Ganetespib showed activity in KRAS-mutant NSCLC as monotherapy and in combinations

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The investigational drug ganetespib, a synthetic second-generation Hsp90 inhibitor, slowed the growth of cancer cells taken from non-small cell lung cancer tumors with a mutation in the KRAS gene. The drug was even more active when combined with traditional lung cancer treatments and other investigational targeted therapies, according to preclinical study data.

David A. Proia, Ph.D., and Jaime Acquaviva, Ph.D., scientists at Synta Pharmaceuticals Corp., presented the data at the AACR-IASLC Joint Conference on Molecular Origins of Lung Cancer: Biology, Therapy and Personalized Medicine, held Jan. 8-11, 2012.

Currently, patients with non-small cell lung cancer (NSCLC) with KRAS mutations have no effective treatment strategy. A phase 2 trial showed tumor shrinkage in more than 60 percent of patients with KRAS-mutant NSCLC at eight weeks after treatment with ganetespib administered once weekly as a monotherapy, indicating the drug's potential effectiveness, according to Proia.

He and his colleagues examined whether ganetespib was effective against several different cell lines of KRAS-mutant NSCLC and confirmed it was effective in 15 different cell lines. They then sought to determine which combination treatments would enhance the activity of ganetespib in this cancer type.

First, the researchers combined ganetespib with several standard-of-care chemotherapies currently available in the clinic for KRAS-mutant NSCLC tumor samples. They found that the combination of ganetespib with alkylating agents, antimitotics and topoisomerase inhibitors resulted in an increased cell death of 1.4-, 1.5- and 2.6-fold, respectively, compared with ganetespib alone.

"We saw great activity with, for example, docetaxel and [ganetespib]," Proia said. "What we are doing now is conducting a large phase 2b/phase 3 trial with docetaxel and [ganetespib] in NSCLC patients. Activity in the KRAS-mutant subpopulation is a coprimary endpoint in this trial."

The researchers also tested ganetespib in combination with two therapies that target pathways known to be involved in NSCLC: a MEK inhibitor or a PI3K/mTOR inhibitor. Results in tumor samples revealed that combining ganetespib with either therapy was also more active in slowing tumor growth compared with ganetespib alone.

"Not only was ganetespib activity enhanced in combination with traditional chemotherapies, which may be understood in terms of the ability of Hsp90 inhibition to block certain resistance or repair mechanisms, but activity was also enhanced in combination with a number of targeted therapies for which recent work has shown very interesting complementary inhibition of signaling pathways," Proia said.

Finally, the researchers further validated their results by combining ganetespib with the PI3K/mTOR inhibitor in mice with KRAS-mutant NSCLC. Both drugs alone promoted tumor shrinkage, but the combination resulted in a greater inhibition of tumor growth.

If further validated, this research could open up avenues for future treatment options for patients with KRAS-mutant NSCLC.

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