Combination therapy might improve outcomes in treatment-resistant liver cancer

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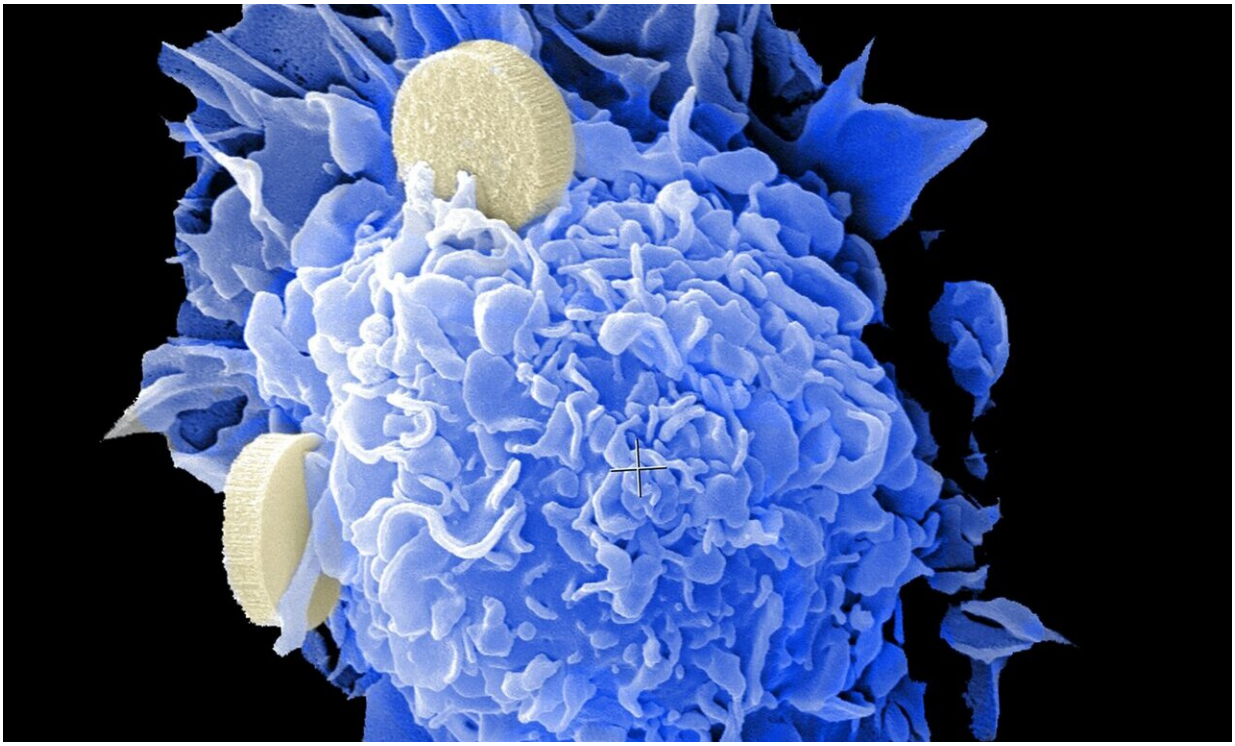

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A combination cancer therapy that is effective against treatment-resistant hepatocellular carcinoma (HCC) by inhibiting tumor growth and increasing survival has been identified by researchers at Massachusetts General Hospital (MGH). In a paper published in the *Journal for ImmunoTherapy of Cancer,* the investigators describe how

the dual therapy—which combines the multikinase inhibitor drug regorafenib to "reprogram" the tumor immune microenvironment, and programmed cell death 1 (PD1) antibodies to stimulate anti-tumor immunity—improved survival in mouse models of HCC beyond what each therapy could have achieved alone.

"The holy grail of immunotherapy in treating solid cancers like HCC is to draw cancer-fighting T-cells inside the tumor," explains Dan G. Duda, DMD, Ph.D., director of translational research in GI Radiation Oncology at MGH and senior author of the study. "We found that regorafenib delivered at the right intermediate dose tricks cancer cells into expressing a chemokine known as CXCL10 which, in turn, triggers intratumoral T-cell infiltration."

HCC, the most common form of liver cancer, is an aggressive gastrointestinal disease that is increasing globally at more than 3% a year. It is the second deadliest form of cancer, responsible for more than 700,000 deaths annually. The encouraging news for patients is the emergence in recent years of combination therapies of anti-vascular endothelial growth factor receptor (anti-VEGFR) inhibitors along with PD1 pathway blockades.

This type of cancer develops a rich new vasculature that feeds tumor progression. This vasculature is highly abnormal, which limits the recruitment and activity of effector T-cells. Anti-VEGFR inhibitors work to control that growth in part by normalizing tumor vasculature and increasing T-cell infiltration into tumors. This concept was first advanced by study co-author Rakesh K. Jain, Ph.D., director of Steele Laboratories for Tumor Biology at MGH, and a pioneer in the fields of vascular biology and cancer therapy. PD1 inhibitors, for their part, restore the immune system's ability to become activated and kill cancer cells by inhibiting the interaction between PD-L1, a protein on the surface of some of the malignant and non-malignant cells in HCC, and

the protein PD1 on the surface of T-cells. This dual treatment strategy has shown in some clinical trials of HCC patients response rates nearly double the 15% to 20% who typically respond to anti-PD1 treatment alone.

"Combination therapy has been a major advance for the field, but it still has limitations in treating liver cancer, as evidenced by the fact so many patients experience recurrence of the disease, even as they are living longer," says Jain. "To address treatment resistance, we suggested that an inhibitor that can target multiple kinases beyond VEGF receptors could be particularly effective. Our research teams were able to show that regorafenib has that unique capability when used at doses that induce both vascular normalization and increased expression of the chemokine CXCL10 in cancer cells. These intratumoral changes induce infiltration of T-cells into tumors where they can more effectively do their job."

Findings from the MGH study are directly informing ongoing clinical trials of regorafenib in cancer patients. Indeed, this work is highly relevant to the future development of treatments for HCC as well as other cancers that metastasize to the liver, according to Duda. "Now that our preclinical study has shown the effectiveness of dual therapy, we need to understand how to combine its components in ways that produce maximum benefit in patients," he says. "Our work has taken a major step in that direction by demonstrating the importance of targeting the immune microenvironment of HCC while using immunotherapy against this deadly cancer."

More information: Kohei Shigeta et al, Regorafenib combined with PD1 blockade increases CD8 T-cell infiltration by inducing CXCL10 expression in hepatocellular carcinoma, *Journal for ImmunoTherapy of Cancer* (2020). DOI: 10.1136/jitc-2020-001435

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