Results of new drug, ASP8273, show response in patients with treatment-resistant NSCLC

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In a second presentation looking at new ways of treating non-small cell lung cancer (NSCLC) that has both the EGFR and T790M mutations, researchers will tell the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, that an oral drug called ASP8273 has caused tumour shrinkage in patients in a phase I clinical trial in Japan.

Mutations of the epidermal growth factor (EGFR) occur in about 30-35% of Asian patients with NSCLC (and in 10-15% of Caucasian patients). EGFR inhibitors called tyrosine kinase inhibitors (TKI), such as erlotinib, gefitinib and afatinib, can be used to treat EGFR-mutated NSCLC. However, these patients will eventually develop resistance to EGFR TKI therapy, rendering their disease resistant to current treatments. A further mutation called T790M accounts for 60% of this acquired resistance.

ASP8273 is a new drug that inhibits the EGFR mutation and the T790M resistance mutation. Earlier research in mice had shown that it caused NSCLC to disappear completely, and so a phase I clinical trial was started in January 2014 to assess the drug's safety and efficacy in humans.

Twenty-four Japanese patients have enrolled so far to receive one of six levels of doses (25, 50, 100, 200, 400 and 600mg) once a day. A further

seven patients have been enrolled into a second group to evaluate doses of 100mg, 200mg and 400mg a day (a dose escalation study), and the researchers are planning to enrol a total of 124 patients. Cancer had progressed in all the patients after prior treatment with EGFR TKI therapy, and most of them had the T790M mutation.

Dr Haruyasu Murakami, of the Shizuoka Cancer Center, Shizuoka, Japan, will tell the meeting: "Preliminary results from this study show a high overall response rate of 78%, with tumours shrinking in seven out of nine patients who had both the EGFR and T790M mutations. While the number of patients is still small, this response is comparable with two other drugs in development that target EGFR - CO-1689 and AZ-9291 - but ASP8273 has fewer safety concerns than these drugs."

The most common adverse reactions to ASP8273 were mild cases of diarrhoea (in half of the patients), nausea and vomiting (in a third of the patients). There were none of the severe respiratory complications, heart problems and high blood sugar levels that have occurred during the clinical trials of the other two drugs. One patient receiving 400mg a day suffered diarrhoea that was severe enough for the dose to be reduced. The four patients who received 600mg a day had dose-limiting toxicities including severe diarrhoea, colitis (inflammation of the colon) and cholangitis (infection of the bile duct). All the patients in the trial who had the T790M mutation remain in the trial without further progression of their disease.

"These data indicate that ASP8273 would be expected to have potential clinical benefits with fewer adverse side-effects compared to CO-1689 and AZ-9291," Dr Murakami will say.

The researchers are continuing to recruit patients to the phase I dose escalation study. "We expect a recommended dose for a phase II trial to be determined soon and then we will start recruiting patients with both

EGFR and T790M mutations immediately in Japan and other Asian countries. At present we are observing partial responses in patients receiving the 100mg dose and they are tolerating it well," he will conclude.

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: "ASP8273 is the fourth EGFR-mutant specific kinase inhibitor in development for NSCLC patients with acquired resistance to EGFR inhibition related to appearance of the T790M mutation. Activity is clearly promising and toxicity is in line with the anticipated mechanism of action, but numbers are small and follow-up is quite immature at present."

More information: Abstract no: LBA 9, "Antitumour activity of ASP8273, an irreversible mutant selective EGFR-TKI, in NSCLC patients with tumours harbouring EGFR activating mutations and T790M resistance mutation". Proffered papers, plenary session 8, Auditorium, 11.00 hrs, Friday 21 November.

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