCs, and poorly differentiated HCCs, enabling resection, ablation, and curative TACE and resulting in complete pathological CR [68, 69].

In general, if systemic therapy is initiated and a response is obtained, it is common practice in oncology to continue the same drug as long as possible. This concept is also applicable to advanced HCC. However, in intermediate-stage HCC, which is a locally advanced HCC without vascular invasion or extrahepatic spread, even if tumor shrinkage is achieved, ablation, curative TACE, and resection are extremely effective options to achieve pathological CR. Patients who achieve cancer- and drug-free status by curative conversion do not need to receive any treatment or worry about adverse events and can enjoy a good quality of life. Therefore, in cases in which Atezo/Bev combination therapy achieves a high degree of tumor shrinkage, curative conversion should always be considered in the tumor shrinkage phase without losing the optimal timing [67-70]. Since patients achieving clinical CR have a long-term survival, especially in intermediate-stage HCC, systemic therapy should be performed based on a different criteria/concept from the conventional sequential systemic therapy for advanced HCC (**Fig. 6**) [71].

Atezo/Bev treatment has a 44% response rate in intermediate-stage HCC [64, 66], indicating that one out of two patients may undergo curative conversion. Due to the high response rate to Atezo/Bev in intermediate-stage HCC, once a deep response is achieved, the patient should not continue receiving the drug until progressive disease (PD) without any treatment strategy, but should switch immediately to a curative treatment while the drug is still effective. This is because it is almost impossible to achieve pathological CR with systemic therapy alone, such as with Atezo/Bev or lenvatinib, and pathological CR cannot be achieved with TACE alone either. Curative conversion should be performed, whenever possible, because even if modified RECIST CR is achieved with systemic therapy, viable cancer cells often remain after resection (existence of drug-resistant clones). In such cases, bevacizumab should be discontinued

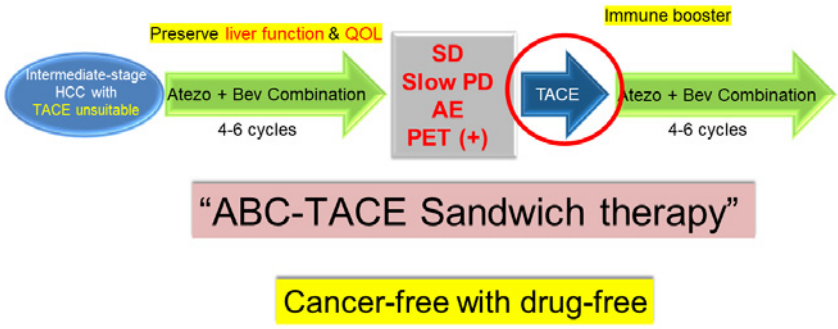

Figure 7. ABC-TACE sandwich therapy.

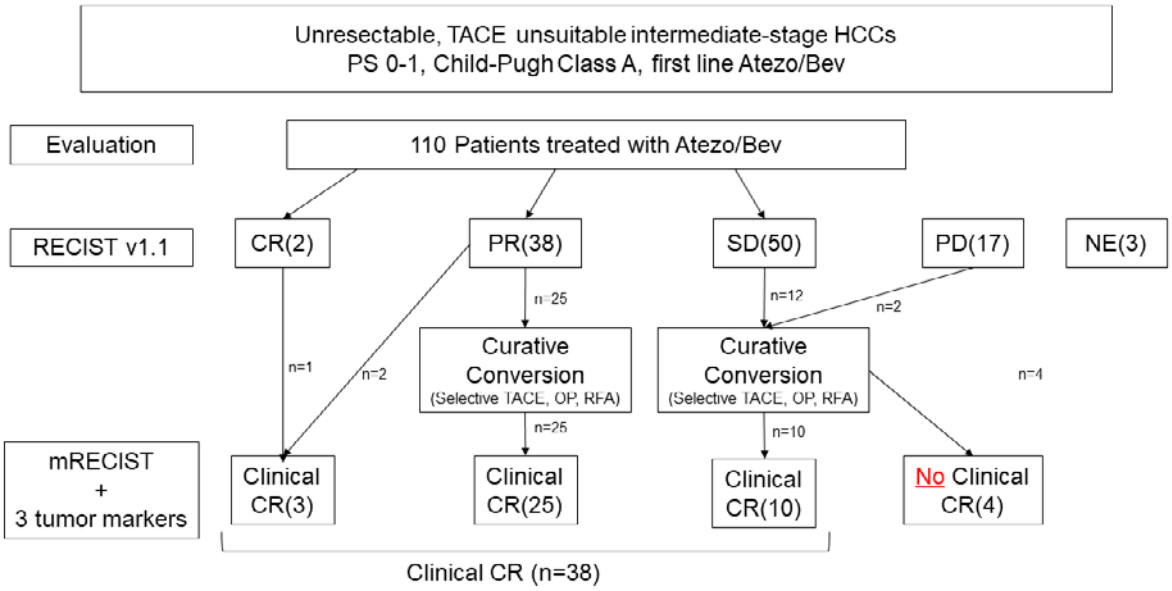

Figure 8. ABC conversion: relationship between response to Atezo/Bev and achievement of clinical CR.

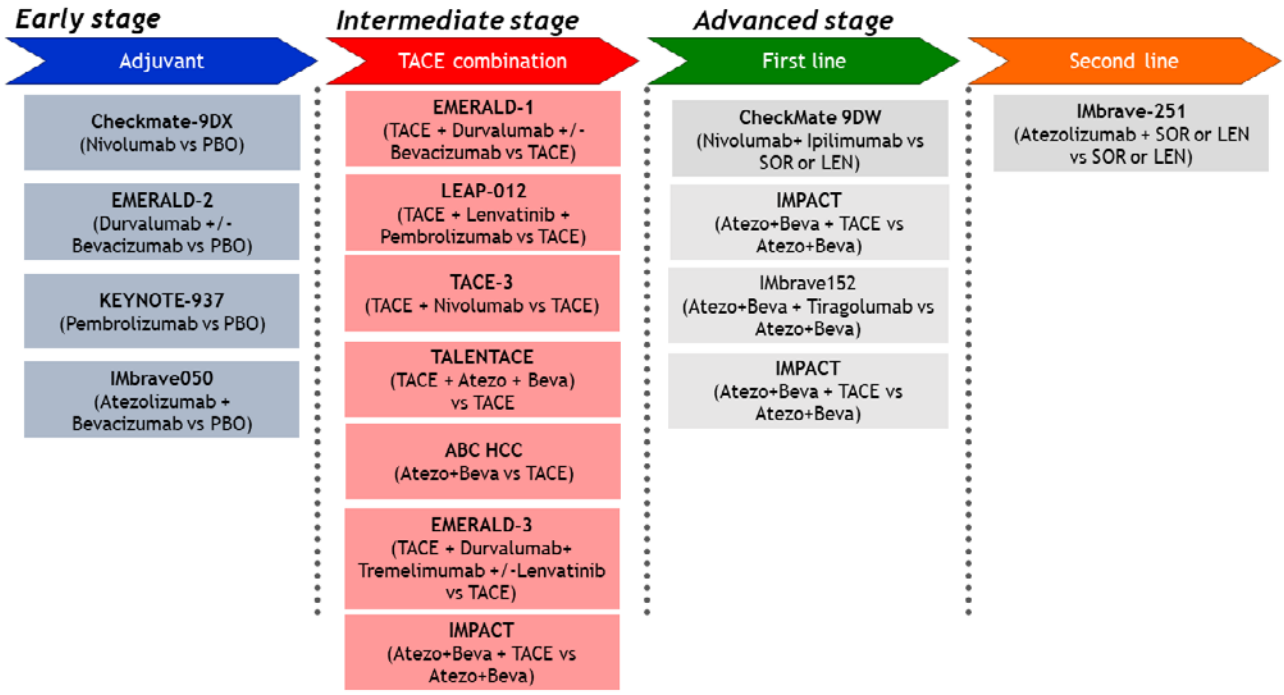

Figure 9. Ongoing phase III clinical trials in hepatocellular carcinoma.

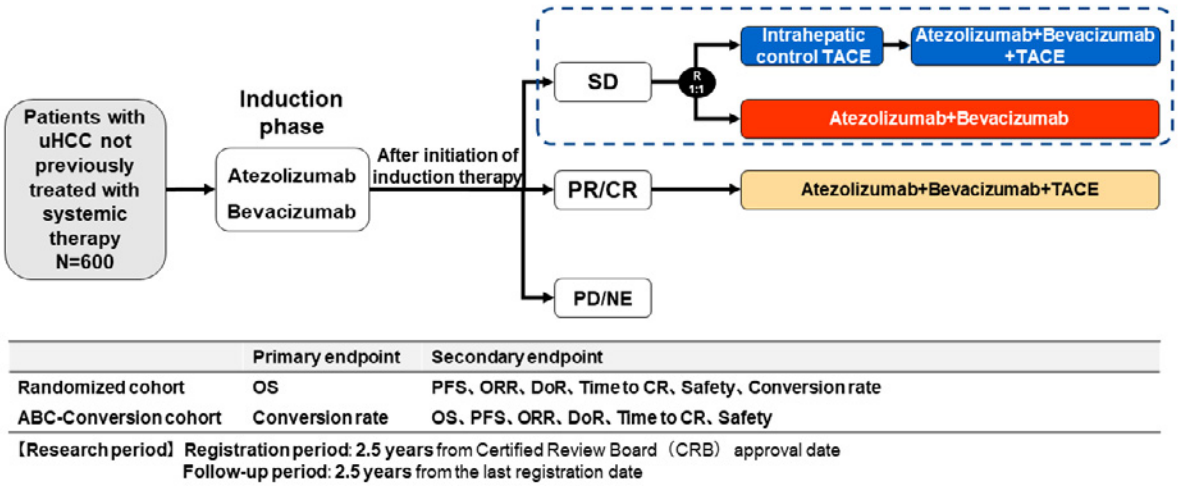

Figure 10. IMPACT trial (phase III study in Japan).

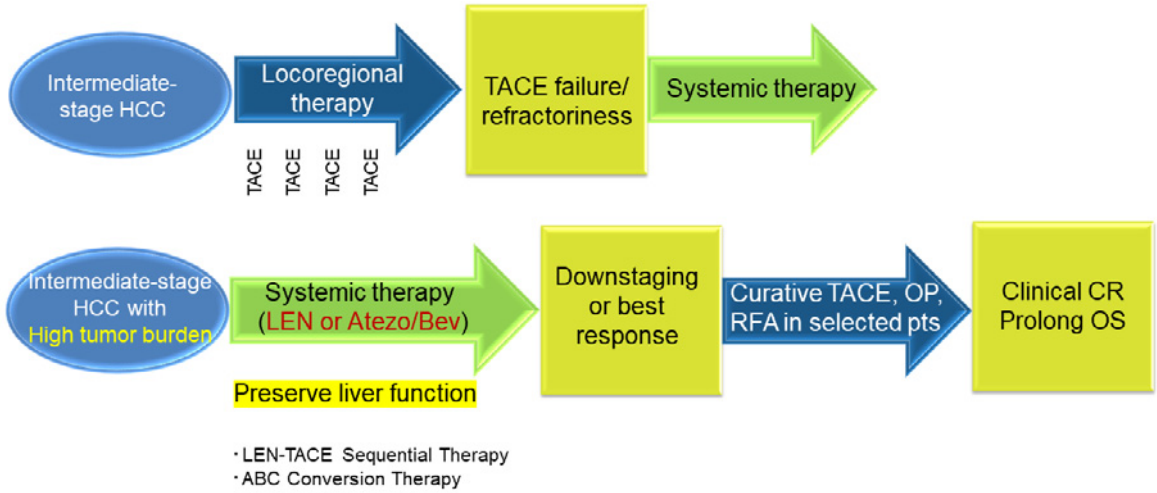

Figure 11. Novel treatment strategy for intermediate-stage HCC.

Table 1. Definition of Clinical CR and Drug-Off Criteria in Immunotherapy Combined with Locoregional Therapy.

Definition of clinical CR
Fulfilling the following two conditions: 1. Achievement of CR per mRECIST/RECISTv1.1 evaluated by CT/MRI 2. Continuous normalization of three tumor markers (AFP/AFPL-3/PIVKA-II) for more than 6 weeks
Drug-off criteria
Fulfilling the following three conditions: 1. Achievement of CR per mRECIST (RECISTv1.1) by super-selective TACE/RFA/MWA 2. Continuous normalization of three tumor markers (AFP/AFP-L3/PIVKA-II) for more than 12-24 weeks 3. Complete disappearance of intra-nodular arterial flow by CEUS

CR, complete response; AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein isoform, lectin affinity; PIVKA-II, protein induced by vitamin K absence or antagonist-II; CEUS, contrast-enhanced ultrasonography
Cited from ref #67.

for at least 6 weeks in the case of resection and for at least 2-3 weeks in the case of ablation or TACE. Nevertheless, combination therapy with Atezo/Bev and locoregional therapy can achieve clinical CR of approximately 35% in intermediate-stage HCC patients not suitable for TACE [67, 68, 70].

In cases of stable disease (SD), slow PD, or drug interruption due to adverse events such as proteinuria or immune-related adverse events [72], TACE should be performed between Atezo/Bev courses to decrease tumor vol-

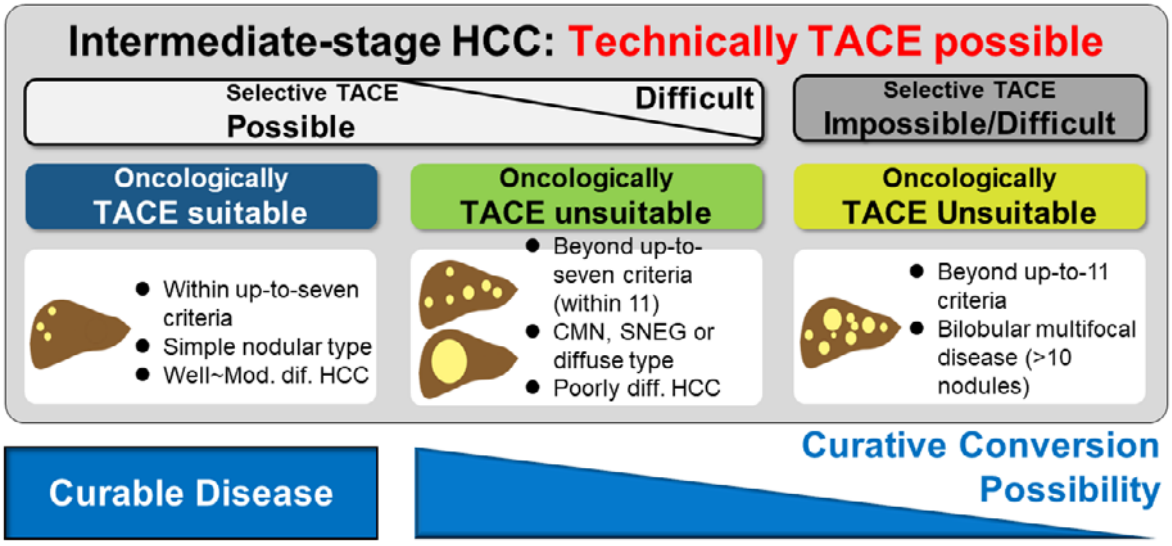

Figure 12. Intermediate-stage HCC: technically TACE possible.

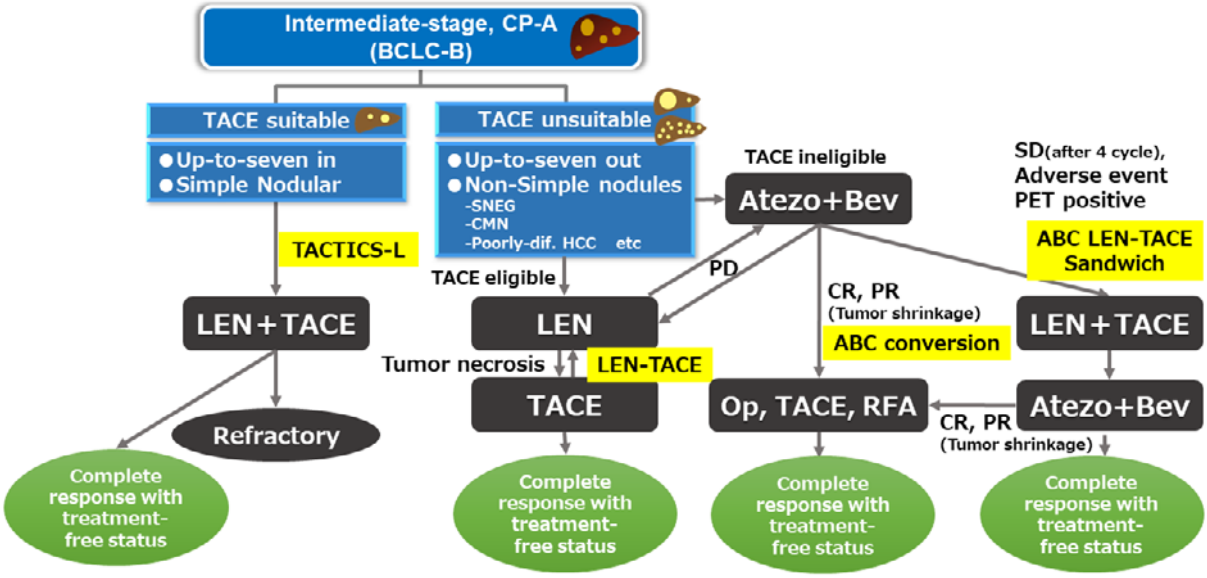

Figure 13. Treatment strategy for intermediate-stage HCC.

ume and induce an immune response by releasing tumor antigens (**Fig. 7**) [73-81]. In such cases, it is recommended to continue Atezo/Bev for at least 4-6 cycles after locoregional therapy whenever possible to increase the rate of pathological CR due to the immunostimulatory effect (ABC-TACE sandwich therapy). Among 38 patients who were cancer-free after ABC conversion, clinical CR was achieved in 10 of 50 SD cases on Atezo/Bev after TACE combination (**Fig. 8**) [67].

OR by systemic therapy is a surrogate marker for OS at the individual patient level [82-84]. Although intermediate-stage HCC is a heterogeneous disease, the combination of systemic therapy and TACE can achieve high ORR and cancer-free with drug-free status [67, 69-71]. The recently introduced Durva+Treme is difficult to use for curative conversion in intermediate-stage disease due to its low CR rate, low ORR, and high PD rate [4, 85].

There are several ongoing clinical trials of TACE in combination with immunotherapy, the results of which are eagerly awaited (**Fig. 9**) [61]. In particular, a phase III study (IMPACT) of ABC conversion in patients with intermediate- and advanced-stage HCC is currently ongoing in Japan (**Fig. 10**) [61].

7. Conclusion

TACE on demand in combination with prior administration of a systemic agent (lenvatinib or Atezo/Bev) has become a common treatment strategy in intermediate-stage HCC (**Fig. 11**). This approach is expected to result in clinical CR and OS prolongation. In some cases, it is possible to achieve drug-free status after clinical CR (**Table 1**). Although curative treatment of intermediate-stage disease is difficult in patients with more than 11 bilobar lesions or

with beyond up-to-11 criteria, TACE is possible in certain patients, or if TACE is not oncologically feasible, curative treatment is possible with drug-preemptive TACE (**Fig. 12** and **13**). All stages of HCC, from early stage to intermediate and advanced stage, currently benefit from systemic therapy combined with locoregional therapy [61].

Conflict of Interest: Lecture: Eli Lilly, Bayer, Eisai, Chugai, Takeda, AstraZeneca; Grants: Taiho, Otsuka, EA Pharma, AbbVie, Eisai, Chugai, GE Healthcare; Advisory Consulting: Chugai, Roche, AstraZeneca, Eisai.

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