Implications of the TACTICS Trial: Establishing the New Concept of Combination/Sequential Systemic Therapy and Transarterial Chemoembolization to Achieve Synergistic Effects

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Introduction

The TACTICS trial was a multicenter, randomized controlled phase 2 trial that explored the clinical efficacy of sorafenib in combination with transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). The trial began in 2010, and its final results were reported in 2022 [1]. Although sorafenib plus TACE improved progression-free survival (PFS), it did not significantly extend overall survival (OS). The OS benefit is difficult to demonstrate in clinical trials of intermediate-stage HCC patients because these patients generally receive aggressive post-trial treatments, which can extend post-progression survival and dilute the benefit obtained from the original trial treatment. However, the median survival benefit of 5.4 months observed in the TACTICS trial can be interpreted as a clinically meaningful result, despite not reaching statistical significance. This result suggests that early intervention with systemic therapy during TACE delays stage progression and that inhibition of tumor proliferation using systemic therapy contributes to maintaining hepatic functional reserve by reducing the number of on-demand TACE sessions required [1].

Many trials have investigated combinations of systemic therapy with TACE; however, they all failed because the unique nature of TACE as a combination of local therapy and systemic therapy, rather than a pure systemic therapy, posed challenges for trial design and endpoint selection. The TACTICS trial was the only such trial to yield both clinically and statistically significant results, and its design and concept have greatly influenced current ongoing clinical trials of combination immunotherapy plus TACE. This editorial discusses the interpretation of the TACTICS trial results and their significance.
Rationale for Combining TACE with Systemic Therapy

TACE consists of the injection of anticancer drugs mixed with Lipiodol into the hepatic artery feeding HCC nodules, followed by injection of an embolic agent, thereby leveraging both the pharmacologic effects of anticancer agents and the necrotic effects of embolic agents. TACE became the standard of care for intermediate-stage HCC based on the results of a meta-analysis of 6 RCTs conducted in the 2000s showing that TACE provided a survival benefit compared with best supportive care [2]. However, because TACE is not a curative therapy but rather a palliative therapy, recurrence or metastasis is common even after tumor necrosis is successfully achieved with TACE, which often leads to repeated TACE sessions. Repeating TACE decreases liver function and limits the survival benefit [3, 4]. Furthermore, as mentioned earlier, because the evidence for TACE was established through a meta-analysis of 6 RCTs of TACE versus no therapy (or best supportive care) at a time when no effective systemic therapy for HCC existed [2], it has become out-of-date, as currently six effective systemic therapy regimens are available [5–11].

The results of the international phase III SHARP trial published in 2007 were the first to demonstrate the efficacy of sorafenib as systemic therapy for HCC [5]. Sorafenib is a multi-kinase inhibitor that suppresses tumor proliferation not only by inhibiting Raf serine/threonine kinases but also by suppressing angiogenesis through the inhibition of VEGFR. Consequently, it extended the duration of stable disease in many patients with HCC, resulting in extended OS.

As described earlier, TACE uses an embolic agent to physically block blood flow and induce tumor necrosis. Because HCC tumors are inherently hypervascular, they are susceptible to blockage of arterial blood flow; when tumors are subjected to hypoxia through blockage of arterial blood flow by embolization, they induce angiogenesis by producing VEGF via HIF1α. Post-TACE progression and biological malignant transformation occur via these VEGF signals, and post-TACE VEGF levels are associated with prognosis [12]. This supports the use of antiangiogenic agents (anti-VEGF drugs) to control post-TACE recurrence and progression. Anti-VEGF drugs may also enhance the response to TACE by improving drug delivery through normalization of the tumor vasculature, reduction of interstitial pressure, and reduction of vascular permeability [13].

Clinical Trials Investigating the Combination of TACE with Molecular Targeted Agents

Many clinical trials have been conducted to test the rationale described above, although most of them failed. Table 1 lists the results of trials investigating the combination of a tyrosine kinase inhibitor with TACE. Among these trials, the TACTICS trial was the only one with both clinically and statistically positive results. The SPACE trial, which investigated sorafenib in combination with drug-eluting beads (DEB)-TACE [14], showed a significant difference in the primary endpoint; however, the result was interpreted as negative from a clinical perspective. The causes of the negative results in each trial are discussed below.

The Post-TACE trial, which was conducted in Japan and Korea [15], was designed to evaluate the effect of sorafenib administered after achieving a complete response by TACE. However, sorafenib was administered a long time after TACE (9 weeks later) rather than immediately after TACE, when the effects of VEGF are strongest; this may partially explain why sorafenib did not yield the expected effect in this trial. In addition, comparison of the Japanese and Korean cohorts showed that sorafenib was effective in the Korean cohort, whereas it provided no benefit whatsoever in the Japanese cohort. This may be because the Korean patients received sorafenib for longer period than the Japanese patients (30.9 weeks vs. 16.1 weeks). At that time, it was common in Japan to immediately discontinue sorafenib when adverse events, such as hand-foot skin syndrome, occurred because Japan did not join the SHARP trial or Asia-Pacific trial [5, 6], and Japanese clinicians were not familiar with the management of such adverse events. This could explain the difference in the duration of treatment and the resulting lack of efficacy in the Post-TACE trial [16, 17].

The SPACE trial investigated the combination of scheduled DEB-TACE with sorafenib. As noted above, this trial showed a statistically significant difference in the primary endpoint of time to progression (TTP) [14]. However, the Kaplan-Meier curves of TTP for the sorafenib plus DEB-TACE group and DEB-TACE alone group almost entirely overlapped, which does not suggest a clinical benefit. The results were not well accepted by clinicians because DEB-TACE was scheduled rather than the on-demand TACE typically used in clinical practice. Problems with endpoint definitions in the trial were also noted. Specifically, event definitions were stricter than those used in clinical practice. For example, Child-Pugh B status was defined as an event; however, in clinical practice, transient impairment of liver function after TACE
### Table 1. Comparison of TACE combination trials

| Trial          | Phase Post-TACE [15] | SPACE [14] | TACE-2 [18] | BRISK-TA [19] | ORIENTAL [20] | TACTICS [1, 25] |
|---------------|-----------------------|------------|-------------|--------------|--------------|-----------------|
| Phase         | Phase 3               | Randomized phase 2 | Phase 2     | Phase 3      | Phase 3      | Randomized phase 2 |
| Agent         | Sorafenib             | Sorafenib  | Sorafenib   | Brivanib     | Orantinib    | Sorafenib       |
| Class         | A                     | A (no ascites) | A           | A and B      | A            | A5-B7           |
| ECOG PS       | 0–1                   | 0          | 0–1         | 0–1          | 0–1          | 0–1             |
| Tumor burden for inclusion criteria | ≤7 cm ≤10 nodules | Unresectable multi-nodules | Not a candidate for resection or transplantation | <4 nodules, ≥5 cm | ≥4 nodules, <1 cm | ≥4 nodules, 1 nodule, >5 cm |
| TACE Procedure | On demand            | Scheduled  | On demand   | On demand    | On demand    | On demand       |
| Progression criteria | RECICL 2004        | MRECIST    | RECIST v1.1 | mRECIST      | TACE discontinuation criteria | RECICL & TACE discontinuation criteria (Intrahepatic new lesion: No PD) |
| PFS or TTP (TACE alone) | 5.4 M (vs. 3.7 M), HR = 0.87, p = 0.252 | 5.6 M (vs. 5.5 M), HR = 0.79, p = 0.072 | 7.9 M (vs. 7.9 M), HR = 0.99, p = 0.94 | 8.4 M (vs. 4.9 M), HR = 0.61, p < 0.0001 | 2.9 M (vs. 2.5 M), p = 0.03 | 25.2 M (vs. 13.5 M), HR = 0.59, p = 0.006 |
| TTUP, TTP, TTTF | –                     | TTUP: 3.0 (vs. 7.4), HR = 1.56, p = 0.99 | –           | TTDP: 12.0 M (vs. 10.9 M), HR = 0.94, p = 0.62 | TTTF: 23.9 M (vs. 19.8 M), HR = 0.88, p = 0.245 | TTUP: 26.7 M (vs. 20.6 M), HR = 0.57, p = 0.02 |
| OS            | 29.7 M (NE), HR = 1.06, p = 0.79 | NE (NE), HR = 0.90, p = 0.29 | 20.9 M (vs. 19.8 M), HR = 0.91, p = 0.57 | 26.4 M (vs. 26.1 M), HR = 0.90, p = 0.52 | 31.1 M (vs. 32.3 M), HR = 1.09, p = 0.435 | 36.2 M (vs. 30.8 M), Δ5.4, HR = 0.86, p = 0.40 |
| DOT           | 17.0 weeks            | 21.0 weeks | 17.1 weeks   | 24.0 weeks   | 43.6 weeks   | 11.27 weeks (28.2 months) |
| Primary endpoint | TTP                  | TTP        | PFS         | OS           | OS           | PF5/OS          |
| Results       | Negative              | Negative   | Negative    | Negative     | Negative     | Positive        |

RECICL, response evaluation criteria in cancer of the liver; RECIST, response evaluation criteria in solid tumors; mRECIST, modified RECIST; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads TACE; TTUP, time to untreatable progression; TTDP, time to disease progression; TTTF, time to treatment failure; HR, hazard ratio; DOT, duration of treatment; PD, progressive disease.
often results in Child-Pugh B status, which does not merit from discontinuation of a TACE combination treatment because TACE can be repeated after recovery of liver function. This overly strict definition of events may be one of the reasons for the negative results of the SPACE trial. In addition, subanalysis by region showed that hazard ratios (HRs) for TTP and OS were significantly better in the Asian population than in the non-Asian population (TTP: HR 0.865 vs. 0.720; OS: HR 1.062 vs. 0.677), and this has been attributed to the longer duration of sorafenib treatment in Asia (30.0 weeks vs. 17.4 weeks).

The TACE2 trial was a phase 3 trial conducted in the UK [18]. In contrast to the SPACE trial, the TACE2 trial investigated the combination of on-demand DEB-TACE plus sorafenib, which is a more clinically acceptable approach. However, the criteria for on-demand TACE are left to the clinician’s discretion, which means that TACE is sometimes performed before or after the detection of progressive disease (PD). Consequently, TACE may have been performed before the efficacy of sorafenib could be confirmed in the trial. It is possible that the clinical efficacy was not purely based on the addition of sorafenib but rather on the effect of additional TACE leading up to PD. This may partly explain the lack of differences in OS and PFS.

The BRISK-TA trial investigating the combination of TACE with brivanib, a novel molecular targeted agent [19], was unfortunately terminated in the middle of the trial because of the negative results of first-line and second-line trials of brivanib, which made it difficult to interpret the trial results. Similarly, the ORIENTAL trial investigated the combination of TACE with orantinib, another novel molecular targeted agent [20]. Interim analysis showed that the primary endpoint of median OS did not meet the criteria for continuation of the trial. Consequently, the trial was terminated, and the results were difficult to interpret.

**Design of the TACTICS Trial**

The TACTICS trial was designed based on lessons learned from the negative results of Post-TACE and SPACE trials (Fig. 1) [16, 17]. Conventional TACE was performed on demand with Lipiodol, which is the global standard and is in accordance with actual clinical practice. Sorafenib was started at 400 mg once daily and titrated up to 800 mg based on tolerability. The treatment plan included interruption of sorafenib for 2 days before and after TACE and resumption of treatment as soon as possible after TACE. Whenever an investigator was con-
Implications of discontinuation of sorafenib, the decision was made by a central review committee, which supported continuation of sorafenib for as long as possible while managing adverse events as well as possible. The co-primary endpoints were PFS and OS, which were evaluated using a gatekeeping strategy. PFS was defined with consideration of the clinical endpoints of TACE, and an event was defined as a state preventing any further benefit from TACE. Specifically, progression was defined as a ≥25% increase in intrahepatic lesions from baseline, extrahepatic spread, or vascular invasion. To prevent discontinuation of TACE due to a transient decline in liver function, transient liver function deterioration to Child-Pugh C was defined as an event. Response was assessed according to RECICL, a method used for locoregional therapy [21, 22], and new intrahepatic lesions were not considered as PD. Meeting the criteria for TACE refractoriness [23, 24] was also considered an event.

**Results of the TACTICS Trial**

The results of the TACTICS trial were presented at ASCO-GI 2018. The primary endpoint of PFS was 25.2 months with TACE plus sorafenib versus 13.5 months with TACE alone (HR, 0.59; \(p = 0.006\)) (Table 2) [25]. OS was not analyzed because the necessary number of events had not been reached at the time according to the statistical plan. Subgroup analysis for PFS showed that TACE plus sorafenib yielded better PFS in all subgroups. The response rate was 71.3% with TACE plus sorafenib versus 61.8% with TACE alone, but the difference was not statistically significant (Table 2). Safety analysis showed that TACE plus sorafenib was well tolerated, with no reports of unknown adverse events. The duration of sorafenib administration was long at 28.2 months, and the median daily dose was somewhat low at 355.2 mg/day. The TACE interval was 24.3 weeks in the TACE plus sorafenib group which was significantly longer than 18 weeks in the TACE alone group (\(p = 0.018\)), indicating that addition of sorafenib increased the TACE interval [25].

The final OS results were presented at ASCO-GI 2021 and subsequently published (Table 2) [1]. Median OS was 5.4 months longer with TACE plus sorafenib than with TACE alone (36.2 months vs. 30.8 months). However, the difference was not statistically significant (\(p = 0.40\)), whereas the final PFS results remained significant. In subgroup analysis, PFS among patients within the up-to-seven (UT7) criteria was 15.2 months in the TACE alone group versus 24.9 months in the TACE plus sorafenib group (HR, 0.756; ΔPFS, 9.7 months), and OS was 31.9 months in the TACE alone group versus 35.6 months in the TACE plus sorafenib group (HR, 0.924; ΔOS, 3.7 months). PFS among patients beyond the UT7 criteria was 9.0 months in the TACE alone group versus 22.1 months in the TACE plus sorafenib group (HR, 0.674; ΔPFS, 13.1 months), and OS was 25.0 months in the TACE alone group versus 36.3 months in the TACE plus sorafenib group (HR, 0.898; ΔOS, 11.3 months). These results suggest that TACE plus sorafenib is more effective in patients beyond the UT7 criteria, namely, those with a greater tumor burden. Among patients with vascular invasion or extrahepatic spread, the time to vascular invasion was 31.3 months in the TACE plus sorafenib group versus 4.0 months in the TACE alone group (HR, 0.28; \(p = 0.007\)), and the time to extrahepatic spread was 20.3

|                | TACE plus sorafenib | TACE alone | HR (\(p\) value) |
|----------------|---------------------|------------|-----------------|
| OS, months     | 36.2                | 30.8       | 0.86 (\(p = 0.40\)) |
| Beyond UT7 criteria | 36.3                | 25.0       | 0.898            |
| Within UT7 criteria | 35.6                | 31.9       | 0.924            |
| PFS            | 25.2                | 13.5       | 0.59 (\(p = 0.006\)) |
| Beyond UT7 criteria | 22.1                | 9.0        | 0.674            |
| Within UT7 criteria | 24.9                | 15.2       | 0.756            |
| CRR, %         | 28.8                | 27.6       | 0.77             |
| ORR, %         | 71.3                | 61.8       | 0.23             |
| DCR, %         | 83.8                | 77.6       | 0.42             |
| TTVI           | 31.3                | 4.0        | 0.28 (\(p = 0.007\)) |
| TTEHS          | 20.3                | 7.1        | 0.19 (\(p = 0.006\)) |
| TTSP           | 25.2                | 7.1        | 0.29 (\(p < 0.001\)) |

OS, overall survival; UT7, up-to-7; PFS, progression-free survival; CRR, complete response rates; ORR, objective response rate; DCR, disease control rate; TTVI, time to vascular invasion; TTEHS, time to extrahepatic spread; TTSP, time to stage progression.
months in the TACE plus sorafenib group versus 7.1 months in the TACE alone group (HR, 0.19; \( p = 0.006 \)) [1]. These figures were significantly better in the TACE plus sorafenib group than in the TACE alone group. Time to stage progression was also significantly longer in the TACE plus sorafenib group than in the TACE alone group at 20.3 months versus 7.1 months, respectively (HR, 0.19; \( p < 0.001 \)) (Table 2). The median interval between TACE sessions was significantly longer in the TACE plus sorafenib group than in the TACE alone group (23.2 weeks vs. 16.1 weeks; \( p = 0.011 \)). The duration of sorafenib treatment in the TACE plus sorafenib group was a relatively long 28.2 months (0.2–78.2 months), considering that the median duration of sorafenib treatment in the SPACE trial was only 21 weeks [5] (Table 1).

Although the TACTICS trial ultimately failed to demonstrate a survival benefit of adding sorafenib to TACE, its results suggest that this combination therapy may slow stage progression; furthermore, the results were obtained using a design in line with actual clinical practice. This led to widespread acceptance of its results, as evidenced by the Clinical Practice Guidelines for Hepatocellular Carcinoma 2021 (5th Edition) established by the Japan Society of Hepatology. A clinical question in the guidelines was, “Is concomitant use of systemic therapy and TACE appropriate?”, and the answer was that “concomitant use of systemic therapy and TACE is recommended,” although the recommendation was weak (recommendation level: weak; strength of evidence: B) [26].

**Implication of the TACTICS Trial**

**Antiangiogenic Agents Enhance the Clinical Efficacy of TACE**

The most significant contribution of the TACTICS trial is that the results suggest that the combination of TACE with an antiangiogenic agent enhances the clinical efficacy of TACE. The results showed that addition of sorafenib to TACE significantly extended PFS. Therefore, addition of sorafenib delayed stage progression, including vascular invasion and extrahepatic spread, by inhibiting tumor progression. One noteworthy characteristic of the study population was that 68% of the patients were within the UT7 criteria and could have been treated adequately with TACE alone. This illustrates that early intervention with sorafenib is still clinically meaningful for such tumors. In addition, the HRs for OS and PFS were better in patients beyond the UT7 criteria than in those within the criteria, which indicates that the additive effect of sorafenib is more meaningful in patients who are unsuitable for TACE because of high tumor burden [26, 27]. These data of TACTICS trial impacted on international guidelines such as updated ESMO, updated AASLD, or updated BCLC treatment algorithms [28–30].

Addition of sorafenib also increased the interval between on-demand TACE sessions in the trial. A longer TACE interval means fewer chances for TACE to deteriorate liver function, which should result in preservation of hepatic functional reserve. This enables a switch to the
next line of treatment and extends post-progression survival.

However, in patients eligible for post-trial treatment because of tumor status, aggressive post-trial treatment extends post-progression survival, which diminishes the direct effect obtained in trials and leads to a lack of difference in OS [31, 32] (Fig. 2). Indeed, the TACTICS trial showed no significant difference in OS, which was the other primary endpoint. One possible reason for this is that 76.3% of patients in the TACE alone group also received post-trial treatment, and nearly half of these patients received sorafenib [1]. Nevertheless, the median survival benefit of 5.4 months can ultimately be interpreted as a clinically significant result.

Importance of Lessons Learned from Negative Trials

The TACTICS trial was designed based on lessons learned from previous negative trials. One reason for the trial’s success was that the trial drug sorafenib was administered prior to TACE as well as immediately after TACE and for as long as possible (median duration of administration: 28.2 months) to maximize its efficacy. Factors that may have contributed to the success of TACE include the use of conventional Lipiodol TACE and performing on-demand TACE with consideration of preserving liver function rather than scheduled TACE. This illustrates the importance of identifying the problems in previous similar clinical trials and applying them to the trial design.

Validity of RECICL in Response Evaluation Criteria in TACE Combination Trial for HCC

RECIST was developed as a standardized method for response evaluation in systemic therapy. However, the criteria are sometimes difficult to apply accurately to the treatment of HCC, which induces tumor necrosis rather than shrinkage. The mRECIST criteria consider the necrotic effects and are widely used in international clinical trials for HCC [33]. However, both RECIST and mRECIST consider new intrahepatic lesions as PD and therefore cannot be used as criteria for discontinuation of TACE because of the multicentric nature of HCC and the regional treatment nature of TACE. The appearance of a new lesion in an area not treated with TACE does not immediately imply treatment failure with a need to switch to the next line of treatment. Another treatment evaluation criteria used in Japan is the RECICL, which was developed by the Committee for Response Evaluation Criteria in Cancer of the Liver of the Japan Liver Cancer As-

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**Fig. 3.** Poorly differentiated HCC: ORR and OS in responders versus non-responders. Subanalysis in the REFLECT trial showed that the response rate to lenvatinib in poorly differentiated HCC was 47.6%, which was significantly higher than the response rate to sorafenib. Responders with poorly differentiated HCC had an extremely long survival period of 40.1 months, whereas non-responders had a shorter survival period of 8.4 months (HR 0.25 [p = 0.003]). Cited from Ref. [32] with permission.
sociation (formerly the Liver Cancer Study Group of Japan) [21, 22]. These criteria were designed to incorporate accurate assessment of viable lesions through bidirectional measurements and to consider the biological characteristics of HCC; their proposed concept of “not considering new intrahepatic lesions as PD” is in line with the definition of PD in actual clinical practice [21, 22]. Incorporating RECICL into the response evaluation criteria for the TACTICS trial eliminated the risk of early discontinuation in patients who could still benefit from TACE, and the positive result of the trial can be attributed to the fact that the trial was continued until the time to unTACEable progression.

**Concept of TACE-Specific PFS**

The definition of PFS used in the TACTICS trial was a newly proposed composite endpoint that was slightly different from that used for conventional systemic therapy. The purpose was to address the fact that typical PFS is not appropriate for determining the efficacy of locoregional therapy such as TACE. Specifically, whereas PD according to RECIST and death are considered events in typical PFS, new intrahepatic lesions that would meet the criteria for PD in RECIST would not be considered to indicate failure of TACE because they do not preclude effective repetition of TACE (i.e., these new lesions should not be interpreted as a reason to discontinue treatment). This clearly demonstrates the importance of the concept of TACE-specific PFS in TACE combination trials [1, 17, 25].

**Combination and Sequential Therapy with TACE and Systemic Therapy**

The success of the TACTICS trial clearly demonstrated the clinical benefits of treatment with antiangiogenic drugs plus TACE, either in combination or in sequence. Lenvatinib was later approved in 2018 [7] and has yielded an extremely high response rate (61% objective response rate) in intermediate-stage HCC [34]. It also yields an extremely high response rate of 47.6% in poorly differentiated HCC [35] and is expected to provide a long-term survival benefit in responders (Fig. 3) [35]. A proof-of-concept study also showed that lenvatinib followed by TACE (LEN-TACE sequential therapy) extends OS [36, 37], and many validation studies have verified this finding [38–41]. Although LEN-TACE sequential therapy is currently more widely used in routine practice than sorafenib-TACE sequential therapy [26, 27, 37], the TACTICS trial provided the theoretical framework for such an approach.

Atezolizumab plus bevacizumab combination therapy, which was approved in 2020, also has a potent tumor-shrinking effect, with an overall response rate of 44% in
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Intermediate-stage HCC [42]. Studies have already shown that cancer-free and treatment-free status can be achieved by inducing tumor shrinkage followed by locoregional therapy, including resection, ablation, or selective TACE [43–45]. In summary, after the clinical benefit of systemic therapy plus sequential TACE was first established in the TACTICS trial, similar studies were performed to validate the efficacy of this approach. In that sense, the TACTICS trial had an extremely large impact on the development of LEN-TACE sequential therapy or ABC conversion therapy (atezolizumab plus bevacizumab followed by curative conversion).

Conclusion

The TACTICS trial is a clinically important trial that demonstrated the potential of a new treatment concept: the combination or sequence of systemic treatment and TACE. A number of trials investigating TACE plus combination immunotherapy are ongoing (Fig. 4), and some of these, the TALENTACE trial (NCT04712643) or TACTICS-L trial (jRCTs031180074), are directly based on the TACTICS trial design. Response assessment for locoregional therapies requires a unique approach, unlike that used for systemic therapy, and the TACTICS trial was regarded as a landmark trial that established a basis for future TACE combination trials.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

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Data Availability Statement

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