NONINTERVENTIONAL STUDY PROTOCOL

Title	Retrospective Assessment of Treatment Patterns and Outcomes Associated with Palbociclib in Combination With Letrozole in Postmenopausal Women With HR+/HER2– Advanced Breast Cancer
Protocol number	A5481064
Protocol version identifier	Version 1.0
Date of last version of protocol	02 June 2016
EU Post Authorisation Study (PAS) register number	Study Not Registered
Active substance	Palbociclib (L01XE33)
Medicinal product	IBRANCE (Palbociclib)
Research question and objectives	The aim of this study is to describe the patient and clinical characteristics, treatment patterns, and clinical outcomes of patients who received palbociclib plus letrozole for the treatment of hormone receptor–positive/human epidermal growth factor receptor 2–negative metastatic breast cancer as part of an expanded access program (EAP). More specifically, data from a medical record review will be used to address the following objectives: ▪ Describe the demographic and clinical characteristics of patients. ▪ Evaluate treatment patterns, including safety of treatment with palbociclib plus letrozole (duration of therapy, cycle delays or dose interruptions, , dose reductions and discontinuation of palbociclib) including reasons for these treatment events to the

	extent documented in the charts, ▪ Receipt of supportive care medications while receiving palbociclib plus letrozole, and additional therapies received for metastatic breast cancer before and after palbociclib plus letrozole.. ▪ Assess palbociclib plus letrozole outcomes, including progression-free survival, overall survival, and objective response rate, and ▪ Assess healthcare resource utilization including hospitalizations and reasons for hospitalization to the extent documented in the charts
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
A+A	A+A Research
AE	Adverse event
AEM	Adverse Event Monitoring
BMI	Body mass index
CRO	Contract Research Organization
DCF	Data collection form
EAP	Expanded access program
ER+	Estrogen receptor–positive
FDA	Food and Drug Administration
HER2–	Human epidermal growth factor receptor 2–negative
HR+	Hormone receptor–positive
IRB	Institutional review board
NIS	Noninterventional Study
OQA	Office of Quality Assurance
PgR+	Progesterone receptor–positive
Pfizer	Pfizer Inc.
PFS	Progression-free survival
RTI-HS	RTI Health Solutions
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
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3. ABSTRACT

Retrospective Assessment of Palbociclib in Combination With Letrozole in Postmenopausal Women With HR+/HER2– Metastatic Breast Cancer

Version 1.0 (24 April 2016)

Background: Breast cancer was diagnosed in approximately 1.7 million women worldwide in 2012, and nearly 522,000 deaths were recorded.[1] In the United States (US), it is estimated that 231,840 women were diagnosed with breast cancer and 40,290 women died from breast cancer in 2015.[2] Women with metastatic breast cancer ultimately experience disease progression on currently available therapies. The 5-year survival of women with metastatic breast cancer is estimated at 24%.[3]

Rationale: Because metastatic breast cancer is incurable with currently available therapies, there is an ongoing unmet need for new treatment strategies in this population. On February 3, 2015, the US Food and Drug Administration (FDA) granted accelerated approval to palbociclib (Ibrance, Pfizer Inc. [Pfizer]) for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor–positive (ER+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer as an initial endocrine-based therapy for their metastatic disease. The approval of palbociclib was based on a phase 2, randomized, multicenter, open-label trial (NCT00721409) in 165 postmenopausal women with ER+/HER2– advanced (locally advanced or metastatic) breast cancer who had not previously received systemic treatment for the advanced disease.[4] Median progression-free survival (PFS) was 20.2 months for the palbociclib-plus-letrozole group (hazard ratio 0.488, 95% confidence interval 0.391-0.48) compared to 10.2 months for the letrozole-only control group.[4] Following the primary efficacy study noted above, and noting rapid and full enrollment of the then ongoing phase 3 studies, Pfizer conducted an expanded access study (A5481034, NCT02142868), to provide access to palbociclib before it became commercially available However, shortly after the EAP began, palbociclib became commercially available, and patients who were still receiving palbociclib plus letrozole were switched to commercially available products and data collection was discontinued. Data from A5481034 were analyzed and reported separately and distinct from the current protocol and related analyses.

Objectives: The objective of the current study is to evaluate the treatment patterns and related outcomes among patients, who had started receiving palbociclib in combination with letrozole for the treatment of HR+/HER2– metastatic breast cancer as part of the EAP, including treatments received before and after participation in the EAP (A5481034). More specifically, the study aims to (1) describe the demographic and clinical characteristics of patients enrolled in the EAP; (2) evaluate safety of palbociclib plus letrozole (including treatment patterns, duration of treatment cycle delays or dose interruptions, dose reductions and discontinuation of palbociclib and reasons for these treatment events, if applicable to the extent documented in the charts, (3) receipt of supportive care medications while receiving palbociclib plus letrozole, and treatments received before and after palbociclib plus letrozole; (4) assess clinical outcomes with palbociclib plus letrozole, including PFS, overall survival, and objective response rate; and (4) resource utilization including hospitalization and reasons

for hospitalization to the extent documented in the charts in patients who had not received any treatment for metastatic breast cancer prior to palbociclib plus letrozole.

Study Design: Non-interventional, retrospective medical record review of patients with postmenopausal HR+/HER2− metastatic breast cancer who were previously enrolled in the EAP (A5481034) in the US.

Population: Centers located in the US who participated in Pfizer's palbociclib EAP will be eligible to retrospectively abstract data from medical records of patients, who had initially started receiving palbociclib plus letrozole for the treatment of HR+/HER2− metastatic breast cancer within the EAP program.

Variables: Patient and physician demographic characteristics, patient clinical characteristics, treatment patterns, PFS, overall survival, objective response rate, and resource utilization including hospitalization rates.

Data Sources: Data will be obtained from patients' medical records (secondary analysis of existing data). This study is a non-interventional retrospective study

Study Size: Study A5481034 included 18 sites. However, it is anticipated that some sites will not agree to participate in this medical record review study. Therefore, data collection will be conducted on a best-effort basis to obtain records for as many as 150 of the 238 EAP participants.

Data Analysis: All study variables will be descriptively analyzed using univariate statistics. Time-to-event outcomes (e.g., time to treatment start, treatment duration, PFS, overall survival) will be described using the Kaplan-Meier method.

Milestones: Key milestones include finalization of the protocol and data collection form (DCF) (May 2016), start of data collection (June 2016), start of data analysis (July 2016), final analytic results (September 2016), and the final study report (October 2016).

4. AMENDMENTS AND UPDATES

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

5. MILESTONES

Milestone	Planned Date
Feasibility (pilots)	June 2016
Final protocol and data collection form	June 2016
Start of data collection	June 2016
End of data collection (planned date on which the raw data set will be first available for analysis)	July 2016
Begin analysis	August 2016
Final analytic results	September 2016
Final study report	October 2016

6. RATIONALE AND BACKGROUND

Breast cancer was diagnosed in approximately 1.7 million women worldwide in 2012, and nearly 522,000 deaths were recorded.[1] The age-standardized incidence of breast cancer in the US is estimated to be 92.9 per 100,000. Age is the main predictor of breast cancer incidence among women. Between 2006 and 2010, approximately 79% of new cases of breast cancer and 88% of breast cancer deaths in the US occurred in women 50 years of age and older.[2] Metastatic breast cancer is incurable with current therapies, and 5-year survival is estimated at 24%.[3]

The presence or absence of hormone and epidermal growth factor receptors in breast tumors are important predictive and prognostic factors. Approximately 70% of invasive breast cancers are HR+ (e.g., ER+ and/or progesterone receptor−positive [PR+]),[4] which indicates the patient may respond well to endocrine therapy.

For postmenopausal women with locally advanced or metastatic HR+/HER2− breast cancer (in the absence of visceral crisis), systemic therapy is most often hormonal, usually consisting of (1) an aromatase inhibitor such as Femara (letrozole), Arimidex (anastrozole), or Aromasin (exemestane); (2) a selective estrogen receptor modulator such as Nolvadex (tamoxifen) or Fareston (toremifene); (3) a selective estrogen receptor down-regulator such as Faslodex (fulvestrant); or (4) a progestin such as Megace (megestrol acetate). Because postmenopausal women with metastatic HR+/HER2− breast cancer ultimately experience disease progression on currently available therapies, there is an ongoing unmet need in this population.

On February 3, 2015, the US FDA granted accelerated approval to palbociclib (Ibrance, Pfizer) for use in combination with letrozole for the treatment of postmenopausal women with HR+/HER2− advanced breast cancer as an initial endocrine-based therapy for their metastatic disease. The approval of palbociclib was based on a randomized, multicenter, open-label trial of palbociclib plus letrozole in 165 postmenopausal women with ER+/HER2− locally advanced or metastatic breast cancer who had not previously received systemic treatment for their advanced disease.[5] In this phase 2 trial, median PFS was 20.2 months for the palbociclib-plus-letrozole group compared to 10.2 months (hazard ratio 0.488, 95% confidence interval 0.391-0.48) for the letrozole-only control group.[5]

In addition to the primary efficacy study noted above, Pfizer also conducted an expanded access study (A5481034) of 238 patients in the US meeting similar inclusion criteria who may have also received prior systemic treatment for breast cancer in any setting. This EAP for palbociclib provided access to palbociclib before it became commercially available. However, shortly after the EAP began, palbociclib became commercially available, and the majority of patients in the palbociclib EAP who were enrolled in late 2014 and early 2015 and still on therapy at the end of the study were anticipated to be switched to commercial supply of the drug by mid-2015. Although patients continued on therapy with the commercially available drug, data collection was discontinued. A new research opportunity therefore exists to collect and analyze a longer term and broader scope of data on patients that initiated palbociclib and letrozole treatment as part of the EAP.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to assess the characteristics, treatment patterns, and clinical outcomes of patients who initially received palbociclib as part of an EAP for the treatment of HR+/HER2− metastatic breast cancer. In addition to providing details of patient treatment while in study A5481034, the study described herein will include information on the EAP enrollees before and after their participation in the EAP. The current study will provide Pfizer with an opportunity to collect supplemental information on the use of palbociclib plus letrozole as well as patterns of use of other therapies received before and after the EAP. Data from a medical record review will be used to address the following objectives:

- Describe the patient demographic and clinical characteristics of patients.
- Evaluate safety of treatment with palbociclib plus letrozole (including treatment patterns, dose reductions, delays and discontinuation in treatment) and the reasons for these treatment events to the extent documented in patients' charts
- Receipt of supportive care medications while receiving palbociclib plus letrozole, and prior and subsequent treatments.
- Assess outcomes associated with palbociclib, including PFS, overall survival, and objective response rate,
- Rates of resource utilization including hospitalization (and the reasons for hospitalizations to the extent documented in patients' charts) in a subgroup of patients who had not received any prior treatment for metastatic breast cancer prior to palbociclib plus letrozole.

8. RESEARCH METHODS

8.1. Study Design

To assess the study objectives described in Section 7, Pfizer's primary study Contract Research Organization (CRO) , RTI Health Solutions (RTI-HS), will conduct a non-interventional retrospective medical record review of the 238 patients (or a sample thereof) originally enrolled in the palbociclib EAP to capture demographic, clinical, and treatment data on each patient. A medical record abstraction will allow for the development of a customized DCF aimed at gathering detailed information tailored to address the specific objectives of this study.

Prior to initiation of data collection activities, RTI-HS, in consultation with Pfizer, will develop a customized DCF to capture detailed data on demographics; disease characteristics; and palbociclib-related treatment patterns, safety, and effectiveness from patients' medical records. The length of the DCF will be consistent with an abstraction time burden of approximately 30 minutes (not to exceed 60 minutes).

During the data collection phase, RTI-HS will recruit sites that participated in study A5481034 to abstract information from the medical records of eligible patients. Contact details for the EAP sites will be provided to RTI-HS by Pfizer for purposes of study recruitment. Pfizer will initiate communication with each of the participating EAP sites, informing them of the study, its goals and objectives, their roles and responsibilities as a participant, as well as introducing them to RTI-HS as the primary facilitator of data collection.

Once all materials have been finalized, and prior to initiating data collection, RTI-HS will obtain approval from one of RTI International's institutional review board (IRB) committees to proceed with the study. RTI-HS will notify Pfizer of any changes to the study design requested by the IRB. Upon receipt of consolidated comments from Pfizer, the RTI-HS team will update and finalize the protocol, which will then be resubmitted to Pfizer for final approval. If a participating site requires additional approval by his or her local IRB, RTI-HS will work in collaboration with him or her to develop and submit the necessary forms for this activity. Note, this study is not intended for regulatory submission purposes.

RTI-HS's subcontracted fieldwork partner, A+A Research (A+A) will be responsible for programming the DCF into a web-based tool and for deploying this to the sites. A+A is a research firm with 20 years of dedicated experience in medical and pharmaceutical research. A+A has offices in Lyons, Paris, London, and Algiers, and has conducted studies in more than 55 countries around the world. A+A has extensive experience conducting research in the field of oncology, particularly with retrospective medical record reviews in the US

If a site agrees to participate in the research, the delegated site staff will be contacted by A+A and directed to the secure website to complete the record abstractions for all eligible patients. Site staff will abstract and provide the de-identified patient record data through direct web-based data entry. It is anticipated that site staff recruited will abstract data for all patients who participated in the palbociclib EAP. A+A personnel will not have direct access to patient record nor will they be entering data into the web based form from any other source.

Key activities that will be implemented by A+A include programming of the DCF for use in a web-based application, administrating data collection via a secure web-based portal, and creating an analyzable data set for delivery to RTI-HS. A+A also will carry out the following activities pertaining to the data collection process:

- Review and comment on the DCF.
- Refine final questionnaire wording (to optimize response and to minimize time burden).
- Program the DCF for the A+A online portal.
- Conduct two pretests to gain direct physician feedback, followed by a debriefing with RTI-HS and Pfizer to enable a final revision of the DCF.
- Conduct all field work
- Construct, review, quality-check, and code open-ended answers in the data set.
- Deliver the final analysis data set.
- Provide central management to oversee all aforementioned tasks and provide weekly updates to RTI-HS and Pfizer.

8.2. Setting

18 sites throughout the US that participated and enrolled patients previously study A5481034 (see Table 1).

Table 1. Eligible Study Sites

Location	Site
1013	Baltimore, MD
1006	Pittsburgh, PA
1017	Vancouver, WA
1018	Bakersfield, CA
1001	Skokie, IL
1029	Seattle, WA
1034	Lake Success, NY
1011	Washington, DC
1009	Washington, DC
1041	Dallas, TX
1052	Jackson, MS

Location	Site
1036	Peoria, IL
1005	Memphis, TN
1027	Metairie, LA
1035	Fairfax, VA
1015	Lawrenceville, GA
1043	Houston, TX
1026	State College, PA

Data will be collected from the patient's initial diagnosis of breast cancer through the end of follow-up (April 30, 2016) or death, whichever occurred first. The study will be composed of the following three distinct study periods (see Figure 1):

(1) Period prior to enrollment in EAP (before September 2014): Beginning with the patient's initial diagnosis of breast cancer through the study index date (defined as enrollment date into the EAP)

(2) While Receiving Palbociclib plus Letrozole as part of EAP (Between September, 2014 and February 2015): Beginning with the patients' enrollment in the EAP (index date) through the patients' disenrollment in the EAP.

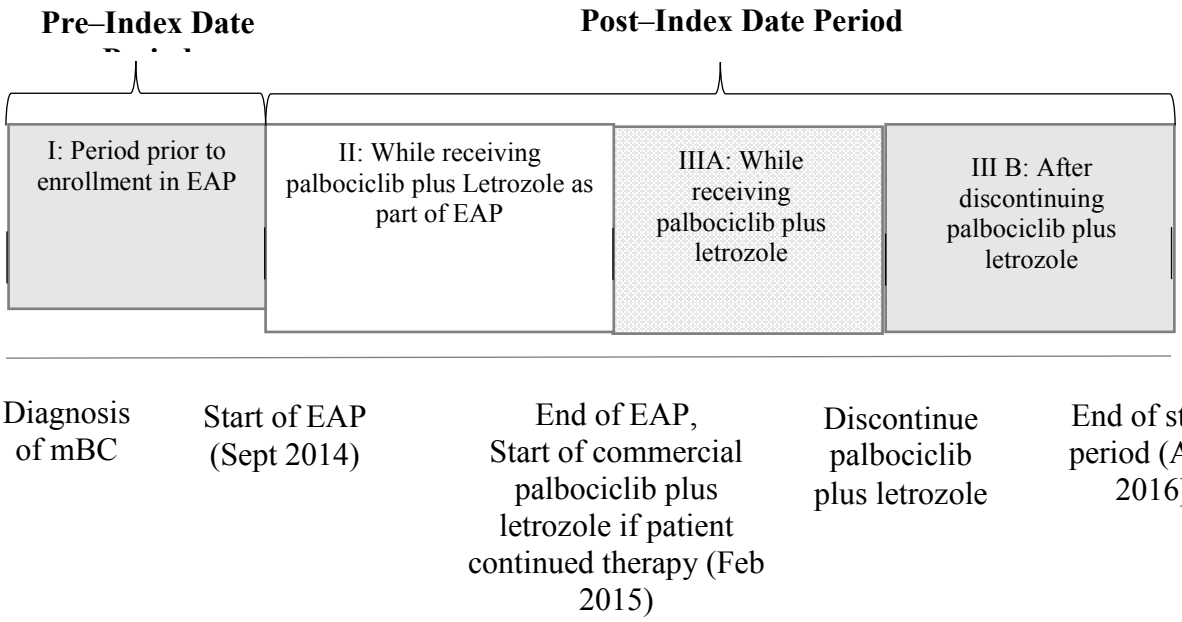
(3) Period following the EAP (Between February 2015 and April 2016): Beginning with the patient's disenrollment from the EAP through the end of follow-up or death, whichever occurs first. The post–EAP period may be composed of time periods on multiple therapies including those after discontinuation of palbociclib plus Letrozole.

   a. A period while the patient continued on commercially available palbociclib plus letrozole.

   b. A period after discontinuation of palbociclib plus letrozole.

Note, some patients could have discontinued palbociclib plus letrozole at the end of the EAP and never received commercially available supply of palbociclib.

Figure 1. Study Period



8.2.1. Inclusion Criteria

Medical records of patients who participated in the EAP (A5481034) will be eligible for abstraction. Therefore, all inclusion criteria used in the EAP will apply for the population selected into the present record review study.

8.2.2. Exclusion Criteria

Patient not enrolled in the EAP (A5481034) will be excluded from this study. Therefore, all exclusion criteria used in the EAP will apply for the population selected into the present record review study

8.3. Variables

All relevant study variables will be gathered using a web-based DCF. Many analysis variables will be directly available from the raw DCF responses, while others will require additional calculation based on combinations of the raw variables. The following sections list and define the anticipated analysis variables that will be collected or created from the DCF responses during the specified study period.

8.3.1.1. Period Prior to Enrollment in EAPSite Characteristics

Characteristics of the sites participating in the study will be obtained, including the following:

- Practice setting (e.g., teaching hospital, nonteaching hospital, community practice).
- Number of patients with metastatic breast cancer treated during the past year.
- Geographic location (e.g., Northeast, Midwest, South, and West).

8.3.1.2. Patient Characteristics

Demographic characteristics of the patients will be abstracted directly from the medical record, including the following:

- Patient vital status (i.e., alive or dead) at the medical record abstraction date.
- Race (i.e., White, Black, Asian, other).
- Ethnicity (i.e., Hispanic/Latino, not Hispanic Latino).
- Date of birth.
- Height (for calculation of body mass index [BMI]).
- Weight (for calculation of BMI) at start of EAP.
- Insurance plan type (i.e., commercial/private, Medicare, other) at end of EAP.

Derived variables will include the following:

- Age at metastatic diagnosis among all patients, calculated as the difference between date of birth and the date of metastatic diagnosis.
- BMI at start of EAP, calculated as weight (in pounds) multiplied by 703 and divide by height (in inches) squared.

8.3.1.3. Baseline Clinical Characteristics

A number of clinical characteristics that describe patients' disease state will be collected and reported. Variables abstracted directly from the medical record will include the following:

- Date of initial diagnosis of breast cancer.
- Clinical stage at initial diagnosis of breast cancer (i.e., local, regional, or advanced).
- Grade at initial breast cancer diagnosis.
- ER status (i.e., positive or negative).
- PgR status (i.e., positive or negative).
- Date of diagnosis of metastatic breast cancer.
- Sites(s) of distant metastases (e.g., adrenal gland, bone, brain) at initial metastatic breast cancer diagnosis.
- Additional sites(s) of distant metastases (e.g., adrenal gland, bone, brain) at time of treatment initiation with palbociclib plus letrozole.
- Patient's performance status, as scored by the physician, at (or nearest to) the date of metastatic diagnosis using the Eastern Cooperative Oncology Group scale.
- Patient's performance status, as scored by the physician, at (or nearest to) time of treatment initiation with palbociclib plus letrozole.

Derived variables will include the following:

- Time from initial diagnosis to diagnosis of metastatic disease, calculated in months, for all patients regardless of whether or not they were diagnosed at early or later stage

8.3.1.4. Comorbidities and Risk Factors

Data on patients' comorbidities and other risk factors will be collected and reported. Variables abstracted directly from the medical record will include the following:

- Presence of comorbidities included in the Charlson Comorbidity Index (except malignancies) and other breast cancer related comorbidities at index date.
- Smoking status (i.e., current smoker, former smoker, nonsmoker, and don't know).

Derived variables will include the following:

- Charlson Comorbidity Index[6]

8.3.1.5. Prior Treatments for Metastatic Breast Cancer

Treatment patterns associated with metastatic breast cancer from the time of patients' diagnosis of metastatic breast cancer until enrollment in the palbociclib EAP will be evaluated. Variables abstracted directly from the medical record will include the following:

- Broad categories of treatment received (i.e., surgery, radiotherapy, chemotherapy, endocrine therapy).
- Total number of therapy lines initiated for the treatment of metastatic breast cancer *prior* to entering the EAP.
- Agent composition of each treatment line *prior* to entering the EAP.
- Start and stop date of each line of treatment.
- Best response (for each line of therapy), in physicians estimation, including complete response, partial response, stable disease ≥ 24 weeks, or stable disease < 24 weeks.
- Date of first disease progression after start of each line of therapy.

Derived variables will include the following:

- Time between discontinuation of previous line to initiation of Nth line will be calculated by subtracting the stop date of the previous line from the date of Nth-line initiation.
- Total duration of each line of therapy line, in months.
- Total duration of pre–index date systemic therapy for treatment of metastatic breast cancer, in months.

8.3.2. : While Receiving Palbociclib Plus Letrozole as part of EAP

The following measures will be assessed during the post–index date period and while the patient continued palbociclib-plus-letrozole treatment on commercial drug supply.

8.3.2.1. Treatment Patterns

Treatment patterns associated with metastatic breast cancer from the time of patients' enrollment in the palbociclib EAP until the permanent discontinuation of palbociclib plus letrozole will be evaluated. Variables abstracted directly from the medical record will include the following:

- Start and stop date of participation in study A5481034.
- Stop date of palbociclib-plus-letrozole treatment.
- Starting dose of palbociclib plus letrozole.
- Dose reduction, including date and new dose.
- Treatment delay, including reason.
- Dose interruption, including delay.
- Reason for dose reductions or treatment delays to the extent documented in charts. Reasons may include AEs (e.g., neutropenia, leukopenia, fatigue, anemia), patient decision, palliative surgery, and palliative radiation.
- Reason for treatment discontinuation to the extent documented in charts. Reasons may include AEs (e.g., neutropenia, leukopenia, fatigue, anemia), patient decision, progressive disease (due to or not due to endocrine resistance), completion of planned course of treatment, or death.
- Receipt of supportive care/concomitant medications, including the following:
  - Pain control.
  - Antiemetics, antibiotics, antifungals, and antivirals.
  - Red blood cell and platelet transfusions.
  - Growth factors.
  -

Derived variables will include the following:

- Time from diagnosis of metastatic breast cancer to date of treatment initiation with palbociclib plus letrozole (index date), in months.
- Total duration of therapy, in months.
  - Total duration of palbociclib plus letrozole administered on EAP, in months.
  - Total duration of palbociclib-plus-letrozole treatment using commercial supply, in months (if applicable).

8.3.2.2. Clinical Outcomes

Finally, clinical outcomes associated with palbociclib plus letrozole will be evaluated. Variables abstracted directly from the medical record will include the following:

- Response (based on tumor assessments carried out as per local practice), including complete response, partial response, stable disease ≥ 24 weeks, or stable disease < 24 weeks.
- Date of first disease progression after start of palbociclib plus letrozole.
- Date of death (collected anytime during the post–index date period).
- Reason for death.

Derived variables will include the following:

- Time to progression (TTP), which will be calculated as time (months) from the index date to first documentation of objective tumor progression
- Progression Free Survival (PFS) which will be calculated as time (months) from the index date to first documentation of objective tumor progression or death due to any cause, whichever occurs first.
- Time to death (overall survival), calculated as time (months) from the index date to the earlier of death or end of follow-up.

8.3.2.3. Resource Utilization

The following data on resource utilization will be collected:

- Total number of hospitalizations for any cause.
- Primary reason for hospitalization (e.g., chemotherapy administration, surgery, non MBC related etc.) to the extent documented in charts.
- Duration of stay.

8.3.3. Following the Discontinuation of Palbociclib Plus Letrozole

The following measures will be assessed during the post–index date period following the discontinuation of palbociclib plus letrozole.

8.3.3.1. Treatment Patterns

We will evaluate treatment patterns associated with metastatic breast cancer from the time the patient discontinues treatment with palbociclib plus letrozole until the end of the most recent record data available or death. Variables abstracted directly from the medical record will include the following:

- Additional/new sites(s) of distant metastases (e.g., adrenal gland, bone, brain) at start of each line of treatment.
- Broad categories of treatment received *after* discontinuation of palbociclib plus letrozole (i.e., surgery, radiotherapy, chemotherapy, endocrine therapy).
- Total number of therapy lines initiated for the treatment of metastatic breast cancer *after* discontinuing palbociclib plus letrozole.

- Agent composition of each treatment line after the discontinuation of palbociclib plus letrozole.
- Start and stop date of each line of treatment.
- Response((based on tumor assessments carried out as per local practice)including complete response, partial response, stable disease ≥ 24 weeks, or stable disease < 24 weeks.
- Date of first disease progression after start of palbociclib plus letrozole.
- Date of death (collected anytime during the post–index date period).
- Reason for death.

Derived variables will include the following:

- Total duration of each line of therapy line, in months.
- Time to progression (PFS), which will be calculated as time (months) from the start of Nth line of therapy to first documentation of objective tumor progression or death due to any cause, whichever occurs first.
- Time to death (overall survival), calculated as time (months) from the start of Nth line of therapy to the earlier of death or end of follow-up.
- Total duration of post–index date systemic therapy for treatment of metastatic breast cancer, in months.

8.4. Data Sources

Medical record abstractions provide a unique opportunity to collect and analyze real-world data outside of the highly controlled settings of clinical trials. The use of record abstraction allows for the development of a highly customized data capture tool (the DCF) that meets the specific needs of this study. In this study, participating site staff will serve as the direct data extractors, therefore allowing for efficient and accurate interpretation of their own notes and records.

8.5. Study Size

The EAP program included 18 sites. However, it is anticipated that some sites will not agree to participate in this medical record review study. Data collection will therefore be conducted on a best-effort basis to obtain record data for as many 150 of the 238 EAP participants.

8.6. Data Management

RTI-HS will perform the analyses described in this proposal using a SAS statistical software application housed on RTI-HS's secure, large-capacity, high-performance Linux mainframe. Experienced RTI-HS programmers and analysts will perform all analyses. To ensure the integrity and quality of the study results, we will follow our programming validation life-cycle process for all analyses. This includes quality-checking programs, logs, and output for accuracy according to relevant standard operating procedures.

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 three steps will be undertaken to achieve this high level of quality:

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

8.6.1. 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.

8.6.2. Validation of SAS Programs

In this section, we describe a variety of programming validation methods, including log review, review of data listings, and independent programming, 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.

8.6.3. 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.

8.6.4. 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 also will have a separate analyst review these listings independent of the programmer.

8.6.5. Independent Programming

For highly complex programming tasks, a second programmer will attempt (if necessary) to independently reproduce output generated by the initial programmer. If the outputs are equivalent, the test will be considered successful. If the outputs are not equivalent, the programmers will evaluate the differences and make appropriate corrections.

8.6.6. 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.

8.6.7. 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 or A+A policies 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.

8.7. Data Analysis

All measures described in Section 8.3 will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations of continuous variables of interest and frequency distributions for categorical variables. Missing and unknown categories for each variable also will be presented. Percentages will be calculated excluding missing values. Time-to-event outcomes (i.e., time to treatment start, treatment duration, PFS, overall survival) will be described using the Kaplan-Meier method. All analyses will be conducted using SAS (version 9.3 or higher) statistical software.

The outlined statistical methods anticipate that the selected sample is randomly drawn from normally distributed populations. However, this study will employ a convenience sample; thus, results may not be generalizable to the entire population with the disease.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan, which will be dated, filed, and maintained by

Pfizer. The statistical analysis plan may modify the plans outlined in the protocol; any major modifications of study measures or analyses would be reflected in a protocol amendment.

8.8. Quality Control

A+A will perform the following data checks for all data collected in the DCF:

- Check for illogical or unusual data (e.g., treatment starting prior to diagnosis).
- Check for speeders (i.e., physicians who seem to skim through the DCF by falling below a certain tolerance time interval of an estimated average duration needed for completing the form).
- Check for responders with a typical unrealistic response pattern, such as always checking the same value in a numerical scale or responding in an erratic, implausible manner to certain questions.
- Check for an extremely high percentage of "Do not know" or "Data not available" responses.
- Check for an extremely high percentage of answering filter questions in a way so as to avoid having to answer subsequent questions in more detail.

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 Assurance (OQA) 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, and provides quality assurance monitoring for compliance with regulatory requirements.

RTI-HS will work closely with the selected subcontractors to establish and ensure a complete integration of procedures for the project. The OQA 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 OQA according to established criteria in standard operating procedures and other applicable procedures. The OQA reports quality assurance observations to the Project Director and facilitates corrective actions, if necessary.

8.9. Strengths and Limitations of the Research Methods

Retrospective medical record review studies are subject to the following general limitations:

- Patients included in the study represent a "convenience" sample, in that the records will be obtained from physicians who are willing to participate in the study. Therefore, study findings may not be generalizable to all the participating EAP patients from A5481034.
- All data captured in the DCF will be limited to information available in the patients' medical records held by the physician participating in the study. Information on

health care services received outside the physician's care setting that is not recorded in the medical record will be unavailable for this study (e.g., treatment for AEs received through primary care rather than the abstracting physician specialist).

- Data will be entered directly by the treating physicians and therefore may be subject to entry errors and resulting inaccuracies in reporting. Although there will be data checks in place to ensure internal consistency of the data, responses will not be validated against the patients' medical records by an independent reviewer.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information, Data Privacy, De-Identification, and Consent

Physicians will be provided with a summary of the protocol, objectives, and methods as well as their rights and responsibilities prior to providing their consent to participate in the study. Physician consent will be obtained electronically prior to participating in the medical record abstraction.

Patient data will be collected retrospectively. No data will be collected prospectively and no contact with any of the EAP enrollees will be required for any aspect of data collection. In addition, all patient data will be de-identified and anonymous, thus patient consent will not be required. Moreover, because the study is retrospective in nature, a requirement of signed informed consent would also require that study include only patients still living at the time of the medical record abstraction; this requirement may bias the sample toward patients with longer survival and more favorable outcomes than would be observed in the general EAP sample. For these reasons, collection of signed informed consent from the patients may yield invalid or, at least, biased data on several key endpoints.

Patient medical record data may contain highly sensitive and private personal health information. Therefore, the following data collection strategies will be implemented to ensure the data collected in this study strictly comply with accepted definitions of de-identified and anonymous data:

- At any point in this study, members of the patient's direct health care team are the only individuals with access to the patient's medical record data containing potentially identifiable information. The study team (i.e., RTI-HS, A+A, and Pfizer) will not view, obtain, or have access to any identifiable health information such as patient name, address, exact date of birth or death, date of health care service encounters, or other personal identifiers.
- Patient identifiers such as name, address, telephone number, e-mail address, health record/beneficiary number, biometric data, and photographs are not relevant to this study and will not be collected or viewed at any point by the study team.
- Major geographic region and facility type will be collected to assess equitable distribution of the physician and record data samples. To eliminate any potential risk

of identifying record information related to patients in rural regions with few patients with HR+/HER2− metastatic breast cancer and few treatment facilities, physician data will not be linkable with the record-level data in the study database. The resulting data will only allow the researchers to assess overall country-level geographic and facility type distributions independently, which include (1) the proportion of physicians in the sample who came from each major geographic region and (2) the proportion of patients who sought treatment at a certain facility type (e.g., outpatient cancer center). However, researchers will not be able to assess the proportion of patients who received treatment at a certain facility type in a specific region as the data are not linked to patients.

As the data used in this study are de-identified and anonymous, this study poses minimal risk to patients whose medical record data are analyzed. With de-identified and anonymous data, the risk of a breach of confidentiality is primarily from malicious system hacking in the presence of suboptimal network security in the case of electronic data collection. Outside of network security risks, identification of a single patient by members of the research investigative team, based on a combination of limited demographic information and treatment information, would require (in addition to malicious intent) access to all medical records in a country or region (including those outside the physicians/sites participating in the study) and an extraordinary analytic effort, except, perhaps, in the case of exceedingly rare conditions which the current study does not include. Based on the study design and data collection procedures, the study team believes there is only a minimal/remote risk of identification of patients.

The physician participants in this study will be subject to different, albeit remote, risks compared with patients. No physician-identifying information (e.g., name, address, practice name) will be collected or retained by RTI-HS unless transmission of this information to RTI-HS is explicitly authorized by the physician. It is conceivable, however, that participation in the study may divert a small amount of physician's time and resources away from clinical activities to allow for their participation in this research. It is expected, however, that these physicians will adequately manage their time.

Records for each patient in the analytic data set will be assigned a random study identification number. The study identification numbers will be generated after the patient data are submitted, on the back-end of the database created by A+A, such that the physician will never see the identifier. Therefore, neither the research team (RTI-HS and A+A) nor the participating physicians maintain a linkable identifier to a specific patient. Only the physicians who directly enter the patient data into the secure, web-based DCF will see (as they would in routine clinical practice) explicit patient identifying information. Only a randomly generated physician identifier will be provided to the analytic team at RTI-HS. Furthermore, A+A's web portal used for data collection is hosted in a secure data center and each physician may access it only with login credentials specifically assigned to them by A+A. This data center offers a secure environment which minimizes the chance of a security breach, thereby allowing access only to authorized persons with valid usernames and passwords.

9.2. Patient Withdrawal

Not applicable as a result of the retrospective, noninterventional nature of this study.

9.3. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/independent ethics committee.

RTI holds a Federal-Wide Assurance (#3331 effective until February 5, 2019) from the Department of Health and Human Services Office for Human Research Protections that allows us to review and approve human subjects protocols through our IRB committees. These committees are also registered with Office for Human Research Protections for both Department of Health and Human Services and FDA-regulated research (registration expires January 22, 2017). Our Federal-Wide Assurance requires IRB review for all studies conducted by RTI that involve human subjects, regardless of the funding source. 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.

RTI currently has three IRB committees available to review research protocols. Each committee meets monthly. One of the IRBs is constituted to review biomedical clinical trials with appropriate medical expertise among its members. These IRBs have been audited by the FDA and are fully compliant with applicable regulatory requirements. The committees review research studies to ensure adherence to appropriate regulations that govern human subjects research, including 45 CFR 46, 21 CFR 50 and 56, and with all applicable International Conference on Harmonization provisions. All studies involving human subjects undergo a continuing IRB review at least once per year.

If a participating physician requires additional approval by his or her local or site-level IRB, RTI-HS will work in collaboration with him or her to develop and submit the necessary forms for this activity.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions, and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution of causality to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution of causality is not necessarily inferred or solely based on a temporal relationship between drug administration and an AE, but must be based on a definitive statement of causality by a health care provider linking drug administration to the AE.

The requirements for reporting safety events on the Noninterventional Study (NIS) Adverse Event Monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and nonserious AEs with explicit attribution to any Pfizer drug that appears in the reviewed information must be recorded on the DCF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

RTI-HS will provide status updates on study progress every 2 weeks via teleconference or e-mail. Once the data analyses are complete, RTI-HS will prepare a final study report presenting a description of the analyses performed and the results obtained. The final study report will synthesize results from the tables generated during the analysis to highlight and interpret the key findings. In addition to the study report, RTI-HS will also prepare a slide set presenting a description of the analyses performed and the results obtained. After delivery of the final study report and slide set, RTI-HS will conduct a 90-minute teleconference and web-based meeting to present the study results to Pfizer. The presentation will be based on the aforementioned slide set.

11.1. Communication of Issues

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

12. REFERENCES

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13. LIST OF TABLES

Not applicable.

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.