**Overall Survival with Palbociclib Plus Aromatase Inhibitor Versus Aromatase Inhibitor Alone in Postmenopausal Women and in Men With HR+/HER2– Metastatic Breast Cancer: A Large Real-World Study in US Clinical Practice**

The P-Reality-X Manuscript, specifically the PAL21190.1144 draft 1, does not provide information about the highest academic degrees of the authors. However, it is important to note that this is a preliminary draft and a formal editorial review and fact check will be conducted in subsequent drafts. The manuscript also includes Figure 2, which displays Kaplan-Meier curves of overall survival.

Based on the new context provided, the work should be attributed to the Department of Global Biometrics and Data Management at Pfizer Inc, specifically to Dr. Benjamin Li, PhD, Dr. Lynn McRoy, MD, and Dr. Connie Chen, PharmD. Additionally, contributions were made by Dr. Rachel M. Layman, MD from The University of Texas MD Anderson Cancer Center, Dr. Massimo Cristofanilli, MD from Weill Cornell Medicine, and Dr. Mylin A. Torres, MD from Winship Cancer Institute, Emory University School of Medicine.

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Requests for reprints should be addressed to Dr. Benjamin Li at Pfizer Inc, Global Biometrics and Data Management, 235 42nd St, New York, NY, 10017, USA. Please note that a formal editorial review and fact check will be performed at a subsequent draft. Other authors' contact information is also provided in the manuscript for further inquiries. The study was sponsored by Pfizer Inc, and editorial/medical writing support was provided by Jill Shults, PhD, of ICON.

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**ABSTRACT**

**Background:**

The study aims to evaluate the overall survival (OS) and real-world progression-free survival (rwPFS) of palbociclib plus an aromatase inhibitor versus an aromatase inhibitor alone in postmenopausal women and men with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer (HR+/HER2– MBC) in routine clinical practice in the United States.   
   
 The study aims to evaluate the overall survival (OS) and real-world progression-free survival (rwPFS) of palbociclib plus an aromatase inhibitor versus an aromatase inhibitor alone in postmenopausal women and men with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC) in routine clinical practice in the United States.

**Methods:**

This study was a retrospective analysis of electronic health records from the Flatiron Health Analysis Database. It included women aged ≥18 years with confirmed hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2‒) metastatic breast cancer who received palbociclib plus an aromatase inhibitor or an aromatase inhibitor alone as first-line therapy. The study utilized three methods for comparative analysis: unadjusted analysis, stabilized inverse probability treatment weighting (sIPTW), and propensity score matching (PSM). Statistical analyses were performed using SAS® Version 9.1.4 or higher.

**Results:**

The study found that in postmenopausal women or men with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2‒) metastatic breast cancer, treatment with palbociclib plus an aromatase inhibitor as first-line therapy resulted in longer overall survival and progression-free survival compared to treatment with an aromatase inhibitor alone. These benefits were observed across various subgroups, including different age groups and disease characteristics. Additionally, a significant proportion of patients in both groups received a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor as second-line treatment.

**Conclusions:**

The authors concluded that treatment with palbociclib plus an aromatase inhibitor (AI) significantly prolonged overall survival and progression-free survival compared to an AI alone in postmenopausal women and men with hormone receptor-positive (HR+) and human epidermal growth factor receptor-2 negative (HER2-) metastatic breast cancer. These results support the use of palbociclib plus an AI as a standard of care for these patients.

**Trial registration number:**

Not applicable.

**BACKGROUND**

Breast cancer accounts for nearly one-third of all cancer cases among women.1 In 2022, approximately 290,560 new cases of breast cancer will be diagnosed, 287,850 among women and 2,710 among men, with an estimated 43,250 and 530 deaths, respectively. Among 6% of breast cancers cases, the breast cancer has spread to distant tissues and is termed metastatic breast cancer (MBC). The 5-year survival rate for MBC is only 29.0%.2  
The majority (68%) of breast cancer cases have a hormone receptor–positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) subtype. As first-line treatment for pre- and postmenopausal women and for men with HR+/HER2‒ MBC, the National Comprehensive Cancer Network treatment guidelines recommend a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in combination with endocrine therapy.3 The CDK4/6 inhibitor, palbociclib, was approved in February 2015 as first-line treatment for HR+/HER2– MBC in combination with an aromatase inhibitor, and approved in February 2016 in combination with fulvestrant for patients who progressed while on prior endocrine therapy.4-6 The palbociclib label was also expanded in 2019 to include men with HR+/HER2– MBC.7 In the phase 3 PALOMA-2 trial, first-line palbociclib plus letrozole versus letrozole plus placebo significantly prolonged median progression-free survival (PFS) in women with estrogen receptor–positive/HER2– MBC.8,9 In the overall survival analysis, median overall survival (OS) was XX months in the palbociclib group versus XX months in the placebo group (hazard ratio=X.XX [95% CI, XX–XX]; P=X.XXX).  
Real-world evidence is used to validate the efficacy and safety of a drug in routine clinical practice.10 Real-world studies also allow for the inclusion of patients underrepresented in clinical trials; thus, real-world data are more generalizable to patients treated in routine care and can help reinforce treatment recommendations.11,12 Specifically, emerging real-world data have demonstrated the safety and effectiveness of a CDK4/6 inhibitor plus endocrine therapy for HR+/HER2

**METHODS**

Study Design and Data Source  
This was a retrospective analysis of electronic health records (EHRs) from the Flatiron Health Analysis Database. Flatiron is a longitudinal database that contains de-identified patient data from structured and unstructured EHRs from >280 cancer clinics (~800 sites of care) representing >2.4 million actively treated US patients with cancer. A patient attrition diagram is presented in Figure 1. See Supplemental Material for information on the states included in the Flatiron Database.  
Inclusion criteria included women aged ≥18 years at Metastatic Breast Cancer (MBC) diagnosis with confirmed Hormone Receptor-positive (HR+)/Human Epidermal Growth Factor Receptor 2-negative (HER2‒) MBC at any point in patient history. Patients also had a date of first prescription (index date) for palbociclib plus an aromatase inhibitor or an aromatase inhibitor alone as first-line therapy for MBC between February 3, 2015 and March 31, 2020 and a potential follow-up for ≥6 months from the index date to the study cutoff date of September 30, 2020. Exclusion criteria included evidence of prior treatment with Cyclin-Dependent Kinase 4/6 (CDK4/6) inhibitors, tamoxifen, raloxifene, toremifene, fulvestrant, or chemotherapy in the metastatic setting; first structured activity >90 days after MBC diagnostic date; and lacks relevant unstructured documents in the Flatiron Health database for review by the abstraction team.  
Operational Rules  
For unstructured data abstraction, Flatiron leverages a hybrid approach that pairs ~1,500 abstractors, including oncology nurses and tumor registrars, with proprietary software called Patient Manager which organizes unstructured documents in predetermined formats. One quality control measure is to have two abstractors complete the same abstraction process for a given patient. In instances when there is abstractor disagreement, the patient is submitted to an in-house review panel for resolution. As of April 2019, Patient Manager completed computer system validated activities in line with the Food and Drug Administration (FDA) Code of Federal Regulations (Principles in 21 CFR Part 11). Flatiron validated Patient Manager as it is a critical electronic system supporting real-world data handling, with the goal of ensuring that systems are designed and tested appropriately to enable good software practices. To process structured data,  
Three methods were utilized and presented for comparative analyses, including an unadjusted analysis (without controlling for confounders), the stabilized inverse probability treatment weighting (sIPTW) method (primary analysis; controlled for observed confounders), and finally the propensity score matching (PSM) method (sensitivity analysis; to assess the robustness of the sIPTW results). The primary sIPTW analysis was used to balance baseline demographic and clinical characteristics between palbociclib plus an aromatase inhibitor and an aromatase inhibitor alone groups. The weighted Cox proportional hazards model was used to compute the hazard ratio and the corresponding 95% CI (95% CI). In addition, propensity scores were generated by a multivariable binomial logistic regression model.23-26 Propensity score matching (PSM) was conducted as a sensitivity analysis to balance baseline demographic and clinical characteristics and to adjust for differences in observed potential confounders between the two cohorts; matches were made using 1:1 nearest neighbor matching without replacement and a caliper of 0.01 (0.01 cm).23 A stratified Cox proportional hazards model was used to compute the hazard ratio and the corresponding 95% CI (95% CI). Survival analyses were summarized using the weighted Kaplan-Meier method. All analyses were performed by using SAS® Version 9.1.4 or higher. An improvement of 25% to a median overall survival (OS) of 50 months (corresponding to a hazard ratio of 0.80) was considered clinically meaningful. Therefore, 750 OS events were required to have at least 80% power to detect a hazard ratio of 0.80 using a two-sided log-rank test at a significance level of 0.05 based on the exponential distribution assumptions of OS for both cohorts.

**RESULTS**

From February 3, 2015 to March 31, 2020, in the Flatiron Database a total of 2888 postmenopausal women or men with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2‒) metastatic breast cancer (MBC) started palbociclib plus an aromatase inhibitor (n=1324) or an aromatase inhibitor alone (n=1564) as first-line therapy. A total of 10 men were included in the palbociclib group and 19 men in the aromatase inhibitor alone group (Table 1). Most patients were treated in the community setting (>90%) versus academic setting. The percentage of patients who initiated palbociclib plus an aromatase inhibitor gradually increased from 2015 to 2019 while the percentage of patients who initiated an aromatase inhibitor alone decreased. More patients treated with palbociclib plus an aromatase inhibitor had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, de novo MBC, a lower mean comorbidity index, and a higher number of metastatic sites compared with patients who received an aromatase inhibitor alone. A higher percentage of patients in the palbociclib group versus aromatase inhibitor group also received letrozole as the first-line aromatase inhibitor (86.1% vs 42.1%), while in the aromatase inhibitor group versus palbociclib group, more patients received anastrozole (47.0% vs 10.8%). Patient characteristics were generally balanced after stabilized inverse probability of treatment weighting (sIPTW) adjustment, and between propensity score–matched groups, with the exception of the first-line aromatase inhibitor received. After sIPTW adjustment, the median age was 70 years in both treatment groups. The majority of patients (~68%) were white in each treatment group, and most patients did not have visceral disease. After sIPTW adjustment, the median duration of follow-up was 23.9 months (interquartile range [IQR], 12.8–38.0) in the palbociclib plus an aromatase inhibitor group and 24.5 months (IQR, 12.0–42.9) in the aromatase inhibitor alone group.  
A consistent rwPFS benefit with palbociclib plus an aromatase inhibitor versus an aromatase inhibitor alone was observed generally across most subgroups examined after sIPTW (Figure 6). In line with OS results, a rwPFS benefit was observed regardless of race and among patients with and without visceral disease or bone-only disease. The benefit of palbociclib plus an aromatase inhibitor varied by age subgroup. Patients aged ≥50 years, including patients aged ≥75 years, had a greater benefit than patients <50 years (≤50 years). Similar rwPFS subgroup results were observed in the PSM-adjusted sensitivity analysis (Figure 7).  
  
Subsequent Treatments  
Subsequent second-line treatments following first-line palbociclib plus aromatase inhibitor or aromatase inhibitor alone after sIPTW analysis are presented in Table 2. A total of 48.9% (48.9%) of patients in the palbociclib group and 65.1% (65.1%) of patients in the aromatase inhibitor alone group had data available on any second-line treatment. Among these patients, 43.1% (43.1%) and 50.5% (50.5%) of patients in the palbociclib group and aromatase inhibitor group, respectively, received a CDK4/6 inhibitor as second-line treatment, and 21.1% (21.1%) and 15.1% (15.1%) received chemotherapy.

**DISCUSSION**

Overall survival (OS) is a key endpoint in clinical oncology research. As stringent inclusion and exclusion criteria only allow for select patients to be enrolled in clinical trials, real-world studies are an essential component to evaluate survival among a heterogeneous population of patients treated with a drug in routine clinical practice. In this retrospective Flatiron Health Analytic Database analysis of postmenopausal women and men with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC), first-line palbociclib plus an aromatase inhibitor significantly prolonged OS and real-world progression-free survival (rwPFS) among all patients and among most subgroups analyzed. Specifically, an OS and rwPFS benefit with palbociclib plus an aromatase inhibitor was observed among patients with and without visceral metastases or bone-only disease, and among subgroups of patients not well represented in breast cancer clinical trials, including Black patients and older patients aged ≥75 years. A landmark analysis of OS at 2, 3, and 4 years showed higher OS rates in the palbociclib plus aromatase inhibitor group compared with the aromatase inhibitor alone group. Selection of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor was also a primary choice as subsequent second-line therapy.  
These findings further support the PALOMA clinical trial data on the effectiveness of palbociclib plus endocrine therapy for HR+/HER2– MBC,8,9,27-29 and are in line with the previous observation of longer OS with palbociclib plus fulvestrant among patients who had disease progression after previous endocrine therapy in PALOMA-3 (absolute difference, 6.9 months).29 These data also add to the body of evidence on the effectiveness of a CDK4/6 inhibitor plus endocrine therapy on OS in MBC in the first- and second-line setting, including a pooled analysis of all CDK4/6 inhibitor trials with published OS results to date.30-33 Results from the current real-world study were available earlier than PALOMA-2 OS results due to many different factors, including that the current study had a greater number of patients, increased statistical power, and included different patients without selective inclusion and exclusion criteria typically observed in clinical trials. <<<Placeholder  
Findings reported in this study are strengthened by the high number of cancer clinics and sites of care across the US that are included in the Flatiron database. Notably, Flatiron data among patients with MBC have been shown to be comparable to SEER and NPCR data of patients with any stage breast cancer across sex and geographical location. Per standards for real-world analyses, this study included prespecified primary and secondary endpoints and a sensitivity analysis. As patients in this observational study were not randomized, differences in baseline and clinical characteristics can be accounted for by using different statistical methods to balance patient demographic and clinical characteristics (ie, sIPTW and PSM). The significant findings observed in the unadjusted analysis were consistent in the sIPTW analysis were further validated by the sensitivity PSM analysis. Furthermore, the overall survival (OS) endpoint includes external data sources, such as the National Death Index, US Social Security Death Index, obituaries, and commercial death data, in addition to health records and has been validated by 2 analyses that confirmed a high sensitivity and specificity of real-world cancer survival data in comparison to the National Death Index.20,22 The real-world progression-free survival (rwPFS) endpoint measured in this study has also been validated in the Flatiron database.35 Overall, real-world evidence is a valuable body of knowledge that is representative of patients in routine clinical practice, can aid in clinical decision making, help expand indications and safety information, and can influence future clinical trial design.10,36,37 The growing evolution in the quality of real-world studies also highlight it as valid component in regulatory decision making.37 Finally, real-world data may also contain helpful information for international health technology assessment practices which play a role in insurance coverage decisions.  
Real-world studies are inherently limited by various factors. First, this study is a retrospective database study of electronic health records which may have missing or erroneous data entry. In addition, some subgroups analyzed may have insufficient sample size (eg, younger patients aged <50 years) to identify significant differences in rwPFS and OS outcomes. Treatment and patient selection bias cannot be excluded since therapy was provided in routine clinical practice and not in a clinical trial setting. Moreover, disease progression was not based on standard criteria (eg, Response Evaluation Criteria in Solid Tumors), but instead was based on the individual treating physician’s clinical assessment or interpretation of radiographic or pathologic results

**CONCLUSIONS**

This is the largest, multisite real-world comparative effectiveness study to date. Treatment with palbociclib plus an aromatase inhibitor (AI) significantly prolonged overall survival (OS) and radiographic progression-free survival (rwPFS) versus an AI alone in a heterogeneous population of postmenopausal women and men with hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC). These results were observed across most subgroups. Overall, these data support first-line palbociclib plus an AI as a standard of care for patients with HR+/HER2– MBC.

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**AUTHOR CONTRIBUTIONS**

Xianchen Liu, Benjamin Li, Lynn McRoy, and Connie Chen contributed to the conception and design, analysis and interpretation of data, and drafting/revision of the article. Hope S. Rugo, Adam Brufsky, Rachel M. Layman, Massimo Cristofanilli, Mylin A. Torres, Giuseppe Curigliano, Richard S. Finn, and Angela DeMichele contributed to the analysis and interpretation of data and drafting/revision of the article. All authors read and approved the final manuscript.

**COMPETING INTERESTS STATEMENT**

Hope S. Rugo reports sponsored research to her institution from Pfizer Inc (Pfizer), Merck, Novartis, Eli Lilly, Roche, Daiichi-Sankyo, Seattle Genetics, Macrogenics, Sermonix, Boehringer Ingelheim, Polyphor, AstraZeneca, Ayala, and Gilead and honoraria from PUMA, Samsung, and Mylan. Adam Brufsky reports advisory/consultancy fees from Pfizer Inc. Rachel M. Layman reports advisory/consultancy fees from Pfizer Inc and Novartis and research/grant funding from Pfizer Inc, Novartis, Eli Lilly, GlaxoSmithKline, and Zentalis. Massimo Cristofanilli reports advisory/consultancy fees (Data Safety Monitoring Board or Advisory Board) from Merck and AstraZeneca, research grant/funding from Pfizer Inc, Menarini, Eli Lilly, and G1 Therapeutics, consulting fees from Novartis, Menarini, Eli Lilly, Sermonix, G1 Therapeutics, Foundation Medicine, AstraZeneca, Pfizer Inc, and Foundation Medicine, and travel support from Foundation Medicine. Mylin A. Torres reports research grant/funding from Pfizer Inc and Genentech, advisory/consulting fees from Centers for Disease Control and Oncohealth, and honoraria from MJH Life Sciences. Giuseppe Curigliano reports consulting fees from Seagen, Roche, Novartis, Lilly, Daiichi Sankyo, Astra Zeneca, Pfizer Inc, Sanofi, Pierre Fabre, and Gilead and fees for Non-CME services (eg, speakers' bureaus) from Lilly, Pfizer Inc, and Daiichi Sankyo. Richard S. Finn reports consulting fees/honoraria from Pfizer Inc and research grant/funding from Pfizer Inc, Eli Lilly, and Novartis. Angela DeMichele reports research grant/funding from Pfizer Inc, Novartis, Calithera, and Genentech. Xianchen Liu, Benjamin Li, Lynn McRoy, and Connie Chen are employees of and stockholders in Pfizer Inc.

**DATA-SHARING STATEMENT**

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See the Pfizer Data Access Program (PDAP) for more information.

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**TABLES**

Text (Chunk 1/1): Table 1. Patient Demographic and Clinical Characteristics  
AI=Aromatase Inhibitor; BC=Breast Cancer; Dx=Diagnosis; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IQR=Interquartile Range; MBC=Metastatic Breast Cancer; NCI=New Comorbidity Index; sIPTW=Stabilized Inverse Probability Treatment Weighting.   
\*Variable used in propensity score matching model.  
†Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.  
‡Bone-only disease was defined as metastatic disease in the bone only.  
§Multiple metastases at the same site were counted as 1 site (e.g., if a patient had 3 bone metastases in the spine, it was considered only 1 site).  
The balance in important prognostic baseline characteristics was assessed using a standardized differences approach, with a standardized difference of ≥0.10 considered indicative of practical significance 23.  
The total patient population for different subgroups varied due to the application of sIPTW. Therefore, the total n number for each subgroup may not have always equaled the N number of the treatment arm (due to rounding error and categorization differences). Calculated percentages were based on the number of patients reported within each subgroup.  
Table 2. Subsequent Second-Line Anticancer Treatments After sIPTW Analysis  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
  
AI=Aromatase Inhibitor; CDK4/6=Cyclin-Dependent Kinase 4/6; sIPTW=Stabilized Inverse Probability of Treatment Weighting.   
\*Includes patients who continued treatment, died, or were censored in the first-line setting.  
†Patients could have received >1 category of second-line treatment.

**FIGURES**

Figure 1. Patient attrition diagram.  
  
Figure 2. Kaplan-Meier curves of overall survival (OS).  
  
AI=aromatase inhibitor; NE=not estimable; PAL=palbociclib; PSM=propensity score matching; sIPTW=stabilized inverse probability of treatment weighting.   
  
Figure 3. Forest plot of overall survival by subgroup after sIPTW (stabilized inverse probability of treatment weighting).  
  
AI=aromatase inhibitor; Dx=diagnosis; ECOG PS=Eastern Cooperative Oncology Group performance status; ND=not documented; PAL=palbociclib; sIPTW=stabilized inverse probability of treatment weighting.   
†Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.  
‡Bone-only disease was defined as metastatic disease in the bone only.  
  
Figure 4. Forest plot of overall survival by subgroup after PSM (propensity score matching).  
  
AI=aromatase inhibitor; Dx=diagnosis; ECOG PS=Eastern Cooperative Oncology Group performance status; ND=not documented; PAL=palbociclib; PSM=propensity score matching.   
†Visceral disease was defined as metastatic disease in the lung and/or liver; patients could have had other sites of metastases. No visceral disease was defined as no lung or liver metastases.  
‡Bone-only disease was defined as metastatic disease in the bone only.  
  
Figure 5. Kaplan-Meier curves of real-world progression-free survival (PFS).

**SUPPLEMENTARY MATERIAL**

Data are derived from 42 distinct states (including Puerto Rico and Washington DC); state-level or geographic filters were not selected. The state is missing for a small proportion of patients for whom the state of residence was not recorded in the physician's records. For de-identification reasons, state is nulled out for all Academic patients and a few low-population states (i.e., Alaska, Montana, North Dakota, South Dakota, Vermont, and Wyoming). Any territories outside of the 50 states, District of Columbia, and Puerto Rico are reported in the State field as NULL.