# Introduction

This study aims to evaluate the overall survival (OS) and real-world progression-free survival (rwPFS) of palbociclib plus aromatase inhibitor (AI) versus AI alone in postmenopausal women and men with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer (MBC) in routine clinical practice in the United States. Palbociclib, a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, was approved in 2015 as first-line treatment for HR+/HER2- MBC in combination with an AI. The study utilizes the Flatiron Health Analytic Database and has the longest index period from palbociclib approval, as well as an extended follow-up time of at least 6 months from the index date to the data cutoff date.  
  
Previous real-world studies have shown the safety and effectiveness of CDK4/6 inhibitors plus endocrine therapy for HR+/HER2- MBC. Comparative effectiveness studies using the Flatiron Database have demonstrated longer rwPFS and OS with palbociclib plus letrozole compared to letrozole alone. However, data on OS in patients treated with palbociclib plus endocrine therapy versus endocrine therapy alone are limited by small sample sizes and short follow-up time.  
  
This study aims to provide further evidence on the efficacy and safety of palbociclib plus AI in routine clinical practice, utilizing a larger sample size and an extended follow-up period. The results of this study will contribute to the understanding of the real-world outcomes of palbociclib treatment in HR+/HER2- MBC patients.

# Background

Breast cancer is a significant public health concern in the United States, with a high incidence and mortality rate. In 2021, it was estimated that there would be 281,550 new cases of female breast cancer and 43,600 deaths. Among breast cancer cases, approximately 6% are classified as metastatic breast cancer (MBC), where the cancer has spread to distant tissues. The 5-year survival rate for MBC is only 29.0%, highlighting the urgent need for effective treatment options.  
  
The majority of breast cancer cases are hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-), accounting for 68% of cases. For patients with first-line HR+/HER2- MBC, the National Comprehensive Cancer Network treatment guidelines recommend the use of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor in combination with endocrine therapy. This treatment approach has shown promising results in clinical trials and has become the standard of care for these patients.  
  
One such CDK4/6 inhibitor is palbociclib, which was approved in 2015 for the first-line treatment of HR+/HER2- MBC in combination with an aromatase inhibitor. In 2016, it was also approved in combination with fulvestrant for patients who had progressed on prior endocrine therapy. The PALOMA-2 trial, a phase 3 study, evaluated the efficacy of palbociclib plus letrozole compared to letrozole plus placebo as first-line treatment for estrogen receptor-positive/HER2- MBC. The trial demonstrated a significant prolongation of median progression-free survival (PFS) with the combination therapy, although overall survival (OS) data are not yet mature.  
  
Real-world evidence plays a crucial role in validating the efficacy and safety of drugs in routine clinical practice. It allows for the inclusion of patients who may be underrepresented in clinical trials and helps to reinforce treatment recommendations. Emerging real-world data on palbociclib have demonstrated its safety and effectiveness when used in combination with endocrine therapy for HR+/HER2- MBC.  
  
Two comparative effectiveness studies using the Flatiron Health Analytic Database showed that palbociclib plus letrozole resulted in longer real-world PFS and OS compared to letrozole alone. These studies also indicated a higher chance of tumor response with the combination therapy. However, the real-world data on OS

# Methods

This study utilized a retrospective analysis of electronic health records (EHRs) from the Flatiron Health Analysis Database as its study design and data source. The Flatiron Health Analysis Database is a longitudinal database that contains de-identified patient data from structured and unstructured EHRs from over 280 cancer clinics, representing more than 800 sites of care. The database includes data from over 2.4 million actively treated US patients with cancer. The study included women aged 18 years or older at the time of metastatic breast cancer (MBC) diagnosis with confirmed hormone receptor-positive (HR+)/HER2-negative MBC at any point in their patient history. The inclusion criteria also required patients to have a date of first prescription for palbociclib plus aromatase inhibitor (AI) or AI alone as first-line therapy for MBC between February 3, 2015, and March 31, 2020, and a potential follow-up of at least 6 months from the index date to the study cutoff date of September 30, 2020. The study excluded patients with prior treatment with certain medications, evidence of disease progression more than 90 days after MBC diagnosis, and lack of relevant unstructured documents in the Flatiron Health database for review.

The primary outcome of the study is overall survival (OS). OS is defined as the time in months from the start of treatment with palbociclib plus AI or AI alone to death. If patients did not die, they were censored at the study cutoff date of September 30, 2020. The secondary outcome is real-world progression-free survival (rwPFS). rwPFS is defined as the number of months from the start of treatment to the date of the first documentation of disease progression or death due to any cause, whichever occurred first. Patients who were last known to be alive and progression-free within the follow-up cutoff date were censored at the date of the last clinic note. Disease progression was determined by the treating clinician based on radiology, laboratory evidence, pathology, or clinical assessment. The duration of follow-up was defined as the number of months from the start of treatment to death due to any cause or the data cutoff date of September 30, 2020. These primary and secondary outcomes will be analyzed using statistical methods such as stabilized inverse probability treatment weighting (sIPTW), weighted Cox proportional hazards model, propensity score matching (PSM), and stratified Cox proportional hazards model. The analysis will be performed using SAS® Version 9.1.4 or higher.

The statistical analyses in this study will focus on comparing the outcomes of two patient cohorts: those receiving palbociclib plus AI (aromatase inhibitor) and those receiving AI alone as first-line therapy for HR+/HER2- metastatic breast cancer (MBC). The study aims to determine the overall survival (OS) and real-world progression-free survival (rwPFS) in these cohorts.  
  
Approximately 3000 patients will be included in the analysis, with a 1:1 ratio between the palbociclib plus AI and AI alone cohorts. The median OS for the AI alone cohort is assumed to be 40 months. A clinically meaningful improvement of 25% to a median OS of 50 months (corresponding to a hazard ratio of 0.80) will be considered. To detect this improvement, 750 OS events will be required, with at least 80% power, using a two-sided log-rank test at a significance level of 0.05.  
  
To balance baseline demographic and clinical characteristics between the two cohorts, stabilized inverse probability treatment weighting (sIPTW) will be used as the primary analysis. The weighted Cox proportional hazards model will be used to compute the hazard ratio and the corresponding 95% confidence interval (CI).  
  
Propensity score matching (PSM) will be conducted as a sensitivity analysis to further balance baseline characteristics and adjust for observed potential confounders. Matches will be made using 1:1 nearest neighbor matching without replacement. A stratified Cox proportional hazards model will be used to compute the hazard ratio and the corresponding 95% CI.  
  
OS and rwPFS will be summarized using the weighted Kaplan-Meier method. The statistical analyses will be performed using SAS® Version 9.1.4 or higher.  
  
In conclusion, the statistical analyses will compare the outcomes of the palbociclib plus AI and AI alone cohorts in terms of OS and rwPFS. Various methods, including sIPTW, PSM, and Cox proportional hazards models, will be used to balance baseline characteristics and compute hazard ratios. The analyses will be performed on a large sample size to ensure sufficient power to detect clinically meaningful differences.

# Results

From February 3, 2015 to March 31, 2020, a total of 2888 postmenopausal women or men with HR+/HER2‒ MBC started palbociclib plus AI (n=1324) or AI alone (n=1564) as first-line therapy. After sIPTW adjustment, the median age was 70 years in both treatment groups, and the majority of patients (~68%) were white in each group. In terms of overall survival (OS), the median OS was significantly longer in the palbociclib group compared to the AI group, with OS rates at 24, 36, and 48 months of 76.6%, 62.9%, and 52.4% in the palbociclib plus AI group, and 65.6%, 54.4%, and 46.8% in the AI alone group. The hazard ratio for OS was 0.76 (95% CI, 0.65–0.87) in favor of the palbociclib group. In terms of real-world progression-free survival (rwPFS), the median rwPFS was significantly longer in the palbociclib group compared to the AI group, with rwPFS rates at 24, 36, and 48 months of 19.3 months (17.5–20.7), 13.9 months (12.5–15.2), and 19.8 months (17.3–21.9) in the palbociclib group, and 14.9 months (12.9–16.9), 0.70 (95% CI, 0.62–0.78), and 0.72 (95% CI, 0.63–0.82) in the AI alone group. These results were consistent across most subgroups examined.

# Discussion

The major findings of the study include a larger sample size compared to previous studies, longer follow-up duration, and improved outcomes with palbociclib plus aromatase inhibitors. Key endpoints include overall survival (OS) and progression-free survival (rwPFS). The study focused on postmenopausal women and men with HR+/HER2- metastatic breast cancer. The study had inclusion criteria of patients receiving palbociclib plus aromatase inhibitors as first-line treatment, while exclusion criteria were not specified. However, it is important to note that the findings may not be generalized to other patient populations and there may be limitations due to the retrospective nature of the analysis.

The study results showed that palbociclib plus aromatase inhibitors were effective in the treatment of HR+/HER2- metastatic breast cancer. In the PALOMA-2 study, the median duration of follow-up was 24.2 months in the palbociclib group and 23.3 months in the letrozole group. The median rwPFS was 20.0 months with palbociclib and 11.9 months with letrozole alone. The median OS was 43.1 months in the letrozole group and not reached in the palbociclib group. These findings were consistent with other real-world palbociclib studies conducted using the Flatiron database. However, it is important to note that this was a retrospective database analysis and the findings may not be generalized to other patient populations.

The current study had a larger sample size of 2888 compared to previous studies with 1430 and 1383 patients. The duration of follow-up in the current study was ≥6 months, while previous studies had follow-up for ≥3 months. In terms of efficacy, the median rwPFS was longer with palbociclib combination therapy compared to letrozole alone in both the current study and previous studies. The median OS was not reached in the palbociclib group, while it was 43.1 months in the letrozole group in the current study. Overall, the findings support the use of palbociclib plus aromatase inhibitors as first-line treatment for HR+/HER2- MBC. However, it is important to note that this study has limitations as it is a retrospective database analysis and the findings may not be generalized to other patient populations.

The study has several strengths, including a large sample size and longer follow-up duration compared to previous studies. The findings support the effectiveness of palbociclib plus aromatase inhibitors as a first-line treatment for HR+/HER2- metastatic breast cancer. However, it is important to note that the study is a retrospective database analysis, which may have limitations in terms of data accuracy and potential biases. Additionally, the findings from the Flatiron Database may not be applicable to other patient populations. Some subgroups may also have insufficient sample size, limiting the generalizability of the results.

# Conclusions

The conclusions of this study were that treatment with palbociclib plus AI significantly prolonged overall survival (OS) and progression-free survival (rwPFS) compared to AI alone in a diverse population of postmenopausal women and men with HR+/HER2- metastatic breast cancer. These results were consistent across various subgroups, and support the use of palbociclib plus AI as a first-line treatment for patients with HR+/HER2- MBC.

# References

The potential references provided in the study include the following:  
  
1. P-Reality OS Extended F/U  
2. Kick-off Discussion Guide  
3. PAL21190.1144  
4. Virtual Kick-off Discussion Guide  
5. Flatiron Real-World Palbociclib + Aromatase Inhibitor (AI) vs AI Alone: Extended Follow-up of Overall Survival  
  
In addition to these references, the study mentions the purpose of the virtual kick-off call, which includes introducing authors to agency/Pfizer personnel assigned to the manuscript, discussing Pfizer guidelines/processes and ICMJE requirements, positioning the paper, agreeing on the scope and content, developing a timeline, and addressing any questions or concerns. The study also highlights the author responsibilities as per ICMJE guidelines and Pfizer policy, emphasizing the need for substantive input and approval of the final version of the manuscript. The manuscript development will be conducted in the Pfizer publication software platform, Datavision, where all author comments will be documented.