Editorial Commentary

Efficacy and challenges of combining transarterial chemoembolization with pembrolizumab in advanced hepatocellular carcinoma: insights from the PETAL study

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We recently read the study by Pinato *et al.* published in *Clinical Cancer Research*, which explores the combination of transarterial chemoembolization (TACE) and pembrolizumab in the treatment of liver-confined hepatocellular carcinoma (HCC) (1). The authors conducted a phase Ib trial, PETAL, to evaluate the safety, preliminary activity, and potential mechanisms of efficacy of TACE combined with pembrolizumab. A total of 15 patients with liver-confined HCC were enrolled in the study. These patients received up to two rounds of TACE followed by pembrolizumab (200 mg every 21 days) starting 30 days post-TACE, continuing until disease progression or unacceptable toxicity for a maximum of 1 year. The authors report that TACE plus pembrolizumab was well-tolerated, with no synergistic toxicities or dose-limiting adverse events observed post-TACE. Treatment-related adverse events occurred in 93% of patients, most commonly skin rash (40%), fatigue, and diarrhea (27%). Encouragingly, the objective response rate (ORR) at 12 weeks post-TACE was 53%, with a median progression-free survival (PFS) of 8.95 months [95% confidence interval (CI): 7.30–not evaluable (NE)], a median duration of response was 7.3 months (95% CI: 6.3–8.3) and a median overall survival (OS) of 33.5 months (95% CI: 11.6–NE).

Liver cancer is a prevalent malignancy worldwide and is ranked as the fourth most commonly diagnosed cancer. Meanwhile, HCC ranks third among malignant tumors in terms of mortality, with over 860,000 new cases diagnosed each year and more than 750,000 deaths attributed to liver cancer annually (2). Pembrolizumab is a humanized monoclonal antibody that works by targeting the programmed cell death-1 (PD-1) pathway, which plays a crucial role in downregulating the immune system and preventing the immune response from attacking cancer cells. Currently, there are numerous studies reporting that pembrolizumab plays an important role in the treatment of various malignancies, including melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, and triple-negative breast cancer, demonstrating good therapeutic responses and lower drug toxicity. Pembrolizumab is often used as a second-line treatment and plays a significant role in the long-term prognosis of patients with advanced HCC. Recent research highlights the promising role of pembrolizumab in the treatment of HCC. Clinical trials indicate that pembrolizumab significantly prolongs OS and PFS in Asian patients with previously treated advanced HCC, with a median OS of 14.6 months compared to 13.0 months for placebo (P=0.018) (3).

Subgroup analysis from the KEYNOTE-240 trial reveals a higher ORR of 20.6% for pembrolizumab versus 2.0% for the placebo group, alongside a median OS of 13.8 months compared to 8.3 months for placebo, underscoring its effectiveness in specific populations (4). The safety profile of pembrolizumab is generally acceptable, with treatment-related adverse events occurring more frequently in the pembrolizumab arm (66.9% *vs.* 49.7% for placebo), though most were of mild to moderate severity (3). Additionally, studies demonstrate that combining pembrolizumab with lenvatinib can yield significant antitumor activity, achieving an ORR of 46% in patients with unresectable HCC (5). However, while pembrolizumab shows encouraging clinical efficacy, its high cost raises concerns regarding cost-effectiveness, with some economic models indicating it may not meet acceptable thresholds for many payers (6). Overall, pembrolizumab presents a valuable therapeutic option for advanced HCC, particularly in second-line settings and specific patient populations, warranting further investigation into its broader applications and economic implications. The current landscape of TACE combined with PD-1 inhibitors in the treatment of HCC demonstrates promising efficacy and safety profiles, reflecting a growing interest in multimodal therapeutic strategies. Studies indicate that combining TACE with PD-1 inhibitors and tyrosine kinase inhibitors (TKIs), such as lenvatinib, significantly improves OS, PFS, ORR, and disease control rate (DCR) in patients with advanced HCC compared to other treatment regimens. A meta-analysis encompassing 1,279 patients showed substantial clinical benefits without increasing the risk of adverse events (7). Patients receiving TACE with PD-1 inhibitors have reported longer median PFS compared to those undergoing monotherapy (8), suggesting enhanced treatment synergy that may lead to effective disease management.

The study by Pinato *et al.* is crucial and has several key advantages. First, it is a registered, well-structured prospective clinical trial (9). While there are existing studies investigating the combination of TACE and PD-1 inhibitors in the treatment of HCC, this is the first early-phase clinical trial to evaluate the safety and preliminary efficacy of TACE in combination with pembrolizumab for HCC, making it highly innovative. Second, the study includes a comprehensive set of outcome measures. In addition to reporting on the safety and toxicity of the treatment, it also incorporates important tumor-related endpoints such as PFS, ORR, and OS. No significant synergistic toxicities were observed, and the treatment demonstrated promising anti-tumor activity, providing valuable data and theoretical support for future phase III and IV clinical trials. Most importantly, the study integrates biomarker assessments to explore the underlying mechanisms of treatment. This includes the dynamics of peripheral T-cell subsets, changes in circulating tumor DNA concentration, targeted transcriptomics of tumor biopsies, correlations with the composition of fecal microbiota, and serum metabolomics analysis. The methodology for the mechanistic discussion is diverse, particularly the observation of changes in T-cell subsets in patients with or without treatment response following immune checkpoint inhibitor (ICI) therapy. This provides support for the synergistic effect of PD-1 inhibitors and TACE on immune cells.

While this study provides important insights, several aspects could be improved to enhance its overall quality. First, the lack of a well-designed control group is a limitation. Receiving a placebo or an alternative established treatment as a control group would help minimize potential confounding factors and strengthen the study's internal validity. While the study presents several angles in exploring mechanisms, the analysis remains somewhat superficial. A more in-depth discussion, coupled with additional *in vivo* and *in vitro* experiments, would lend further support to the findings and provide a more comprehensive understanding of the underlying mechanisms. Meanwhile, it is important to note that HCC patient populations vary across regions, each exhibiting distinct disease profiles, risk factors, and progression patterns. These regional differences can influence treatment choices and drug selection (10). Since most of the people in this study were white, the benefits of these therapies for Asian populations remain to be further validated.

Many studies have reported that combination therapies, including TKIs with PD-1 inhibitors, bispecific antibodies, and combinations of local and systemic treatments, generally demonstrate superior efficacy and tolerability in HCC patients (11,12). Currently, there is broad consensus on the combination of TACE with TKIs and PD-1 inhibitors for the treatment of advanced HCC (13). A study on the combination of TACE with PD-1 inhibitors and molecular targeted therapies in patients with advanced HCC reported favorable efficacy, with a median PFS and median OS of 9.5 and 19.2 months, respectively (14). Another study also reported better outcomes including a median PFS of 9.9 months and median OS of 22.6 months in the combination therapy (15). Both studies used a combination of TACE with PD-1 inhibitors and molecular

targeted drugs. The majority of patients in these studies were in Barcelona Clinic Liver Cancer (BCLC) stage C and only a few patients were in BCLC stage B. However, in this study, nearly half of the enrolled HCC patients were in BCLC stage A, and the rest were in BCLC stage B. Although the tumor burden of these patients was relatively low, the median PFS (8.95 months) was noticeably shorter than in the aforementioned studies. Based on the results obtained, the necessity of conducting a phase II clinical trial on the combination of TACE and pembrolizumab should be reconsidered and further rigorously evaluated. Expanding this study to include TKIs may help determine the most effective treatment regimen for advanced HCC.

Despite these areas for improvement, the study carries substantial clinical value. As the first clinical report on the combination of TACE and pembrolizumab in HCC treatment, it provides critical data to support future phase II clinical trials. Furthermore, the findings offer valuable insights for clinical decision-making. With the growing array of therapeutic options for advanced HCC, it is anticipated that more patients will benefit from these emerging treatment strategies in the near future.

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Footnote

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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.

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