Targeted investigational therapy potential to overcome crizotinib resistance in lung cancers

October 20 2013

PF-06463922, an investigational drug being developed by Pfizer Inc., has the potential to become a new treatment option for patients who have lung cancer harboring abnormalities in the ALK gene, according to preclinical results presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held Oct. 19-23.

About 3 to 5 percent of lung cancers harbor ALK gene abnormalities. The drug crizotinib (Xalkori), which blocks ALK protein kinase activity, was approved in August 2011 by the U.S. Food and Drug Administration for the treatment of patients who have these lung cancers. Although robust responses to crizotinib are observed for lung cancers harboring ALK gene abnormalities, the majority eventually become resistant to the effects of the drug. In many cases, resistance arises because of genetic mutations in ALK.

"Resistance to targeted therapies such as crizotinib is a major challenge when treating patients with cancer," said Tod Smeal, Ph.D., associate research fellow in the Oncology Research Unit at Pfizer Inc. in San Diego, Calif. "Our goal is to take advantage of everything we have learned about designing drugs that target kinases like ALK and the ways in which lung cancers become resistant to crizotinib to develop the best next-generation ALK inhibitor we can.

"Our preclinical studies suggest that we are making progress toward achieving our goal: PF-06463922 has potent ALK-inhibiting activity, it is capable of inhibiting all the crizotinib-resistant ALK mutants so far detected in patients, and it can efficiently access the brain. We are excited about these preclinical results and very hopeful that they will translate into meaningful responses in the clinic."

After carefully designing PF-06463922, Smeal and colleagues first showed in cell assays that it potently inhibited the activity of ALK and all eight of the mutant forms of ALK known to cause resistance to crizotinib in patients with lung cancer. They then showed that PF-06463922 inhibited the growth of tumors harboring three of the crizotinib-resistant ALK mutants, including the most resistant ALK mutant, G1202R, in mice.

Further analysis indicated that PF-06463922 readily entered the brains of mice, rats, and dogs. In mice, levels of PF-06463922 in the brain were 20-30 percent of levels of PF-06463922 in the blood. This is potentially clinically relevant because a significant number of lung cancer patients will develop brain metastasis during the course of their disease, according to Smeal, although he noted that it will be important to see if these results in animals hold true in humans.

Smeal and colleagues also found that PF-06463922 potently inhibited the protein ROS1, a close relative of ALK recently implicated in a number of cancer types, including some lung and brain cancers. Further, PF-06463922 had antitumor effects in two mouse models of cancers driven by ROS1 gene abnormalities, leading the researchers to suggest that PF-06463922 has potential as a treatment for this subgroup of cancers, in addition to its promise as a new treatment for ALK-driven cancers.

More information: Abstract Number: A277

Presenter: Tod Smeal, Ph.D.

Title: PF-06463922, a novel ROS1/ALK inhibitor, demonstrates sub-nanomolar potency against oncogenic ROS1 fusions and capable of blocking the resistant ROS1G2032R mutant in preclinical tumor models

Authors: Helen Y. Zou, Lars R. Engstrom, Qiuhua Li, Melissa West Lu, Ruth Wei Tang, Hui Wang, Konstantinos Tsaparikos, Sergei Timofeevski, Justine Lam, Shinji Yamazaki, Wenyue Hu, Hovhannes Gukasyan, Nathan Lee, Ted W. Johnson, Valeria Fantin, Tod Smeal. Pfizer, Inc., San Diego, CA

The oncogenic ROS1 gene fusion (Fig-ROS1) was first identified in glioblastoma cells over two decades ago. Recently, ROS1 gene rearrangements were further discovered in a variety of human cancers, including lung adenocarcinoma, cholangiocarcinoma, ovarian cancer, gastric adenocarcinoma, colorectal cancer, inflammatory myofibroblastic tumor, angiosarcoma, and epithelioid hemangioendothelioma, providing additional evidence for ROS1 as an attractive cancer target. The 1st generation Met/ALK/ROS1 inhibitor XALKORI ® (crizotinib) has demonstrated promising clinical response in ROS1 fusion positive NSCLC. But similar to what was seen with acquired ALK secondary resistant mutations in XALKORI refractory patients, a ROS1 kinase domain mutant—ROS1G2032R has been identified in a ROS1 positive NSCLC patient who developed resistance to XALKORI. Therefore, there is an urgent need to develop agents that can overcome this type of resistance.

PF-06463922 is a novel, orally available, ATP-competitive small molecule inhibitor of ROS1/ALK with exquisite potency against ROS1 kinase. PF-06463922 inhibited the catalytic activity of recombinant ROS1 with a mean Ki of

Abstract Number: PR10/B107
Presenter: Tod Smeal, Ph.D.

Title: Is CNS availability for oncology a no-brainer? Discovery of PF-06463922, a novel small molecule inhibitor of ALK/ROS1 with pre-clinical brain availability and broad spectrum potency against ALK-resistant mutations

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Oncogenic fusions of Anaplastic Lymphoma Kinase (ALK) define a subset of human lung adenocarcinoma. The 1st generation ALK inhibitor crizotinib demonstrated impressive clinical benefit in ALK-fusion positive lung cancers and was approved by the FDA for the treatment of ALK-fusion positive NSCLC in 2011. However, as seen with most kinase inhibitors, patients treated with crizotinib eventually develop resistance to therapy. Acquired ALK kinase domain mutations and disease progression in the central nervous system (CNS) are reported as main contributors to patient relapse after ALK inhibitor therapy. Preclinically, crizotinib lacks significant brain penetration and does not potently inhibit activity of ALK kinase domain mutants, so a drug discovery program was initiated aimed to develop a second generation ALK inhibitor that is more potent than existing ALK inhibitors, capable of inhibiting the resistant ALK mutants and penetrating the blood-brain-barrier. These objectives present a considerable challenge in kinase inhibitor chemical space.

Here we report that PF-06463922, a novel small molecule ATP-competitive inhibitor of ALK/ROS1, showed exquisite potencies against non-mutant ALK (Ki