



Combination makes strength: a narrative review of transarterial radioembolization plus immune checkpoint inhibitors for hepatocellular carcinoma

Rusi Chen¹, Giovanni Monaco¹, Bernardo Stefanini^{1^}, Mariarosaria Marseglia^{2^}, Stefania De Lorenzo^{3^}, Francesco Tovoli^{1,2^}

¹Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; ²Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ³Oncology Unit, Azienda USL Bologna, Bologna, Italy

Contributions: (I) Conception and design: R Chen, B Stefanini; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: R Chen, G Monaco, B Stefanini, S De Lorenzo; (V) Data analysis and interpretation: F Tovoli, M Marseglia; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Francesco Tovoli, MD. Department of Medical and Surgical Sciences, University of Bologna, Via Massarenti 9, 40134 Bologna, BO, Italy; Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. Email: francesco.tovoli@unibo.it.

Background and Objective: Immune checkpoint inhibitors (ICIs) and transarterial radioembolization (TARE) are now regarded as promising and versatile therapies for hepatocellular carcinoma (HCC). Combining TARE and ICIs may offer synergistic antineoplastic effects by integrating local and systemic tumor control. This review critically discusses recent preclinical evidence supporting the TARE-ICI combination strategy, completed and ongoing clinical trials, and the challenges in identifying optimal target populations and treatment protocols.

Methods: A comprehensive literature search was conducted in multiple electronic databases (PubMed, Scopus, and Web of Science) from January 1999 to January 2024. The first part of the search was directed at identifying concluded studies regarding the TARE-ICIs combination. The second part aimed at identifying ongoing clinical trials exploring the Clinicaltrials.gov database.

Key Content and Findings: The combination of TARE and ICIs is a promising strategy, supported by preclinical evidence of immune activation post-TARE and potential synergies with ICIs. Early-phase clinical trials have reported encouraging efficacy. However, significant heterogeneity exists among these studies, particularly concerning target populations and treatment schedules.

Conclusions: The current evidence on TARE-ICI is favorable and promising in improving outcomes of patients with HCC. Further conclusive and higher levels of evidence are pending.

Keywords: Hepatocellular carcinoma (HCC); immunotherapy; radioembolization; selective internal radiotherapy; immune checkpoint inhibitors (ICIs)

Submitted Feb 29, 2024. Accepted for publication Jul 28, 2024. Published online Oct 08, 2024.

doi: 10.21037/cco-24-27

View this article at: <https://dx.doi.org/10.21037/cco-24-27>

[^] ORCID: Bernardo Stefanini, 0000-0003-3800-5678; Mariarosaria Marseglia, 0000-0002-5829-4537; Stefania De Lorenzo, 0000-0002-4866-4864; Francesco Tovoli, 0000-0002-8350-1155.

Introduction

Background

Hepatocellular carcinoma (HCC) is a significant global health challenge, responsible for over 800,000 deaths annually (1). Despite the expansion of the therapeutic arsenal over the past two decades, the 5-year survival rate for this cancer continues to be low (17%) (1). Treatment options for advanced stage are the fastest growing sector among treatment options for HCC. The introduction of immune checkpoint inhibitors (ICIs) marked a revolutionary shift in therapy. Notably, in the last 5 years, combinations such as atezolizumab with bevacizumab (2), sintilimab with bevacizumab (3), durvalumab and tremelimumab (4) have shown superiority over sorafenib. Additionally, single-agent ICIs tislelizumab (5) and durvalumab (4) have reached non-inferiority to sorafenib.

Despite these advancements, the radiological response rates for HCC remain between 10–15% for single agents and up to 30% for combination regimens (6).

Alongside systemic anti-cancer treatments, transarterial radioembolization (TARE) has emerged as a significant innovation in HCC management. TARE, a type of intra-arterial brachytherapy using Yttrium-90 (Y90)-labeled resin or glass particles (SIR-Spheres or TheraSphere, respectively) was approved by the Food and Drug Administration (FDA) in 2021 for patients with unresectable HCC (7,8).

This method offers versatility in targeting lesion size, customizing radiation doses, and potential benefits over other locoregional treatments, particularly in the presence of portal vein thrombosis (9,10).

Looking ahead, combining ICIs with locoregional treatments such as TARE holds promise for both advanced and earlier stages of HCC. This strategy aims to increase the number of patients eligible for curative interventions, including liver transplantation (11). Specifically, integrating TARE with ICIs may convert an immunosuppressive tumor microenvironment (TME) into an immune-supportive setting, enhancing the efficacy of ICIs and mitigating the adverse effects of embolization-induced hypoxia (especially when ICIs are combined with anti-angiogenic agents) (11–15).

Rationale and knowledge gap

The combination of TARE with ICIs has a strong preclinical rationale and holds significant theoretical potential in clinical practice. However, clinical data remain

sparse. A comprehensive collection of both clinical and preclinical data is needed to provide practical information on this topic, helping clinicians understand the current limitations and future directions.

Objective

In this review, we will summarize the current evidence regarding the use of TARE in HCC, examine the data supporting its combination with ICIs, and discuss ongoing studies evaluating this promising therapeutic approach. We present this article in accordance with the Narrative Review reporting checklist (available at <https://cco.amegroups.com/article/view/10.21037/cco-24-27/rc>).

Methods

We searched the PubMed, Scopus, and Web of Science databases from January 1999 to January 2024 using the following query: “hepatocellular carcinoma” AND (“transarterial radioembolization” OR “selective internal radiotherapy”) AND (“immune checkpoint inhibitors” OR “immunotherapy” OR “nivolumab” OR “atezolizumab” OR “durvalumab” OR “tremelimumab”). Following the removal of duplicate articles, this search yielded 98 results. After excluding non-original articles and non-English language studies, 11 studies were included in this review. Overall survival (OS), progression-free survival (PFS), response rate, and safety were considered outcome of special interest. The baseline characteristics of the study populations were also analyzed.

Moreover, to report and describe the ongoing clinical trials of TARE + ICIs, we accessed Clinicaltrials.gov in January 2024, selecting the following options for condition/disease: “Liver cancer”, “Hepatocellular carcinoma”, “Hepatocellular cancer”, “Hepatocellular carcinoma Non-resectable”, “Hepatocellular carcinoma/(HCC/)”. We identified seven ongoing studies. The search and selection of articles were conducted independently by R.C., G.M., and M.M., and then reviewed by B.S., S.D.L., and F.T. Consensus was obtained after discussion with the senior author (F.T.).

The search strategy summary is provided in *Table 1*.

Discussion

Current role of TARE in HCC

TARE faced setbacks in recent Phase 3 randomized

Table 1 The search strategy summary

Items	Specification
Date of search	15 January 2024
Databases and other sources searched	PubMed, Scopus, Web of Science, Clinicaltrials.gov
Search terms used	“transarterial radioembolization”; “selective internal radiotherapy”; “hepatocellular carcinoma”; “immune checkpoint inhibitors”; “immunotherapy”; “nivolumab”; “atezolizumab”; “durvalumab”; “tremelimumab”
Timeframe	Inception of database to July 2023
Inclusion criteria	Original articles relevant to TARE and immunotherapy in English language
Selection process	The search and selection of articles were conducted by R.C., G.M., M.M. These were then reviewed by B.S., S.D.L., and F.T. Search and selection was conducted independently, consensus was obtained after discussion with the senior author (F.T.)

TARE, transarterial radioembolization.

controlled trials SARAH and SIRveNIB, which reported negative outcomes when TARE was compared to sorafenib, then the standard treatment for advanced-stage HCC (16,17). Additionally, the Phase 3 SORAMIC trial showed that adding TARE to sorafenib did not confer a survival advantage over sorafenib monotherapy (18). These trials were hindered by poor patient selection, enrolling individuals with extensive liver neoplastic occupation (up to 70%), who had a limited chance of achieving a meaningful response and an increased risk of radiation-induced liver damage.

With immune-based combinations emerging as the new standard of care, innovative associations of TARE and systemic therapies are now under investigation. Today, TARE can be applied across nearly all Barcelona Clinic for Liver Cancer (BCLC) stages, provided patients have preserved liver function (Child-Pugh A–B7), normal serum bilirubin levels, limited tumor load (less than 50% liver involvement), and a low percentage of lung shunt (19) (*Figure 1*).

In early-stage HCC (BCLC-0 or -A), an ablative dose of Y90 can be delivered to up to two liver segments for radiation segmentectomy. This is considered a third option for non-surgical candidates with lesions in locations unsuitable for ablation (20). Based on the results of the LEGACY trial, the latest BCLC update now consider as a viable treatment option for early-stage HCC with a single nodule less than 8 cm (21).

In the BCLC-B class, TARE exhibits a safety profile similar to that of transarterial chemoembolization (TACE), making it suitable for patients with portal vein thrombosis due to its lower risk of hepatic failure compared to TACE (22). Unlike TACE, TARE causes less significant vascular blockage due to the smaller diameter of Y90 microspheres, resulting in

a lower ischemic effect and a threefold lower incidence of postembolization syndrome (23). Given the available data, Y90 treatment is safe for patients with compromised portal circulation at the level of the first-order portal branches (24).

TARE is also applicable in advanced HCC (BCLC-C), particularly for patients with neoplastic vascular invasion. Several studies indicate its potential for downstaging disease in patients with portal vein tumor thrombus, especially in those with thrombus in the portal vein branch and preserved liver function (24–27).

Pre-clinical rationale for combination treatment (TARE + ICI)

Several studies in recent years have demonstrated the concept of immune activation following TARE. Since the early 2000s, radiation has been hypothesized to promote an anti-tumoral immune response by increasing tumor antigen presentation, as shown by increased tumor cell major histocompatibility class I (MHC I) expression following external γ -beam radiation (28). Observations of the abscopal effect, where distant oncological responses occur after local therapy (29,30) further support the idea of significant immune stimulation triggered by interventional procedures, particularly irradiation (31).

In 2019, Chew *et al.* (32) analyzed the immune profile of surgically resected HCC downstaged with TARE. They observed increased CD56⁺ natural killer (NK) cells, CD8⁺CD56⁺ natural killer T (NKT) cells, granzyme B (GB)⁺ CD8⁺ T cells, and CD4⁺ T cells in Y90 TARE-treated HCC specimens compared to treatment-naïve patients. Additionally, the authors found a higher expression

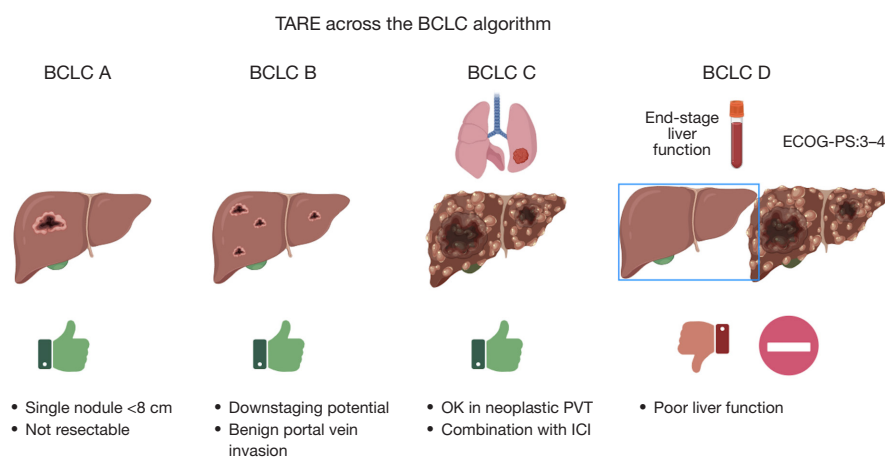


Figure 1 Possible applications of transarterial radioembolization across the BCLC stages. TARE, transarterial radioembolization; BCLC, Barcelona Clinic for Liver Cancer; ECOG-PS, Eastern Cooperation Group-performance status; PVT, portal vein thrombosis; ICI, immune checkpoint inhibitor.

of chemotactic cytokines CCL5 and CXCL16, which are associated with the recruitment and homing of activated T cells. Comparing peripheral blood mononuclear cells (PBMCs) before and after TARE, the authors noted an increase in tumor necrosis factor (TNF)- α expression on both CD8⁺ and CD4⁺ T cells one month after TARE, as well as a higher percentage of antigen-presenting cells 3 months post-TARE, indicating systemic immune activation. Interestingly, patients with sustained objective responses post-TARE exhibited higher pre- and post-TARE percentages of CD8⁺ T cells expressing PD-1 and TIM3, markers of T cell exhaustion that may indicate higher peripheral T cell activation.

A more recent study retrospectively analyzed 60 patients treated with partial hepatectomy for HCC, with about half undergoing pre-operative TACE or TARE (33). TARE-treated patients showed a significant increase in CD3⁺ tumor-infiltrating lymphocytes (TILs) and GB expression compared to those receiving TACE. The type of immune infiltrate was influenced by the dose of irradiation, with lower doses (<100 Gy) associated with a higher peri-tumoral CD3⁺ TIL ratio and higher doses (>100 Gy) associated with more intra-tumoral CD4⁺ cells. In this study, although pre-operative TARE generated significant modifications of the TME while pre-operative TACE did not, neither treatment improved OS or PFS after partial hepatectomy compared to the surgery-only group, confirming previous observations (34-37). These findings suggest that the immune cells recruited locally after TARE may not acquire full functionality, failing to generate a robust anti-tumor response in the remaining liver tissue.

Combination regimens with ICIs or other immunotherapies may, at least partially, overcome these resistance mechanisms (Figure 2) (38).

Rivoltini *et al.* (39) later observed an increase in circulating CD3⁺ T cells, GB⁺ CD8⁺ T cells, CD4⁺ T cells, and Tregs in the peripheral blood of TARE patients, peaking at 1-month post-treatment and decreasing at 3 and 6 months. Notably, these TARE-induced T cells exhibited high levels of PD-1 and LAG-3, especially in responders, suggesting a potentially dysfunctional immune response with immediate anti-tumoral activity but lacking long-term immunological memory. In this context, the timely delivery of ICIs against the PD-1/PD-L1 or LAG-3 pathways may restore the anti-tumoral immune response and guarantee long-term clinical outcomes (11).

Locoregional treatments can also induce immunosuppressive factors (IL-6, VEGF, HIF-1 α , TGF- β , PD-1, and PD-L1), which may stimulate Treg accumulation and cause lymphopenia, leading to tumor progression (12,13,15). Consistent with this evidence, a German study found that TARE caused severe impairment of the cellular immune response, with decreased lymphocyte proliferation and interferon- γ production lasting until day 28 post-therapy (40). Lymphopenia was affecting all subsets (CD3⁺, CD4⁺, CD8⁺ T cells, B cells and NK cells), and also included a reduction in the percentage of activated HLA-DR⁺ monocytes and of CD45RO⁺ memory T cells. The authors proposed that the drop of lymphocyte counts was a result of radiation induced DNA damages on the circulating lymphocytes.

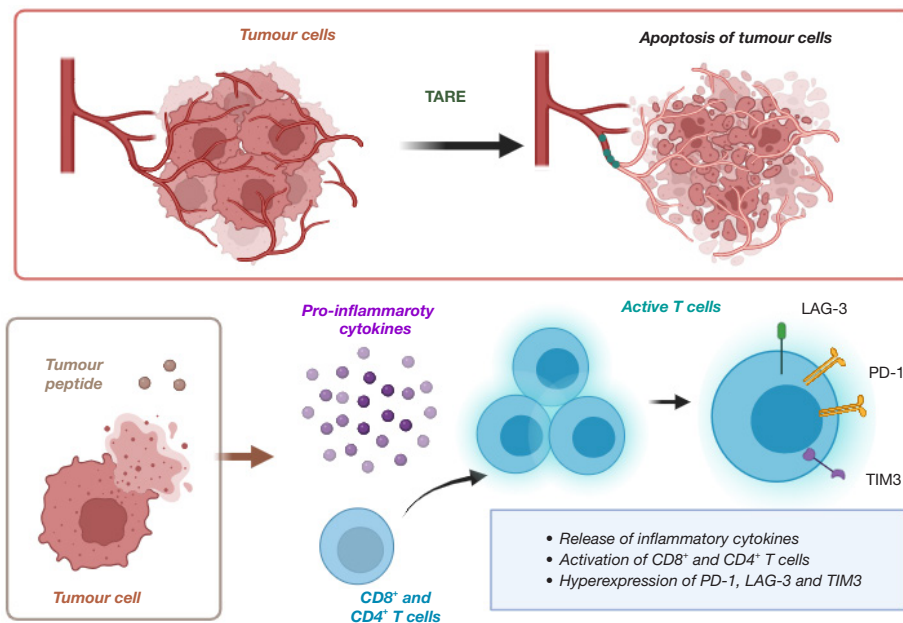


Figure 2 Mechanism of potential synergistic effects between of TARE and immune checkpoint inhibitors, based on preclinical evidence. TARE may induce apoptosis of tumour cells, with the release of tumours peptides. These tumour-associated antigens, together with pro-inflammatory cytokines lead to activation of T-lymphocytes. Lymphocytes activation in counterbalanced by the expression of immune checkpoints such as PD-1, TIM3, and LAG-3. Immune checkpoints physiologically prevent uncontrolled immune proliferation, but can be inappropriately be activated by tumour cells leading to tumour immune escape, which can be prevented using immune checkpoint inhibitors. TARE, transarterial radioembolization; PD-1, programmed death-1; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; LAG-3, lymphocyte-activation gene 3.

Although more research is needed and some data are conflicting, the potential synergistic benefit of combining TARE with ICIs has generated growing interest, particularly regarding their clinical application.

Evidence from concluded studies

Published clinical evidence regarding the combination of TARE and systemic treatment is still limited, particularly in the context of combining TARE with ICIs. *Table 2* summarizes the published studies investigating this combination strategy for HCC.

Tai *et al.* published the results of a Phase II trial combining TARE with nivolumab 240 mg every 2 weeks, starting 21 days after the procedure. Among the 36 patients with advanced HCC who received TARE and nivolumab, the authors reported an objective response rate (ORR) of 30.6% [95% confidence interval (CI): 16.4–48.1%], with only one complete response (CR) (41). A similar study by de la Torre-Aláez *et al.* involved 41 patients who received nivolumab after TARE, achieving a remarkable ORR of

41.5%. However, it is noteworthy that only a quarter of the patients in this study were classified as BCLC-C (42).

Marinelli *et al.* conducted a retrospective study analyzing a cohort of patients who received nivolumab approximately within 60 days before TARE until the date of the procedure. Nivolumab was then resumed following the same schedule. Among the 21 enrolled patients, the median OS was 12.0 months, with a median follow-up of 8.8 months. While the ORR of the targeted lesion was highly encouraging, the ORR for the overall disease was 20%, with a median time-to-progression of 4.3 months (43).

Zhan *et al.* analyzed a similar cohort of 26 patients (18 receiving only nivolumab, 8 receiving nivolumab plus ipilimumab) who were exposed to systemic treatment before receiving TARE (44). This single-center retrospective study, conducted between 2015 and 2018, primarily focused on the safety profile but also provided efficacy data, showing a median OS of 16.5 and 17.2 months from TARE and the first dose of immunotherapy, respectively. Interestingly, the study included 6 patients with impaired liver function (Child-Pugh B) without reporting concerning adverse

Table 2 Concluded studies regarding combination strategies of TARE and ICIs for hepatocellular carcinoma

Reference	Study design	Phase	Country	Microspheres	Systemic therapy	Schedule of immunotherapy administration	Patients	Radiologic criteria of response	ORR	Median OS
Tai <i>et al.</i> (41)	Prospective, monocentric	II	Singapore	Resin	Nivolumab	Adjuvant (after 21 days)	36 (BCLC-B, -C)	RECIST 1.1	30.6%	16.9 months
de la Torre-Aláez <i>et al.</i> (42)	Prospective, monocentric	II	Spain	Resin	Nivolumab	Adjuvant (after 21 days)	42 (BCLC-B 31, -C 11)	RECIST 1.1	41.5%	20.9 months
Marinelli <i>et al.</i> (43)	Retrospective, monocentric	NA	US	Glass/resin	Nivolumab	Periprocedural (from 60 days before to concurrent, then adjuvant)	21 (BCLC-B, -C)	mRECIST	40% at 1 month, 20% at 6 months	12.0 months
Zhan <i>et al.</i> (44)	Retrospective, monocentric	NA	US	Glass/resin	Nivolumab or nivolumab/ipilimumab	Adjuvant (within 90 days from TARE)	26 (BCLC-B, -C)	mRECIST	26%	17.2 months
Yu <i>et al.</i> (45)	Retrospective, monocentric	NA	US	Glass	Atezolizumab/bevacizumab	Periprocedural	10 (BCLC-B 4; -C 6)	mRECIST	Not reported	Not reached

TARE, transarterial radioembolization; ICI, immune checkpoint inhibitor; ORR, objective response rate (evaluated on the overall tumour burden); OS, overall survival; NA, not applicable; BCLC, Barcelona Clinic for Liver Cancer.

events (44).

Yu *et al.* recently published a small retrospective study involving patients with advanced HCC treated with TARE combined with atezolizumab and bevacizumab. In this study, patients received atezolizumab-bevacizumab before TARE (with bevacizumab stopped 3 weeks before TARE). Systemic treatment was reintroduced 1 to 2 months after TARE (45). Although the study included only 10 patients with a median follow-up of 12 months, the results were remarkable, with both PFS and OS not reached, and only 4 of 10 patients developing progression during the study period.

The highest ORR for a combination of ICI plus TARE was recently reported by Lee *et al.* in the SOLID trial, an open-label Phase I–II trial evaluating the safety and efficacy of durvalumab plus TARE. In this trial, 20 out of 24 patients achieved either partial response (PR) or CR. Notably, patients with extrahepatic disease were excluded from this trial (46). Despite the significant improvement in ORR, the median OS for the BCLC-C class population remained quite poor (9.5 months), especially compared to similar studies. This discrepancy between radiological response and OS was attributed to several patients dying before developing radiological progression. This finding could be related to the inclusion of a relatively high number of patients with negative prognostic tumor features and the administration of a relatively high dose of radiation (median: 191 Gy).

Ongoing trials and future scenarios

Studies investigating single-agent nivolumab in patients with advanced HCC demonstrated an ORR ranging from 15% to 20%, compared to 30–40% in prospective studies involving combinations with TARE. These findings align with preclinical evidence, suggesting a potential advantage in combination strategies. However, it remains unclear whether this benefit is synergistic or merely additive.

Recently, the interest around combining loco-regional treatment with ICIs heightened after the success of the EMERALD-1 trial. Interest in combining loco-regional treatments with ICIs has increased, particularly after the success of the EMERALD-1 trial. This was the first randomized clinical trial to demonstrate a benefit in PFS when systemic treatment (durvalumab plus bevacizumab) was administered following TACE compared to TACE alone in patients with unresectable but TACE-eligible HCC (47).

Given the economic implications of both TARE and ICIs, future trials should aim to achieve either a prolonged OS or a substantial increase in ORR. Additionally, the rate of conversion to curative treatments is another important endpoint to consider.

Ongoing trials (reported in Table 3) emphasize ORR as the primary efficacy outcome. Various combinatorial regimens are currently being evaluated, including single-agent pembrolizumab and dual regimens (48–53).

Among the dual regimens, durvalumab plus

Table 3 Ongoing clinical trials of combination strategies of TARE and ICIs for hepatocellular carcinoma

NCT	Systemic therapy	Primary outcome	BCLC stage	Phase	Estimated number of patients	Date of completion (estimated)
NCT04541173 (48)	Atezolizumab/bevacizumab (adjuvant)	PFS	Up to C (no extrahepatic disease)	II	128	Study terminated due to low accrual
NCT05063565 (49)	Durvalumab + tremelimumab (adjuvant)	ORR	Up to C (no extrahepatic or Vp3/Vp4)	II	100	July 2027
NCT04605731 (50)	Durvalumab + tremelimumab (adjuvant)	Safety	Up to C (no extrahepatic disease)	I	32	December 2024
NCT04522544 (51)	Durvalumab + tremelimumab (adjuvant)	ORR	Up to B	II	55	September 2025
NCT06040099 (52)	Durvalumab + bevacizumab (adjuvant)	PFS	Up to C (no extrahepatic or Vp3/Vp4)	II	100	September 2026
NCT03099564 (53)	Pembrolizumab (adjuvant)	PFS	Up to C (no extrahepatic disease)	I	30	March 2024

TARE, transarterial radioembolization; ICI, immune checkpoint inhibitor; NCT, National Clinical Trial; BCLC, Barcelona Clinic for Liver Cancer; PFS, progression-free survival; ORR, objective response rate; Vp3, neoplastic portal vein invasion in one of the main branch; Vp4, neoplastic portal vein invasion in the portal trunk.

tremelimumab and atezolizumab plus bevacizumab are particularly noteworthy as they are already approved for treating unresectable HCC. Despite the potential, an open-label, multi-center, randomized Phase II study comparing Y90 TARE followed by bevacizumab and atezolizumab to Y90 TARE alone in unresectable advanced HCC (NCT04541173) was recently terminated due to low accrual, highlighting the challenges in obtaining data from prospective trials.

Currently, three studies are exploring the combination of TARE and durvalumab-tremelimumab (NCT05063565, NCT04522544, NCT04605731). In particular, the ROWAN study (NCT05063565) is a global open-label, prospective, multi-center Phase II trial designed to assess the safety and efficacy of glass microspheres administered before initiation of durvalumab with tremelimumab in HCC patients who are unsuitable for curative procedures. This study will enroll about 100 patients using ORR as the primary endpoint. Interestingly, this study includes dosimetry data (pre-treatment and post-treatment volumes and absorbed doses; correlation between tumoral absorbed doses and impact on tumor response, survival, and safety) amongst its many secondary endpoints. The IMMUNWIN trial (NCT04522544) adopted a different study design. Patients with intermediate-stage HCC will be randomized into two experimental arms, one receiving TARE + durvalumab + tremelimumab, the other arm receiving TACE + durvalumab + tremelimumab. This study aims

to determine the ideal transarterial treatment to pair with ICIs. The primary endpoint is the proportion of patients with a best response of complete or PR at 6 months. Finally, NCT04605731 is a Phase 1b study focusing on safety endpoints (including dose-limiting toxicities and adverse events) for durvalumab plus tremelimumab following TARE. Patients receive standard radioembolization with 90Y resin spheres, followed by durvalumab and tremelimumab. Durvalumab cycles continue in the absence of disease progression or unacceptable toxicities. For patients accepting to undergo serial biopsies, exploratory aims of this study include the association of response and survival outcomes with next generation sequencing results, and genomic evolutions in tumor tissue through comparison of baseline and post-combination immunotherapy treatment tumor biopsies.

Conclusions

Several encouraging preclinical studies have emerged in recent years, supporting the synergistic role of loco-regional treatments and ICIs. Although promising results have been reported, the currently available evidence is still insufficient to provide strong recommendations for clinical practice. The relatively low number of patients included in prospective studies, heterogeneity in patient selection, treatment schedules, and clinical settings (ranging from peri-treatment approaches to purely adjuvant regimens)

remain significant issues.

Future studies should address and clarify at least four pivotal aspects. First, define patient selection to clearly identify which patients are suitable candidates for TARE, avoiding those with extensive liver invasion to prevent repeating the mistakes that contributed to the failure of previous Phase 3 TARE trials. Second, determine the most effective ICI monotherapies or combinations to use alongside TARE. Third, to establish the best treatment schedules (neoadjuvant, peri-procedural, or adjuvant) for combining TARE with ICIs. Fourth, to assess whether TARE provides superior benefits compared to other loco-regional techniques, particularly TACE, when combined with ICIs.

Ongoing studies will hopefully provide answers to some of these questions and further clarify the role of combining TARE with ICIs in clinical practice.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://cco.amegroups.com/article/view/10.21037/cco-24-27/rc>

Peer Review File: Available at <https://cco.amegroups.com/article/view/10.21037/cco-24-27/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://cco.amegroups.com/article/view/10.21037/cco-24-27/coif>). F.T. received consulting fees from ROCHE, Eisai, Ipsen, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Roche. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International

License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209-49.
2. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020;382:1894-905.
3. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. *Lancet Oncol* 2021;22:977-90.
4. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evid* 2022;1:EVIDoa2100070.
5. Qin S, Kudo M, Meyer T, et al. Tislelizumab vs Sorafenib as First-Line Treatment for Unresectable Hepatocellular Carcinoma: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2023;9:1651-9.
6. Stefanini B, Ielasi L, Chen R, et al. TKIs in combination with immunotherapy for hepatocellular carcinoma. *Expert Rev Anticancer Ther* 2023;23:279-91.
7. Health C for D and R. TheraSphere™ – P200029. FDA. Available online: <https://www.fda.gov/medical-devices/recently-approved-devices/theraspheretm-p200029> (2021, accessed 31 May 2024).
8. <https://fyra.io>. Sirtex Medical Receives FDA Approval to Conduct DOORwaY90 Study of SIR-Spheres in Unresectable HCC. *Endovascular Today*. Available online: <https://evtoday.com/news/sirtex-medical-receives-fda-approval-to-conduct-doorway90-study-of-sir-spheres-in-unresectable-hcc> (accessed 31 May 2024).
9. Lau WY, Sangro B, Chen PJ, et al. Treatment for hepatocellular carcinoma with portal vein tumor thrombosis: the emerging role for radioembolization using yttrium-90. *Oncology* 2013;84:311-8.
10. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008;47:71-81.

11. Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2021;18:293-313.
12. Zhang J, Li H, Gao D, et al. A prognosis and impact factor analysis of DC-CIK cell therapy for patients with hepatocellular carcinoma undergoing postoperative TACE. *Cancer Biol Ther* 2018;19:475-83.
13. Lee HL, Jang JW, Lee SW, et al. Inflammatory cytokines and change of Th1/Th2 balance as prognostic indicators for hepatocellular carcinoma in patients treated with transarterial chemoembolization. *Sci Rep* 2019;9:3260.
14. Chen ME, Chen PT, Chen WC, et al. The role of PD-L1 in the radiation response and prognosis for esophageal squamous cell carcinoma related to IL-6 and T-cell immunosuppression. *Oncotarget* 2016;7:7913-24.
15. Duan XH, Li H, Han XW, et al. Upregulation of IL-6 is involved in moderate hyperthermia induced proliferation and invasion of hepatocellular carcinoma cells. *Eur J Pharmacol* 2018;833:230-6.
16. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017;18:1624-36.
17. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. *J Clin Oncol* 2018;36:1913-21.
18. Rieke J, Klumpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol* 2019;71:1164-74.
19. Matsumoto MM, Mouli S, Saxena P, et al. Comparing Real World, Personalized, Multidisciplinary Tumor Board Recommendations with BCLC Algorithm: 321-Patient Analysis. *Cardiovasc Intervent Radiol* 2021;44:1070-80.
20. Izzo F, Granata V, Grassi R, et al. Radiofrequency Ablation and Microwave Ablation in Liver Tumors: An Update. *Oncologist* 2019;24:e990-e1005.
21. Salem R, Johnson GE, Kim E, et al. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. *Hepatology* 2021;74:2342-52.
22. Dhondt E, Lambert B, Hermie L, et al. (90) Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. *Radiology* 2022;303:699-710.
23. Goin JE, Dancey JE, Roberts CA, et al. Comparison of post-embolization syndrome in the treatment of patients with unresectable hepatocellular carcinoma: trans-catheter arterial chemoembolization versus yttrium-90 glass microspheres. *World J Nucl Med* 2004;3:49-56.
24. Jia Z, Jiang G, Tian F, et al. A systematic review on the safety and effectiveness of yttrium-90 radioembolization for hepatocellular carcinoma with portal vein tumor thrombosis. *Saudi J Gastroenterol* 2016;22:353-9.
25. Tabone M, Calvo A, Russolillo N, et al. Downstaging unresectable hepatocellular carcinoma by radioembolization using 90-yttrium resin microspheres: a single center experience. *J Gastrointest Oncol* 2020;11:84-90.
26. Serenari M, Cappelli A, Cucchetti A, et al. Deceased Donor Liver Transplantation After Radioembolization for Hepatocellular Carcinoma and Portal Vein Tumoral Thrombosis: A Pilot Study. *Liver Transpl* 2021;27:1758-66.
27. Bargellini I, Scalise P, Boni G, et al. Yttrium-90 Radioembolization for Hepatocellular Carcinoma with Portal Vein Invasion: Validation of the Milan Prognostic Score. *J Vasc Interv Radiol* 2020;31:2028-32.
28. Reits EA, Hodge JW, Herberts CA, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med* 2006;203:1259-71.
29. Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. *Curr Probl Cancer* 2016;40:10-24.
30. Chino F, Pollis KE, Choi S, et al. Stereotactic Body Radiation Therapy-Induced Abscopal Effect on Hepatocellular Carcinoma After Treatment for Lung Cancer: A Case Report. *Hepatology* 2018;68:1653-5.
31. Powerski M, Drewes R, Omari J, et al. Intra-hepatic Abscopal Effect Following Radioembolization of Hepatic Metastases. *Cardiovasc Intervent Radiol* 2020;43:1641-9.
32. Chew V, Lee YH, Pan L, et al. Immune activation underlies a sustained clinical response to Yttrium-90 radioembolisation in hepatocellular carcinoma. *Gut* 2019;68:335-46.
33. Craciun L, de Wind R, Demetter P, et al. Retrospective analysis of the immunogenic effects of intra-arterial locoregional therapies in hepatocellular carcinoma: a rationale for combining selective internal radiation therapy (SIRT) and immunotherapy. *BMC Cancer* 2020;20:135.
34. Lemaire M, Lucidi V, Bouazza F, et al. Selective internal

- radiation therapy (SIRT) before partial hepatectomy or radiofrequency destruction for treatment of hepatocellular carcinoma in cirrhotic patients: a feasibility and safety pilot study. *HPB (Oxford)* 2018;20:641-8.
35. Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. *Ann Surg* 2009;249:195-202.
 36. Yoo H, Kim JH, Ko GY, et al. Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization only before major hepatectomy for patients with hepatocellular carcinoma. *Ann Surg Oncol* 2011;18:1251-7.
 37. Si T, Chen Y, Ma D, et al. Preoperative transarterial chemoembolization for resectable hepatocellular carcinoma in Asia area: a meta-analysis of random controlled trials. *Scand J Gastroenterol* 2016;51:1512-9.
 38. Wehrenberg-Klee E, Goyal L. Combining systemic and local therapies for hepatocellular carcinoma. *Lancet Gastroenterol Hepatol* 2021;6:976-8.
 39. Rivoltini L, Bhoori S, Camisaschi C, et al. Y(90)-radioembolisation in hepatocellular carcinoma induces immune responses calling for early treatment with multiple checkpoint blockers. *Gut* 2023;72:406-7.
 40. Domouchtsidou A, Barsegian V, Mueller SP, et al. Impaired lymphocyte function in patients with hepatic malignancies after selective internal radiotherapy. *Cancer Immunol Immunother* 2018;67:843-53.
 41. Tai D, Loke K, Gogna A, et al. Radioembolisation with Y90-resin microspheres followed by nivolumab for advanced hepatocellular carcinoma (CA 209-678): a single arm, single centre, phase 2 trial. *Lancet Gastroenterol Hepatol* 2021;6:1025-35.
 42. de la Torre-Aláez M, Matilla A, Varela M, et al. Nivolumab after selective internal radiation therapy for the treatment of hepatocellular carcinoma: a phase 2, single-arm study. *J Immunother Cancer* 2022;10:e005457.
 43. Marinelli B, Cedillo M, Pasik SD, et al. Safety and Efficacy of Locoregional Treatment during Immunotherapy with Nivolumab for Hepatocellular Carcinoma: A Retrospective Study of 41 Interventions in 29 Patients. *J Vasc Interv Radiol* 2020;31:1729-1738.e1.
 44. Zhan C, Ruohoniemi D, Shanbhogue KP, et al. Safety of Combined Yttrium-90 Radioembolization and Immune Checkpoint Inhibitor Immunotherapy for Hepatocellular Carcinoma. *J Vasc Interv Radiol* 2020;31:25-34.
 45. Yu Q, Wang Y, Ungchusri E, et al. Combination of transarterial radioembolization with atezolizumab and bevacizumab for intermediate and advanced staged hepatocellular carcinoma: A preliminary report of safety and feasibility. *J Interv Med* 2023;6:187-93.
 46. Lee YB, Nam JY, Cho EJ, et al. A Phase I/IIa Trial of Yttrium-90 Radioembolization in Combination with Durvalumab for Locally Advanced Unresectable Hepatocellular Carcinoma. *Clin Cancer Res* 2023;29:3650-8.
 47. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: A phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. *J Clin Oncol* 2024;42:LBA432.
 48. He AR. A Randomized Phase II Study of Atezolizumab and Bevacizumab With Y-90 TARE in Patients With Unresectable Hepatocellular Carcinoma (HCC). Clinical Trial Registration NCT04541173, [clinicaltrials.gov](https://clinicaltrials.gov/study/NCT04541173). Available online: <https://clinicaltrials.gov/study/NCT04541173> (10 May 2023, accessed 1 January 2024).
 49. Boston Scientific Corporation. An Open-Label, Prospective, Multi-Center Clinical Trial to Evaluate the Efficacy and Safety of TheraSphere™ Followed by Durvalumab (Imfinzi®) With Tremelimumab (Imjudo®) for Hepatocellular Carcinoma (HCC). Clinical Trial Registration NCT05063565, [clinicaltrials.gov](https://clinicaltrials.gov/study/NCT05063565). Available online: <https://clinicaltrials.gov/study/NCT05063565> (25 January 2024, accessed 1 January 2024).
 50. City of Hope Medical Center. A Phase Ib Study of Durvalumab (Medi4736) and Tremelimumab Following Radioembolization in Patients With Unresectable Locally Advanced Hepatocellular Carcinoma. Clinical Trial Registration NCT04605731, [clinicaltrials.gov](https://clinicaltrials.gov/study/NCT04605731). Available online: <https://clinicaltrials.gov/study/NCT04605731> (29 January 2024, accessed 1 January 2024).
 51. Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest. A Phase II Study of Immunotherapy With Durvalumab (MEDI4736) and Tremelimumab in Combination With Either Y-90 SIRT or TACE for Intermediate Stage HCC With Pick-the-winner Design. Clinical Trial Registration NCT04522544, [clinicaltrials.gov](https://clinicaltrials.gov/study/NCT04522544). Available online: <https://clinicaltrials.gov/study/NCT04522544> (29 August 2023, accessed 1 January 2024).
 52. AstraZeneca. Phase II Single-Arm Study of Durvalumab and Bevacizumab Following Transarterial Radioembolization Using Yttrium-90 Glass Microspheres (TheraSphere™) in Unresectable Hepatocellular

- Carcinoma Amenable to Locoregional Therapy. Clinical Trial Registration NCT06040099, clinicaltrials.gov. Available online: <https://clinicaltrials.gov/study/NCT06040099> (5 January 2024, accessed 1 January 2024).
53. Somasundaram A. A Pilot Study of Pembrolizumab in Combination With Y90 Radioembolization in Subjects

With Poor Prognosis Hepatocellular Carcinoma With Preserved Liver Function. HCRN: GI15-225. Clinical Trial Registration NCT03099564, clinicaltrials.gov. Available online: <https://clinicaltrials.gov/study/NCT03099564> (3 February 2023, accessed 1 January 2024).

Cite this article as: Chen R, Monaco G, Stefanini B, Marseglia M, De Lorenzo S, Tovoli F. Combination makes strength: a narrative review of transarterial radioembolization plus immune checkpoint inhibitors for hepatocellular carcinoma. *Chin Clin Oncol* 2024;13(5):71. doi: 10.21037/cco-24-27