**ABOUT XALKORI**

XALKORI® (crizotinib) is an oral medicine that inhibits the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase.¹

XALKORI is the first ALK inhibitor approved in the U.S. and is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ALK-positive as detected by an FDA-approved test. The U.S. indication is not limited to any specific line of therapy.

To date, over 6,000 patients have been treated with XALKORI in the U.S. since the FDA approval in 2011.²

**TARGETING ALK IN LUNG CANCER**

Originally discovered as an oncogenic driver in a type of lymphoma, ALK gene alterations were also found to be among key drivers of tumor development in cancers such as NSCLC and rare sarcomas.³ By inhibiting ALK, XALKORI blocks signaling in a number of cell pathways that are believed to be critical for the growth and survival of tumor cells.⁴,⁵

In ALK-positive lung cancer, a normally dormant gene named ALK is fused with another gene, predominantly “EML4.” This genetic alteration creates the ALK fusion gene and ultimately, the production of the ALK fusion protein, which is responsible for tumor growth.⁵,⁶

Only biomarker testing can determine which patients have ALK-positive NSCLC. In the U.S., the Abbott ALK FISH test is the only FDA approved test for detecting ALK.

**NSCLC CLINICAL STUDIES & EFFICACY**

Pfizer has conducted two Phase 3 studies of XALKORI in advanced NSCLC patients:

**PROFILE 1007** met the primary objective of significantly prolonging progression-free survival (PFS) compared with pemetrexed or docetaxel. The study enrolled 347 patients from clinical sites globally.⁷ This study is still under follow-up, but no longer recruiting participants. Results of PROFILE 1007 were published in the June 20, 2013 issue of the *New England Journal of Medicine* (NEJM).

- In PROFILE 1007, XALKORI achieved median PFS of 7.7 months (n=173) compared to 3.0 months [HR =0.49 (95% CI 0.37, 0.64); p <0.001] with standard-of-care second-line chemotherapy (pemetrexed or docetaxel) (n=174) in previously treated patients with advanced ALK-positive NSCLC.⁸
  - Median PFS was 7.7 months for patients treated with XALKORI compared with 3.0 months for those treated with chemotherapy.⁸
  - Median duration of response was 7.4 months (95% CI, 6.1 to 9.7) for patients treated with XALKORI and 5.6 months (95% CI, 3.4 to 8.3) in those treated with chemotherapy.⁸
  - The objective response rate was 65 percent (95% CI, 58 to 72; P=0.001) for patients treated with XALKORI and 20 percent (95% CI, 14 to 26; P=0.001) in those treated with chemotherapy.⁸
  - Median overall survival was 20.3 months (95% CI, 18.1 to not reached) in patients treated with XALKORI and 22.8 months (95% CI, 18.6 to not reached) in those treated with chemotherapy (hazard ratio, 1.02; 95% CI, 0.68 to 1.54; P=0.54).⁸

**PROFILE 1014** met the primary objective of significantly prolonging PFS in previously untreated patients with ALK-positive advanced non-squamous NSCLC when compared to standard platinum-based chemotherapy regimens. The study enrolled 343 participants from clinical sites globally.⁹ This study is still under follow-up, but no longer recruiting participants. Results of PROFILE 1014 were published in the December 4, 2014 issue of NEJM.
**ROLE IN ROS1-POSITIVE ADVANCED NSCLC**

Occurring in approximately one percent of NSCLC cases, ROS1-positive NSCLC represents a particular molecular subgroup of NSCLC.

Efficacy and safety data from an expansion cohort of a global Phase 1 study evaluating XALKORI in patients with ROS1-positive advanced NSCLC were published in the September 27, 2014 issue of NEJM.

- **Study 1001** is a Phase 1, safety, pharmacokinetic and pharmacodynamic study of XALKORI in patients with advanced cancer. There are subsets of the Phase 1 study evaluating XALKORI in patients with ALK, MET or ROS1-positive advanced NSCLC. The study is currently recruiting participants.10

In April 2015, Pfizer announced that XALKORI received Breakthrough Therapy designation by the U.S. Food and Drug Administration (FDA) for the treatment of patients with ROS1-positive NSCLC. Pfizer will work closely with the FDA on the development of XALKORI for ROS1-positive NSCLC and provide the information needed to support a potential regulatory submission.

**SAFETY PROFILE**

**IMPORTANT SAFETY INFORMATION**

**Hepatotoxicity:** Across three main clinical trials fatal hepatotoxicity occurred in 0.2% of patients. Monitor with periodic liver testing. Temporarily suspend, dose reduce, or permanently discontinue XALKORI.

**Pneumonitis:** Across three main clinical trials interstitial lung disease (ILD)/pneumonitis occurred in 2% of patients. Permanently discontinue in patients with ILD/pneumonitis.

**QT Interval Prolongation:** Across three main clinical trials QT interval prolongation occurred in 2.7% of patients. Monitor with electrocardiograms and electrolytes in patients who have a history of or predisposition for QTc prolongation, or who are taking medications that prolong QT. Temporarily suspend, dose reduce, or permanently discontinue XALKORI.

**Bradycardia:** XALKORI can cause bradycardia. Across three main clinical trials 11% of patients experienced a heart rate of less than 50 beats per minute. Monitor heart rate and blood pressure regularly. Temporarily suspend, dose reduce, or permanently discontinue XALKORI.

**Embryofetal Toxicity:** XALKORI can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI.

**Adverse Reactions:** Across three main clinical trials the most common adverse reactions (≥25%) were vision disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue.

In a phase 3 study in patients with previously treated ALK-positive metastatic NSCLC randomized to XALKORI (n=172) or chemotherapy (n=171), serious adverse reactions were reported in 37.2% of patients treated with XALKORI. The most frequent serious adverse reactions reported in patients treated with XALKORI were pneumonia (4.1%), pulmonary embolism (3.5%), dyspnea (2.3%), and ILD (2.9%). Fatal adverse reactions in XALKORI-treated patients occurred in 9 (5%) patients, consisting of: acute respiratory distress syndrome, arrhythmia, dyspnea, ILD, pneumonia, pneumonitis, pulmonary embolism, respiratory failure, and sepsis. Grade 3 or 4 events occurring at a higher incidence with XALKORI than with chemotherapy and at greater than 2%, were syncope (3%), QT prolongation (3%), and pulmonary embolism (5%). Elevation of ALT of any grade occurred in 76% of patients and grade 3 or 4 in 17% of patients. Neutropenia of any grade occurred in 49% of patients and grade 3 or 4 in 12% of patients. Lymphopenia of any grade occurred in 51% of patients and grade 3 or 4 in 9% of patients. Renal cysts occurred in 4% and neuropathy occurred in 19% of patients treated with 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. Dose reduction may be needed for co-administered drugs that are predominantly metabolized by CYP3A.

**Nursing Mothers:** Given the potential for serious adverse reactions in nursing infants, consider whether to discontinue nursing or discontinue XALKORI.

**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 (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, please visit www.XALKORI.com.

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2 Pfizer data on file.