Sequencing of drug combinations could amplify the anti-tumor immune response in liver cancer

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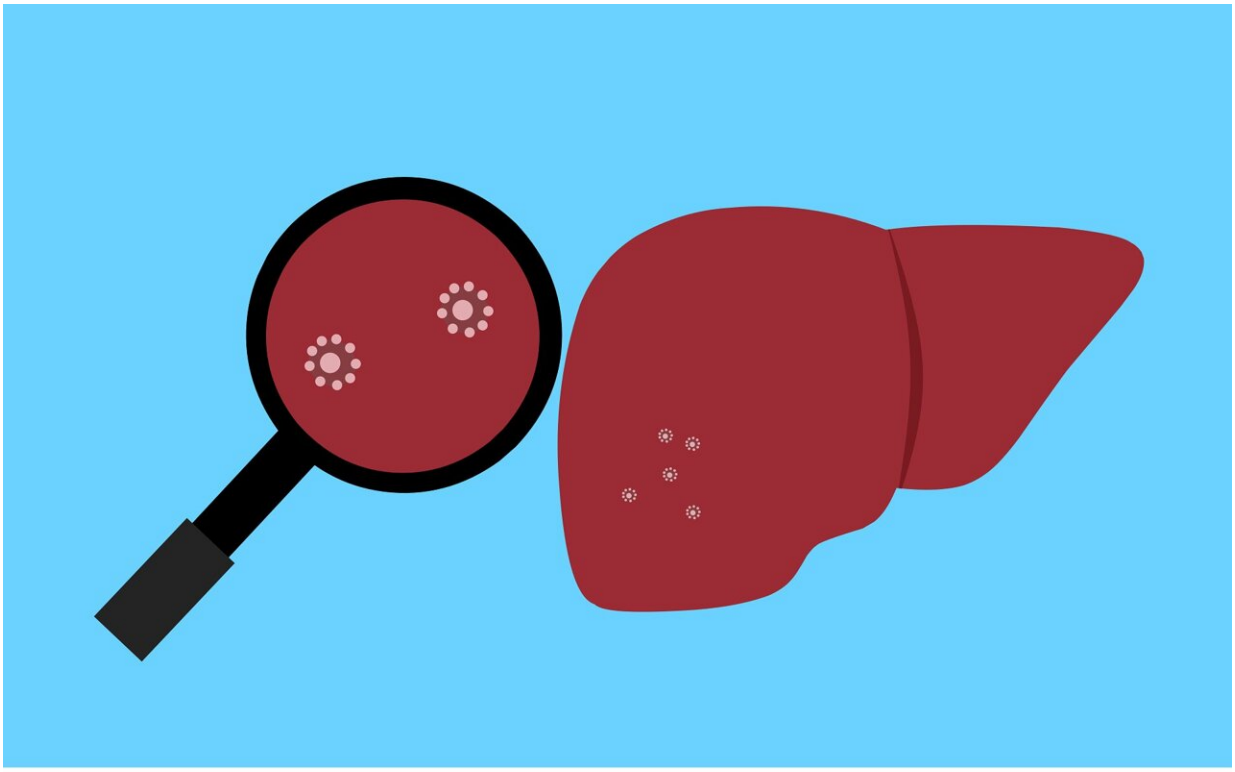

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A new therapeutic strategy for hepatocellular cancer (HCC) that initially

primes the tumor with an immune checkpoint inhibitor before using a multikinase inhibitor drug showed great promise for treating patients with the deadly disease, a Massachusetts General Hospital (MGH) study found. In a paper published in *Journal of the National Cancer Institute*, researchers reported that the new sequencing approach enhanced the effectiveness of the dual drug therapy, potentially allowing de-escalation of the prolonged use of medications and thus reducing toxic drug exposure.

"A regimen of a multikinase inhibitor followed by immune checkpoint blockade, alone or in combination, has historically been the way to test new treatment approaches in HCC patients," says Dan G. Duda, DMD, Ph.D., director of translational research in GI Radiation Oncology at MGH and senior author of the study. "No one knew, however, what the effect might be of reversing the sequence of these therapies."

Duda decided to find out by conducting a retrospective analysis of patients who had been treated under the reversed, non-standard sequence. After learning that it produced favorable outcomes in a cohort of 25 HCC patients, Duda's team expanded its research to preclinical models of HCC in mice. "We discovered that using an immune checkpoint blockade first served to amplify the immune system response , which enhanced the effectiveness of sorafenib, a standard multikinase inhibitor drug with anti-VEGFR (vascular endothelial growth factor receptor) activity, and produced superior results," he notes.

HCC is the second deadliest form of cancer, responsible for more than 700,000 deaths globally each year, and the most common form of liver cancer. Sorafenib became the first systemic treatment for liver cancer around 15 years ago. As an anti-VEGFR inhibitor, it works to control cancerous growth by targeting new blood vessels that feed the tumor and allow its progression. For their part, immune checkpoint inhibitors like programmed cell death 1 (PD1) antibodies restore the immune system's

ability to become activated and kill cancer cells. In a major discovery last year, Duda's lab found that immune checkpoint blockade also helps to reprogram the tumor vascular microenvironment, leading to greater T-cell infiltration and activation in HCC when used concomitantly with a multikinase inhibitor. It was that discovery that encouraged the MGH team to change the sequencing of the immune checkpoint inhibitor and multikinase inhibitor to see what would happen in preclinical models.

"We determined that increasing $CD8^+$ T cell infiltration mediates the benefit of sorafenib therapy when given sequentially, meaning after anti-PD-1 therapy priming," says Duda. "The feasibility of this approach was verified by our finding that the depletion of the $CD8^+$ T cells erased the benefits of sorafenib in this model."

Duda believes the new treatment strategy could have applicability in other forms of liver cancer, particularly metastatic colorectal cancer, where a recent Japanese study showed the effectiveness of combining immunotherapy with regorafenib, another type of multikinase inhibitor. "Unlike chemotherapy, which is geared to using the maximum tolerated dose, we're employing a 'less is more' approach which uses the body's immune system to reprogram the tumor environment," says Duda. "And that shows great promise of reducing the doses needed for therapy as well as the toxicity that often accompanies extended use of these medicines."

More information: Hiroto Kikuchi et al, Increased CD8+ T-Cell Infiltration and Efficacy for Multikinase Inhibitors after PD-1 Blockade in Hepatocellular Carcinoma, *JNCI: Journal of the National Cancer Institute* (2022). DOI: 10.1093/jnci/djac051

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