Sandwich-model perioperative therapy ushers in a new era of chronic disease management in hepatocellular carcinoma

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Liver cancer represents a significant and growing global health burden, currently ranking as the sixth most common cancer and the third leading cause of cancer-related deaths worldwide.[1] A comprehensive analysis by The Lancet Liver Cancer Commission projects that if current trends continue, the annual number of new liver cancer cases will nearly double from approximately 870,000 in 2022 to about 1.52 million by 2050; concurrently, annual mortality is expected to rise from 760,000 to 1.37 million during the same period.[2] For patients undergoing resection for hepatocellular carcinoma (HCC), postoperative recurrence remains a paramount challenge, occurring in up to 80% of patients after resection, particularly in individuals with high-risk features such as large tumor size, multifocal disease, or vascular invasion. This high recurrence rate underscores an urgent clinical need to develop effective multidisciplinary strategies, including perioperative systemic therapies, to improve overall survival outcomes.

The integration of immune checkpoint inhibitors (ICIs) with anti-angiogenic agents has emerged as a promising therapeutic strategy across various malignancies, including HCC, by leveraging synergistic mechanisms to enhance anti-tumor immunity and normalize the tumor microenvironment. Specifically, the combination of atezolizumab (an anti-PD-L1 antibody) and bevacizumab (an anti-VEGF antibody) has demonstrated notable efficacy in advanced HCC, leading to its adoption as a treatment strategy with significant potential in unresectable cases. The phase 3 IMbrave050 trial investigated this combination as an adjuvant therapy in patients with resectable HCC who were at high risk of recurrence. At the prespecified interim analysis (October 21, 2022), the regimen showed a statistically significant improvement in recurrence-free survival (RFS) compared to active surveillance, with a hazard ratio (HR) of 0.72 (95% CI 0.53–0.98; p=0.012).[3] However, subsequent updated results (May 3, 2024) revealed that the initial RFS benefit was not sustained, with an updated HR of 0.90 (95% CI 0.72–1.12).[4] The IMbrave050 trial revealed that adjuvant atezolizumab plus bevacizumab, while initially improving RFS, did not sustain this benefit in updated analyses—suggesting that adjuvant immunotherapy alone may be insufficient to achieve durable

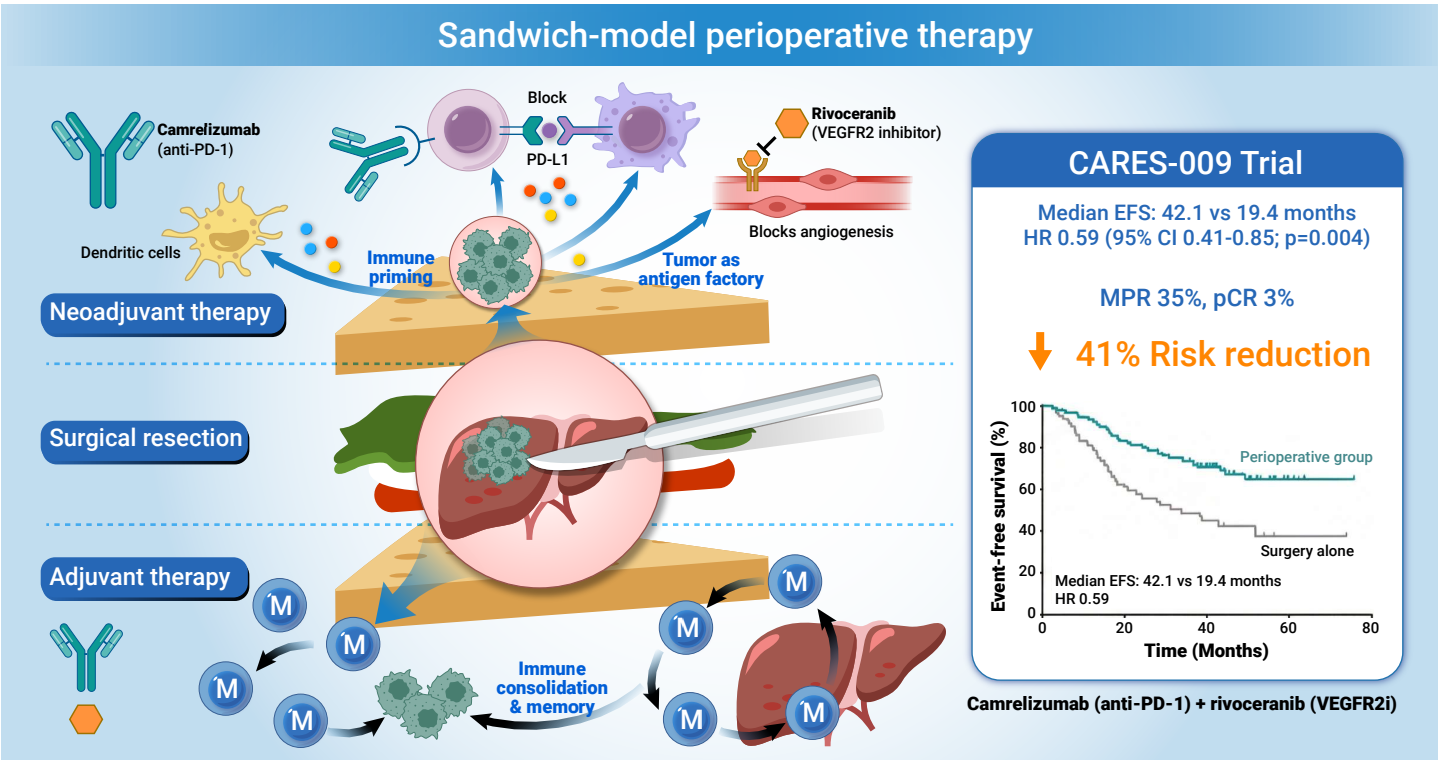

Figure 1. Sandwich-model perioperative therapy.

disease control in HCC. This has spurred interest in integrated perioperative strategies, which combine neoadjuvant and adjuvant therapy to maximize antitumor immune activation and address micrometastatic disease more comprehensively. The "sandwich" approach—neoadjuvant therapy followed by resection and adjuvant therapy—may synergistically enhance tumor-specific immunity by leveraging the intact tumor as a source of antigens pre-surgery, while postoperative consolidation targets residual disease and promotes long-term immunological memory (Figure 1). Inspired by this model, the Zhongshan Hospital team initiated the CARES-009 trial, evaluating perioperative camrelizumab (an anti-PD-1 antibody) plus rivoceranib (a VEGFR-2 inhibitor) in patients with resectable HCC at intermediate or high risk of recurrence.[5]

CARES-009 represents the first phase 3 randomized trial to investigate a perioperative combination of immunotherapy and anti-angiogenic therapy—specifically, camrelizumab plus rivoceranib—in patients with resectable HCC at intermediate or high risk of recurrence. This multicenter

study, conducted across 16 Chinese HCC centers, adopted an innovative "sandwich" therapeutic model utilizing domestically developed agents. Eligible patients were randomized 1:1 to receive either the perioperative combination regimen or surgery alone. In the experimental arm, participants received two cycles of neoadjuvant camrelizumab and rivoceranib prior to surgery, followed by radical resection and subsequent adjuvant therapy for up to 15 cycles, resulting in a total perioperative treatment duration of approximately 12 months.

In patients with resectable hepatocellular carcinoma (HCC) at intermediate or high risk of recurrence, perioperative "sandwich" therapy significantly prolonged event-free survival (EFS), with a median EFS of 42.1 months compared to 19.4 months in the surgery-alone group, corresponding to a hazard ratio (HR) of 0.59 (95% CI: 0.41–0.85; p = 0.004) and a 41% reduction in the risk of disease progression, recurrence, or death (Figure 1). The EFS rates at 1, 2, and 3 years were 79.4%, 58.8%, and 55.2%, respectively, for the perioperative therapy group, versus 62.0%, 47.4%, and 39.5% for the surgery-alone group, indicating that over half of the treated patients remained event-free at the 3-year mark. Moreover, perioperative treatment markedly improved pathological outcomes, achieving a major pathological response (MPR) rate of 35%—significantly higher than the 8% observed in the surgery-alone group—including five patients who attained a pathological complete response (pCR) with no viable tumor cells in the resected specimen.

The CARES-009 trial provides a compelling new paradigm for HCC management, but its underlying mechanisms warrant deeper discussion. The superiority of the "sandwich" model over a purely adjuvant approach likely stems from its unique immunological priming mechanism. During the neoadjuvant phase, the intact primary tumor functions as an in-situ antigen factory, continuously releasing a diverse repertoire of tumor neoantigens that are captured and processed by dendritic cells for cross-presentation to T lymphocytes. Concurrently, the anti-angiogenic agent rivoceranib normalizes the chaotic tumor vasculature, alleviating intratumoral hypoxia and transforming the immunosuppressive tumor microenvironment into one that is permissive for immune cell infiltration. This vascular normalization enhances the trafficking and penetration of effector T cells into the tumor bed, while the PD-1 blockade by camrelizumab reinvigorates exhausted T cells, unleashing a potent, broad-spectrum anti-tumor immune response. This preoperative "immune priming" generates a large pool of tumor-specific effector and memory T cells, establishing a robust immunological memory that persists beyond surgery and is critical for eradicating residual micrometastatic disease during the adjuvant phase.

This mechanism provides an explanation for the discrepancy between the sustained benefit observed in CARES-009 and the attenuated effect in IMbrave050. In the adjuvant-only setting of IMbrave050, immunotherapy was initiated after the primary antigen source—the tumor—had been surgically removed. Without the continuous antigenic stimulation from the intact tumor, the immune system may not have been adequately "trained" to mount a durable anti-tumor response, resulting in a narrower and less persistent immune activation that waned over time. The "pre-emptive strike" strategy of CARES-009, by contrast, ensures that the immune system is maximally primed before resection, generating a more resilient and long-lasting anti-tumor immunity that translates into a more durable and sustained clinical benefit.

However, the clinical feasibility of this intensive approach must be carefully considered. In the trial, 38% of patients in the perioperative group experienced grade 3 or higher adverse events, and two treatment-related deaths occurred during the neoadjuvant phase—one due to hepatic failure assessed as possibly related to treatment, and one due to combined hepatic and renal failure with indeterminate causality. This underscores the critical importance of meticulous patient selection, close monitoring of liver function, timely dose adjustments, and effective multidisciplinary supportive care. Despite this treatment intensity, the substantial survival benefit, particularly in a high-risk population, supports the clinical value of this approach.

Several limitations of the CARES-009 trial should be acknowledged. The study population was predominantly Chinese with HBV-associated HCC, which may limit generalizability. The absence of a neoadjuvant-only or adjuvant-only comparator arm limits the ability to dissect the individual contribution of each treatment phase. Future research should prioritize long-term OS follow-up to confirm the ultimate survival benefit, validation of the "sandwich" model in diverse etiological and ethnic populations, and the identification of predictive biomarkers—such as circulating tumor DNA (ctDNA) or the degree of pathological response—to personalize therapy and potentially de-escalate treatment for excellent responders. Additionally, integrating other modalities, such as locoregional therapies, into the "sandwich" framework could be explored to further optimize outcomes across the spectrum of resectable HCC.[5]

In conclusion, the CARES-009 trial heralds a new era for perioperative HCC therapy. By transforming treatment from a single surgical event into a systematic, long-term chronic disease management process through the "sandwich" model of neoadjuvant therapy, surgical resection, and adjuvant consolidation, it offers renewed hope for improving outcomes in this challenging and lethal malignancy.

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DECLARATION OF INTERESTS

The authors declare no competing interests.