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AKT inhibitor AZD5363 well tolerated, yielded partial response in patients with advanced solid tumors

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The investigational drug AZD5363, which has shown activity in preclinical studies, was well tolerated in humans, and two patients with advanced solid tumors showed partial response, according to data presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

"PI3K/AKT signaling is very important in cancer cells," said Udai Banerji, M.D., Ph.D., clinical senior lecturer at the Institute of Cancer Research and The Royal Marsden NHS Foundation Trust in London, United Kingdom. "This signaling pathway is highjacked by abnormalities or mutations in genes that can cause a normal cell to behave like a cancer cell."

AZD5363 is a new-generation drug inhibiting the three forms of the AKT protein: AKT1, AKT2 and AKT3. It has shown promising results in several tumor cell lines and animal studies. In prior clinical trials, AKT inhibitors have almost always been tested in continuous dosing schedules, resulting in excessive toxicity, according to Banerji.

Banerji and colleagues conducted two phase I studies and administered AZD5363 to the patients in two schedules: continuous dosing seven days a week and intermittent dosing with four days on and three days off.

Among the 92 patients recruited thus far, an intermittent dosing schedule

of 480 mg twice a day was generally well tolerated. Side effects included high blood sugar, rash and diarrhea. "But what is important about these side effects, such as raised blood sugar, is that these are known consequences of targeting the AKT pathway," said Banerji. "This provides proof of principle that the drug is working."

Using pharmacokinetics studies, the team determined that the dose achieved in the patients' blood was comparable to the dose used in preclinical studies in which they saw positive outcomes. More than 30 percent reduction was seen in the levels of two proteins, pPRAS40 and pGSK3 beta, in plucked hair and blood samples collected from the patients, suggesting that the drug successfully inhibited AKT.

One patient with ovarian cancer and one with cervical cancer showed partial response to treatment. Both had a mutation in either AKT1 or PIK3CA in their cancers. A third patient with ovarian cancer with a PIK3CA mutation had prolonged stable disease.

"What is very gratifying is that a response like this to a single agent is not something we see very often," said Banerji. "Also, these data support the growing realization that AKT inhibitors are beneficial when administered intermittently and not continuously."

Encouraged by these results, AstraZeneca recently initiated two phase Ib studies with patients with prostate and breast cancers. AZD5363 was discovered by AstraZeneca subsequent to collaboration with Astex Therapeutics and its collaboration with The Institute of Cancer Research .

Provided by American Association for Cancer Research

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