First demonstration of anti-cancer activity for an IDH1 mutation inhibitor

18 November 2014

A phase I trial of the first drug designed to inhibit the cancer-causing activity of a mutated enzyme known as isocitrate dehydrogenase (IDH) 1, which is involved in cell metabolism, has shown clinical activity in patients with advanced acute myeloid leukaemia (AML) with the IDH1 mutation.

Professor Daniel Pollyea, M.D. will tell the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, today (Wednesday) that early results from the phase 1 clinical trial of the drug AG-120, an oral, selective and potent inhibitor of the mutated form of the IDH1 enzyme, have shown that the drug was well tolerated with encouraging clinical activity in patients with advanced IDH1 mutation positive AML.

"This is the first study in humans of an inhibitor of mutant IDH1 and the first demonstration of clinical activity of AG-120 in AML patients whose cancers have the IDH1 mutation. Although the data are early, we are encouraged to see evidence of clinical activity, as the primary objectives of Phase I studies are to determine safety and tolerability," Prof Pollyea, who is clinical director of leukemia services and assistant professor of medicine at the University of Colorado, USA, will say.

Mutations in IDH1 lead to a cascade of metabolic events in cells that contribute to malignancy. Mutant IDH1 produces an excess amount of 2-hydroxyglutarate (2-HG), which is a substance that is normally present in cells in low levels. When 2-HG is present in excessive amounts, it prevents them from maturing into normal functioning cells, leading to cancer. In the phase 1 study, AG-120 was able to reduce 2-HG levels in diseased cells to normal levels, allowing them to mature into normal cells. IDH1 mutations have been identified in a range of solid tumours, such as chondrosarcoma, cholangiocarcinoma and gliomas, and haematologic cancers (cancers of the blood), such as AML and myelodysplastic syndromes (MDS).

The first clinical trial of AG-120 in haematologic cancers started in March 2014 and, as of the data cut-off date of October 17, 2014, 17 patients with relapsed and/or refractory AML had been enrolled into one of four dose groups, with each group receiving the drug in tablet form at different and increasing dose levels: 100mg twice a day, 300mg once a day, 500mg once a day and 800 mg once a day over continuous 28-day cycles. There are between four to five patients in each group. The median number of prior treatments before entering the study was two.

In the first four groups of patients treated in the trial with AG-120, results from 14 evaluable patients showed seven patients whose cancers responded to the drug, including four complete remissions (no sign of cancer remaining). Three patients had not reached the time in their treatment for bone marrow assessments in the first 28-day treatment cycle, and so were not evaluable. AG-120 has been well tolerated by patients to date, and the researchers are continuing to increase the dose; the maximum tolerated dose has not been reached yet.

"These data suggest that using AG-120 to inhibit the IDH1 mutation has the potential to stop the production of 2HG, and encourage cancerous cells to become mature, functioning blood cells. AML is a devastating disease that has historically been very difficult to treat, and these findings suggest that AG-120 has the potential to transform therapy for patients with IDH1-mutant positive AML," Prof Pollyea will say.

The phase 1 trial is enrolling patients with difficult to treat AML whose cancers have failed to respond to previous treatment and/or have relapsed, or who are over the age of 60 with untreated AML or myelodysplastic syndromes (or MDS). All harbour the IDH1 mutation. The prognosis for these cancers is poor: overall, only 25% of patients diagnosed with AML will live for five years, but among patients over the age of 60, who tend to respond less well to

treatments, about 12% are alive after five years.

The researchers are continuing to conduct the phase I study with the aim of fully understanding the safety of the drug, determining the maximum tolerated dose and assessing its efficacy in treating AML and MDS.

Professor Jean-Charles Soria, chair of the scientific committee for the EORTC-NCI-AACR Symposium and chair of the Drug Development Department at Gustave Roussy Cancer campus, France, commented: "AG120 is an oral inhibitor of mutant IDH1. In this first-in-man trial, AG120 appears well tolerated, and has demonstrated, in a limited set of molecularly selected AML patients, indisputable clinical activity."

More information: Abstract no: LBA 1, "Clinical safety and activity in a phase I trial of AG-120, a first in class, selective, potent inhibitor of the IDH1-mutant protein, in patients with IDH1 mutant positive advanced haematologic malignancies". Proffered papers, plenary session 2, Auditorium, 13.15 hrs, Wednesday 19 November.

Provided by ECCO-the European CanCer Organisation