Pfizer Logo

# Three Year Follow-Up Data from Phase 3 CROWN Trial of Pfizer's LORBRENA® (lorlatinib) Confirm Prolonged Progression-Free Survival in First-Line ALK-Positive Advanced Lung Cancer

Friday, April 08, 2022 - 01:00pm

NEW YORK, NY, April 8, 2022 – Pfizer Inc. (NYSE: PFE) announced updated results from the Phase 3 CROWN trial, which evaluated LORBRENA® (lorlatinib, available in Europe under the brand name LORVIQUA) versus XALKORI® (crizotinib) in people with previously untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). This analysis reported after a median follow-up of three years, LORBRENA continued to demonstrate meaningful improvement in progression-free survival (PFS) assessed by blinded independent central review (BICR), the primary endpoint, compared to XALKORI (HR, 0.27; 95% CI, 0.18–0.39), corresponding to a 73% reduction in the rate of progression or death. These data will be presented on April 12, 2022, at the American Association for Cancer Research (AACR) Annual Meeting 2022 (Abstract # CT223 / 2).

"The long-term results from the CROWN trial confirm LORBRENA's compelling safety and efficacy profile in the first-line setting, providing sustained benefit for up to three years for this patient population," said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. "Since its first-line approval based on the initial groundbreaking CROWN trial results, LORBRENA has solidified its place as a practice-changing medicine, and these updated data add to the growing body of evidence supporting its use from the onset of metastatic disease."

"Approximately 25-40% of people with ALK-positive advanced non-small cell lung cancer either have brain metastases at diagnosis or develop brain metastases within two years after initial diagnosis, and biomarker-driven medicines like LORBRENA have transformed the way we treat this typically aggressive disease," said Professor Benjamin Solomon, MBBS, Ph.D., Department of Medical Oncology at the Peter MacCallum Cancer Centre in Melbourne, Australia. "The new results from the CROWN trial confirm LORBRENA as a treatment option that significantly improves outcomes for people with previously untreated ALK-positive advanced NSCLC."

In this analysis, 64% of people treated with LORBRENA were without disease progression after three years (95% CI, 55-71, n=149) compared to 19% for people treated with XALKORI after the same amount of time (95% CI, 12-27, n=147). As a secondary endpoint, the objective response rate (ORR) was 77% with LORBRENA (95% CI, 70-84) and 59% with XALKORI (95% CI, 50-67). Additionally, LORBRENA treatment resulted in a 92% reduction in the rate of intracranial progression (HR, 0.08; 95% CI, 0.04–0.17). The intracranial objective response rate (IC-ORR) for people with measurable brain metastases at baseline was 83%

(95% CI, 59–96, n=15) with LORBRENA and 23% (95% CI, 5–54, n=3) with XALKORI, with an intracranial complete response rate of 72% and 8%, respectively. In people without brain metastases at baseline, LORBRENA demonstrated a 98% reduction in the rate of intracranial progression (HR 0.02; 95% CI, 0.002-0.136).

The safety profile observed in the three-year follow-up analysis was consistent with the established safety profiles of LORBRENA and XALKORI. In the initial 2020 analysis of the CROWN trial, the most frequent adverse events (AEs) in ?20% of 149 patients treated with LORBRENA were edema, weight gain, peripheral neuropathy, cognitive effects, diarrhea, dyspnea, and hypertriglyceridemia. Serious AEs occurred in 34% of people treated with LORBRENA; the most frequently reported serious AEs were pneumonia, dyspnea, respiratory failure, cognitive effects, and pyrexia. Fatal AEs occurred in 3.4% of people treated with LORBRENA. Permanent discontinuation of LORBRENA due to AEs occurred in 6.7% of people.

In the Phase 3 CROWN trial, patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. The primary endpoint of the CROWN trial was PFS assessed by BICR. Secondary endpoints included overall survival (OS) and time to Intracranial Progression (IC-TTP) in patients with and without baseline brain metastasis, tumor assessment related data by BICR, including ORR, duration of response (DOR) and time to treatment response (TTR). Additional secondary endpoints included PFS by investigator assessment, ORR by investigator assessment, safety, and quality of life (QOL). In patients with Central Nervous System (CNS) metastases at baseline, additional outcome measures were IC-ORR, IC-DOR and IC-TTR, by BICR. The trial is continuing to further evaluate the secondary endpoint of OS, which was not mature at the time of analysis.

In findings published in the *New England Journal of Medicine* in 2020, the CROWN trial met its primary endpoint by demonstrating significantly improved PFS by BICR, as compared to XALKORI in people with previously untreated ALK-positive advanced NSCLC (HR 0.28; 95% CI, 0.19 to 0.41; stratified 1-sided p<0.001).

**About Non-Small Cell Lung Cancer (NSCLC)**
Lung cancer is the number one cause of cancer-related death around the world.[1] NSCLC accounts for approximately 80-85% of lung cancers,[2] with ALK-positive tumors occurring in about 3-5% of NSCLC cases.[3] Approximately 25-40% of people with ALK-positive advanced NSCLC may develop brain metastases within two years from initial diagnosis.[4]

**About LORBRENA® (lorlatinib)**
LORBRENA is a Tyrosine Kinase Inhibitor (TKI) that has been shown to be highly active in preclinical lung cancer models harboring chromosomal rearrangements of ALK. LORBRENA was specifically developed to inhibit tumor mutations that drive resistance to other ALK inhibitors and to penetrate the blood brain barrier. LORBRENA is approved in the U.S. by the Food and Drug Administration (FDA) for the treatment of adults with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.

**The full U.S. prescribing information for LORBRENA can be found here.**

**IMPORTANT LORBRENA® (lorlatinib) SAFETY INFORMATION FROM THE U.S. PRESCRIBING INFORMATION**

**Contraindications:** LORBRENA is contraindicated in patients taking strong CYP3A inducers, due to the potential for serious hepatotoxicity.

**Risk of Serious Hepatotoxicity with Concomitant Use of Strong CYP3A Inducers:** Severe hepatotoxicity

occurred in 10 of 12 healthy subjects receiving a single dose of LORBRENA with multiple daily doses of rifampin, a strong CYP3A inducer. Grade 4 ALT or AST elevations occurred in 50% of subjects, Grade 3 in 33% of subjects, and Grade 2 in 8% of subjects. ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days (7 to 34 days); median time to recovery in subjects with Grade 3 or 4 or Grade 2 ALT or AST elevations was 18 days and 7 days, respectively. LORBRENA is contraindicated in patients taking strong CYP3A inducers. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating LORBRENA.

**Central Nervous System (CNS) Effects:** A broad spectrum of CNS effects can occur; overall, CNS effects occurred in 52% of the 476 patients receiving LORBRENA. These included seizures (1.9%, sometimes in conjunction with other neurologic findings), psychotic effects (7%; 0.6% severe [Grade 3 or 4]), and changes in cognitive function (28%; 2.9% severe), mood (including suicidal ideation) (21%; 1.7% severe), speech (11%; 0.6% severe), mental status (1.3%; 1.1% severe), and sleep (12%). Median time to first onset of any CNS effect was 1.4 months (1 day to 3.4 years). Overall, 2.1% and 10% of patients required permanent or temporary discontinuation of LORBRENA, respectively, for a CNS effect; 8% required dose reduction. Withhold and resume at same or reduced dose or permanently discontinue based on severity.

**Hyperlipidemia:** Increases in serum cholesterol and triglycerides can occur. Grade 3 or 4 elevations in total cholesterol occurred in 18% and Grade 3 or 4 elevations in triglycerides occurred in 19% of the 476 patients who received LORBRENA. Median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia. Approximately 4% and 7% of patients required temporary discontinuation and 1% and 3% of patients required dose reduction of LORBRENA for elevations in cholesterol and in triglycerides in Study B7461001 and Study B7461006, respectively. Eighty-three percent of patients required initiation of lipid-lowering medications, with a median time to onset of start of such medications of 17 days. Initiate or increase the dose of lipid-lowering agents in patients with hyperlipidemia. Monitor serum cholesterol and triglycerides before initiating LORBRENA, 1 and 2 months after initiating LORBRENA, and periodically thereafter. Withhold and resume at same dose for the first occurrence; resume at same or reduced dose of LORBRENA for recurrence based on severity.

**Atrioventricular (AV) Block:** PR interval prolongation and AV block can occur. In 476 patients who received LORBRENA at a dose of 100 mg orally once daily and who had a baseline electrocardiography (ECG), 1.9% experienced AV block and 0.2% experienced Grade 3 AV block and underwent pacemaker placement. Monitor ECG prior to initiating LORBRENA and periodically thereafter. Withhold and resume at reduced or same dose in patients who undergo pacemaker placement. Permanently discontinue for recurrence in patients without a pacemaker.

**Interstitial Lung Disease (ILD)/Pneumonitis:** Severe or life-threatening pulmonary adverse reactions consistent with ILD/pneumonitis can occur. ILD/pneumonitis occurred in 1.9% of patients, including Grade 3 or 4 ILD/pneumonitis in 0.6% of patients. Four patients (0.8%) discontinued LORBRENA for ILD/pneumonitis. Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold LORBRENA in patients with suspected ILD/pneumonitis. Permanently discontinue LORBRENA for treatment-related ILD/pneumonitis of any severity.

**Hypertension:** Hypertension can occur. Hypertension occurred in 13% of patients, including Grade 3 or 4 in 6% of patients. Median time to onset of hypertension was 6.4 months (1 day to 2.8 years), and 2.3% of patients temporarily discontinued LORBRENA for hypertension. Control blood pressure prior to initiating LORBRENA. Monitor blood pressure after 2 weeks and at least monthly thereafter. Withhold and resume at reduced dose or permanently discontinue based on severity.

**Hyperglycemia:** Hyperglycemia can occur. Hyperglycemia occurred in 9% of patients, including Grade 3 or 4 in 3.2% of patients. Median time to onset of hyperglycemia was 4.8 months (1 day to 2.9 years), and 0.8% of patients temporarily discontinued LORBRENA for hyperglycemia. Assess fasting serum glucose prior to initiating LORBRENA and monitor periodically thereafter. Withhold and resume at reduced dose or permanently discontinue based on severity.

**Embryo-fetal Toxicity:** LORBRENA can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective non-hormonal method of contraception, since LORBRENA can render hormonal contraceptives ineffective, during treatment with LORBRENA and for at least 6 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with LORBRENA and for 3 months after the final dose.

**Adverse Reactions:** In the pooled safety population of 476 patients who received 100 mg LORBRENA once daily, the most frequent (? 20%) adverse reactions were edema (56%), peripheral neuropathy (44%), weight gain (31%), cognitive effects (28%), fatigue (27%), dyspnea (27%), arthralgia (24%), diarrhea (23%), mood effects (21%), and cough (21%). The most frequent (? 20%) Grade 3-4 laboratory abnormalities in patients receiving LORBRENA were hypercholesterolemia (21%) and hypertriglyceridemia (21%).

In previously untreated patients, serious adverse reactions occurred in 34% of the 149 patients treated with LORBRENA; the most frequently reported serious adverse reactions were pneumonia (4.7%), dyspnea (2.7%), respiratory failure (2.7%), cognitive effects (2.0%), and pyrexia (2.0%). Fatal adverse reactions occurred in 3.4% of patients and included pneumonia (0.7%), respiratory failure (0.7%), cardiac failure acute (0.7%), pulmonary embolism (0.7%), and sudden death (0.7%). In the Phase 1/2 study, serious adverse reactions occurred in 32% of the 295 patients; the most frequently reported serious adverse reactions were pneumonia (3.4%), dyspnea (2.7%), pyrexia (2%), mental status changes (1.4%), and respiratory failure (1.4%). Fatal adverse reactions occurred in 2.7% of patients and included pneumonia (0.7%), myocardial infarction (0.7%), acute pulmonary edema (0.3%), embolism (0.3%), peripheral artery occlusion (0.3%), and respiratory distress (0.3%).

**Drug Interactions:** LORBRENA is contraindicated in patients taking strong CYP3A inducers. Avoid concomitant use with moderate CYP3A inducers, strong CYP3A inhibitors, and fluconazole. If concomitant use of moderate CYP3A inducers cannot be avoided, increase the LORBRENA dose as recommended. If concomitant use with a strong CYP3A inhibitor or fluconazole cannot be avoided, reduce the LORBRENA dose as recommended. Avoid concomitant use of LORBRENA with CYP3A substrates and P-gp substrates, which may reduce the efficacy of these substrates.

**Lactation:** Because of the potential for serious adverse reactions in breastfed infants, instruct women not to breastfeed during treatment with LORBRENA and for 7 days after the final dose.

**Hepatic Impairment:** No dose adjustment is recommended for patients with mild hepatic impairment. The recommended dose of LORBRENA has not been established for patients with moderate or severe hepatic impairment.

**Renal Impairment:** Reduce the dose of LORBRENA for patients with severe renal impairment. No dose adjustment is recommended for patients with mild or moderate renal impairment.

**About Pfizer Oncology**
At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference in the lives of people living with cancer. Today, we have an industry-leading portfolio of 24 approved

innovative cancer medicines and biosimilars across more than 30 indications, including breast, genitourinary, colorectal, blood and lung cancers, as well as melanoma.

**About Pfizer: Breakthroughs That Change Patients' Lives**
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, including innovative medicines and vaccines. 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 170 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 April 8, 2022. 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 LORBRENA® (lorlatinib), 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, uncertainties regarding the commercial success of LORBRENA; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when any drug applications may be filed in any additional jurisdictions for LORBRENA for the treatment of patients with ALK-positive advanced NSCLC or in any jurisdictions for any other potential indications for LORBRENA; whether and when any such other applications may be approved by regulatory authorities, which will depend on a myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether LORBRENA will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of LORBRENA; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; 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, 2021 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] World Health Organization. International Agency for Research on Cancer. GLOBOCAN 2020: Lung fact sheet. https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf. Accessed January 2022.
[2] American Cancer Society. What is lung cancer? https://www.cancer.org/cancer/lung-cancer/about/what-is.html. Accessed January 2022.

[3] Garber K. ALK, lung cancer, and personalized therapy: portent of the future? J Natl Cancer Inst. 2010;102:672-675.
[4] Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK—rearranged non—small—cell lung cancers. Lung Cancer. 2015;88(1):108—111.

Media Relations: +1 (212) 733-1226 PfizerMediaRelations@Pfizer.com Investor Relations: +1 (212) 733-4848 IR@Pfizer.com