



# Pfizer Announces U.S. FDA Acceptance and Priority Review of Supplemental New Drug Application for XALKORI® (crizotinib) for the Treatment of Patients with ROS1-Positive Metastatic Non-Small Cell Lung Cancer

Tuesday, December 08, 2015 - 06:01am

Pfizer Inc. (NYSE:PFE) today announced that the U.S. Food and Drug Administration (FDA) has accepted and granted Priority Review for a supplemental New Drug Application (sNDA) for XALKORI® (crizotinib) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. In April 2015, XALKORI received Breakthrough Therapy designation by the FDA for this potential indication. If approved, XALKORI would be the first FDA-approved biomarker-driven therapy for the treatment of ROS1-positive metastatic NSCLC. XALKORI is currently indicated for patients with metastatic NSCLC whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. The projected FDA action date is April 2016.

Priority Review status accelerates FDA review time from 10 months to a goal of six months from the day of acceptance of filing and is given to drugs that may offer major advances in treatment or may provide a treatment for which no adequate therapy exists.

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“ROS1 represents the second molecular subgroup of NSCLC in which XALKORI has demonstrated a level of anti-tumor activity that can potentially make a meaningful

difference for patients,” said Dr. Mace Rothenberg, senior vice president of Clinical Development and Medical Affairs and chief medical officer for Pfizer Oncology. “The development of XALKORI in this subgroup of patients is an example of the capability of precision medicine to identify treatments for patients whose tumors contain rare genetic mutations, such as ROS1-positive metastatic NSCLC.”

ROS1 rearrangement occurs when the ROS1 gene attaches to another gene and changes the way each gene normally functions, which can contribute to cancer-cell growth. Epidemiology data suggest that ROS1 rearrangements occur in approximately one percent of NSCLC cases. Of the estimated 1.5 million new cases of NSCLC worldwide each year, roughly 15,000 may be driven by oncogenic ROS1 fusions. 2,3

The submission to the FDA is based on data from a multicenter, single-arm Phase 1 study (Study 1001) that evaluated XALKORI in 53 patients with ROS1-positive metastatic NSCLC.<sup>3</sup> Data from 50 of these patients were published in the November 20, 2014 issue of *The New England Journal of Medicine* and showed that XALKORI exhibited marked anti-tumor activity in patients with ROS1-positive metastatic NSCLC. Additionally, the safety profile of XALKORI in ROS1-positive metastatic NSCLC was consistent with that observed in patients with ALK-positive metastatic NSCLC. 4

#### 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 whose tumors are anaplastic lymphoma kinase-positive as detected by an FDA-approved test. XALKORI has received approval in more than 85 countries including Australia, Canada, China, Japan, South Korea and the European Union.

#### XALKORI® Important Safety Information

**Hepatotoxicity:** Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of patients treated with XALKORI across clinical trials (n=1669). Transaminase elevations generally occurred within the first 2 months. Monitor with liver function tests including ALT 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=1669), 2.9% of XALKORI-treated patients had any grade ILD, 1.1% had Grade 3/4, and 0.5% had fatal ILD. These cases 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=1560), 2.1% of patients had QTcF (corrected QT by the Fridericia method)  $\geq 500$  ms and 5.0% had an increase from baseline QTcF  $\geq 60$  ms by automated machine-read evaluation of ECG. Avoid use in patients with congenital long QT syndrome. Consider periodic monitoring with 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  $\geq 60$  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  $\leq 480$  ms, then resume at a reduced dose.

Bradycardia: Symptomatic bradycardia can occur. Across clinical trials, bradycardia occurred in 12.3% of patients treated with XALKORI (N=1669). 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  $\geq 60$  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  $\geq 60$  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=1669). 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 62% of 1669 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.

**Embryofetal 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.

**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  $\geq 25\%$  and more commonly ( $\geq 5\%$ ) 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  $\geq 2\%$  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 breast feed 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:** Administer XALKORI at a starting dose of 250 mg taken orally once daily in patients with severe renal impairment (CL<sub>cr</sub> <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](http://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](http://www.pfizer.com).

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At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as

one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more, please visit us at [www.pfizer.com](http://www.pfizer.com).

DISCLOSURE NOTICE: The information contained in this release is as of December 8, 2015. 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 a potential new indication for XALKORI for the treatment of patients with metastatic non-small cell lung cancer whose tumors are ROS1-positive (the "Potential Indication"), 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, without limitation, the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when any applications may be filed with other regulatory authorities for XALKORI for the Potential Indication; whether and when the FDA may approve the sNDA for the Potential Indication and whether and when other regulatory authorities may approve any such other 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 XALKORI for the Potential Indication; 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, 2014 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](http://www.sec.gov) and [www.pfizer.com](http://www.pfizer.com).

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<sup>1</sup> U.S. Food and Drug Administration. Priority Review. Available at:<http://www.fda.gov/forpatients/approvals/fast/ucm405405.htm>. Accessed November 5, 2015. <sup>2</sup> Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. *Oncologist* 2013;18:865-75. <sup>3</sup> American Cancer Society. Detailed Guide: What is Lung Cancer - Non-Small Cell? Available at:<http://www.cancer.org/cancer/lungcancer-non->

smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer.  
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Media: Sally Beatty, 212-733-6566 or Investors: Ryan Crowe, 212-733-8160