Mesothelioma drug slows disease progression in patients with an inactive NF2 gene

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Preliminary findings from the first trial of a new drug for patients with mesothelioma show that it has some success in preventing the spread of the deadly disease in patients lacking an active tumour suppressor gene called NF2. The study is presented at the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today (Friday).

Mesothelioma, which is usually caused by exposure to asbestos, has few treatment options and patients usually die within 9-17 months of diagnosis. Previous research has shown that the gene NF2, which produces a protein called merlin, is frequently inactivated in approximately 50% of mesotheliomas. Merlin negatively regulates another protein called focal adhesion kinase (FAK) in mesothelioma, and so when NF2 and merlin are inactivated, the activity of FAK is increased and mesothelioma cells become invasive and start to spread. When NF2 and merlin activity is restored, FAK activity and cell invasion are decreased.

Professor Jean-Charles Soria, Professor of Medicine and Medical Oncology at South Paris University and head of early drug development at the Institut Gustave Roussy in Paris (France), said: "This suggested that if we could inhibit FAK in mesothelioma patients, it might slow or stop the spread of the disease. Pre-clinical work has shown that an agent, currently known as GSK2256098, is a potent and specific inhibitor of FAK. Early in the clinical study presented today, a patient with mesothelioma, who had progressed quickly on prior therapies, had

prolonged stable disease while on GSK2256098, which is suggestive of clinical activity."

Prof Soria and colleagues at nine centres in France, Australia and the United Kingdom recruited 29 mesothelioma patients to the phase I study of GSK2256098, starting in July 2010. The study is continuing.

The mesothelioma patients took the drug orally in capsule form twice a day at doses ranging from 300 - 1500 mg, with the majority (22) taking 1000 mg a day. There were no complete or partial responses; 14 patients had stable disease, nine had progressive disease, three had non-measurable disease, and three left the study before evaluation of response. Overall, patients had an average of 17 weeks before the disease progressed.

However, in patients in whom merlin was inactivated, the average time before the disease progressed was 24 weeks, compared to 11 weeks in patients with active merlin and nearly 11 weeks in patients in whom the activity of merlin was unknown.

Adverse side-effects were mainly low grade and tolerable.

"These findings are important but preliminary," said Prof Soria. "They show that merlin is a potential biomarker in mesothelioma that may enable us to identify a subset of patients who could benefit from GSK2256098 and have longer, progression-free survival. Mesothelioma is a deadly disease without many treatment options, and therefore identification of novel and effective therapies is needed."

The researchers will accumulate and analyse further data, and larger clinical trials will be needed to confirm these findings. In addition, other cancers such as melanoma and meningioma (tumours of the membranes around the central nervous system) show loss of NF2 and merlin

function, and so researchers are also investigating whether the findings from this trial may be relevant to other cancers.

Professor Stefan Sleijfer, the scientific chair of the EORTC-NCI-AACR Symposium, from Erasmus University Medical Centre (The Netherlands), commented: "This study strongly suggests that inactivation of merlin may act as a marker to identify patients who may benefit from this compound. Furthermore, better insight into the role of merlin in mesothelioma may lead to novel targets of treatment. This is highly needed given the detrimental prognosis of patients suffering from mesothelioma."

More information: Abstract no: 610. Poster session, Phase I trials, 09.00 hrs, Friday 9 November.

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