Non-Interventional Study Protocol
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Comparative assessment of overall survival in Medicare patients with HR+/HER2− metastatic breast cancer treated with palbociclib in combination with aromatase inhibitor (AI) vs. AI alone

Statistical Analysis Plan
(SAP)

Version: 1

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LIST OF ABBREVIATIONS

Abbreviation	Term
1L	first line
ACS	American Community Survey
AI	aromatase inhibitor
AJCC	American Joint Committee on Cancer
CDK4/6	cyclin-dependent kinase 4 and 6
CI	confidence interval
CPH	Cox proportional hazards
EOD	Extent of Disease
ER	estrogen receptor
ET	endocrine therapy
HCPCS	Healthcare Common Procedure Coding System
HER2	human epidermal growth factor receptor 2
HMO	health maintenance organization
HR	hormone receptor
IPTW	inverse probability of treatment weighting
LIS	low-income subsidy
mBC	metastatic breast cancer
N/A	not applicable or not available
NAACCR	North American Association of Central Cancer Registries
NCI	National Cancer Institute
NCICI	National Cancer Institute Comorbidity Index
NHIA	NAACCR Hispanic Identification Algorithm
NOS	not otherwise specified
OS	overall survival
CCI	[redacted]
PR	progesterone receptor
PS	propensity score
PSM	propensity score matching
RPSFT	Rank Preserving Structural Failure Time
SEER	Surveillance, Epidemiology, and End Results
sIPTW	stabilized inverse probability of treatment weighting
SSA	Social Security Administration
CCI	[redacted]
US	United States

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable

2 INTRODUCTION

Nearly 70% of all metastatic breast cancer (mBC) cases are of the hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) subtype. Endocrine therapies (ETs), such as aromatase inhibitors (AIs), tamoxifen, and fulvestrant, have remained the mainstay of therapy for patients with HR+/HER2− mBC for nearly 2 decades; however, in recent years, several newer targeted therapies, particularly the class of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, have become available: palbociclib (February 2015), ribociclib (March 2017), and abemaciclib (September 2017). Phase 3 clinical studies have shown that CDK4/6 inhibitors used in combination with an AI in first line (1L) in HR+/HER2− mBC significantly increased progression-free survival compared with AI monotherapy. However, evidence on the secondary endpoint of overall survival (OS) from the clinical studies is mixed across different CDK4/6 inhibitors. In the phase 3 trial PALOMA-2, palbociclib + letrozole in the 1L setting demonstrated a numerical improvement but not a statistically significant OS increase, with median OS of 53.9 months for palbociclib + letrozole versus 51.2 months for letrozole alone (hazard ratio, 0.956; 95% confidence interval [CI], 0.78-1.18) (Finn et al., 2022). Likewise, in PALOMA-3, treatment with palbociclib + fulvestrant, after progression or relapse during previous ET, yielded a clinically important but not statistically significant survival improvement over fulvestrant monotherapy (median OS, 34.9 vs. 28.0 months; hazard ratio, 0.81; 95% CI, 0.64-1.03) (Turner et al., 2018). In a post hoc analysis of PALOMA trials, time to chemotherapy initiation was considerably longer for patients treated with palbociclib + letrozole (in PALOMA-2) and palbociclib + fulvestrant (in PALOMA-3) versus the respective non-palbociclib control groups (Rugo et al., 2022b). Further, an exploratory analysis of PALOMA-3 trial patients showed that patients who had not been treated with a prior chemotherapy for advanced breast cancer had improved OS with the palbociclib combination therapy versus the control group (median OS, 39.7 vs. 29.5 months; hazard ratio, 0.75; 95% CI, 0.56-1.01) (Rugo et al., 2021).

Data from at least 2 observational studies have shown possible OS benefits in relatively older patient populations. Results from P-Reality-X, a real-world evidence study conducted using data from the Flatiron electronic health record (median age, 70 years for palbociclib treatment group), also reported improved OS, specifically for patients receiving palbociclib + AI compared with AI alone. After stabilized inverse probability of treatment weighting, median OS (95% CI) is significantly longer among palbociclib compared with AI recipients (49.1 [45.2-57.7] vs. 43.2 [37.6-48.0] months; hazard ratio, 0.76 [95% CI, 0.65-0.87]; $P < 0.0001$) (Rugo et al., 2022a). In another study of older

patients (median age, 74 years for both the treatment arms: palbociclib + letrozole and letrozole alone), the palbociclib group was shown to have significantly better OS than the letrozole alone group (hazard ratio, 0.55 [95% CI, 0.42-0.72]; P < 0.001) (Rugo et al., 2023). In a recent observational study of an Medicare population of patients with diagnosis of de novo HR+/HER2− mBC using data from the Surveillance, Epidemiology, and End Results (SEER)–Medicare during an early period of CDK4/6 inhibitors use (2015-2017), Goyal et al. (2023) analyzed the effect of the CDK4/6 inhibitors (as a class) on OS and reported that combination therapy with ET and a CDK4/6 inhibitor is independently associated with improved OS compared with ET alone (hazard ratio, 0.59; 95% CI, 0.42-0.82). The majority (≥ 90%) of patients in the CDK4/6 inhibitor group (median age, 70 years) in this study were taking palbociclib (Trapani and Mayer, 2023).

Because the evidence from real-world populations are often underrepresented in clinical trials (Lewis et al., 2003; Loree et al., 2019; Murthy et al., 2004; Talarico et al., 2004), and because 2 additional years of SEER-Medicare data have now become available allowing for more sample size and additional follow-up we seek to understand current data on potential survival benefits among the primary cohort of patients treated with palbociclib + AI compared with AI alone after de novo mBC diagnosis. A description of the SEER-Medicare database is provided in Section 2.1.

2.1 STUDY DESIGN

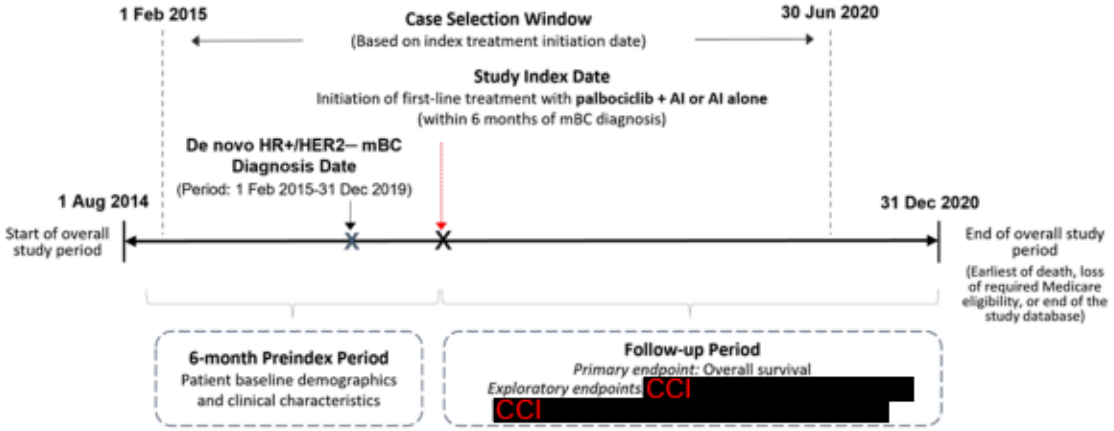
*This study will encompass a retrospective cohort analysis using clinical and administrative claims data from the linked SEER-Medicare database (providing SEER data are available through 2019 and linked Medicare claims are available through 2020) for patients with diagnosis of HR+/HER2− mBC at initial presentation. The study will assess the rates of OS in patients 65 years or older with diagnosis of de novo mBC from 2015-2019 who initiated 1L systemic therapy with palbociclib + AI or AI alone following the first approval of palbociclib in February 2015. **Figure 2-1** presents a graphical schema of the study design (drawn for a hypothetical patient and not to scale).*

Based on the study schema presented below, the following key study definitions will apply:

- ***De novo mBC diagnosis date window:** From 1 February 2015 through 31 December 2019*
- ***Study index date:** The date of 1L treatment initiation with palbociclib + AI or AI alone after the de novo mBC diagnosis*
- ***Case selection window:** From 1 February 2015 through 30 June 2020 – for the date of 1L treatment initiation (study index date)*

- ***Baseline period:*** *The 6-month period before the study index date (to assess patient baseline demographic and clinical characteristics)*
- ***Study follow-up:*** *All patients will be followed from their study index date through the earliest of the following: death, disenrollment from Medicare Part A (hospital insurance), Part B (medical insurance), or Part D (prescription drug insurance), enrollment in a health maintenance organization (HMO) plan, or end of the study database (31 December 2020).*
- ***Overall study period:*** *From 1 August 2014 (to allow up to 6 months of look back period for any patient with index date in February 2015) through 31 December 2020 (accounting for a minimum 6 months of potential follow-up for any patient with index date in June 2020).*

Figure 2-1. Study Design Schematic (Depiction for a Hypothetical Patient)



AI = aromatase inhibitor; HER2– = human epidermal growth factor receptor 2–negative; HR+ = hormone receptor–positive; mBC = metastatic breast cancer.

Note: Figure not drawn to scale.

Study Population

The study population will represent Medicare beneficiaries (men or women) with diagnosis of HR+/HER2− mBC at initial presentation (i.e., de novo), as identified in the SEER-Medicare database.

Data Source

The SEER-Medicare database is composed of 2 large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer: (1) the SEER registry data that contain information about an incident cancer diagnosis and (2) linked Medicare data that contain longitudinal information on Medicare enrollment and

specific healthcare services received in different settings (e.g., hospitals, physician offices, outpatient clinics, nursing homes), as well as prescription drug utilization. The linkage of these 2 data sources results in a unique source of information that can be used for an array of epidemiological research, including health services use and survival outcomes, among older patients with cancer in the United States (US) Medicare population.

The SEER registries are part of the SEER Program, which is an epidemiologic surveillance system consisting of population-based tumor registries in certain states and metropolitan areas designed to track cancer incidence and survival in the US. The SEER registries collect information on nearly all (98%) newly diagnosed cancer cases, including breast cancer, in persons residing in SEER areas. SEER areas have been shown to be nationally representative (Nattinger et al., 1997) and the 21 registries represented in the SEER data linkage available for this study (SEER-21) capture over one-third (35%) of the total US population (Enewold et al., 2020). In contrast to the entire population of the US, the SEER Program encompasses a population that displays greater racial and ethnic diversity, along with a higher representation of individuals facing economic disadvantages (Enewold et al., 2020).

The SEER registry data released as part of SEER-Medicare are included in a customized file known as the SEER-Medicare Cancer file. The information collected on each SEER-reported cancer diagnosis includes patient-level demographic characteristics, date of diagnosis, clinical data about the tumor (e.g., stage, grade, size, estrogen receptor [ER] status, progesterone receptor [PR] status, and HER2 status), and cause and date of death. Linkage with Medicare data provides a database of persons generally aged 65 years and older with detailed information on incident cancer linked with comprehensive longitudinal healthcare utilization data from Medicare fee-for-service. In SEER-Medicare, the Medicare date of death information is collected from multiple sources, including the Social Security Administration (SSA), Railroad Retirement Board, and Medicare Common Working File; the Medicare date of death information is known to be complete for the given enrollment year (e.g., 2020 enrollment data will capture deaths occurring in 2020). Because almost all (99%) Medicare deaths are validated (98% through SSA), the vital status information available in the linked SEER-Medicare data make it one of the most authoritative data sources to examine survival outcomes in Medicare beneficiaries with an incident of cancer diagnosis in the US.

The linkage of SEER-Medicare data is managed by the National Cancer Institute (NCI), in collaboration with the contributing SEER registries and the Centers for Medicare & Medicaid Services. Investigators must submit a detailed application to the NCI for obtaining access to the required study data, which must be used under the terms of a data use agreement. Based on the most recent data linkage by the NCI, released in December

2022, SEER data are linked with Medicare patients aged ≥ 65 years with an incident (de novo) cancer diagnosis from 1999-2019, with linked claims and survival data available through 2020. The reason for the 3-year gap between cancer diagnosis and integration into the SEER-Medicare database stems from a 2-year period required for complete case reporting to the SEER Program, coupled with one extra year to process the data linkage. Information contained within the linked Medicare claims data, including dates and types of treatment utilization (including prescription drugs), make it possible to retrospectively "follow" patients after the date of their initial diagnosis reported in the SEER registry. Additional details on the structure, content, and application of the SEER-Medicare data can be found in the literature (Enewold et al., 2020; Warren et al., 2002).

2.2 STUDY OBJECTIVES

Following the work of Goyal et al. (2023), this retrospective, noninterventional study aims to assess OS in Medicare patients with HR+/HER2− de novo mBC who initiated 1L treatment with palbociclib + AI combination therapy versus AI alone. Specifically, the key objectives of this study are as follows:

Primary objective:

- *To compare OS of 1L palbociclib + AI versus AI alone for women or men with de novo HR+/HER2– mBC in the SEER-Medicare database who are ≥ 65 years old*

Exploratory objectives:

CCI [redacted]

- *To measure time to chemotherapy, if enough follow-up time is available to assess this measure.*

3 HYPOTHESES AND DECISION RULES

The primary objective of this study is to demonstrate superiority of palbociclib + AI over AI monotherapy in prolonging OS for women and men aged ≥ 65 years with HR+/HER2– mBC as 1L treatment in the US clinical practice setting. The study is designed to test the null hypothesis H_0: $\lambda \geq 1$ versus alternative hypothesis H_a: $\lambda < 1$, palbociclib + AI cohort vs. AI monotherapy cohort, where λ stands for the hazard ratio.

4 ANALYSIS SETS/POPULATIONS

The patient section criteria that define the study population or analysis set are described in this section.

4.1 FULL ANALYSIS SET

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. *De novo metastatic (stage IV) disease at initial breast cancer diagnosis during 2015-2019 (Howlader et al., 2018):*
    - *Incident breast cancer diagnosis will be identified using the SEER Site Recode 26000, which includes cases classified as "breast" according to the International Classification of Diseases for Oncology, 3rd Edition codes: C50.0-C50.9, excluding histology codes 9050-9055, 9140, and 9590-9992 (National Cancer Institute, 2023b).*
    - *Staging at diagnosis will be determined using criteria applicable during the specific period. Specifically, the American Joint Committee on Cancer (AJCC) staging 7th edition variable will be used to classify diagnoses in year 2015, the derived SEER combined stage group variable will be used to classify diagnoses in years 2016-2017, and the derived Extent of Disease (EOD) stage group variable will be used to classify diagnoses in years 2018-2019.*
2. *Age ≥ 65 years at diagnosis*
3. *"Age" as the reason for Medicare entitlement*
4. *Breast cancer recorded as the first cancer (coded as tumor sequence "1") or the only cancer (coded as tumor sequence "0") confirming no evidence of another, previous primary cancer diagnosis.*
5. *HR+/HER2− molecular subtype at diagnosis, using the SEER breast subtype variable (defined according to ER/PR and HER2 status)*
6. *Initiated 1L systemic therapy with a CDK4/6 inhibitor + AI or AI alone*
    - *Subsequently, and differing from Goyal et al. (2023), to assess the primary objective, the study cohort will be restricted to patients initiating 1L therapy with palbociclib + AI or AI alone within 6 months of mBC diagnosis:*
        - *It is assumed that most patients will initiate a systemic treatment within a few months of the diagnosis, and those who did not receive treatment*

within 6 months may have meaningful unobserved characteristics that likely influenced their treatment decisions.

7. *To ensure complete data for identifying the 1L of therapy, patients will be required to have continuous enrollment in Medicare Parts A and B and have prescription drug coverage (Part D) with no HMO participation from date of diagnosis until they initiate the 1L therapy, and they are allowed up to 6 months to initiate first-line therapy.*
8. *Continuously enrolled in Medicare Parts A and B with no HMO participation for ≥ 6 months* before *the index date*
    - *Because HMOs are not obligated to provide information about healthcare encounters (i.e., administrative procedure and diagnosis codes) to the Medicare system, patients who were enrolled in an HMO during study period may have incomplete data on service utilization, which may affect the accuracy of measurement for comorbid conditions and receipt of systemic therapy lines.*

Exclusion Criteria

Patients will be excluded if their mBC diagnosis was first recorded in a death certificate or at the time of autopsy.

4.2 SAFETY ANALYSIS SET

Not applicable.

4.3 OTHER ANALYSIS SET

Not applicable.

4.4 SUBGROUPS

To help better explain the results and to generate additional contextual data, subgroup analyses may be performed. As exploratory analyses, these subgroups may include age groups, metastatic sites, receipt of subsequent treatments, and other patient characteristics as appropriate, and the analyses will be conducted based on availability of the data and adequate sample sizes.

5 ENDPOINTS AND COVARIATES

The endpoints and covariates that will be defined by the data abstracted from the medical records are described in this section.

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

As the primary endpoint, OS will be defined as time in months from initiation of 1L therapy to death from any cause. For details on endpoint definition, please refer to Table 5-1.

5.2 SAFETY ENDPOINTS

Not applicable.

5.3 EXPLORATORY ENDPOINTS

As exploratory endpoints, CCI [redacted], and time to chemotherapy will be assessed. For details on endpoint definitions, please refer to Table 5-1.

5.4 STUDY ENDPOINTS

The endpoints or study outcomes to be analyzed for each study objective and the associated definitions are described in Table 5-1.

Table 5-1. Definition of Endpoints

Variable	Role/objective	Definition
Overall survival in 1L	Primary	The *time in months from initiation of 1L therapy* (palbociclib + AI or AI alone) *to all-cause death*. Patients who did not die will be censored at the end of study follow-up as defined in Section 2.1.
CCI [redacted]		

Variable	Role/objective	Definition
CCI [redacted]		
Time to chemotherapy	Exploratory	*Time in months from the study index date to first initiation of chemotherapy in any subsequent therapy lines.* Patients who did not initiate chemotherapy treatment as of last follow-up will be censored at the end of the follow-up.

1L = first line; AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6;
CCI [redacted]

5.5 EXPOSURE VARIABLES AND COVARIATES

The exposure and other covariates to be analyzed as part of the study objectives and associated definitions are described in Table 5-2. *For covariates, categories may be further combined if appropriate for statistical purposes.*

Table 5-2. Definitions of Exposure Variables

Variable	Role/objective	Definition
Exposure variables		
1L treatment type	Primary	*Patients initiating 1L therapy with one of the following regimens (to be identified in the Prescription Drug Event file using the generic drug names and HCPCS procedure codes, as applicable):* • *Palbociclib + AI* • *AI alone* *AI will include the following individual agents:* • *Anastrozole (HCPCS code: S0170)* • *Letrozole (HCPCS code: N/A)* • *Exemestane (HCPCS code: S0156)* ***Therapy line definition:** For each patient, the 1L therapy will be defined as all agents administered within a 60-day period after treatment initiation. The 1L therapy will start on the date the first agent will be*

Variable	Role/objective	Definition
		administered (or filled) and will be considered to have ended upon occurrence of the earliest of any of the following: treatment switch to a new regimen or a gap of more than 90 days in administration or refill of any of the 1L regimen drugs. The start and end dates of the second and subsequent therapy lines will be defined in a similar fashion. The rules defining "treatment switch to a new regimen" are presented in Appendix 1.
Subsequent treatment	Exploratory	*All subsequent treatment lines for patients initiating 1L therapy with palbociclib + AI or AI alone, including a description of treatment switch from AI alone to palbociclib + AI.*
Control variables/covariates		
Tumor grade at diagnosis	Clinical characteristic (assessed at mBC diagnosis)	*The tumor grade will be summarized as below:* • *Grade 1 (lowest grade; well differentiated)* • *Grade 2* • *Grade 3* • *Grade unknown*
Metastatic site involvement at diagnosis	Clinical characteristic (assessed at mBC diagnosis)	*The SEER-defined metastatic site variables will be used to describe involvement of any of the following sites at diagnosis:* • *Bone* • *Brain* • *Liver* • *Lung* • *An additional variable will be created to describe presence of visceral metastases using the composite of liver and lung.*
NCI Comorbidity Index (NCICI) Score	Clinical characteristic (assessed within the 6 months period before index date)	*The comorbidity burden during the 6-month baseline period will be assessed using the NCI's comorbidity index, which is described in the Klabunde adaptation of the Charlson Comorbidity Index, version 2021 (Klabunde et al., 2007; National Cancer Institute, 2023a). NCICI scores will be reported as continuous and categorical variables:* • *Score 0* • *0 < Score ≤ 1* • *Score > 1*

Variable	Role/objective	Definition
		The specific comorbidities represented in the NCICI include the following: • *Acute myocardial infarction* • *History of myocardial infarction* • *Congestive heart failure* • *Peripheral vascular disease* • *Cerebrovascular disease* • *Chronic obstructive pulmonary disease* • *Dementia* • *Paralysis (hemiplegia or paraplegia)* • *Diabetes without complications* • *Diabetes with complications* • *Renal disease* • *Mild liver disease* • *Moderate/severe liver disease* • *Peptic ulcer disease* • *Rheumatologic disease* • *AIDS*
Age	*Demographics (assessed at mBC diagnosis and at index date)*	*Age at diagnosis will be assessed as continuous and categorical variables:* • *65-69 years* • *70-74 years* • *75-79 years* • *≥ 80 years*
Year of diagnosis	*Demographics (assessed at mBC diagnosis)*	*Year of de novo mBC diagnosis will be described as a categorical variable:* • *2015* • *2016* • *2017* • *2018* • *2019*

Variable	Role/objective	Definition
Race	*Demographics (assessed at mBC diagnosis)*	*Race will be defined using the SEER Race Recode variable and categorized as follows:* • *American Indian/Alaska native* • *Asian or Pacific Islander* • *Black* • *White* • *Other or unknown* *These categories may be further combined for statistical purposes as below:* • *White* • *Non-White*
Origin/ethnicity	*Demographics (assessed at mBC diagnosis)*	*Ethnicity will be defined using the SEER Origin Recode variable defined by the NAACCR Hispanic Identification Algorithm (NHIA) and categorized as follows:* • *Hispanic (Spanish-Hispanic-Latino)* • *Non-Hispanic (non-Spanish-Hispanic-Latino)*
Race-ethnicity	*Demographics (assessed at mBC diagnosis)*	*Race will be defined using the SEER Race Recode variable, and ethnicity will be defined using the SEER Origin Recode variable defined by the NAACCR Hispanic Identification Algorithm (NHIA) and categorized as follows:* • *American Indian/Alaska native/unknown* • *Hispanic* • *Non-Hispanic Asian or Pacific Islander* • *Non-Hispanic Black* • *Non-Hispanic White*

Variable	Role/objective	Definition

Marital status	*Demographics (assessed at mBC diagnosis)*	*Marital status will be categorized as follows:*
		• *Married*
		• *Not married*
		  ○ *Single (never married)*
		  ○ *Unmarried living with domestic partner*
		  ○ *Divorced*
		  ○ *Separated*
		  ○ *Widowed*
		• *Unknown*
		These categories may be further combined for statistical purposes as below:
		• *Single (never married)*
		• *Married/unmarried living with domestic partner*
		• *Divorced/separated/widowed*
		• *Unknown*

Geographic region	*Demographics (assessed at mBC diagnosis)*	*The geographic region of patients' county of residence will be defined according to the rural-urban continuum code (version year 2013) and categorized as follows:* • ***Big metro:*** *Counties in metropolitan areas ≥ 1 million population* • ***Metro:*** *Counties in metropolitan areas of 250,000 to 1 million population* • ***Urban:*** *Counties in metropolitan areas of < 250,000 population* • ***Less urban:*** *Nonmetropolitan counties adjacent to a metropolitan area* • ***Rural:*** *Nonmetropolitan counties not adjacent to a metropolitan area* *These categories may be further combined for statistical purposes as below:* • *Large urban (big metro and metro areas)* • *Small urban (urban and less urban areas)* • *Rural*

Variable	Role/objective	Definition
Household income	*Demographics (assessed using the latest available ACS data: 2008-2012)*	*The median household income based on patients' census tract of residence will be defined according to American Community Survey data (2008-2012). Data will be categorized using quartile distribution as follows:* • *Quartile 1 (e.g., < $55,000)* • *Quartile 2 (e.g., $55,000-$64,999)* • *Quartile 3 (e.g., $65,000-$74,999)* • *Quartile 4 (e.g., $75,000+)* • *Missing/unknown*
LIS coverage	*Demographics (assessed during 6 months before index date)*	*Patient's enrollment in an LIS plan during the 6-month baseline period will be assessed and summarized as a binary variable:* • *Any LIS coverage* • *No LIS coverage*
Medicaid (dual) eligibility	*Demographics (assessed as available in the data at mBC diagnosis or treatment)* *[Not to be used in propensity score model]*	*Medicare with Medicaid (dual) eligibility status will be summarized according to primary payer/insurance carrier at the time of initial diagnosis and/or treatment at the reporting facility:* • *Medicaid* • *No Medicaid*

1L = first line; ACS = American Community Survey; AI = aromatase inhibitor; HCPCS = Healthcare Common Procedure Coding System; LIS = low-income subsidy; mBC = metastatic breast cancer; N/A = not applicable; NAACCR = North American Association of Central Cancer Registries; NCI = National Cancer Institute; NCICI = NCI Comorbidity Index; NHIA = NAACCR Hispanic Identification Algorithm; SEER = Surveillance, Epidemiology, and End Results.

6 HANDLING OF MISSING VALUES

No imputation for missing values will be performed. Number and percentage of patients with missing data on all key study measures will be reported.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Means with standard deviations, medians with interquartile range, and min/max values will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Baseline patient demographics (e.g., age, race, marital status) and clinical characteristics (e.g., metastatic sites, NCICI) will be descriptively analyzed and reported. Unadjusted and/or weighted Kaplan-Meier curves will be drawn to illustrate time-to-event endpoints.

All analyses will be performed separately for the primary and exploratory objectives described in Section 2.2, and any computations and generation of tables, listings, and data for figures will be conducted using SAS statistical software, version 9.4 or later (SAS Institute; Cary, North Carolina).

7.2 STATISTICAL ANALYSES

7.3 ANALYSES FOR PRIMARY OBJECTIVE

For the primary objective, the association between primary independent variable (treatment type: palbociclib + AI or AI alone) and the outcome variable (OS) will be assessed using unadjusted Kaplan-Meier analysis and multivariable methods. The primary method of analysis to account for observed confounders will be stabilized inverse probability of treatment weighting (sIPTW). Additionally, as sensitivity analyses, multivariable Cox proportional hazards (CPH) regression and propensity score matching (PSM) will be performed. *Both IPTW and PSM are propensity score (PS)-based methods commonly used to achieve balance between treatment and control groups in retrospective cohort study designs.* All methods are described below in detail.

Kaplan-Meier Analysis

Time-to-event outcome (i.e., OS) will be described using unadjusted Kaplan-Meier analyses; median time-to-event (in months) and landmark probabilities of event at various timepoints (e.g., 12 months, 24 months) will be estimated, along with 95% CIs and log-rank *P* values. Graphical displays of the data will also be generated as appropriate. Kaplan-Meier analysis may also be performed using the stabilized weights or among the PS-matched groups (see details in this section below), and the weighted or PS-matched survival curves may be drawn.

Cox Proportional Hazards Regression

The CPH regression model may be used to estimate a hazard ratio of the OS, along with 95% CI, for the primary exposure—a dichotomous variable indicating whether the patient received AI + palbociclib versus AI alone—and for each of the control variables included in the model, indicating higher or lower rate of death (relative to a reference category) at any given point in time after the index date. The patient demographic and clinical characteristics that will be considered for confounding adjustment in the model are described earlier in Table 5-2.

Propensity Score Estimation

As the first step in implementation of PS-based methods (IPTW and PSM), the PS (i.e., the estimated probability of treatment assignment) will be obtained from a logistic regression model where the treatment assignment (treatment vs. control) will be regressed on a set of covariates or confounders. The baseline covariates or control variables that will be considered for adjustment in the multivariable logistic regression for deriving treatment probabilities (i.e., PSs for IPTW and PSM) are described earlier in Table 5-2. The following variables will be included in the model: age group, race, year of mBC diagnosis, marital status, geographic status of residence, median household income, LIS coverage, tumor grade at initial diagnosis, involvement of metastatic sites at initial diagnosis (bone, brain, liver, and lung as independent binary variables), and NCICI score category. If any covariates are identified to have missing data, they may be coded as "missing" or "unknown" and included as categorical variables in the model.

Covariate Balancing

The following process will be implemented to determine whether there is sufficient overlap between the patient populations of the 2 treatment cohorts:

- Compute the standardized mean difference in PS for each level of each baseline covariate
- Graphically assess differences in the full distribution of each covariate between 2 treatment cohorts
- An absolute standardized mean difference < 0.1 indicates negligible difference and is considered a good balance

Covariate balance will be examined using both IPTW and PSM techniques as described below. Subsequently, depending on the quality of balance, the endpoint (OS) may be assessed using one or both techniques (Austin, 2014; Buchanan et al., 2014).

IPTW: The general approach for an IPTW analysis involves calculating the inverse probability weights and then using these weights to estimate the treatment effect. The IPTW for each patient is the inverse of their PS for their respective treatment group. For exposed individuals, the weight is 1/PS, and for unexposed individuals, it is 1/(1 − PS). The treatment weights derived from the PSs might be large because patients receiving palbociclib + AI treatment may have PSs closer to 0, while patients receiving AI monotherapy may have scores closer to 1. Consequently, extreme weights and inflated variance can occur. To mitigate this potential problem, we will calculate sIPTW, as suggested by Pezzi et al. (2016), Xu et al. (2010), and Shiba and Kawahara (2021). By employing sIPTW, the point estimates of the treatment effect will remain unaffected compared with unstabilized weights while leading to a more accurate estimation of the variance. Once the stabilized inverse probability weights are calculated for each individual, they will be used to estimate the average treatment effect by comparing the weighted outcomes between the treatment (palbociclib + AI) and control (AI alone) groups. For Kaplan-Meier analysis, sIPTW will be applied to assess weighted median OS and 95% CI; weighted survival curves will be drawn and weighted landmark probabilities of event at various timepoints will be estimated (e.g., 12 months and 24 months). For assessing weighted estimate of hazard ratio for the treatment type (AI + palbociclib vs. AI alone), sIPTW will be applied to the Cox proportional hazards model. Variance will be estimated using robust variance estimation method to account for the weighted nature of the data. Point estimate (i.e., hazard ratio) will be derived along with 95% CI; any covariates with residual imbalance may be adjusted for in this step.

PSM: In the PSM technique, each patient in the palbociclib +AI cohort will be matched to a patient in the AI alone cohort using a 1-to-1 matching with no replacement, using the nearest neighbor method to match by closest propensity scores (with a caliper of 0.01). As described above, median OS, landmark probabilities of event at various timepoints, and 95% CI for the matched cohorts will be assessed, and the hazard ratio will be assessed using the univariate CPH model. To plot survival functions and to test for differences between AI + palbociclib and AI alone, the Kaplan-Meier estimator will be used. Given the matched nature of the study cohorts, the CPH analysis will use a robust variance estimator to account for the clustering within paired sets.

All patients will be followed from the start of therapy line through the earliest of the following: death; disenrollment from Medicare Parts A, B, or D; enrollment in an HMO plan; or end of the study database (31 December 2020). Section 7.6 discusses potential sensitivity analyses (e.g., adjusting for subsequent treatments received).

7.4 ANALYSES FOR EXPLORATORY OBJECTIVES

Exploratory study measures CCI [redacted]

[redacted]

7.5 SUBGROUP ANALYSES

Further, to help better explain the results and to generate additional contextual data, subgroup assessments may be performed according to age groups, race/ethnicity, comorbidity score, metastatic sites, dual Medicare/Medicaid eligibility, and other patient characteristics as appropriate and based on availability of the data and adequate sample sizes.

7.6 SENSITIVITY ANALYSES

To test for the robustness of the results for the primary objective, sensitivity analyses will be performed using multivariable CPH analysis and PSM as described earlier in Section 7.3. *Another sensitivity analysis may be performed for a subset of patients who initiated their 1L therapy within 3 months of de novo mBC diagnosis (vs. within 6 months of diagnosis as planned for the main analysis). Additionally, a sensitivity analysis may be considered to adjust for subsequent treatment with CDK4/6 inhibitors using methods such as the Rank Preserving Structural Failure Time (RPSFT) (Robins et al., 1991). Further, considering that the information on patients vital status is up to date and complete as of the end of study period (Dec 2020), the definition of the end of study follow-up may be revisited to disregard the criteria of continuous enrollment in Medicare Parts A, B, and D and enrollment in an HMO; consequently, a sensitivity analysis may be performed to examine if changing this definition has any effect on the OS endpoint.*

In the sensitivity analysis involving adjustment for patients on AI monotherapy who switch to palbociclib + AI combination, the following strategies may be considered (Kang et al., 2022):

- **Estimand strategy:** Take the hypothetical strategy for the intercurrent event of "treatment switch" as if subsequent treatment with CDK4/6 inhibitors in the AI monotherapy cohort during any time of the observation period had not occurred.
- **Intercurrent events:** All data will be used regardless of the occurrence of intercurrent events (concomitant or subsequent treatments) except for the use of CDK4/6 inhibitors in the AI monotherapy cohort as a subsequent treatment.
- **Population-level summary:** Summary of OS adjusting for subsequent CDK4/6 inhibitors will be provided. After RPSFT, primary analyses will be repeated with modified survival times for the patients who switched from AI monotherapy to palbociclib + AI combination.

7.7 SAFETY ANALYSES

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

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9 APPENDICES

9.1 APPENDIX 1: RULES FOR DEFINING CHANGE IN THERAPY LINE

Condition	*Rule*
Switch to a completely new agent or combination of agents	*Change in therapy line*
Switching between CDK4/6 inhibitors (e.g., palbociclib to ribociclib or abemaciclib)	*Change in therapy line*
Therapy suspended for greater than 90 days	*Change in therapy line*
*Addition of a new agent to an existing treatment regimen**	*Change in therapy line*
Removal of an agent from a combination regimen	*Not a change in therapy line*
Exception to switching within the same treatment class	
Anastrozole to letrozole (or vice versa)	*Not a change in therapy line*
Anastrozole to exemestane (or vice versa)	*Not a change in therapy line*
Letrozole to exemestane (or vice versa)	*Not a change in therapy line*

CDK4/6 = cyclin-dependent kinase 4 and 6.

** A treatment regimen is defined as combination of all agents administered within a 30-day period from the date of initiation of the first agent, with the exception of CDK4/6 inhibitors, for which a 60-day period will be allowed to account for insurance coverage delays. Addition of a new agent after 30 days (or 60 days for CDK4/6 inhibitors) will be considered a change in therapy line. A given therapy line will be considered to have ended upon occurrence of the earliest of any of the following: switch to a new treatment regimen or a gap of more than 90 days in administration or refill of any of the first line regimen drugs.*

9.2 APPENDIX 2: LIST OF SYSTEMIC THERAPY AGENTS

Therapy agents	*HCPCS codes*
CDK4/6 inhibitors	
Palbociclib	*N/A*
Ribociclib	*N/A*
Abemaciclib	*N/A*
Aromatase inhibitors	
Anastrozole	*S0170*
Letrozole	*N/A*
Exemestane	*S0156*
Other hormonal therapy	
Fulvestrant	*J9393, J9394, J9395, C9120*
Tamoxifen	*S0187*
Toremifene	*N/A*
Kinase inhibitor	
Everolimus	*J7527, J8561*
Specific chemotherapy agents	
Doxorubicin (all forms)	*C9415, J9000, J9001, J9002, Q2048, Q2049, Q2050*
Epirubicin	*C1167, J9178, J9180*
Eribulin	*C9280, J9179*
Gemcitabine	*J9198, J9201*
Capecitabine	*J8520, J8521*
Docetaxel	*J9170, J9171*
Paclitaxel (all forms)	*C9127, C9431, J9264, J9265, J9267, J9259*
Cyclophosphamide	*C9420, C9087, C9421, J8530, J9070, J9071, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097*
Fluorouracil	*J9190*
Cisplatin	*C9418, J9060, J9062*
Carboplatin	*J9045*
Oxaliplatin	*C9205, J9263*
Methotrexate	*J8610, J9250, J9260*
Vinorelbine	*C9440, J9390*
Vinblastine	*J9360*

Therapy agents	*HCPCS codes*
Leuprolide	*C9430, J1950, J9217, J9218, J9219, J1952*
Irinotecan	*C9474, J9205, J9206*
Ixabepilone	*C9240, J9207*
Etoposide	*C9414, C9425, J8560, J9181, J9182*
Mitomycin	*C9432, J9280, J9290, J9291, J9281, C9064*
NOS chemotherapy agent	*J8999, J9999*
Other targeted therapies	
Olaparib	*N/A*
Alpelisib	*N/A*
Lapatinib	*N/A*
Tucatinib	*N/A*
Neratinib	*N/A*
Larotrectinib	*N/A*
Entrectinib	*N/A*
Talazoparib	*N/A*
Trastuzumab (all forms)	*C9131, J9316, J9354, J9355, J9356, J9358, Q5112, Q5113, Q5114, Q5116, Q5117*
Pertuzumab	*C9292, J9306, J9316*
Bevacizumab	*Q2024, C9257, C9214, Q5118, Q5107, C9142, Q5126, Q5129, S0116, J9035*
Pembrolizumab	*C9027, J9271*
Atezolizumab	*C9483, J9022*
Sacituzumab	*C9066, J9317*
Nivolumab	*C9453, J9299, J9298*

CDK4/6 = cyclin-dependent kinase 4 and 6; HCPCS = Healthcare Common Procedure Coding System; N/A = not available; NOS = not otherwise specified.

Note: All treatments will be identified using a combination of HCPCS codes and the generic drug names in the Medicare Prescription Drug Event file that are linked to corresponding National Drug Codes assigned to each drug. Treatments with no applicable HCPCS codes will only be identified using generic drug names.