

Metabolic inhibitor IACS-6274 shows early antitumor effects in underserved patients

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The glutaminase (GLS1) inhibitor IACS-6274, discovered and developed by The University of Texas MD Anderson Cancer Center's Therapeutics Discovery division, appears to be well-tolerated with successful target inhibition and early signs of anti-tumor activity in a biomarker-driven Phase I trial. Interim results of the study will be presented at the 2021 American Society for Clinical Oncology (ASCO) Annual Meeting on June 4.

On the trial, 17 of 20 evaluable patients achieved a best response of stable disease, with a disease control rate of 60% at 12 weeks. Six patients with biomarker-defined advanced cancers had meaningful durable disease stabilization for greater than six months, with evidence of tumor shrinkage.

Comprehensive pharmacokinetics (PK) and pharmacodynamics (PD) analyses on serial tumor and/or [blood samples](#) from trial participants established a robust PK/PD relationship across dose levels. Using a clinical assay developed in-house to measure [metabolic activity](#) in patients' blood mononuclear cells, the team also observed strong inhibition of glutamine metabolism at the recommended Phase II dose level, suggesting IACS-6274 robustly functions as intended to block GLS1 activity.

This represents the first major clinical data reported by MD Anderson's Therapeutics Discovery division, a unique group of clinicians, researchers and drug development experts working collaboratively to

advance impactful new therapies. By working seamlessly with MD Anderson physicians, the team gains unique clinical insights that aid in the development of impactful medicines.

"Within Therapeutics Discovery, we have focused our efforts to develop new therapies that meet the needs of our patients," said principal investigator Timothy A. Yap, M.B.B.S., Ph.D., associate professor of Investigational Cancer Therapeutics and medical director of the Institute for Applied Cancer Science (IACS). "Our comprehensive efforts to understand and advance IACS-6274 identified select groups of underserved patients as those most likely to benefit from treatment, and we are encouraged by the early results thus far in the study."

Developing a therapy for underserved patient groups

The development of IACS-6274, previously known as IPN60090, was led by a team of scientists and drug development experts in the IACS and Translational Research to Advance Therapeutics and Innovation in Oncology (TRACTION) platforms, both engines within Therapeutics Discovery.

IACS-6274 was selected for development based on its potency, selectivity and PK profile to provide sustained GLS-1 inhibition in patients. The research team then conducted patient-driven translational studies to identify unique populations of patients likely to respond.

Based on these studies, priority indications for the trial include non-small cell lung cancers (NSCLC) with KEAP1/NFEL2L2 mutations, ovarian cancers with low expression of asparagine synthetase (ASNS) and tumors with immune checkpoint inhibitor resistance. Additional insights have revealed that cancers with STK11 and NF1 mutations may respond to GLS1 inhibitors, so the trial also has enrolled those patients.

Evaluating IACS-6274 in a Phase I clinical trial

The first-in-human dose-escalation study was conducted by MD Anderson's Phase I Clinical Trials Program in the Department of Investigational Cancer Therapeutics. The study was designed to evaluate the safety and tolerability of IACS-6274, to identify the maximum tolerated dose and to establish a recommended Phase II dose. Secondary objectives included PK, PD, anti-tumor activity and correlation of biomarkers with clinical outcomes.

The study has enrolled 22 patients with a median age of 63.5, all of whom had received at least two prior therapies. Sixteen patients (73%) are female and six (27%) are male. The trial included patients with different tumor and molecular subtypes, including many of the identified priority patient populations.

The six patients with durable stable disease included those with advanced ASNS-low ovarian cancer, melanoma resistant to anti-PD-1 therapies, NF1-mutant leiomyosarcoma and STK11-mutant NSCLC.

The most common side effects were mild transient visual disturbances. Less common grade 3 toxicities at higher dose levels included reversible nausea, vomiting and fatigue. One patient experienced dose-limiting acute renal failure and posterior reversible encephalopathy syndrome (PRES) at the highest dose level, which fully resolved.

"IACS-6274 appears to be safe and well-tolerated at our recommended Phase II dose, with early signs of anti-tumor activity in patients with certain molecular features," Yap said. "As the study progresses and we continue to learn from those participating, we will work to explore rational combination therapies that are predicted to maximize the benefits for distinct groups of patients based on key biomarkers of response."

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

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