Early trial of new multi-kinase inhibitor shows impressive activity in medullary thyroid cancer

Geneva, Switzerland: Preliminary trials of a new multi-kinase inhibitor have indicated it has impressive tumour shrinkage activity in patients with a difficult to treat type of thyroid cancer. The results have put the drug’s development on a fast track, prompting the accelerated initiation of a large phase III trial.

The compound, XL184, targets cell growth and migration, as well as blood vessel growth (angiogenesis), through inhibition of MET kinase, VEGFR and RET kinase.

In a study presented today (Thursday 23 October) at the 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Geneva, 84 patients with a variety of advanced tumours that were not amenable to standard therapy were administered XL184 for either the first five days of a 14-day cycle or daily throughout the cycle. The group included 36 patients with advanced medullary thyroid cancer, for which no treatment is known to work. Response to the drug was assessed at 28 days and subsequently every eight weeks.

The impact on tumour shrinkage was particularly notable in the medullary thyroid cancer patients, where the overall disease control rate – the percentage of patients with either a partial response to the drug or prolonged stable disease for more than three months – was 84% in the 25 patients who have been followed for at least three months, said the study’s presenter, Professor Steven Sherman, chair of the Department of Endocrine Neoplasia and Hormonal Disorders at M.D. Anderson Cancer Center in Houston (Texas, USA).

“Partial response, where tumours shrink by at least 30%, was achieved in 55% of the 22 patients with measurable disease who have been followed for at least three months. Most of the others experienced prolonged stable disease beyond three months, and for most of these patients there was actually tumour shrinkage. That is an impressive result for an early trial in this type of cancer,” Professor Sherman said.

Three of the medullary thyroid cancer patients had unmeasurable disease. Tumour biomarkers such as plasma calcitonin and CEA [2] dropped significantly after therapy in most of the patients.

Of the 84 patients, including patients with diverse cancers, disease stabilisation for at least three months was seen in 28 cases. In sixteen of those cases, the disease was stable for six months or more, the study found. The most common adverse effects of the drug included diarrhoea (24%), nausea (18%) and fatigue (15%).

In a preclinical study presented on Friday at the conference, XL184 showed encouraging results in boosting sensitivity to erlotinib and gefitinib in drug-resistant lung cancer. Gefitinib and erlotinib belong to a class of targeted drugs that zero in on the epidermal growth factor receptor (EGFR) gene, which is mutated in many non-small cell lung cancers. MET kinase, which is inhibited by XL184, is implicated in the resistance to EGFR kinase inhibitors.
In the study, mice were grafted with human EGFR mutant and MET amplified non-small cell lung cancer tumours that were made resistant to gefitinib.

“Neither agent was effective alone, but tumour regression occurred in all animals when they were treated with a combination of erlotinib and XL184,” said the mouse study’s leader, Professor Pasi Janne, an assistant professor of medicine at Harvard University Medical School in Boston (Massachusetts, USA).

A clinical trial has now been initiated, testing XL184 with or without erlotinib in non-small cell lung cancer patients who have developed resistance to erlotinib. The phase III trial of XL184 in medullary thyroid cancer patients involves using the drug alone. XL184 is also being studied in glioblastoma.

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Abstract nos: 379, poster session in the poster area, 12.00-15.00 hrs CEST, Thursday 23 October.

552, poster session in the poster area, 12.00-15.00 hrs CEST, Friday 24 October.

Notes:

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From 09.00 hrs CEST Tuesday 21 October to 14.30 hrs CEST Friday 24 October
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