Gene testing identifies lung cancer patients who benefit from ALK-inhibitor drug

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Results of a new study in non-small cell lung cancer showed that patients with specific oncogenic rearrangements of the anaplastic lymphoma kinase (ALK) gene within the short arm of chromosome 2 of their tumors had a much greater response to a new therapy - an ALK-inhibitor.

Findings were presented at the AACR-IASLC Joint Conference on Molecular Origins of Lung Cancer, held here from Jan. 11-14, 2010.

D. Ross Camidge, M.D., Ph.D., clinical director of the Thoracic Oncology Program at the University of Colorado, said this study and its results are an example of how all lung cancers are not created equal.

"This helps prove the principle that there may be many different molecularly defined diseases lurking under the same non-small cell lung cancer umbrella, each of which may derive considerable benefit from drugs that are highly specific to these molecular abnormalities if only we knew what they were. Here we have begun to move away from a one-size-fits-all treatment by testing lung cancers for specific genetic changes in advance of choosing the treatment for them," Camidge said.

This study also represents a paradigm shift in cancer drug development as scientists now start to test their molecular hypotheses about which patients a targeted drug may or may not work on from the very first time the drug is tried out in humans, according to Camidge.

"If your hypothesis is right, the results can be dramatic and you could shave three to five years off the time from discovery to FDA approval by really focusing on who will benefit the most," he said. "This potentially means getting the right drug to the right patients far quicker than the oncology community has done previously."

Camidge and colleagues have been testing PF-02341066, a small molecule synthesized as an inhibitor of both ALK and cMET in a Phase I trial since 2006. The initial Phase I findings for this targeted drug were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, which was held in Orlando last June.

Study results presented at ASCO explored the initial determination of the appropriate dose of PF-02341066 in patients with all different types of cancers, followed by additional testing of the drug within the same study only in cancers proven to express markers of either ALK or cMET activation. In 2007, ALK gene rearrangements, which had previously been reported only in rare lymphomas, were reported in lung cancer and the study was amended to adapt to this emerging data.

Thus far, 31 ALK-positive lung cancer patients have been enrolled in the Phase I study. These patients were heavily treated; 65 percent received more than two prior treatment regimens. Patients with the ALK rearrangement had a 65 percent overall response rate, including 19 patients who had a partial response and one patient who had a complete response.

Patients remained on therapy for a median of 24 weeks, with many still on treatment. Accurate measurements of progression-free survival have not yet been reached.
Adverse events associated with PF-02341066 at the 250 mg twice-daily dose have been mild and include gastrointestinal and dark-light vision disturbances.

Exploration of the drug in cMET positive patients continues, but striking clinical responses in ALK-positive lung cancers have already been noted. On the basis of these results, a Phase III study of PF-02341066 in ALK-positive lung cancer compared to standard chemotherapy has now begun.

At this year's AACR-IASLC Joint Conference on Molecular Origins of Lung, Camidge will present updated data on ALK-positive lung cancer patients treated with PF-02341066 and will explore the change in philosophy this trial represents in terms of modern cancer drug development.

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