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Real-World Evidence Supports Effectiveness of First-line IBRANCE® (palbociclib) Combination Therapy in HR+, HER2- Metastatic Breast Cancer

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First large-scale comparative effectiveness analysis of a CDK 4/6 inhibitor plus letrozole evaluating progression-free and overall survival versus letrozole alone

NEW YORK--(BUSINESS WIRE)-- Pfizer Inc. (NYSE:PFE) today announced the peer-reviewed publication of real-world evidence (RWE) demonstrating that first-line therapy with IBRANCE® (palbociclib) in combination with letrozole was associated with improved real-world progression-free survival (rwPFS) and overall survival (OS) in women with hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (mBC) compared with letrozole alone. These findings represent the first comprehensive comparative effectiveness analysis of survival outcomes for a CDK 4/6 inhibitor in routine clinical practice and were published online in *Breast Cancer Research*.

At a median follow-up of approximately two years and after balancing for baseline demographic and clinical characteristics, median rwPFS was 20.0 months with IBRANCE plus letrozole versus 11.9 months with letrozole alone (HR 0.58: 95% CI, 0.49 to 0.69; p<0.0001) in this observational, retrospective real-world analysis. Median OS was not reached among patients in the IBRANCE group and was 43.1 months among patients in the letrozole group (HR 0.66: 95% CI, 0.53 to 0.82; P=0.0002). These findings represent a 42% reduction in the risk of progression and a 34% reduction in the risk of death.

“Real-world evidence is woven into the fabric of how we innovate and advance care for patients with breast cancer, supporting our randomized clinical trials,” said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. “With more than six years of patient experience, a positive benefit-risk profile, strong clinical data and robust real-world data, the totality of evidence solidifies the role of IBRANCE plus endocrine therapy as a treatment for patients with HR+, HER2- metastatic breast cancer.”

The analysis also showed the two-year OS rate was 78.3% in the IBRANCE group and 68.0% with letrozole. The rwPFS and OS benefits were generally consistent across all subgroups, including younger patients (18-50 years of age) and site or extent of metastases.

“Real-world evidence is increasingly used to complement traditional randomized clinical trial data to better understand a therapy’s effectiveness in routine clinical practice and inform treatment decisions,” said Angela DeMichele, M.D., lead researcher and Professor in Breast Cancer Excellence in the Perelman School of Medicine at the University of Pennsylvania. “The findings from this landmark real-world study align with the positive impact that I have seen in my own patients treated with IBRANCE combination therapy.”

The data for this retrospective observational analysis was collected from the Flatiron Health de-identified longitudinal database, which includes patient records from Flatiron's network of more than 280 community cancer clinics and partnerships with major academic cancer centers across the U.S. This real-world cohort includes more than 1,400 women with HR+, HER2- mBC with any extent of visceral disease. Safety data were not collected as part of this analysis.

The data from this real-world analysis is consistent with available data from the Phase 3 PALOMA-2 trial, which studied IBRANCE plus letrozole versus placebo plus letrozole as initial endocrine-based therapy in post-menopausal women with estrogen-receptor positive (ER+), HER2- mBC. However, this observational analysis differs from the randomized clinical trial in several ways. The studies have different endpoints and there are inherent limitations in real-world observational studies, including lack of randomization, lack of uniform timing or type of clinical assessments and challenges with missing data. OS data is being collected in the PALOMA-2 randomized clinical trial but is not yet mature.

About the IBRANCE Real-World Evidence Program

Since the initial approval by the U.S. Food and Drug Administration more than six years ago, IBRANCE has been prescribed to more than 380,000 patients across more than 100 countries. With this breadth of real-world experience, Pfizer is working to build the most extensive body of RWE for a CDK 4/6 inhibitor. This RWE program is generating data from multiple studies involving more than 4,000 patients around the world and continues to expand. These studies – IRIS, POLARIS, MARIA, and MADELINE – include diverse patient populations treated in everyday clinical practice and are collecting data related to clinical outcomes, translational data and quality of life endpoints, which complement the data generated from the PALOMA randomized clinical trials. Pfizer will continue to share new data from these studies with the scientific community as results becomes available.

About IBRANCE® (palbociclib) 125 mg tablets and capsules

IBRANCE is an oral inhibitor of CDKs 4 and 6,[1] which are key regulators of the cell cycle that trigger cellular progression.[2,3] In the U.S., IBRANCE is indicated for the treatment of adult patients with HR+, HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or in men; or with fulvestrant in patients with disease progression following endocrine therapy.

The full U.S. Prescribing Information for the IBRANCE tablets and the IBRANCE capsules can be found here and here.

IMPORTANT IBRANCE® (palbociclib) SAFETY INFORMATION FROM THE U.S. PRESCRIBING INFORMATION

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Severe, life-threatening, or fatal **interstitial lung disease (ILD) and/or pneumonitis** can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4, and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis.

Based on the mechanism of action, IBRANCE can cause **fetal harm**. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may **impair fertility in males** and has the potential to cause genotoxicity. Advise male patients to consider sperm preservation before taking IBRANCE. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women **not to breastfeed** during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

The **most common adverse reactions(?10%)** of any grade reported in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

The **most frequently reported Grade ?3 adverse reactions (?5%)** in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

The **most common adverse reactions (?10%)** of any grade reported in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

The **most frequently reported Grade ?3 adverse reactions (?5%)** in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 1%) and leukopenia (31% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 40%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (43% vs 48%), and increased alanine aminotransferase (36% vs 34%).

Avoid concurrent use of **strong CYP3A inhibitors**. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of **strong CYP3A inducers**. The dose of **sensitive CYP3A substrates** with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

For patients with **severe hepatic impairment** (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg. The pharmacokinetics of IBRANCE **have not been studied** in patients **requiring hemodialysis**.

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 March 25, 2021. 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 IBRANCE® (palbociclib), 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 IBRANCE; 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 drug applications may be filed in any jurisdictions for any other potential indications for IBRANCE; whether and when any such applications may be approved by regulatory authorities, which will depend on 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 such product candidate 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 IBRANCE; 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, 2020 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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[1] IBRANCE® (palbociclib) Prescribing Information. New York. NY: Pfizer Inc: 2019.
[2] Weinberg, RA. pRb and Control of the Cell Cycle Clock. In: Weinberg RA, ed. *The Biology of Cancer*. 2nd ed. New York, NY: Garland Science; 2014:275-329.
[3] Sotillo E, Grana X. Escape from Cellular Quiescence. In: Enders GH, ed. Cell Cycle Deregulation in Cancer. New York, NY: Humana Press; 2010:3-22.

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