New investigational epigenetic therapy shows clinical activity against several blood cancers

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Patients with a variety of hematological, or blood, cancers benefited from treatment with OTX015, a member of a new class of investigational epigenetic therapies that block the activity of bromodomain and extraterminal (BET)-bromodomain proteins, according to results of a phase I clinical trial presented here at the AACR Annual Meeting 2014, April 5-9.

BET-bromodomain proteins have an important role in controlling whether a gene is turned on or off. They work by attaching to special epigenetic flags on the genome. The positioning of many epigenetic flags is abnormal in many different types of cancer, and this can inappropriately turn genes on or off, helping drive these cancers.

"OTX015 is a potent, small-molecule inhibitor of the BET-bromodomain proteins BRD2, 3, and 4," said Esteban Cvitkovic, M.D., professor of oncology and founder of OncoEthix. "Preclinical data showed that it may be effective against a wide range of hematologic malignancies. This ongoing study is designed to determine the recommended dose and schedule of OTX015 to be given orally as a single agent to patients with hematologic malignancies.

"We have been excited to see that several leukemia and lymphoma patients, having failed all available standard therapies, have durable, objective responses to monotherapy with oral OTX015 at doses that have little or no toxicity," added Cvitkovic. "As far as we know, this is the first clinical evidence that BET-bromodomain inhibitors, a new

family of anticancer agents, may have a role in the treatment of human malignancies."

So far, Cvitkovic and colleagues have enrolled 42 patients in their clinical trial, 21 with acute leukemia—mainly acute myelogenous leukemia (AML)—and 21 with other hematological malignancies, including diffuse large B-cell lymphoma (DLBCL) and multiple myeloma. These patients were assigned to a single dose of 10 mg, 20 mg, 40 mg, or 80 mg of OTX015 daily, or to two 40 mg doses of OTX015 daily. There were from three to six patients with acute leukemia and three to six patients with another hematological malignancy assigned to each dosing regimen.

Of the 38 patients for whom data are mature enough to allow evaluation, the researchers saw clinically meaningful activity in seven. Four of these seven patients received a single dose of 80 mg of OTX015 daily, one received 10 mg daily, and the other two received 40 mg daily. Treatment of three of these seven patients is ongoing, between two and six months from the start of treatment.

Among the patients who benefited clinically are four with AML. One is experiencing an ongoing complete response, which means the patient's bone marrow and blood returned entirely to normal. A second is experiencing a complete response with incomplete recovery, meaning there are no leukemia cells detectable in the bone marrow and blood but only partial recovery of normal blood cells. The researchers saw a significant decrease in the number of leukemia cells in bone marrow and blood for the two other patients with AML. They also saw partial responses in two lymphoma patients, one with DLBCL and one with lymphoplasmacytic lymphoma. A patient with follicular lymphoma has an ongoing minor response with clinical symptom clearance.

No dose-limiting toxicities have been observed so far in patients with

leukemia, according to Cvitkovic, while thrombocytopenia is emerging as a dose-limiting toxicity for patients with other hematological malignancies. Enrollment in the trial is continuing, with patients being assigned to single doses of 120 mg OTX015 daily.

Other sporadic adverse events reported so far have been increased blood glucose in previously diabetic patients, mild to moderate digestive symptoms, and fall of platelet counts. No cumulative toxicity has been observed.

"With dose escalation still ongoing, we have yet to determine the optimal dosing and schedule for monotherapy with OTX015," said Cvitkovic. "Given that, we are very pleased to have already seen clear evidence of antineoplastic activity."

Provided by American Association for Cancer Research

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