Pfizer’s XALKORI® (crizotinib) Receives FDA Breakthrough Therapy Designation in Two New Indications

Tuesday, May 29, 2018 - 04:00am

XALKORI is the First Tyrosine Kinase Inhibitor to Receive Breakthrough Designation for the Treatment of Patients with Previously-treated Metastatic Non-Small Cell Lung Cancer with MET Exon 14 Alterations Additional Breakthrough Therapy Designation for the Treatment of Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma that is ALK-positive

Pfizer Inc. (NYSE:PFE) announced today that the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation for XALKORI® (crizotinib) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with MET exon 14 alterations with disease progression on or after platinum-based chemotherapy. The FDA also granted Breakthrough Therapy designation for XALKORI for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) that is anaplastic lymphoma kinase (ALK)-positive.

MET is a transmembrane tyrosine receptor kinase which is expressed in several types of cells. In patients with NSCLC, MET exon 14 alterations occur in approximately three percent of NSCLC tumors.1 Anaplastic large cell lymphoma is a rare type of non-Hodgkin lymphoma, divided into ALK-positive or ALK-negative disease.2,3 Despite the activity of chemotherapy, many patients with ALCL relapse or require alternative treatment approaches.4

“Biomarker-driven therapies have changed the way we treat cancer, helping to ensure that patients receive the right medicine for their disease,” said Mace Rothenberg, M.D.,

chief development officer, Oncology, Pfizer Global Product Development. “These Breakthrough Therapy designations for XALKORI exemplify our commitment to precision medicine development and delivering medicines that have the potential to transform the lives of patients whose cancers carry these genomic alterations.”

XALKORI is currently approved in the U.S. for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive or ROS1-positive as detected by an FDA-approved test. XALKORI became a first-line standard of care for ALK-positive metastatic NSCLC in its first approved indication and has proven to be a practice-changing treatment for patients with ALK-positive and ROS1-positive NSCLC, globally. It is the only FDA-approved treatment indicated for both ALK-positive and ROS1-positive metastatic NSCLC. If approved in patients with metastatic NSCLC with MET exon 14 alterations, XALKORI will be the only TKI with demonstrated efficacy in three separate biomarker-driven indications in NSCLC.

The Breakthrough Therapy designation for patients with metastatic NSCLC with MET exon 14 alterations was supported by results from an expansion cohort of the Phase 1 PROFILE 1001 study, in which XALKORI showed antitumor activity.5

The designation for patients with relapsed or refractory systemic ALCL that is ALK-positive was supported by the results from Study ADVL0912 (NCT00939770) and Study A8081013 (NCT01121588). Study ADVL0912 is a Phase 1/2 study conducted by the Children’s Oncology Group evaluating the maximum dose that is safe and tolerable, and assessing preliminary clinical activity in pediatric patients with relapsed or refractory solid tumors and ALCL. Study A8081013 evaluated XALKORI in pediatric and adult patients with advanced malignancies known to be ALK-positive other than NSCLC and included patients with relapsed/refractory ALCL. These two studies showed compelling antitumor activity in pediatric and adult patients who received XALKORI.6,7

Please visit clinicaltrials.gov for more information on these studies.

The FDA’s Breakthrough Therapy designation is intended to expedite the development and review of a medicine if it is intended to treat a serious or life-threatening disease and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies. The Breakthrough Therapy designation is distinct from the FDA’s other mechanisms to expedite drug development and review.8

About MET Alterations in Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer deaths worldwide.9 NSCLC accounts for about 85 percent of lung cancer cases and remains difficult to treat, particularly in the metastatic setting.10 Approximately 75 percent of NSCLC patients are diagnosed late with metastatic or advanced disease where the five-year survival rate is only five percent.11,12

MET is a transmembrane tyrosine receptor kinase which is expressed in several types of cells. In patients with NSCLC, MET exon 14 alterations occur in approximately three percent of NSCLC tumors.1

About Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin lymphoma (NHL), but one of the more common subtypes of T-cell lymphoma. ALCL comprises about two percent of all NHLs and approximately 20 percent of all T-cell lymphomas.2,3 Patients with systemic ALCL are divided into two groups, ALK-positive or ALK-negative. Both of these lymphomas are treated as aggressive (fast-growing) lymphomas, yet many patients still relapse or require alternative treatment approaches. ALK-positive ALCL usually affects children and young adults.4

About XALKORI® (crizotinib)

XALKORI is a tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test. XALKORI has received approval for patients with ALK-positive NSCLC in more than 90 countries including Australia, Canada, China, Japan, South Korea and the European Union. XALKORI is also approved for ROS1-positive NSCLC in more than 60 countries.

XALKORI® Important Safety Information

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%), esophagitis (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: Crizotinib concentrations increased in patients with pre-existing moderate (any AST and total bilirubin >1.5x ULN and ≤3x ULN) or severe (any AST and total bilirubin >3x ULN) hepatic impairment. Reduce XALKORI dose in patients with moderate or severe hepatic impairment. The recommended dose of XALKORI in patients with pre-existing moderate hepatic impairment is 200 mg orally twice daily or with pre-existing severe hepatic impairment is 250 mg orally once daily.

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.

For more information and full prescribing information, please visit www.XALKORI.com.

About Pfizer in Lung Cancer

Pfizer Oncology is committed to addressing the unmet needs of patients with lung cancer, the leading cause of cancer-related deaths worldwide and a particularly difficult-to-treat disease. Pfizer strives to address the diverse and evolving needs of patients with non-small cell lung cancer (NSCLC) by developing efficacious and tolerable therapies, including biomarker-driven therapies and immuno-oncology (IO) agents and combinations. By combining leading scientific insights with a patient-centric approach, Pfizer is continually advancing its work to match the right patient with the right medicine at the right time. Through our growing research pipeline and collaboration efforts, we are committed to delivering renewed hope to patients living with NSCLC.

About Pfizer Oncology

Pfizer Oncology is committed to pursuing innovative treatments that have a meaningful impact on people living with cancer. Our growing pipeline of biologics, small molecules, and immunotherapies is focused on identifying and translating the best scientific breakthroughs into clinical application for patients across a diverse array of solid tumors and hematologic cancers. Today, we have 10 approved oncology medicines and 14 assets currently in clinical development. By maximizing our internal scientific resources and collaborating with other companies, government and academic institutions, as well as patients and non-profit and professional organizations, we are bringing together the brightest and most enterprising minds to take on the toughest cancers. Together we can accelerate breakthrough treatments to patients around the world and work to redefine life with cancer.

Pfizer Inc.: Working together for a healthier world ®

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, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube, and like us on Facebook at Facebook.com/Pfizer.

DISCLOSURE NOTICE: The information contained in this release is as of May 29, 2018. 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 XALKORI (crizotinib) and a potential new indication for the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma that is ALK-positive (the “Potential Indication”), including their 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 trial commencement completion dates and] regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations, and, even when we view data as sufficient to support the safety and/or effectiveness of a product candidate, regulatory authorities may not share our views and may require additional data or may deny approval altogether; 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 the FDA or other regulatory authorities for XALKORI for the Potential Indication; 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 and, if approved, whether XALKORI will be commercially successful; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of XALKORI, including 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, 2017 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 .

# # # # #

1 Lovly, C., P. Paik. 2017. MET Exon 14 Skipping Mutations in Lung Cancer. My Cancer Genome https://www.mycancergenome.org/content/disease/lung-cancer/met/343/. (Updated June 15). Accessed May 2018.

2 Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64(2):83-103.

3 Drexler HG, Gignac SM, von Wasielewski R, et al. Pathobiology of NPM-ALK and variant fusion genes in anaplastic large cell lymphoma and other lymphomas. Leukemia 2000;14:1533–59.

4 Lymphoma Research Foundation. Getting the Facts. Anaplastic Large Cell Lymphoma. https://www.lymphoma.org/wp-

content/uploads/2018/04/LRF_FACTSHEET_ANAPLASTIC_LARGE_CELL_LYMPHOMA.pdf. Accessed May 2018.

5 Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC). Alexander E. Drilon et al. Journal of Clinical Oncology 2016 34:15_suppl, 108-108

6 Gambacorti-Passerini C, Orlov S, Zhang L, et al. Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. Am J Hematol. 2018;93:607–614.

7 P. Mossé, Yael & D. Voss, Stephan & S. Lim, Megan & Rolland, Delphine & Minard, Charles & Fox, Elizabeth & Adamson, Peter & Wilner, Keith & Blaney, Susan & J. Weigel, Brenda. (2017). Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. Journal of Clinical Oncology. 35. JCO.2017.73.483.

8 U.S. Food and Drug Administration Fact Sheet: Breakthrough Therapies. Available at: https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFD Accessed May 2018.

9 The International Agency for Research on Cancer, the World Health Organization. GLOBOCAN 2008. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx (select "Lung" from the drop-down menu). Accessed May 2018.

10 Reade CA, Ganti AK. EGFR targeted therapy in non-small cell lung cancer: potential role of cetuximab. Biologics. 2009; 3: 215–224.

11 Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest. 2005;128(1):452–462.

12 American Cancer Society. Detailed Guide: Lung Cancer (Non-Small Cell). Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-survival-rates. Accessed May 2018.

Pfizer Media: Jessica Smith, 212-733-6213 Jessica.M.Smith@pfizer.com or Pfizer Investor: Ryan Crowe, 212-733-8160 Ryan.Crowe@pfizer.com