Researchers advance new therapy with potential benefit for underserved patients with lung and ovarian cancers

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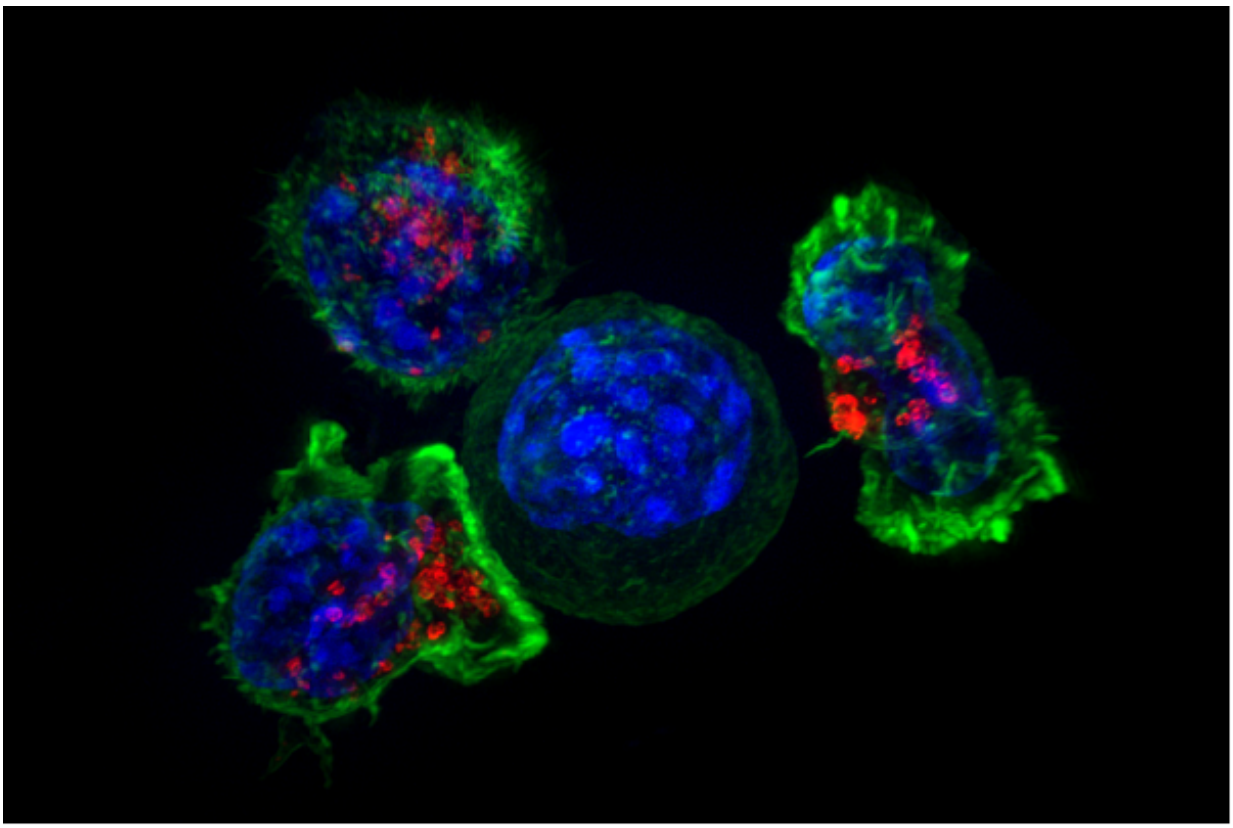

Killer T cells surround a cancer cell. Credit: NIH

In a first-time disclosure of IPN60090, a small-molecule inhibitor of the metabolic enzyme glutaminase (GLS1), researchers from The University

of Texas MD Anderson Cancer Center's Therapeutics Discovery division and Ipsen Biopharmaceuticals reported the preclinical discovery and early-stage clinical development of this novel drug. IPN60090, now under investigation in a Phase I trial, may hold benefit for certain patients with lung and ovarian cancers.

MD Anderson's GLS1 program was initiated and advanced by a team of scientists in the Institute for Applied Cancer Science (IACS) and Translational Research to Advance Therapeutics and Innovation in Oncology (TRACTION) platforms, both engines within Therapeutics Discovery. Development of the program continues in collaboration with Ipsen, which licensed the therapeutic in 2018.

Findings and information about the ongoing trial will be presented today at the 2020 American Association for Cancer Research Virtual Annual Meeting I by Jeffrey Kovacs, Ph.D., institute group leader with TRACTION and co-leader of the GLS1 program.

"This effort is a great example of our strategy within Therapeutics Discovery, taking a comprehensive approach to personalized medicine," said Kovacs. "Our preclinical data suggest that IPN60090 may be effective in underserved groups of patients who need better treatment options, and we look forward to results from our ongoing clinical trials."

Dysregulation of cellular metabolism is a hallmark of cancer development, and the GLS1 enzyme plays a key role in many metabolic processes. Thus, it makes an attractive target for cancer therapy, explained Kovacs.

IACS drug-discovery scientists identified IPN60090 as a potent and selective inhibitor of GLS1 suitable for clinical trials, and translational researchers in TRACTION demonstrated its activity against subsets of lung and ovarian cancer preclinical models.

Further analysis revealed biomarkers of response, which have been leveraged to identify patients most likely to benefit. In lung cancers, mutations in the KEAP1 and NFE2L2 genes, which regulate response to oxidative stress, sensitize cells to treatment with IPN60090. Similarly, low expression of the metabolic protein asparagine synthetase (ASNS) in ovarian cancers predicts response to IPN60090 in preclinical models.

"Identifying these putative predictive biomarkers of response is critical for our ongoing clinical efforts to ensure that we're able to offer patients the most relevant therapies," said Timothy A. Yap, M.B.B.S., Ph.D., F.R.C.P., associate professor of Investigational Cancer Therapeutics and medical director of IACS. "These patient groups in particular, which represent distinct niches within those cancer types, are in need of more effective treatment options."

For example, patients with lung cancers harboring KEAP1/NRF2 mutations have not benefited from treatment with immune checkpoint inhibitors and have poorer outcomes overall, explained Yap, who leads the IPN60090 clinical trial at MD Anderson.

IPN60090 currently is under investigation in a Phase I dose-escalation and dose-expansion study for patients with advanced solid tumors that harbor KEAP1/NFE2L2 mutations or have low ASNS levels. The team has developed novel CLIA-certified assays to identify patients likely to benefit and monitor how effectively the drug is acting. Initial data from the clinical trial indicate that IPN60090 is effectively inhibiting GLS1 activity in peripheral blood mononuclear cells from patients.

Future trial cohorts plan to investigate IPN60090 in combination with checkpoint inhibitors, chemotherapy and targeted therapies identified by the researchers as having potential synergistic benefits with GLS1 inhibition.

The ongoing research is supported by Ipsen through a global licensing and development agreement. The research is managed according to MD Anderson's Institutional Conflict of Interest Management and Monitoring Plan. Kovacs is a co-inventor on material and method-of-use patent applications related to IPN60090. The Therapeutics Discovery division is supported in part by MD Anderson's Moon Shots Program.

Provided by University of Texas M. D. Anderson Cancer Center