Pfizer Presents Promising Data from Next Generation ALK/ROS1 Inhibitor in Advanced Non-Small Cell Lung Cancer

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Study Results Presented as Oral Abstract at ASCO 2016

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Pfizer Inc. (NYSE:PFE) today announced encouraging new data from a Phase 1/2 study of lorlatinib, the proposed generic name for PF-06463922, Pfizer’s investigational, next-generation ALK/ROS1 tyrosine kinase inhibitor. The study showed clinical response in patients with ALK-positive or ROS1-positive advanced non-small cell lung cancer (NSCLC), including patients with brain metastases. These data were presented today in an oral presentation at the 52nd Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

The results presented are from the dose escalation component of an ongoing Phase 1 study of patients with ALK-positive or ROS1-positive NSCLC, with or without brain metastases, who were treatment-naïve or had disease progression after at least one prior tyrosine kinase inhibitor (TKI). Among patients with ALK-positive metastatic NSCLC, the overall response rate (ORR) with lorlatinib was 46 percent, with three patients achieving complete responses and 16 patients achieving a partial response (95% CI: 31-63). The median progression free survival (PFS) was 11.4 months (95% CI: 3.4 – 16.6). The majority of patients had received two or more prior ALK TKIs. Additionally, lorlatinib showed the ability to decrease the size of brain metastases in patients with ALK-positive

or ROS1-positive metastatic NSCLC.

“Many patients with ALK-positive or ROS1-positive metastatic NSCLC will progress beyond initial therapy and potentially develop brain metastases,” said Benjamin Solomon, MBBS, Associate Professor, Peter MacCallum Cancer Centre, Australia. “These early data suggest lorlatinib may be effective in a broad range of patients, including those who are heavily pre-treated or develop brain metastases. We are encouraged by these results and look forward to further investigating the full effects of lorlatinib in ALK-positive and ROS1-positive NSCLC.”

“We are excited by these data and the potential of lorlatinib to overcome resistance to ALK inhibitors, which remains a significant challenge for patients with ALK-positive NSCLC,” said Mace Rothenberg, MD, senior vice president, head of development, Pfizer Oncology. “Pfizer pioneered precision medicine in ALK-positive advanced NSCLC through the introduction of XALKORI® (crizotinib), which is widely recognized as a first-line standard of care for these patients, and we are committed to developing next-generation treatments that meet these patients’ evolving needs.”

In the phase 1 portion of the study, patients received lorlatinib on a continuous basis, once or twice daily. The primary objective was to identify the maximum tolerated dose and recommended Phase 2 dose. Patients were treated across 10 dose levels (10–200 mg). The recommended Phase 2 dose was 100 mg once daily. Other objectives included safety and efficacy by RECIST v1.1 including intracranial activity. Of 54 patients treated as of January 15, 2016, 41 were ALK-positive, 12 were ROS1-positive and one was unconfirmed. The majority of patients were previously treated with a TKI, including 20 with one prior TKI and 27 with more than one TKI. Additionally, 39 patients had brain metastases at baseline.

The most common treatment-related adverse events (AEs) were hypercholesterolemia (69%) and peripheral edema (37%). Hypercholesterolemia was the most common (11%) grade 3 or higher treatment-related AE and the most frequent reason for dose delay or reduction. No patients discontinued due to treatment-related AEs. At the recommended Phase 2 dose, 4 out of 17 patients (24%) experienced a treatment-related AE of any grade that led to a dose delay or hold.

The ongoing Phase 2 study is expected to enroll a total of 240 patients across six cohorts (five for ALK-positive and one for ROS1-positive patients with NSCLC), with enrollment defined by degree and type of prior treatment.

About Lorlatinib

Lorlatinib, the proposed generic name for PF-06463922, is an investigational next-generation ALK/ROS1 tyrosine kinase inhibitor that has been shown to be highly active in preclinical lung cancer models harboring chromosomal rearrangements of both ALK and ROS1. Lorlatinib was specifically designed to inhibit tumor mutations that drive resistance to other ALK inhibitors and to penetrate the blood brain barrier. A Phase 1/2 clinical trial of lorlatinib in patients with ALK-positive or ROS1-positive advanced NSCLC is currently ongoing. Lorlatinib has not yet been approved by any regulatory agency.

About XALKORI® (crizotinib)

XALKORI is a kinase inhibitor indicated in the U.S. for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive.

XALKORI Important Safety Information (US)

Hepatotoxicity: Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1719). Transaminase elevations generally occurred within the first 2 months. Monitor liver function tests, including ALT, AST, and total bilirubin, every 2 weeks during the first 2 months of treatment, then once a month, and as clinically indicated, with more frequent repeat testing for increased liver transaminases, alkaline phosphatase, or total bilirubin in patients who develop transaminase elevations. Permanently discontinue for ALT/AST elevation >3 times ULN with concurrent total bilirubin elevation >1.5 times ULN (in the absence of cholestasis or hemolysis); otherwise, temporarily suspend and dose-reduce XALKORI as indicated.

Interstitial Lung Disease (Pneumonitis): Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur. Across clinical trials (n=1719), 2.9% of XALKORI-treated patients had any grade ILD, 1.0% had Grade 3/4, and 0.5% had fatal ILD. ILD generally occurred within 3 months after initiation of treatment. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes and permanently discontinue XALKORI in patients with drug-related ILD/pneumonitis.

QT Interval Prolongation: QTc prolongation can occur. Across clinical trials (n=1616), 2.1% of patients had QTcF (corrected QT by the Fridericia method) ≥500 ms and 5.0% had an increase from baseline QTcF ≥60 ms by automated machine-read evaluation of ECGs. Avoid use in patients with congenital long QT syndrome. Monitor ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that prolong the QT interval. Permanently

discontinue XALKORI in patients who develop QTc >500 ms or ≥60 ms change from baseline with Torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia. Withhold XALKORI in patients who develop QTc >500 ms on at least 2 separate ECGs until recovery to a QTc ≤480 ms, then resume at a reduced dose.

Bradycardia: Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 12.7% of patients treated with XALKORI (n=1719). Avoid use in combination with other agents known to cause bradycardia. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm, re-evaluate the use of concomitant medications, and adjust the dose of XALKORI. Permanently discontinue for life-threatening bradycardia due to XALKORI; however, if associated with concomitant medications known to cause bradycardia or hypotension, hold XALKORI until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm. If concomitant medications can be adjusted or discontinued, restart XALKORI at 250 mg once daily with frequent monitoring.

Severe Visual Loss: Across clinical trials, the incidence of Grade 4 visual field defect with vision loss was 0.2% (n=1719). Discontinue XALKORI in patients with new onset of severe visual loss (best corrected vision less than 20/200 in one or both eyes). Perform an ophthalmological evaluation. There is insufficient information to characterize the risks of resumption of XALKORI in patients with a severe visual loss; a decision to resume should consider the potential benefits to the patient.

Vision Disorders: Most commonly visual impairment, photopsia, blurred vision or vitreous floaters, occurred in 63.1% of 1719 patients. The majority (95%) of these patients had Grade 1 visual adverse reactions. 0.8% of patients had Grade 3 and 0.2% had Grade 4 visual impairment. The majority of patients on the XALKORI arms in Studies 1 and 2 (>50%) reported visual disturbances which occurred at a frequency of 4-7 days each week, lasted up to 1 minute, and had mild or no impact on daily activities.

Embryo-Fetal Toxicity: XALKORI can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to the fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 45 days (females) or 90 days (males) respectively, following the final dose of XALKORI.

ROS1-positive Metastatic NSCLC: Safety was evaluated in 50 patients with ROS1-positive metastatic NSCLC from a single-arm study, and was generally consistent with the safety profile of XALKORI evaluated in patients with ALK-positive metastatic NSCLC. Vision disorders occurred in 92% of patients in the ROS1 study; 90% of patients had Grade 1 vision disorders and 2% had Grade 2.

Adverse Reactions: Safety was evaluated in a phase 3 study in previously untreated patients with ALK-positive metastatic NSCLC randomized to XALKORI (n=171) or chemotherapy (n=169). Serious adverse events were reported in 34% of patients treated with XALKORI, the most frequent were dyspnea (4.1%) and pulmonary embolism (2.9%). Fatal adverse events in XALKORI-treated patients occurred in 2.3% of patients, consisting of septic shock, acute respiratory failure, and diabetic ketoacidosis. Common adverse reactions (all grades) occurring in ≥25% and more commonly (≥5%) in patients treated with XALKORI vs chemotherapy were vision disorder (71% vs 10%), diarrhea (61% vs 13%), edema (49% vs 12%), vomiting (46% vs 36%), constipation (43% vs 30%), upper respiratory infection (32% vs 12%), dysgeusia (26% vs 5%), and abdominal pain (26% vs 12%). Grade 3/4 reactions occurring at a ≥2% higher incidence with XALKORI vs chemotherapy were QT prolongation (2% vs 0%), and constipation (2% vs 0%). In patients treated with XALKORI vs chemotherapy, the following occurred: elevation of ALT (any grade [79% vs 33%] or Grade 3/4 [15% vs 2%]); elevation of AST (any grade [66% vs 28%] or Grade 3/4 [8% vs 1%]); neutropenia (any grade [52% vs 59%] or Grade 3/4 [11% vs 16%]); lymphopenia (any grade [48% vs 53%] or Grade 3/4 [7% vs 13%]); hypophosphatemia (any grade [32% vs 21%] or Grade 3/4 [10% vs 6%]). In patients treated with XALKORI vs chemotherapy, renal cysts occurred (5% vs 1%). Nausea (56%), decreased appetite (30%), fatigue (29%), and neuropathy (21%) also occurred in patients taking XALKORI.

Drug Interactions: Exercise caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice which may increase plasma concentrations of crizotinib. Avoid concomitant use of strong CYP3A inducers and inhibitors. Avoid concomitant use of CYP3A substrates with narrow therapeutic range in patients taking XALKORI. If concomitant use of CYP3A substrates with narrow therapeutic range is required in patients taking XALKORI, dose reductions of the CYP3A substrates may be required due to adverse reactions.

Lactation: Because of the potential for adverse reactions in breastfed infants, advise females not to breastfeed during treatment with XALKORI and for 45 days after the final dose.

Hepatic Impairment: XALKORI has not been studied in patients with hepatic impairment. As crizotinib is extensively metabolized in the liver, hepatic impairment is likely to increase plasma crizotinib concentrations. Use caution in patients with hepatic impairment.

Renal Impairment: Decreases in estimated glomerular filtration rate occurred in patients treated with XALKORI. Administer XALKORI at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment (CLcr <30 mL/min) not requiring dialysis. No starting dose adjustment is needed for patients with mild and moderate renal impairment.

For more information and full Prescribing Information, visit www.XALKORI.com.

About Pfizer Oncology

Pfizer Oncology is committed to the discovery, investigation and development of innovative treatment options to improve the outlook for cancer patients worldwide. Our strong pipeline of biologics and small molecules, one of the most robust in the industry, is studied with precise focus on identifying and translating the best scientific breakthroughs into clinical application for patients across a wide range of cancers. By working collaboratively with academic institutions, individual researchers, cooperative research groups, governments, and licensing partners, Pfizer Oncology strives to cure or control cancer with breakthrough medicines, to deliver the right drug for each patient at the right time. For more information, please visit www.pfizer.com.

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DISCLOSURE NOTICE: The information contained in this release is as of June 6, 2016. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about lorlatinib, Pfizer's investigational, next-generation ALK/ROS1 tyrosine kinase inhibitor, including its potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical study commencement and completion dates as well as the possibility of unfavorable study results, including unfavorable new clinical data and additional analyses of existing clinical data; risks associated with interim data; whether and when any applications may be filed with regulatory authorities for lorlatinib; whether and when regulatory authorities may approve any such applications, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of lorlatinib; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2015 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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