# 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 includes an extended follow-up time of at least 6 months from the index date to the data cutoff date.  
  
The importance of real-world evidence is highlighted, as it validates the efficacy and safety of a drug in routine clinical practice. Real-world studies also allow for the inclusion of underrepresented patients and reinforce treatment recommendations. Previous real-world data 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, real-world 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 address these limitations by including the longest index period from palbociclib approval and an extended follow-up time of at least 6 months.

# Background

The study is a retrospective analysis of electronic health records (EHRs) from the Flatiron Health Analysis Database. The database contains de-identified patient data from structured and unstructured EHRs from over 280 cancer clinics, representing more than 2.4 million actively treated US patients with cancer. The purpose of the study is to fill the existing gap in knowledge by analyzing the EHRs to gain insights and understanding in the field of cancer treatment. The key findings and theories of previous studies are not mentioned in the provided context. The study includes a detailed definition of visceral disease and bone-only disease, as well as how multiple metastases at the same site are counted. The balance in important prognostic baseline characteristics was assessed using a standardized differences approach. The total patient population for different subgroups varied due to the application of sIPTW, which may have resulted in rounding errors and categorization differences. Calculated percentages were based on the number of patients reported within each subgroup.

# Methods

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

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 study aims to determine the median OS for both treatment cohorts and assess if there is a clinically meaningful improvement in OS with palbociclib plus AI compared to AI alone. Statistical analyses, including stabilized inverse probability treatment weighting (sIPTW) and propensity score matching (PSM), will be used to analyze and compare the hazard ratios and 95% confidence intervals between the two cohorts.

The secondary outcome of the study is rwPFS, which stands for real-world progression-free survival. rwPFS is defined as the number of months from the start of treatment with palbociclib plus AI or AI alone to the date of the first documentation of a real-world progressive disease or death due to any cause, whichever occurs first. Patients who were last known to be alive and progression-free within the follow-up cut-off 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. The study will use statistical analyses such as stabilized inverse probability treatment weighting (sIPTW) and propensity score matching (PSM) to compare the rwPFS outcomes between the two treatment cohorts.

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, providing 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.  
  
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.

# Results

The study included a total of 2888 postmenopausal women or men with HR+/HER2‒ MBC who started palbociclib plus AI (n=1324) or AI alone (n=1564) as first-line therapy from February 3, 2015 to March 31, 2020. Out of these, 10 men were included in the palbociclib group and 19 men in the AI alone group. After 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 unadjusted analysis of the full cohort showed that median OS was significantly longer in the palbociclib group compared to the AI group (P<0.0001). After adjustment, the OS (95% CI) was 49.1 months (45.2–57.7) in the palbociclib group and 43.2 months (37.6–48.0) in the AI group, with a hazard ratio of 0.76 (95% CI, 0.65–0.87; P<0.0001). The OS rates at 24, 36, and 48 months were 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 propensity score matching (PSM) analysis also showed a significant improvement in OS with palbociclib plus AI compared to AI alone, with an OS (95% CI) of 57.8 months (47.2–not estimable) in the palbociclib group and 43.5 months (37.6–48.9) in the AI group, and a hazard ratio of 0.72 (95% CI, 0.62–0.83; P<0.0001).  
  
For real-world progression-free survival (rwPFS), the unadjusted analysis showed that median rwPFS was significantly longer in the palbociclib group compared to the AI group (P<0.0001). After adjustment, the rwPFS (95% CI) was 19.3 months (17.5–20.7)

# Discussion

The major findings of the study include a longer median rwPFS and improved OS with palbociclib plus aromatase inhibitors compared to letrozole alone. The study had a larger sample size compared to previous studies conducted using the Flatiron database. The inclusion criteria included postmenopausal women and men with HR+/HER2- MBC, while the exclusion criteria were not mentioned in the provided context. 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 study.

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. Additionally, some subgroups may have insufficient sample size.

The study has several strengths, including a larger sample size compared to previous studies using the Flatiron database. The study also had a longer follow-up period, which provides more robust data. The findings from this study support the effectiveness of palbociclib plus aromatase inhibitors as a first-line treatment for HR+/HER2- MBC. However, there are limitations to consider, such as the retrospective nature of the analysis and the potential lack of generalizability to other patient populations. Additionally, some subgroups may have had insufficient sample size, which could limit the interpretation 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- metastatic breast cancer.

# Reference

Figure 1, P-Reality OS Extended F/U, Kick-off Discussion Guide, PAL21190.1144, Table S2, Virtual Kick-off Discussion Guide