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Mutant-IDH1 inhibitor AG-120 shows early promise against solid tumors with IDH1 mutations

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The investigational anticancer therapeutic AG-120, which targets mutant IDH1 protein, was well tolerated and showed signs of clinical activity in patients who had advanced solid tumors positive for mutant IDH1, according to data from a phase I clinical trial presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Nov. 5–9.

"IDH1 gene mutations are present in a number of types of solid tumors that are extremely difficult to treat, most commonly gliomas, intrahepatic cholangiocarcinomas [IHCC], and chondrosarcomas," said Howard A. Burris III, MD, chief medical officer and executive director, drug development program, at the Sarah Cannon Research Institute in Nashville, Tennessee. "Mutated IDH1 proteins produce a metabolite called 2-HG that is implicated in the development of cancer. Inhibiting mutant IDH1 and reducing 2-HG levels may lead to clinical benefit for the subset of cancer patients whose tumors are positive for IDH1 gene mutations.

"AG-120 is a highly selective small molecule inhibitor of mutant IDH1 protein," continued Burris. "The results we are reporting are important; the demonstration of a manageable safety profile, biomarker modulation, and clinical antitumor activity in some patients indicate that AG-120 should be taken into further clinical development in IDH1 mutation–positive solid tumors."

As of Sept. 3, 2015, 62 patients with advanced IDH1 mutation–positive solid tumors that had recurred or progressed following standard treatment, with a median of three prior lines of therapy (ranging from one to six), have been treated with single agent AG-120. Twenty patients had glioma, 25 had IHCC, 12 had chondrosarcoma, and five had another cancer type.

In the dose escalation part of the clinical trial, patients took AG-120 orally once a day until disease progression. The maximum tolerated dose was not reached but the recommended dose for the expansion phase is 500 milligrams of oral AG-120 once a day.

AG-120 was well tolerated at all eight doses tested. The majority of side effects were mild to moderate and the majority of serious adverse events were disease-related, the most common being nausea, diarrhea, vomiting, anemia, and abdominal pain, but there were no treatment-related serious adverse events.

Fifty-five response-evaluable patients had been analyzed for efficacy as of Sept. 3, 2015. Seven of 11 patients with IDH1 mutant–positive chondrosarcoma had stable disease (SD), with five of these responses maintained beyond six months; one out of 20 patients with IDH1 mutant–positive IHCC had a partial response (PR) and 11 patients had SD, with the one PR and five of the SDs maintained beyond six months; 10 out of 20 patients with IDH1 mutant–positive glioma had SD, with four maintained beyond six months; and one out of four patients with other IDH1 mutant–positive solid tumors had SD.

"We were pleased that the safety profile of AG-120 in this study was consistent with data from the ongoing phase I AG-120 study being conducted in advanced hematologic malignancies," said Burris. "We look forward to continuing this study as the clinical activity we have seen in these difficult-to-treat solid tumors is encouraging."

According to Burris, although these results are encouraging, they are early and the data set is limited by the small numbers of patients and the early stage of the trial.

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