A drug that inhibits the Notch signalling process is active in a range of advanced cancers

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Munich, Germany: A new anti-cancer drug that inhibits a key cell signalling process involved in many different cancers has shown that it is capable of stopping the progression of cancer and shrinking tumours. Importantly, it has been able to do this in rare cancers that are less well-studied such as adenoid cystic carcinoma.

Dr Christophe Massard, a senior medical oncology consultant and chair of the Early Drug Development programme at the Institut Gustave Roussy Cancer Campus (Villejuif, France) told the 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany, today (Friday) that results from a phase I clinical trial in 103 patients showed that the drug LY3039478 was successful in inhibiting the Notch signalling pathway in patients with alterations in the Notch protein.

Patients in the trial had a range of cancers, including breast, colon, parotid (salivary gland) and sarcoma, which were all advanced or had started to spread to other parts of the body (metastasise). After treatment with LY3039478, the tumour shrank in one patient with breast cancer and the disease stabilised and did not progress in another 29 patients. In addition, using PET scanning, researchers found two more cases where the tumours had shrunk: in a patient with adenoid cystic carcinoma and a patient with testicular cancer.

Dr Massard said: "Research suggests that the Notch signalling pathway plays a role in helping cancer cells to grow, divide and spread around the body; it is also involved in angiogenesis, the process by which tumours grow new blood vessels, and it may contribute to tumours becoming resistant to chemotherapy. Notch signalling that is unregulated due to mutations in the Notch protein is implicated in a number of cancers.

The Notch signalling pathway involves four Notch receptors (NOTCH1, 2, 3 and 4) - proteins that sit on the membranes of cells, including cancer cells, and transfer messages across the cell membrane. LY3039478 is able to inhibit all four receptors. The results from this phase I trial prove that LY3039478 has the effect on tumours that was expected, by inhibiting the Notch signalling and thereby preventing cancer cell growth and proliferation.

"Notch was evaluated as a target for anti-cancer drugs several years ago, with promising results in lymphoma and rare cancers. However, because of gastrointestinal toxicity, the development of several Notch-inhibition compounds was stopped," said Dr Massard. "In this trial we have worked closely with gastrointestinal specialists to manage the toxic effects of the drug."

Side effects from the drug were manageable, the most common being diarrhoea (in 48% of patients), vomiting (40%), nausea (38%), loss of strength (25%) and decreased appetite (21%). Other, less common side effects included weight loss, dry skin and mouth, and hair loss.

The clinical trial also established that the recommended dose for a phase II clinical trial as 50 mg three times a week for 28 days, repeated until the disease starts to progress. The drug is taken orally.

"This was a proof of concept trial that has shown that LY3039478 is successful in inhibiting unregulated Notch signalling, resulting in

encouraging signs of preliminary clinical activity in several advanced and metastatic cancers. One of the interesting results with implications for some patients is that the drug was active against rare cancers such as adenoid cystic carcinoma," concluded Dr Massard.

The phase I trial is continuing and there are plans for a further trial in advanced and metastatic cancers to test the drug in combination with other anti-cancer drugs such as taladegib (in breast cancer), abemaciclib (colon cancer), cisplatin (cholangiocarcinoma) and gemcitabine and carboplatin (soft tissue sarcoma).

Dr Kapil Dhingra, a member of the executive committee for the Symposium and managing member of KAPital Consulting LLC (USA), commented: "Notch signalling is an important contributor to the development of a variety of cancers. However, successful development of drugs against this pathway has been challenging, in part due to unacceptable side effects. While preliminary, the results of the phase I study of LY3039478 show evidence of anti-tumour activity in a number of different tumour types with a manageable safety profile. These results warrant further investigation of this drug in clinical trials."

Provided by ECCO-the European CanCer Organisation

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