AZD9291 shows clinical activity in non-small cell lung cancer patients with leptomeningeal disease

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The epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) AZD9291 crossed the blood-brain barrier and showed clinical activity in heavily pretreated non-small cell lung cancer (NSCLC) patients with leptomeningeal disease, a disease in which lung cancer cells spread to the membranes surrounding the brain and spinal cord, according to data from a phase I BLOOM clinical trial presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Nov. 5–9.

"Leptomeningeal disease at initial diagnosis of NSCLC is rare; however, as their lung cancer progresses, up to 15 percent of patients will develop this devastating complication. Additionally, an increased risk of central nervous system [CNS] involvement has been reported among patients with EGFR-mutant NSCLC, in particular those treated with a first-generation EGFR-TKI," said Dae Ho Lee, MD, PhD, associate professor in the Department of Oncology in the University of Ulsan College of Medicine and Asan Medical Center, Seoul, Korea.

"Patients with EGFR-mutated NSCLC and leptomeningeal disease have an average survival of seven to 11 months, and currently there is no established effective treatment for this condition," he added.

"Preclinical studies and anecdotal patient reports have indicated that AZD9291, an oral EGFR-TKI that selectively acts against lung tumors driven by specific mutations in the EGFR gene, including the T790M resistance mutation, crosses the blood-brain barrier that usually prevents drugs from having an effect in the brain, and had activity against brain tumors with EGFR mutations," Lee explained. Based on the preclinical evidence and anecdotal reports of activity in brain metastases, the decision was made to study AZD9291 in NSCLC patients with leptomeningeal disease or brain metastases in a clinical trial in order to assess its antitumor efficacy and safety in this setting, he said.

Of the 13 heavily pretreated EGFR-mutant NSCLC patients that Lee and colleagues enrolled in the phase I trial, 10 had received other EGFR-TKIs as prior therapies, and seven had received radiotherapy to the brain. Four patients had T790M-positive disease detected in their plasma, and two had DNA with the T790M mutation detected in their cerebrospinal fluid (CSF). All patients received 160 mg of AZD9291 once daily until disease progression. Treatment beyond progression was allowed at investigator discretion.

"There is no standardized way to measure response of leptomeningeal disease to therapy, but a combination of clearing cancer cells from the fluid surrounding the brain (CSF cytology), changes on brain MRI imaging, and improvement in neurologic symptoms is likely to be the best composite endpoint to assess clinical benefit," Lee said.

As of Oct. 12, 2015, 11 patients were evaluable for response. Of these patients, six patients had improvements in brain imaging and three of seven patients with abnormal neurological exams at baseline had symptomatic improvement, as judged by the investigator. One patient had confirmed clearance and four patients had unconfirmed clearance of cancer cells from the CSF, according to Lee.

Eight of nine patients from whom pre- and post-treatment CSF samples were available had a decrease in EGFR-mutant DNA, with the decrease being more than 50 percent in five of them.

Adverse events were consistent with those

published previously, Lee said.

"Our results show that AZD9291 is a well-tolerated compound in this difficult-to-treat setting, and demonstrated that it crosses the blood-brain barrier. Although preliminary, these results show encouraging activity and a manageable safety profile in a patient population with few treatment options. The results support further investigation of AZD9291 in central nervous system disease," Lee said.

"This phase I, open-label, non-randomized study enrolled a small number of patients. As there are no recognized endpoints to measure response in leptomeningeal disease, we have collected several outcomes for a composite measure of efficacy. These are preliminary results, and a longer follow-up is needed to fully understand the potential for AZD9291 in CNS disease associated with EGFR-mutated NSCLC," Lee added.

Provided by American Association for Cancer Research

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