Molecular Therapy
Oncology
Commentary

Cracking the code for more effective treatments for hepatocellular carcinomas: Promise and a path for immunovirotherapy

Emil Lou[1,2,3]

https://doi.org/10.1016/j.omton.2025.200955

In their recent publication "Enhancing Immune Response and Survival in Hepatocellular Carcinoma with Novel Oncolytic Jurona Virus and Immune Checkpoint Blockade," Tesfay et al. report their evaluation of an oncolytic form of Jurona virus (JURV) and characterize its use in multiple versions of mouse models (syngeneic and xenograft) of hepatocellular carcinomas (HCCs).[1] Immunotherapies are being actively used for the treatment of patients with this cancer; at the same time, much of the biology of HCC remains unknown regarding immune composition and potential susceptibilities to immuno-oncologic (IO) strategies.

For historical perspective, advancements in the development of effective therapeutic options for HCC have lagged far behind compared to gastrointestinal (GI) cancers, until relatively recently. The SHARP trial, a phase 3 trial published in 2008 that randomized 602 patients with advanced HCC to either sorafenib (an oral kinase inhibitor) or placebo, demonstrated superior median overall survival (10.7 vs. 7.9 months for placebo) and median time to radiologic progression (5.5 vs. 2.8 months).[2] However, its success was in inducing cytostasis, improvement in mere weeks to months compared to best supportive care represented by placebo, and was only evaluated in patients who had the least severe amount of cirrhosis (class A using the Child-Pugh form of classification).[2] For nearly a decade, that drug remained the only viable treatment option for unresectable and/or metastatic forms of HCC, offering a highly modest treatment effect compared to the significant inroads being made in upper and lower GI cancers in particular. Combination treatment strategies adding regional chemoembolization to sorafenib improved disease control rates, but they also provided limited and extremely incremental improvements at best. Over the last decade, however, long-awaited human trials of multi-kinase inhibitors and investigation of immune checkpoint inhibitors were undertaken, borrowing from use and utility in metastatic colorectal cancers (CRC) in particular, with more improvement in patient outcomes than had been accomplished during any previous period of time.[3]

Enter the promise of immunovirotherapy. In their report, Tesfay et al. focus their study on a novel oncolytic form of JURV, a vesiculovirus selected for its relatively fast replication rate, tropism, and low human seroprevalence.[1] The authors assessed at least five cell lines derived from HCC, demonstrating 30% reduction in cell viability across several multiplicities of infection. For their *in vivo* studies, they utilized the approach of intratumoral injection that has become prevalent for a host of recent human clinical trials examining effects of engineered oncolytic viruses across a spectrum of tumor types.[4] The treatment strategy for the JURV used in this study consisted of three intratumoral doses into human xenografts.

The abscopal effect—the principle that the administration of a cancer-directed therapy at one site would subsequently have indirect positive effects against additional tumors systemically, without direct intervention—has remained an elusive but long sought after holy grail of cancer therapeutic strategies. Can intratumoral injections of next-generation oncolytic viruses provide the advances to prove the abscopal effect exists and can they be leveraged in a meaningful way, especially in potentially immuno-privileged compartments such as the liver? The answer to this question is going to be complex and not entirely solved in the scope of this or other single studies. Rather, the challenge is to channel new and emerging technologies—measurement and assessment of cell-free DNA, as just one example—with increased understanding of compartment-specific tumor biology and determination of the effects of commonly used checkpoint inhibitors deployed at a proper time and tumoral space. Tumor-agnostic approvals of immune checkpoint inhibitors (ICIs) include deficient mismatch repair/microsatellite instability high and high tumor mutational burden, while in some forms of cancer, prominently for metastatic gastroesophageal cancers among GI cancers, ICI use has been predicated on the presence and extent of PD-L1 surface checkpoint expression. ICI are increasingly used for metastatic HCCs, but without requirement or validation to date of predictive biomarkers for success. Will this change in the near future? With the maturation of comprehensive genomic profiling, more studies may be performed to analyze biomarkers prevalent in HCC that may be actionable. At the same time, the unique aspects of clinical diagnosis and management of HCC, all the way to the vagaries of the liver microenvironment created by cirrhosis and other causative factors of

[1]Department of Medicine, Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN, USA; [2]Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA; [3]Graduate Faculty, Integrative Biology and Physiology Department, University of Minnesota, Minneapolis, MN, USA

Correspondence: Emil Lou, Division of Hematology, Oncology and Transplantation, Mayo Mail Code 480, 420 Delaware Street SE, Minneapolis, MN 55455, USA.

E-mail: emil-lou@umn.edu

Published by Elsevier Inc. on behalf of The American Society of Gene and Cell Therapy.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HCC, may not create the best mix for the success of kinase inhibitors and/or checkpoint inhibitors when used as single agents. Experiences from colorectal tumors that metastasize to the liver have provided insight into the unique nature of the hepatic microenvironment, and parallels can be drawn for improving approaches to treating primary hepatic tumors such as HCC. Studies investigating the efficacy of multi-kinase inhibitors such as regorafenib and anti-programmed cell death protein (PD-1) ICIs such as nivolumab in CRCs have determined that these agents are most effective in non-liver CRC metastases.[5] Perhaps not coincidentally, these two agents were investigated in HCC and are now in widespread use and US Food and Drug Administration (FDA) approved for treating patients with unresectable or metastatic cases of HCC. What we do not yet know in a clinically meaningful way is what molecular or cellular factors distinguish the immune suppressive microenvironment in the hepatic parenchyma that allows these tumors to fend off these molecular-targeted approaches. Just as important, can newer strategies such as immunovirotherapy successfully recraft the tumor microenvironment in a way that makes HCC more susceptible to such agents?

The field of oncolytic viral therapy of cancer is over 100 years old in concept, if not in execution. Like many older things made new, the field has fluctuated over the past 2 decades, with a high point in 2015 being the first FDA approval of an oncolytic virus, talimogene laherparepvec, for cancer therapy. This virus is administered via injection in non-resectable cases of melanoma, and it opened the door to the expansion of exploration of this and other engineered viruses for other tumor types. This approach provides a fertile field for exploring oncolytic viruses such as the novel JURV, described by Tesfay et al. as a means to an end, part of a larger strategy and growing movement in oncology to modulate the tumor microenvironment, to induce a non-inflamed "cold" microenvironment to be converted to an inflammatory-rich "hot" state susceptible to immunotherapeutic treatments. The work reported by Tesfay et al. provides a meaningful contribution to the field of IO treatment strategies in a fast-moving field at the intersection of gastroenterology, oncology, and developmental therapeutics. The authors should be congratulated for this thought-provoking work.

ACKNOWLEDGMENTS

E.L. reports support and research grants from the American Cancer Society (RSG-22-022-01-CDP), 2022–2026, and the University of Minnesota Clinical Center for the Study of Pancreatic Disease, part of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC), funded by the National Institute of Diabetes and Digestive and Kidney Diseases (5U01DK126300-03); consultant for and/or financial interests in Ryght, Inc., Myer Research, and Primum; and compensation for the scientific review of proposed printed content from Elsevier and The Johns Hopkins University Press. He is/has been an institutional principal investigator for clinical trials sponsored by Celgene, Novocure, Intima Bioscience, and the National Cancer Institute. He is part of the University of Minnesota membership in the Caris Life Sciences Precision Oncology Alliance.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Tesfay, M.Z., Zhang, Y., Ferdous, K.U., Taylor, M.A., Cios, A., Shelton, R.S., Simoes, C.C., Watters, C.R., Barro, O., Elliott, N.M., et al. (2024). Enhancing immune response and survival in hepatocellular carcinoma with novel oncolytic Jurona virus and immune checkpoint blockade. Mol. Ther. Oncol. *32*, 200913. https://doi.org/10.1016/j.omton.2024.200913.

2. Llovet, J.M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J.F., de Oliveira, A.C., Santoro, A., Raoul, J.L., Forner, A., et al. (2008). Sorafenib in advanced hepatocellular carcinoma. N. Engl. J. Med. *359*, 378–390. https://doi.org/10.1056/NEJMoa0708857.

3. Yang, C., Zhang, H., Zhang, L., Zhu, A.X., Bernards, R., Qin, W., and Wang, C. (2023). Evolving therapeutic landscape of advanced hepatocellular carcinoma. Nat. Rev. Gastroenterol. Hepatol. *20*, 203–222. https://doi.org/10.1038/s41575-022-00704-9.

4. Lawler, S.E., Speranza, M.C., Cho, C.F., and Chiocca, E.A. (2017). Oncolytic Viruses in Cancer Treatment: A Review. JAMA Oncol. *3*, 841–849. https://doi.org/10.1001/jamaoncol.2016.2064.

5. Fakih, M., Sandhu, J., Lim, D., Li, X., Li, S., and Wang, C. (2023). Regorafenib, Ipilimumab, and Nivolumab for Patients With Microsatellite Stable Colorectal Cancer and Disease Progression With Prior Chemotherapy: A Phase 1 Nonrandomized Clinical Trial. JAMA Oncol. *9*, 627–634. https://doi.org/10.1001/jamaoncol.2022.7845.