Novel AKT pathway inhibitor, ARQ 092, demonstrated safety, effective target inhibition

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Researchers have confirmed that the novel oral agent ARQ 092 inhibits the AKT pathway and has a manageable safety profile in patients with a variety of advanced solid tumors, according to phase I data presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

"AKT is a signal transduction pathway crucially involved in the growth, survival and metabolism of cancer cells," said Mansoor N. Saleh, M.D., professor of medicine at the University of Alabama Comprehensive Cancer Center in Birmingham and director of research at Georgia Cancer Specialists in Atlanta. "Many of the signaling pathways disrupted by commonly seen cancer-causing mutations merge into the AKT pathway. In addition, the AKT pathway is often amplified and mutated in patients who relapse following initial therapy.

"This means that the AKT pathway is a potential treatment target for numerous cancer types, either at diagnosis or when they become resistant to initial therapies."

Saleh and his colleagues tested the safety and activity of ARQ 092 in patients with a broad range of advanced or metastatic solid tumors, including colorectal, endometrial and neuroendocrine cancers. They assigned patients in the first cohort to a dose of 10 mg every other day and enrolled subsequent patients into cohorts of three to six patients who were assigned to a dose escalation schedule with the drug.

"This class of agents has two common toxicities, namely skin toxicity and hyperglycemia, a rise in blood sugar levels," Saleh said. "Based on data presented with other AKT inhibitors, skin toxicity has been the dose-limiting side effect and often resulted in drug discontinuation."

To date, Saleh and colleagues have observed no dose-limiting skin toxicity. In addition, they have observed that with ARQ 092, blood sugar levels rise before patients experience skin toxicity, and they have been able to treat the hyperglycemia, thus allowing the patients to continue on the experimental drug.

"When we see hyperglycemia, we know that the drug is active in patients," Saleh said. "We can ameliorate the high blood sugar, potentially allowing us to achieve drug levels that will be therapeutically active."

Currently, the maximum tolerated dose has not been reached in this ongoing trial, but Saleh and colleagues have confirmed that the 80-mg dose once a day is not well tolerated. Seven patients have remained stable on the drug for more than four months. Four patients with advanced and refractory solid tumors have had stable disease for longer than six months, according to Saleh.

Once the maximum tolerated dose is identified, Saleh and colleagues plan to test the drug for efficacy.

"We will also explore the drug activity in patients with a high level of AKT in the tumor to identify the patient populations that can robustly benefit from our treatment," he said.

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