MedicalXpress

New NTRK-targeted therapy shows early promise against tumors with NTRK gene fusions

November 9 2015

The investigational anticancer therapeutic LOXO-101, which targets a family of proteins called neurotrophic tyrosine kinase receptors (NTRKs), was safe, tolerable, and showed signs of clinical activity in patients who had tumors with a specific type of NTRK genetic alteration called a gene fusion, 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.

"Prior studies have shown that NTRK gene fusions drive the growth of tumors in preclinical models and are found in a wide array of tumor types," said David S. Hong, MD, deputy chair and associate professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center in Houston. "These preliminary results from the first-in-human clinical trial of the NTRK-targeted investigational agent LOXO-101 help to validate NTRK gene fusions as drivers of several cancer types and suggest that LOXO-101 is a safe, tolerable, and potentially effective option for these patients."

As of Oct. 20, 2015, among the 30 patients so far enrolled in the phase I clinical trial, there were six who had tumors positive for an NTRK gene fusion. As of that date, three of these six patients have had their disease assessed since starting LOXO-101 and all three had a partial response at first disease assessment, as assessed by RECIST 1.1 criteria. These three patients are the only patients on the trial to have responded. All three

partial responses are ongoing. The other three patients with NTRK fusions are still on study and will have their disease assessed in the coming weeks, according to Hong.

"We are particularly excited by the fact that we have seen dramatic responses for patients with different types of tumors positive for NTRK gene fusions, as this looks like a potential targeted, or precision, therapy that could be effective at the level of the matching genetic alteration regardless of the cancer type," said Hong. "Building from these data, a phase II basket trial testing LOXO-101 as a treatment for patients with any type of tumor positive for an NTRK gene fusion recently opened."

All patients enrolled in the current clinical trial had solid tumors that were not responding to standard therapy. The trial is a standard 3 + 3 dose escalation phase I clinical trial and LOXO-101 is taken orally once or twice a day in 28-day cycles.

LOXO-101 was well tolerated at all five doses tested so far: 50 mg, 100 mg, and 200 mg once a day, and 100 mg and 150 mg twice a day. The maximum-tolerated dose has not been defined. The most common reported adverse events have been grade 1 and 2 fatigue, dizziness, anemia, and nausea.

The three response-evaluable patients with NTRK gene fusion–positive tumors received either 100 mg or 150 mg of LOXO-101 twice a day and are still on study. One patient with an undifferentiated sarcoma with an LMNA-NTRK1 gene fusion has a confirmed partial response ongoing at eight months. One patient with a c-kit-negative gastrointestinal stromal tumor with an ETV6-NTRK3 gene fusion has a confirmed partial response ongoing at four months. One patient with a mammary analogue secretory carcinoma of the salivary glands with an ETV6-NTRK3 gene fusion has a partial response ongoing at three months.

Hong explained that the major limitation of the current study is that it is a small phase I clinical trial that has assessed only three patients with NTRK gene fusion–positive tumors. He added that although these results are extremely promising, they need validating in larger studies.

Provided by American Association for Cancer Research