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Letter

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Comment on the Article "Prognostic Usefulness of Clinical Complete Response after PD-1 Inhibitor-Based Combination Therapy for Unresectable Hepatocellular Carcinoma"

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Dear Editor,

We read with profound interest the multicenter study (GUIDANCE006) by Ma et al. [1] recently published in *Liver Cancer*. By analyzing a robust cohort of 1,266 patients with initially unresectable hepatocellular carcinoma (HCC), the authors convincingly demonstrated that achieving a clinical complete response (cCR) following PD-1 inhibitor-based combination therapy (incorporating interventional and antiangiogenic modalities) serves as an independent, highly reliable prognostic indicator for prolonged overall survival and progression-free survival [1]. The authors must be commended for providing such compelling real-world evidence. However, transitioning these clinical observations into personalized precision medicine requires decoding the underlying molecular and biological nuances. In this regard, we believe several microenvironmental, spatial, and epigenetic dimensions warrant deeper scientific discussion.

First, the study broadly categorizes both transarterial chemoembolization (TACE) and hepatic artery infusion chemotherapy (HAIC) under the umbrella of "interventional therapy" combined with PD-1 inhibitors [1]. While both are effective cytoreductive tools, their biological impact on the tumor immune microenvironment is fundamentally divergent. TACE primarily induces severe localized hypoxia via embolic ischemia. Such abrupt hypoxic stress typically stabilizes hypoxia-inducible factors and upregulates vascular endothelial growth factor. As demonstrated in recent studies, this hypoxia-driven signaling axis actively recruits and maintains pro-tumorigenic innate immune cells, particularly myeloid-derived suppressor cells and regulatory T cells, thereby fostering an intensely immunosuppressive niche [2]. In stark contrast, HAIC relies on continuous, high-concentration chemotherapeutic perfusion without severe ischemia, potentially favoring immunogenic cell death and enhanced neoantigen presentation. We strongly advocate that future cohorts should explicitly stratify these two modalities. Furthermore, integrating single-cell RNA sequencing on longitudinal biopsies could delineate how TACE-induced hypoxia versus HAIC-induced immunogenic cell death uniquely reshapes the evolutionary trajectories of $CD8^+$ T cells, which is vital for optimizing cCR rates.

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Second, a fascinating paradox within the study is the discrepancy between radiological and pathological evaluations. Among the 121 patients who achieved a cCR and subsequently underwent hepatectomy, a striking 21.5% failed to achieve a pathological complete response, harboring viable microscopic residual disease [1]. This highlights the limitations of standard imaging in detecting immune-evasive clonal subpopulations. We hypothesize that these 21.5% of viable clones are shielded within an "immune-excluded" spatial niche, heavily orchestrated by cancer-associated fibroblasts and a dense extracellular matrix barrier. These physical and metabolic walls effectively exclude effector T cells, rendering the clones invisible to radiology but resilient to PD-1 blockade. To unravel this phenomenon, we suggest applying spatial transcriptomics [3] on these specific microscopic residual disease-positive explants. High-resolution spatial mapping would precisely identify the stromal cell phenotypes shielding these viable HCC cells, thereby discovering novel targets to break down the cancer-associated fibroblast-mediated barrier and convert a mere cCR into a true pathological complete response.

Lastly, the authors perceptively suggest in their discussion that circulating tumor DNA profiling could assist in monitoring residual disease and guiding the discontinuation of PD-1 inhibitors [1]. We suggest elevating this concept by moving beyond traditional tumor markers (AFP and PIVKA-II) and single-gene mutations, to establish the framework of "molecular complete response." Highly sensitive cell-free DNA methylation profiling captures early, broad-spectrum epigenetic alterations that reflect the entire "field effect" of the liver microenvironment, often predating radiological and protein marker changes [4]. By longitudinally monitoring HCC-specific cell-free DNA methylation signatures, clinicians could definitively differentiate true tumor eradication from radiological pseudoprogression. This epigenetic liquid biopsy approach would serve as an ultrasensitive molecular yardstick, providing a safer and more precise biological rationale for when to safely discontinue immunotherapy in patients who have seemingly achieved a cCR.

In conclusion, Ma et al. [1] have established a pivotal clinical milestone by validating the prognostic utility of cCR in advanced HCC. Augmenting such large-scale clinical frameworks with targeted spatial transcriptomic profiling, differentiation of local hypoxic versus immunogenic therapies, and epigenetic circulating tumor DNA monitoring represents the indispensable next step toward truly curative strategies for initially unresectable HCC.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mulin Liu: conceptualization and manuscript draft. Qin Zheng and Juan Fu: manuscript revision and final approval.

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