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Research Progress of TACE Combined with Immunotherapy and Anti-Vascular Triple Therapy in Unresectable Hepatocellular Carcinoma

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Abstract

Unresectable hepatocellular carcinoma (HCC) is a highly prevalent malignancy with a poor prognosis. Because it is often diagnosed at an advanced stage and treatment options are limited, it poses a serious threat to patient health. Traditional modalities such as surgical resection and various local therapies have limited applicability for most patients, underscoring the urgent need for more effective systemic strategies. In recent years, triple therapy combining transarterial chemoembolization (TACE), immune checkpoint inhibitors, and anti-angiogenic therapy has become a focus of investigation. This approach has shown potential to improve tumor control and patient survival. This review synthesizes the latest clinical trial data and foundational research on TACE combined with immunotherapy and anti-angiogenic therapy for unresectable HCC and outlines prospects for future development.

Keywords

Hepatocellular Carcinoma, Unresectable, Transarterial Chemoembolization, Immunotherapy, Anti-Angiogenic Therapy

1. Introduction

HCC is a leading cause of cancer mortality worldwide—it is the sixth most common malignancy and the third leading cause of cancer death globally [1]. Only about 30% of patients are eligible for potentially curative therapies (resection or ablation), so most require non-surgical treatments [2] [3]. Notably, HCC incidence continues to rise, especially in Asia, which now accounts for roughly 70% -

75% of global liver cancer cases [1]. For patients with intermediate to advanced disease who are not candidates for resection or ablation, TACE has long been the standard liver-directed therapy (primarily for Barcelona Clinic Liver Cancer stage B). At the same time, stage migration and individualized strategies are increasingly emphasized by recent guidelines [4] [5]. However, conventional monotherapies—TACE alone or systemic therapy alone, often yield limited long-term control. This underscores an unmet need to enhance efficacy without compromising hepatic reserve [6].

Past attempts to combine TACE with molecular targeted therapy yielded limited success. For example, the phase III TACE-2 trial found no improvement in progression-free survival by adding sorafenib to TACE (median PFS ~8 months in both arms; HR ~0.99, P = 0.94), mirroring earlier negative studies with concurrent sorafenib. These setbacks underscored the need for more effective partners to augment TACE [7] [8]. Now, the advent of immune checkpoint inhibitors (ICIs) and modern anti-angiogenic agents has reinvigorated interest in TACE-based combination strategies. Recent randomized trials have begun to translate this concept into clinical benefit. In EMERALD-1, adding durvalumab (anti-PD-L1) plus bevacizumab (anti-VEGF) to TACE significantly improved progression-free survival (PFS) versus TACE with placebo (median 15.0 vs 8.2 months; HR 0.77, P = 0.032) [5]. Notably, a durvalumab-only arm in that study did not improve PFS over placebo (HR 0.94), underlining the necessity of pairing ICI with anti-VEGF in the post-TACE microenvironment [9]. The LEAP-012 phase III trial further showed that TACE combined with lenvatinib (multi-kinase VEGF inhibitor) and pembrolizumab (anti-PD-1) prolonged PFS (14.6 vs 10.0 months; HR 0.66; P = 0.0002), with a safety profile consistent with known effects of the components [10]. Most recently, the TALENTACE international phase III study reported that on-demand TACE (repeat TACE sessions administered as needed based on imaging evidence of residual or recurrent viable tumor) plus atezolizumab (anti-PD-L1) and bevacizumab improved TACE-specific PFS (11.3 vs 7.0 months; HR 0.71, P = 0.009) and objective response rate (ORR 49.1% vs 33.9%) over on-demand TACE alone, although overall survival data remain immature (median ~34.5 vs 35.4 months at first analysis) [11]. Collectively, these studies suggest that a TACE-anchored "triple therapy" (TACE + ICI + anti-vascular agent) can raise response rates and delay progression in unresectable HCC (uHCC), with safety profiles consistent with the component therapies.

In this review, we synthesize global progress from the past five years on TACE-based triple therapy for uHCC, including its mechanistic underpinnings, key efficacy outcomes, comparative strategic approaches, and current challenges for research and practice.

2. Mechanistic Rationale for Triple Therapy

2.1. Immunogenic Effects of TACE and Vascular Normalization

TACE causes acute tumor ischemia and necrosis, releasing damage-associated

molecular patterns (DAMPs) and tumor neoantigens into the microenvironment. These DAMPs (e.g., calreticulin, HMGB1) and antigens can be taken up by dendritic cells, priming tumor-specific T-cell responses. In effect, TACE may function as an *in situ* vaccine, and embolization has been associated with transient augmentation of antigen-specific immunity and rises in inflammatory cytokines (e.g., IL-6, IL-17) [12]-[15]. These findings support the idea that TACE can spark antitumor immunity, which could be harnessed by ICIs.

However, TACE also induces profound hypoxia. Hypoxia drives VEGF expression and PD-L1 upregulation via HIF-1α-dependent pathways, and recruits suppressive immune cells (myeloid-derived suppressor cells, Tregs, M2 macrophages). Indeed, studies of resected tumors show that TACE-treated HCCs have higher PD-L1 expression on tumor and immune cells compared to untreated tumors [16]-[18]. This adaptive immune resistance likely limits the efficacy of TACE alone. Anti-VEGF therapies (e.g., bevacizumab) and VEGF-pathway TKIs (lenvatinib, others) can counteract these effects. At optimal dosing, anti-angiogenics transiently "normalize" the tumor vasculature, decreasing vessel permeability and interstitial pressure, thereby improving perfusion and reducing hypoxia. Better perfusion allows chemotherapy, oxygen, and immune cells to reach the tumor more effectively, and limits hypoxia-driven immunosuppression. This concept is supported by experimental data: anti-VEGF treatment in HCC models increases infiltration of $CD8^+$ T cells and other effectors, and creates a positive feedback loop whereby activated Th1-type T cells further reinforce vascular normalization [19]-[22].

In parallel, VEGF blockade directly reprograms the immune microenvironment. VEGF is a pleiotropic immunomodulator: it impairs dendritic-cell maturation, supports the expansion of myeloid suppressors and Tregs, and blunts cytotoxic T-cell activity. Blocking VEGF (or related FGF/PDGF via TKIs) restores dendritic-cell function and decreases immunosuppressive cells. For example, transcriptomic analyses of HCC samples reveal that lenvatinib enriches interferon-γ/T-cell gene signatures and reduces inhibitory macrophage markers; it also lowers levels of resistance-associated cytokines like IL-8 and Ang-2. *In vitro* and animal studies further show that lenvatinib shifts tumor-associated macrophages from an M2-like (suppressive) to an M1-like (pro-inflammatory) phenotype. Thus, anti-angiogenic agents in triple therapy serve as immune modulators that amplify the "antigenic spark" of TACE by fostering a more permissive TME for effector T cells [23]-[26].

2.2. PD-1/PD-L1 Upregulation and Checkpoint Blockade

Programmed death-ligand 1 (PD-L1) is an immune checkpoint extensively upregulated in HCC and associated with immune escape. In HCC, PD-L1 expression is induced by oncogenic pathways (e.g., MAPK, β-catenin) and inflammatory signals [27]-[29]. Notably, TACE-induced hypoxia directly increases PD-L1: animal models and patient samples demonstrate that PD-L1 (and PD-1) mRNA and pro-

tein levels rise after embolization [16]. Clinically, higher PD-L1 expression in resected HCC has been associated with increased recurrence risk in some cohorts, though the prognostic impact specifically after TACE remains uncertain. Introducing anti-PD-1/PD-L1 therapy with or shortly after TACE can block this escape mechanism. By unleashing $CD8^+$ T cells on newly exposed tumor antigens, ICIs can convert the transient immune activation from TACE into broader tumor control [12] [30].

2.3. Timing and Scheduling Considerations

Optimizing the sequencing of TACE relative to immunotherapy and anti-angiogenics is an area of active investigation. The concept of a "vascular normalization window" suggests that anti-angiogenic drugs should be administered at a time that transiently maximizes perfusion (typically achieved with moderate dosing over several days to weeks) [31] [32]. Outside the optimal "normalization window," anti-VEGF therapy can paradoxically worsen tumor hypoxia by over-pruning vessels. For example, high-dose or prolonged VEGF blockade can excessively prune tumor vasculature, increasing hypoxia and promoting compensatory angiogenesis [33]. In practice, protocols have varied: trials such as EMERALD-1 and LEAP-012 integrated ICIs and VEGF-pathway blockade at or shortly after the first TACE, whereas TALENTACE used an on-demand TACE strategy with systemic therapy initiated soon after each TACE [9] [10] [34]. Some clinical designs (e.g., TACTICS and TACTICS-L) deliberately administered VEGF-targeted therapy 2-21 days before the first TACE to exploit putative vascular normalization [35] [36]. Others have tried induction TKI therapy before the first TACE, but such approaches risk delaying tumor debulking.

Currently, most contemporary phase 3 protocols initiate systemic agents at or around the first TACE rather than after multiple TACE cycles. Whether TACE should be repeated on a fixed schedule or "on demand" (based on imaging response) remains under study; TALENTACE indicates that on-demand TACE can be paired with combined systemic therapy. Ultimately, optimal timing likely varies by patient factors and drug characteristics, and remains an important focus for future research.

2.4. TACE Technique: cTACE vs. DEB-TACE

The choice of embolic modality may also influence triple-therapy outcomes. Both conventional TACE (cTACE) and drug-eluting bead TACE (DEB-TACE) achieve tumor ischemia but differ in delivery characteristics and adverse-event profiles [37]. Some studies indicate that DEB-TACE produces higher local drug exposure with lower systemic spillover. In the triple-therapy context, DEB-TACE may offer more controlled intratumoral drug release; however, evidence for reduced hypoxia is limited [38]. In practice, major trials have allowed either cTACE or DEB-TACE per investigator/site selection. DEB-TACE may be preferred when minimizing post-embolization syndrome is a priority [39]. Regardless of the embolic

used, TACE-induced tumor necrosis and antigen release can help prime anti-tumor immunity.

2.5. Biomarkers and Other Mechanisms

Beyond VEGF/PD-L1, several other pathways and biomarkers are under investigation. TACE can activate the cGAS-STING pathway in tumor cells, further stimulating interferon responses; however, evidence in HCC is preliminary. Early data suggest that pro-inflammatory/angiogenic cytokines such as IL-6 and IL-8 increase around embolization and may be associated with resistance or early progression [40] [41]. Radiomic and immunologic predictors of response to TACE (with or without immunotherapy) are also being explored [42]. For example, dynamic changes in the neutrophil-to-lymphocyte ratio (NLR) after TACE have been linked to response and survival, and high expression of exhaustion markers such as TIM-3 correlates with worse prognosis in HCC [43]-[45]. Ultimately, no validated biomarker yet guides which patients need triple therapy, but ongoing translational studies are actively seeking signatures (genomic, immunologic, imaging) that predict benefit.

3. Clinical Evidence: Efficacy and Safety

3.1. Phase 3 Trial Results

EMERALD-1 (TACE + durvalumab ± bevacizumab)—In this global, randomized, double-blind phase 3 trial (NCT03778957), embolization-eligible uHCC patients received protocol-defined TACE and were assigned to durvalumab plus bevacizumab, durvalumab plus placebo, or placebo. The primary endpoint was blinded independent central review (BICR)-assessed PFS. In the Lancet report, median PFS was 15.0 months with durvalumab + bevacizumab + TACE versus 8.2 months with TACE + placebo (HR 0.77; P = 0.032); the durvalumab-only arm did not improve PFS. Confirmed objective response also improved with durvalumab + bevacizumab versus TACE alone (≈44% vs ≈30% in prespecified analyses), while overall survival data remained immature but trended favorably. Grade 3 - 4 adverse events were more frequent with the triple regimen, with hypertension among the most common high-grade events and no treatment-related deaths in that arm. These results establish a PFS benefit of durvalumab + bevacizumab + TACE over TACE alone and support the synergy concept [9].

LEAP-012 (TACE + lenvatinib + pembrolizumab)—This multicenter, randomized, double-blind phase 3 trial (NCT04246177) assigned patients with unresectable, non-metastatic HCC eligible for embolization to TACE plus lenvatinib + pembrolizumab versus TACE plus dual placebo; the primary endpoints were BICR-assessed PFS and OS. Reported in early 2025, the combination significantly improved median PFS (14.6 vs 10.0 months; HR 0.66; one-sided P = 0.0002). At 24 months, estimated OS rates were 75% vs 69% (HR 0.80; one-sided P = 0.087), indicating a numerical trend that did not meet the pre-specified boundary. Grade ≥3 toxicities were more frequent with the triple regimen (71% vs 32%), with hy-

pertension (24% vs 7%) and decreased platelet count (11% vs 6%) among the most common high-grade events; treatment-related deaths occurred in 2% vs <1%. In summary, LEAP-012 demonstrated a substantial PFS benefit with added toxicity, and longer follow-up is needed for definitive OS results [10].

TALENTACE (TACE + atezolizumab/bevacizumab)—This open-label Asian (China/Japan) phase 3 study randomized patients with systemically untreated, intermediate- to high-burden uHCC to on-demand cTACE plus atezolizumab/bevacizumab vs cTACE alone, with the primary endpoint of TACE-PFS (investigator-assessed). Preliminary ESMO GI 2025 results showed a significant TACE-PFS improvement (median 11.3 vs 7.0 months; HR 0.71; P = 0.009); RECIST 1.1 ORR was higher with the combination; OS data were immature without a definitive difference at this cut, and safety was consistent with the known profiles of the agents without new signals. Overall, these data support that adding ICI + anti-VEGF to TACE can delay progression and increase response, in line with EMERALD-1 and LEAP-012 [11].

3.2. Phase 2 and Real-World Evidence

Several smaller studies and retrospective analyses further support triple-therapy efficacy. A propensity-matched study in BMC Cancer (2024) compared TACE + lenvatinib + camrelizumab versus TACE alone in 222 patients: the triple group had markedly higher ORR (88.6% vs 28.6%), longer median PFS (12.7 vs 6.1 months) and OS (19.4 vs 13.0 months) [46]. Another two-centre series reported that DEB-TACE + lenvatinib + camrelizumab yielded longer PFS and OS than DEB-TACE-based doublet therapy (about 10 vs 6 months for PFS) [47]. Meta-analyses echo these findings, generally showing improved tumour control and survival with TACE-based triple therapy over TACE or doublet regimens, though most included cohorts were Asian and HBV-predominant [48]. Consequently, prospective trials remain essential.

Doublet combinations (TACE + ICI or TACE + TKI) have also been explored. Small prospective studies of TACE + pembrolizumab and randomized studies of TACE + sorafenib show activity in selected settings, but overall the signal has not matched the robustness seen with modern triples [35] [49] [50]. In practice, triple regimens now dominate research pipelines, and multiple ongoing trials are testing other ICI/anti-VEGF pairs and CTLA-4-containing backbones with TACE.

3.3. Safety

Safety across the phase III programs aligns with the known profiles of TACE, ICIs, and anti-angiogenic therapies. Each component contributes its expected toxicities, and combinations must be managed to avoid additive harm to liver function. In general, triplet therapy increases the frequency of Grade ≥3 adverse events compared to TACE alone or TACE + placebo, largely due to well-known VEGF-inhibitor or TKI side effects and the additive impact of TACE (post-embolization syndrome). Importantly, however, no new safety signals have emerged, and treat-

ment-related mortality has remained low and comparable between arms when patients are properly selected (typically Child-Pugh A liver function).

In summary, triple therapy does increase toxicity compared to TACE alone, and careful patient monitoring is required. The most common added toxicities come from the systemic agents: hypertension, hand-foot skin reactions or diarrhea (TKIs), proteinuria and bleeding risk (bevacizumab), and ICIs. Post-embolization symptoms can be worse when systemic therapy is ongoing (e.g., fever, fatigue). However, with proactive management - including blood pressure control, thyroid function monitoring, dermatologic care, and prompt immunosuppressive treatment for grade ≥2 immune toxicities - these side effects are generally manageable. Importantly, rates of treatment discontinuation due to AEs have been relatively low (in LEAP-012, 18% discontinued all treatment on triplet vs 5% on control) [10]. No trial reported a significant excess of fatal AEs with triplets. For example, in EMERALD-1 no treatment-related deaths occurred on triplet [9]. This indicates that with proper patient selection (favoring those with robust performance status and liver function) and multidisciplinary toxicity management, the benefit-risk profile of triple therapy is favorable.

4. Integration Strategies and Comparative Approaches

4.1. Systemic Agent Selection

Multiple ICI/anti-VEGF combinations are available, and the optimal choice with TACE is not fully established. Atezolizumab/bevacizumab is the current standard first-line systemic therapy for advanced HCC; its use with TACE (as in TALENTACE) is logical [11] [51] [52]. In practice, selection may depend on region (some approvals vary by country), side-effect profiles, and cost. For example, bevacizumab carries gastrointestinal/variceal bleeding risk, whereas lenvatinib commonly causes fatigue and hypertension [53] [54]. No head-to-head randomized data exist comparing different triple regimens; cross-trial comparisons should be avoided [55]. For example: 1) blinding/design: double-blind, placebo-controlled phase III in EMERALD-1/LEAP-012 vs. open-label randomized in TALENTACE; 2) eligibility: LEAP-012 restricted to Child-Pugh A, no PVT, and lesions treatable in 1 - 2 TACE sessions; EMERALD-1 allowed Child-Pugh A-B7 and excluded only major PVT; TALENTACE excluded extrahepatic disease but enriched for higher tumor burden (diameter + number ≥ 6). Beyond PD-(L)1 inhibitors, CTLA-4 blockade (e.g., tremelimumab) is being tested with TACE in ongoing studies and could expand options if positive.

4.2. DEB-TACE vs cTACE

DEB-TACE has been postulated to synergize with systemic therapy by enabling sustained intratumoral chemotherapy release [56]. Limited data suggest that TACE—including DEB-TACE in some series—combined with lenvatinib plus camrelizumab yields high response rates [57]. In major ongoing trials, randomized head-to-head comparisons of DEB-TACE versus cTACE within triple regi-

mens have not been performed; instead, the TACE modality (cTACE or DEB-TACE) is pre-specified per site and delivered according to local practice [58]. DEB-TACE may attenuate post-procedural VEGF elevation relative to cTACE, potentially moderating hypoxia-driven inflammatory signaling; however, this has not been validated specifically within triple-therapy regimens. In summary, both embolic types are acceptable; interventional teams should prioritize super-selective, high-quality TACE technique to optimize local control.

5. Discussion

Recent evidence positions TACE-based triple therapy as a significant advance in managing unresectable HCC. The combination of locoregional and systemic modalities is supported by complementary mechanisms. TACE triggers tumor-antigen release and inflammation, while concurrent VEGF inhibition and PD-(L)1 blockade counteracts the ensuing immunosuppression [59]-[62]. Clinically, this synergy translates into improved intermediate outcomes. Phase III trials (EMERALD-1, LEAP-012, TALENTACE) consistently show that adding an ICI plus an anti-VEGF agent to TACE extends PFS and increases response rates compared with TACE alone [9]-[11]. Retrospective studies and meta-analyses broadly echo these findings [63] [64], whereas prior attempts at TACE plus single-agent targeted therapy did not yield similar benefits [7] [8].

Despite these encouraging results, overall survival benefits remain to be proven. Interim OS analyses have trended favorably but not reached significance, underscoring the need for longer follow-up. From a safety perspective, adding systemic therapy predictably increases high-grade toxicity, particularly hypertension, hand-foot reactions, and immune-related events. However, adverse events have generally been consistent with known drug profiles, manageable with standard interventions, and have not led to unexpected complications or excess fatalities [9] [10]. Importantly, careful patient selection is critical to maintain a favorable benefit-risk balance. In practice, "careful patient selection" has meant enrolling only those with favorable baseline features. All three trials included unresectable, locoregional HCC (no extrahepatic metastases) in otherwise fit patients. Key eligibility criteria were generally: preserved liver function (Child-Pugh A, with EMERALD-1 also allowing B7) and good performance status (ECOG 0-1), measurable HCC confined to the liver, and no major portal vein tumor thrombus beyond segmental branches. For example: EMERALD-1: Unresectable HCC amenable to TACE, Child-Pugh A-B7, ECOG 0-1, no extrahepatic disease, measurable by mRECIST; patients with Vp3/Vp4 thrombosis were excluded. LEAP-012: Intermediate-stage, unresectable HCC, Child-Pugh A only, ECOG 0-1, no portal vein thrombosis or metastases. Crucially, all tumors had to be treatable with 1-2 TACE sessions. These strict criteria suggest that ideal candidates for triple therapy are otherwise fit patients with bulky, multifocal liver tumors that are not curatively resectable but still amenable to locoregional treatment. Patients with poor liver function, extensive metastases, or diffuse vascular invasion were generally excluded.

Biomarkers and selection: Beyond clinical criteria, novel biomarkers are being explored to predict which patients might benefit. Circulating tumor DNA (ctDNA) is one promising avenue. For instance, ultra-deep sequencing of ctDNA for common HCC driver mutations (CTNNB1, TP53, ARID1A, etc.) has been shown to stratify outcomes after locoregional therapy. In one study, detection of these mutations in plasma prior to TACE predicted poorer survival [65]. This suggests ctDNA could help predict which tumors are likely to progress despite TACE. Similarly, radiomics—quantitative image analysis, offers non-invasive predictors. Recent models using pre-treatment CT or MRI features have discriminated responders from non-responders to immunotherapy in HCC. In one report, specific CT texture features differed significantly between partial responders and non-responders to checkpoint inhibitors, and an XGBoost model using these radiomic features accurately forecasted short-term immunotherapy efficacy [66]. Integrating such biomarkers (ctDNA levels/mutations, radiomic signatures, etc.) into trials could improve patient selection by identifying tumors likely to respond to or resist triple therapy.

Looking ahead, several practical questions merit further research. The optimal timing and sequencing of TACE and systemic agents remain unsettled: while current phase III protocols often start ICIs/anti-VEGF at or soon after the first TACE, future studies may clarify whether priming or maintenance approaches improve outcomes. Biomarker-driven patient selection is another key area: as yet, no validated marker predicts which patients benefit most from triple therapy [37] [67]. Exploratory signals such as post-TACE neutrophil-to-lymphocyte ratio or checkpoint expression warrant prospective evaluation [44] [68]. Additionally, the broad application of triple therapy must consider resource implications, patient comorbidities, and regional treatment availability.

In summary, TACE combined with ICIs and anti-angiogenic therapy is a mechanistically sound and clinically promising approach for unresectable HCC. It achieves deeper tumor control by simultaneously eliciting immune activation and removing inhibitory signals [59] [61]. Ongoing and planned trials, along with translational biomarker research, should refine how to best integrate these modalities. Such efforts will be essential to fully harness the potential of triple therapy and establish it as a standard option for appropriate patients.

6. Summary

Transarterial chemoembolization combined with immune checkpoint inhibitors and anti-angiogenic therapy offers a synergistic treatment paradigm for unresectable HCC. This triple therapy amplifies TACE-induced immune activation and counteracts hypoxia-driven immunosuppression, leading to improved tumor control and progression-free survival in recent trials. Although the enhanced efficacy is accompanied by increased toxicity, careful patient selection and proactive adverse-event management have generally maintained a favorable benefit-risk balance. Notably, systemic atezolizumab-bevacizumab is now a standard first-line

therapy in advanced HCC, underscoring the value of simultaneously targeting immune checkpoints and angiogenesis. Integrating such agents with locoregional TACE thus represents a logical extension that has demonstrated improved outcomes. Continued efforts should focus on optimizing treatment sequencing, drug selection, and biomarker-driven strategies to fully realize the potential of this multimodal approach.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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