Ganetespib shows potency against ALK-positive lung cancer and overcomes crizotinib resistance

March 26 2013

A drug that indirectly impairs the function of several cancer-driving proteins, including anaplastic lymphoma kinase (ALK), may be an effective new treatment for patients with ALK—positive non-small cell lung cancer.

The drug, ganetespib, may also be effective for treating patients who have become resistant to the only FDA-approved targeted therapy for this disease, crizotinib, according to data published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Lung cancer, a leading cause of death, is no longer thought of as a single disease, but rather as a group of diseases, each with a distinct genetic profile," according to David Proia, Ph.D., associate director of cancer biology at Synta Pharmaceuticals Corporation, the company that funded the research. "This realization has paved the way for the design of new treatments tailored to the specific biological characteristics of a patient's tumor.

"For example, patients with lung cancer caused by alterations in the ALK protein typically respond well to crizotinib, which blocks that activity of the modified ALK and consequently kills off the cancer cells," said Proia. "However, as is the case for many cancer drugs, most patients treated with crizotinib eventually become resistant to the drug."

Proia and colleagues investigated ganetespib as an alternative treatment for ALK-positive non-small cell lung cancer (NSCLC). Ganetespib targets heat shock protein 90 (Hsp90), a chaperone for many different proteins, including ALK, to ensure proper functioning. When Hsp90 is blocked, ALK can no longer work properly and is destroyed by the cell. Once ALK is lost, the cancer cells die and the tumors shrink.

Ganetespib had 30 times greater potency than crizotinib against a cultured ALK-positive NSCLC cell line, resulting in the complete loss of ALK protein expression. In addition, the drug was active against ALK-positive lung cancer cell lines that had become resistant to the effects of crizotinib.

The researchers then compared ganetespib and crizotinib in mice xenografted with human ALK-positive NSCLC cancer cells. Ganetespib displayed greater antitumor activity and prolonged animal survival as compared to crizotinib. It was also shown that ganetespib had meaningful activity in a patient with ALK-driven NSCLC who had responded to, and then progressed, following crizotinib therapy.

"Ganetespib therapy represents a new option for treating ALK-dependent lung cancer in sequence with direct ALK inhibitors and/or for treating patients who relapse following direct ALK inhibitor therapy," said Proia.

Provided by American Association for Cancer Research