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)

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Study Information

Title	Assessment of overall survival in Medicare patients with HR+/HER2− metastatic breast cancer treated with palbociclib
Protocol number	A5481182
Protocol version identifier	1.0
Date	Version 1.0: 6 September 2023
Active substance	Palbociclib
Medicinal product	Ibrance
Research question and objectives	The primary objective of this study is: • To compare overall survival (OS) of first-line palbociclib + aromatase inhibitor (AI) versus AI alone for women or men with HR+/HER2− de novo metastatic breast cancer (mBC) in the SEER-Medicare data
Authors	**RTI Health Solutions:**  **Pfizer:**  *Please refer to Section 3 Responsible Parties for detailed author affiliation and contact details.*

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2 LIST OF ABBREVIATIONS

Abbreviation	Term
1L	first line
2L	second line
ACS	American Community Survey
AI	aromatase inhibitor
AJCC	American Joint Committee on Cancer
CDK4/6	cyclin-dependent kinase 4 and 6
CFR	Code of Federal Regulations
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
HER2–	human epidermal growth factor receptor 2–negative
HMO	health maintenance organization
HR+	hormone receptor–positive
IEC	independent ethics committee
IPTW	inverse probability of treatment weighting
IRB	institutional review board
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	National Cancer Institute Comorbidity Index
NHIA	NAACCR Hispanic Identification Algorithm
NOS	not otherwise specified
OQ	Office of Quality
OS	overall survival

Abbreviation	Term
CCI [redacted]	
PR	progesterone receptor
PS	propensity score
PSM	propensity score matching
RPSFT	Rank Preserving Structural Failure Time
RTI-HS	RTI Health Solutions
SEER	Surveillance, Epidemiology, and End Results
sIPTW	stabilized inverse probability of treatment weighting
SSA	Social Security Administration
CCI [redacted]	
US	United States

[redacted]

3 RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job title	Affiliation	Address
PPD			

4 ABSTRACT

Not applicable.

5 AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason

6 MILESTONES

Milestone	Planned date/anticipated timeline
Kickoff meeting	3 May 2023
Acquire study data	Quarter 3, 2023
Final study protocol	Quarter 3, 2023
Data analysis	Quarter 2, 2024
Prepare study report	Quarter 4, 2024

7 RATIONALE AND BACKGROUND

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, 39.7 vs. 29.7 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 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 9.4.

8 OBJECTIVES AND RESEARCH QUESTIONS

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

9 RESEARCH METHODS

9.1 Study Design

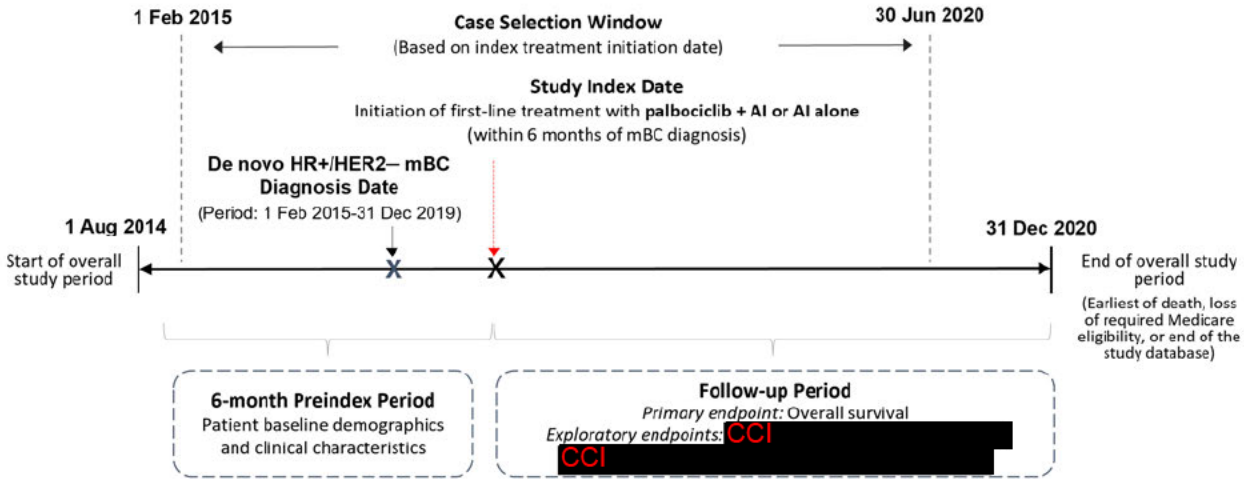
This study will encompass a retrospective cohort analysis using clinical and administrative claims data from the linked SEER-Medicare database (providing SEER data are available through 2019 and linked Medicare claims are available through 2020) for patients with diagnosis of HR+/HER2− mBC at initial 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 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 (index period):** 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 an index date in February 2015) through 31 December 2020 (accounting for a minimum 6 months of potential follow-up for any patient with an index date in June 2020).

Figure 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.

9.2 Setting

9.2.1 Inclusion Criteria

The following inclusion criteria will be applied:

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 estrogen receptor [ER]/progesterone receptor [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.

9.2.2 Exclusion Criteria

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

9.3 Variables

All relevant study variables will be gathered or calculated from raw variables contained in the SEER-Medicare database. The following sections list and define the anticipated key analysis variables that will be collected or created from the study database. For covariates, categories may be further combined if appropriate for statistical purposes.

Table 1. Study Outcomes and Stratification Variables with Associated Definitions

Variable name	Type	Definition/categories
Outcome variables		
Overall survival	Outcome (primary objective)	Time in months from the study index date to all-cause death
CCI		

Variable name	Type	Definition/categories
CCI [redacted]		
Time to chemotherapy	Outcome (exploratory objective)	Time in months from the study index date to first initiation of chemotherapy in any subsequent therapy lines
Exposure variable		
1L Treatment type	Exposure (primary objective)	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 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

Variable name	Type	Definition/categories
		defining "treatment switch to a new regimen" are presented in Annex 2.
Subsequent treatment	Exposure (exploratory objective)	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 or 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.
National Cancer Institute's (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 • $0 < \text{Score} \leq 1$ • Score > 1 The specific comorbidities represented in the NCICI include the following: • Acute myocardial infarction

Variable name	Type	Definition/categories
		• 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 (categories may be collapsed based on final sample size): • 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 name	Type	Definition/categories
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

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

Variable name	Type	Definition/categories
		○ 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 name	Type	Definition/categories
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)	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; 2L = second line; ACS = American Community Survey; AI = aromatase inhibitor; CDK4/6 = cyclin-dependent kinase 4 and 6; 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; CCI [redacted]; SEER = Surveillance, Epidemiology, and End Results; CCI [redacted].

9.4 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, ER status, 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 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).

9.5 Study Size

Because the sample size available for analysis is dictated by eligible patients available in the study database, no formal sample size estimations were performed.

9.6 Data Management

The analyses described in this proposal will be performed using a SAS statistical software application housed on a secure, large-capacity, high-performance Linux mainframe. Experienced programmers and analysts at RTI Health Solutions (RTI-HS) will perform all analyses. To ensure the integrity and quality of the study results, we will follow a programming validation life cycle process for all analyses. This includes quality-checking programs, logs, and output for accuracy according to relevant standard operating procedures. Because this secondary data analysis will use structured data only, no further human review of the raw data is planned.

To ensure the integrity and quality of study results, RTI-HS implements several practice standards for statistical programming, database management, and documentation for all projects involving databases analyses. The following 3 steps will be undertaken to achieve this high level of quality:

- Documentation of SAS programming
- Validation of SAS programs
- Database storage and retention

9.6.1 Documentation of SAS Programming

To ensure smooth transitions of analytic methods and work among programmers, reviewers, and other project personnel, documentation of the following information will be created for each SAS program:

- Project name
- Program name
- Program purpose
- Program author
- Date the program was completed
- Descriptions of subsequent changes and/or enhancements, with name of programmer and date for each

This information will be incorporated into each program in the form of a header. In addition to documenting this information in a general program header, each program will include detailed comments throughout to describe the purpose and method of specific programming statements.

9.6.2 Validation of SAS Programs

RTI-HS employs a variety of programming validation methods, including log review, review of data listings, and independent programming (if needed to validate any complex coding), which will be used to ensure that our SAS programs function as intended. The validation methods described in this section are not exhaustive, and additional measures will be implemented as appropriate.

9.6.3 Log Review

Programmers will review all SAS log files. This procedure is a widely accepted, basic level of program validation. The following issues must be addressed as part of a log review:

- No errors should appear in a log file.
- If warning messages or messages related to uninitialized variables are permitted in the log file, the programmer will document why they are permitted.
- The programmer will account for the number of observations reported at each executed data step, especially when the number of observations increases or decreases.
- The log file will contain all lines of the program as it was saved at the time of execution, and it will contain only those lines of code.

9.6.4 Review of Data Listings and Tables of Summary Statistics

Because an error-free log file does not necessarily demonstrate that a SAS program has functioned as intended, programmers will produce cell frequencies, means, and other summary statistics on specific data items to demonstrate that the program results are valid. Where appropriate, we will also have a separate analyst review these listings independent of the programmer.

9.6.5 Validation Documentation

For each SAS program used to produce final study outputs for presentation, RTI-HS will complete and store a formal SAS validation document.

9.6.6 Database Storage and Retention

RTI-HS will store in a secure location all copies of the original data files, as applicable. Data files stored on CD, DVD, or other media will be kept in a locked storage unit. Original data files will be transferred from media disks to dedicated project space on a Linux server. To ensure the integrity of the original files, they will be stored on our Linux server in a designated folder that cannot be overwritten. Data sets derived from the original files during the data cleaning process will be stored in a separate folder.

After project completion, all data sets (either raw or derived) used in this project will be retained for a period of at least 5 years, unless specific Pfizer protocols explicitly prohibit this. If any data cleaning activities or other analyses need to be repeated for any reason, this retention procedure will allow quick and efficient access to the data sets.

9.7 Data Analyses

All analyses, including 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).

Baseline patient demographics (e.g., age, race, marital status) and clinical characteristics (e.g., metastatic sites, NCICI) will be descriptively analyzed and reported. Means with standard deviations, medians with interquartile range, and minimum/maximum 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.

9.7.1 Analyses of the 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 an appropriate multivariable method. The primary method of analysis will be determined following an assessment of the balance in baseline characteristics between the 2 treatment groups. Specifically, we would explore the following methods: 1) multivariable Cox proportional hazards regression, 2) the inverse probability of treatment weighting (IPTW), and 3) propensity score matching (PSM). 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. The baseline covariates or control variables that will be considered for adjustment in the multivariable Cox proportional hazards (CPH) regression and in logistic regression for deriving treatment probabilities (i.e., PSs for IPTW and PSM) are described earlier in Table 1. The multivariable CPH model will generate a hazard ratio, along with 95% CI, for each of the covariates included in the model, indicating higher or lower rate of death (relative to a reference category) at any given point in time following the index date. The final lists of variables to be used in the model will be discussed and determined during analysis development and will be recorded in the SAP prior to final analysis.

The general approach for an IPTW analysis involves calculating the inverse probability weights and then using these weights to estimate the treatment effect. As the first step, 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 treatment weights derived from the PS might exhibit instability due to the fact that patients receiving palbociclib + AI treatment could have PS closer to 0, while patients receiving AI monotherapy might have scores closer to 1. Consequently, extreme weights and inflated variance can occur. To mitigate this potential problem, we will calculate stabilized IPTW (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, but it can lead 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.

In the PSM technique, each subject in the palbociclib + AI cohort will be matched to a subject in the AI alone cohort using a 1-to-1 matching with no replacement, using the nearest neighbor matching algorithm with potential use of a caliper (no larger than 0.1 standard deviation).

Covariate balance will be examined before any adjustment for the PS and after adjusting for the PS (using both sIPTW and PSM techniques). If no significant differences are observed among all baseline measures between the treatment groups, the treatment effect that is calculated from the 2 methods based on the weighted and matched population can be considered to be the true effect. Subsequently, depending on the quality of balance, the endpoint (OS) may be assessed using one or both techniques, in addition to the multivariable CPH regression analysis (Austin, 2014; Buchanan et al., 2014).

For the assessment of OS, Kaplan-Meier analysis may also be performed using the stabilized weights or among the PS matched groups, and the weighted or PS-matched survival curves may be drawn. Subsequently, Cox regression analysis may be performed using the stabilized weights or among the PS-matched groups. Point estimate (i.e., hazard ratio) will be derived, as applicable, along with 95% CI and *P* value using robust variance estimation. Any covariates with residual imbalance may be adjusted for in this step.

All patients will be followed from the start of therapy line through death or the end of available study follow-up, whichever is earliest. Section 9.7.3 discusses potential sensitivity analyses; e.g., adjusting for subsequent treatments received.

9.7.2 Analyses for Exploratory Objectives

Exploratory study measures CCI [redacted]

9.7.3 Sensitivity and Subgroup Analyses

To test for the robustness of the results for the primary objective, sensitivity analyses will be performed, which may involve reanalysis of the data using an alternate methodology to that employed in the primary method of analysis. For instance, after the assessment of quality of covariate balance, if multivariable Cox regression is determined to be the suitable method for primary analysis, PS-based analysis (IPTW or PSM or both) may be performed as sensitivity analysis to test the difference in OS between the treatment groups (refer to Section 9.7.1 for details on the 3 methods under consideration). 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). 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.

Further, to help better explain the results and to generate additional contextual data, subgroup analyses may be performed as appropriate. As exploratory analyses, these subgroups may include age groups, metastatic sites, and other patient characteristics as appropriate (e.g., race/ethnicity, NCICI score, dual Medicare/Medicaid eligibility), and the analyses will be conducted based on availability of the data and adequate sample sizes.

9.8 Quality Control

RTI-HS and its staff strive to meet the highest standards of professional performance and continuously improve our products and services. To ensure quality, we work with our clients to define requirements and clarify expectations, and we pledge that our products and services will comply with these requirements, meet or exceed client expectations, and deliver exceptional value.

The RTI-HS Office of Quality (OQ) is an independent unit that reports to the Vice President of RTI-HS and provides training on applicable regulations and guidelines, implements and maintains a series of standard operating procedures, and provides quality assurance monitoring for compliance with regulatory requirements.

RTI-HS will work closely with selected subcontractors, if applicable, to establish and ensure a complete integration of procedures for the project. The OQ will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation. Audits are conducted by the OQ according to established criteria in standard operating procedures and other applicable procedures. The OQ reports quality assurance observations to the project director and facilitates corrective actions, if necessary.

9.9 Strengths and Limitations of Research Methods

This study is based on the analysis of the SEER-Medicare database—a database with a diverse array of demographic and clinical information on patients with incident diagnosis of cancer in the Medicare population in the US who are generally 65 years or older. The linkage of Medicare claims data with SEER registry data provides confirmatory data on cancer diagnoses along with precise dates, which in turn make it possible to attribute treatments as specific lines of therapy in alignment with their approved indications and guideline recommendations; this substantially minimizes the risk of misclassification—an inherent limitation in many other commonly used population-based administrative claims data sources in the US. The availability of up-to-date validated vital statistics data, as described in Section 9.4, further makes the database a unique and authoritative data resource for evaluation of survival outcomes in older patients with cancer, especially those represented in the US Medicare population.

There are certain limitations that are typically inherent in studies based on secondary data sources and are applicable to this current study as well:

- Patients are not randomized to treatment and control groups, and as such, the lack of random assignment may lead to selection bias. We plan to adjust for differences in baseline characteristics and risk factors that are observable in the database, but imbalances in many unobserved characteristics (e.g., performance status, laboratory test results, genetic mutations) may introduce unmeasured confounding.
- The US-labelled indication for palbociclib includes patients who were initially diagnosed at an earlier stage but later progressed to have advanced or metastatic disease; however, this analysis will be restricted to patients with de novo metastatic disease given limitation of the data source. This could potentially limit the generalizability of study findings beyond patients who are not diagnosed at the metastatic stage, but would be an appropriate approach in consideration of the fact that SEER does not collect information about progression or recurrences, and proxy methods to identify recurrences in the SEER-Medicare database are shown to have low sensitivity and specificity, especially among older patients (Hassett et al., 2014; Warren et al., 2016).
- Patients on Medicare Advantage or HMO plans cannot be analyzed because Medicare data do not contain comprehensive claims records for these patients, who make up 32% to 42% of the Medicare population, with higher uptake in certain geographic regions, potentially affecting generalizability of our findings.
- The planned survival analysis will be based on an intent-to-treat approach, regardless of changes to their exposure status during the follow-up, which may influence the survival outcome.
- Because the treatment regimens will be defined using a claims-based algorithm, it is reasonable to assume some risk of misclassification—even though the algorithm rules will be drawn from previously published methods.

The SEER-Medicare database used for this study, however, remains a unique—and the most authoritative—data source to examine survival outcomes in older patients with diagnosis of cancer at the US Medicare population level.

9.10 Other Aspects

Not Applicable.

10 PROTECTION OF HUMAN SUBJECTS

This study will be subjected to a project-level evaluation by the institutional review board (IRB) at RTI International, of which RTI-HS is a business unit. RTI International holds a Federal-Wide Assurance (#3331) from the Department of Health and Human Services' Office for Human Research Protections that allows us to review and approve human subjects protocols through these IRB

committees. The IRB has been audited by the Food and Drug Administration and is fully compliant with applicable regulatory requirements. The committee reviews research studies to ensure adherence to appropriate regulations that govern human subjects research, including 45 CFR 46 and 21 CFR 50 and 56, and to all applicable Helsinki Declarations and provisions of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. All studies involving human subjects undergo a continuing IRB review at least once per year. Depending on the level of risk and nature of the research, a study may be ruled as exempt from IRB review by an IRB chair or designated IRB member. Studies that are not exempt must be approved either by an IRB chair or designated IRB member (if the study qualifies for expedited review) or by a full IRB committee. Because this study involves use of existing, secondary data with no more than minimal risk to the patient, a waiver of informed consent will be requested.

10.1 Patient Information

Because the data used in this study are deidentified and anonymous, this study poses minimal risk to patients whose medical data are analyzed.

10.2 Patient Consent

Not applicable.

10.3 Patient Withdrawal

Not applicable.

10.4 Institutional Review Board/Independent Ethics Committee

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms, if applicable) from the relevant IRBs or independent ethics committees (IECs). All correspondence with the IRB or IEC must be retained. Copies of IRB or IEC approvals must be forwarded to Pfizer.

10.5 Ethical Conduct of the Study

Not applicable.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Upon study completion and finalization of the study report, the results of this noninterventional study will be submitted for publication (abstract, manuscript, or both). Publications will comply with internal Pfizer standards and the recommendations of the International Committee of Medical Journal Editors.

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ANNEX 1. LIST OF STANDALONE DOCUMENTS

Not applicable.

ANNEX 2. ADDITIONAL INFORMATION

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

1L = first 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 1L regimen drugs.

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

Therapy agents	**HCPCS codes**
Oxaliplatin	C9205, J9263
Methotrexate	J8610, J9250, J9260
Vinorelbine	C9440, J9390
Vinblastine	J9360
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.