NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Retrospective, Multicenter, Observational Study to Evaluate Overall Survival in Japanese Patients With HR+/HER2- Advanced Breast Cancer Treated with Palbociclib Plus Letrozole
Protocol number	A5481154
Protocol version identifier	Amendment 1
Date	07 April 2022
Active substance	Palbociclib (L01XE33)
Medicinal product	Palbociclib (IBRANCE)
Research question and objectives	To evaluate overall survival in Japanese patients with HR+/HER2- advanced breast cancer who have been treated with palbociclib plus letrozole in first-line setting
Author	PPD (NI study lead) PPD, Pfizer Oncology Japan PPD PPD Pfizer Oncology Japan

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Term
ABC	advanced breast cancer
AE	adverse event
AEM	adverse event monitoring
CDK	cyclin-dependent kinase
CI	confidence interval
CRF	case report form
CSA	clinical study agreement
DCF	data clarification form
DCT	data collection tool
ET	endocrine therapy
HER2-	human epidermal growth factor receptor 2-negative
HR+	hormone receptor–positive
IEC	independent ethics committee
IRB	institutional review board
LET	letrozole
LSLV	last subject last visit
MHLW	Minister of Health, Labour and Welfare
NI	non-interventional
NIS	non-interventional study
OS	overall survival
PAL	Palbociclib
PFS	progression-free survival
SAP	statistical analysis plan

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Organization of study operationwill be prepared as Appendix 1.

4. ABSTRACT

Not applicable

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1	07 April 2022	Section 9.2.1	description revised	To clarify inclusion criteria
Amendment 1	07 April 2022	Sections 9.6.2, 10.2, and 12	descriptions revised	Based on the findings of Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
Amendment 1	07 April 2022	Sections 9.10.1, 10.6, 10.7, 10.8	Sections added	Based on the findings of IRB/IEC
Amendment 1	07 April 2022	Section 9.7.5	Section added	To conduct interim analysis based on the data at the second data collection
Amendment 1	07 April 2022	Section 6	description revised	To conduct interim analysis based on the data at the second data collection
Amendment 1	07 April 2022		Other minor edits were made	

6. MILESTONES

Milestone	Planned date

Start of data collection	15 December 2020
Completion of interim analysis	15 December 2022
End of data collection	31 December 2024
Final study report	30 November 2025

7. RATIONALE AND BACKGROUND

Breast cancer is the most common cancer in women in Japan, with nearly 86,500 new cases diagnosed in 2018 and breast cancer is the fifth leading cause of cancer-related death in Japanese females [1]. Breast cancer prevalence rate of Japanese women by age group began to increase from the 30s, peaked in the latter half of the 40s, after that it remained almost constant, and gradually decreased from the late sixties[2]. Hormone receptor–positive (HR+) breast cancer accounts for approximately 71% of new cases worldwide[3]. Endocrine therapy has been a mainstay of HR+ breast cancer treatment and recommended by the Japanese Breast Cancer Society and international guidelines for initial treatment of HR+ disease[4, 5]. However, hormonal blockade alone provides only modest benefit in women with advanced breast cancer (ABC), with many patients having de novo or acquired resistance to endocrine therapy.

Palbociclib is a selective, oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that prevents cell proliferation by blocking cell cycle progression from the G1 to the S phase. In Japan, palbociclib was approved in 2017 for the treatment of HR+/human epidermal growth factor receptor 2-negative (HER2-) inoperable or recurrent breast cancer. The safety and efficacy of palbociclib were investigated in 2 phase 3, randomized, double-blind, placebo-controlled, multicenter trials (PALOMA-2, -3) and have shown significant activity in the first- or subsequent line treatment of HR+/HER2- ABC when combined with endocrine therapy (ET), demonstrated an approximate doubling of progression-free survival (PFS) when compared to ET alone[6, 7]. In Japanese patients with HR+/HER2− ABC, a phase 2, single-arm, open-label study of palbociclib in combination with letrozole as first-line treatment was conducted, and the combination treatment demonstrated effectively 75.0% (90% CI, 61.3%-84.4%) of investigator-assessed 1-year progression-free survival (PFS) probability, with a manageable safety profile[8].

There is limited data regarding the effectiveness of standard subsequent line therapies (chemotherapy, targeted agents or ET) after progression on CDK4/6 inhibitor-based regimens. Recent analyses in the overall population from PALOMA-2 and PALOMA-3 have shown that the type of subsequent therapy was similar between the palbociclib plus ET and placebo plus ET groups and that PFS improvement associated with palbociclib plus ET was retained in subsequent lines of therapy[9, 10]. While overall survival (OS) data are not yet available for Paloma-2, Paloma-3 has demonstrated that in patients sensitive to endocrine therapy, this combination therapy also brings about longer OS than fulvestrant monotherapy

(39.7 months vs 29.7 months; Hazard ratio, 0.92; 95% CI, 0.55–0.94) suggesting that progression on palbociclib has no significant effect on the therapeutic benefit derived from subsequent treatments received [10]. Although these findings in the overall population suggest that the treatment benefit of subsequent therapy was not compromised by palbociclib, in the postmenopausal woman with moderately pre-treated HR+/HER2- ABC, limited benefit from post palbociclib treatment are reported[11].

Real-world data in the United States demonstrated that palbociclib plus letrozole significantly prolonged progression-free survival by 45% versus letrozole alone (P < .0001) and significantly improved overall survival by 48% versus letrozole alone (P < .0001), according to a retrospective analysis of electronic health records[12].

The data on the effectiveness of palbociclib containing treatment sequence in Japanese patients are very limited. The health insurance system, available treatment option and healthcare outcomes are different in countries[13]. These differences may influence clinical outcomes of palbociclib in each country. To explore the effectiveness of palbociclib as first-line treatment in Japan, this non-interventional study was planned to follow up the OS and also to investigate the type and duration of subsequent therapies after palbociclib treatment in the phase 2 study conducted in Japan.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective

To evaluate overall survival (OS) in Japanese patients with HR+/HER2- advanced breast cancer who have been treated with palbociclib plus letrozole in first-line setting

Secondary objective

To describe the type and duration of subsequent therapy after palbociclib plus letrozole treatment in Japanese patients with HR+/HER2- advanced breast cancer

9. RESEARCH METHODS

9.1. Study design

This is a retrospective, multicenter, observational study in Japan. The primary objective is to evaluate OS in Japanese patients with HR+/HER2- advanced breast cancer who have been treated with palbociclib plus letrozole. This observational study was planned as follow-up study of Japanese phase 2 study of palbociclib (NCT01684215, phase 2 portion of A5481010 study, hereafter described as J-Ph2).

In J-Ph2, 43 patients were enrolled, and 42 patients were treated with palbociclib plus letrozole. At the study completion of J-Ph2 [Last Subject Last Visit (LSLV): 25 October 2018], 8 deaths were reported. Of the remaining 34 patients without death reported, 4 patients refused further follow-up and 30 patients were under follow-up for survival.

For the 30 patients under follow-up for survival in J-Ph2, OS and subsequent therapy data will be retrospectively collected from individual patient medical records (See Section 9.3 and 9.4 for detail). If the patient had been transferred to another hospital, the investigator will be asked to collect data as much as possible from the hospital. The investigator will complete paper-based case report forms (CRFs) at study initiation at each study site and at an annual reporting period set by the sponsor. Patient demographics and other relevant data collected in J-Ph2 will be used and matched with data collected in this study through patient IDs for analysis.

For 8 patients with OS events confirmed in J-Ph2 and 4 patients who refused further follow-up in J-Ph2, data collected in J-Ph2 will be used for analysis.

9.2. Setting

Thirty patients who participated, treated with palbociclib plus letrozole, and under follow-up for survival in J-Ph2 will be enrolled in this study for data collection. See Appendix 2 for inclusion and exclusion criteria in J-Ph2.

9.2.1. Inclusion criteria

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

1. Participated, treated with palbociclib plus letrozole in J-Ph2, and was under follow-up for survival at the study completion of J-Ph2.

2. For patients who are still alive and have routine visits to the study site, evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study. For patients who are still alive and had been transferred to another hospital, evidence that the patient has been informed of all pertinent aspects of the study and oral or written informed consent is obtained. For patients who had already passed away, the conduct of this study will be disclosed, and the patients' legally acceptable representatives will be guaranteed an opportunity to refuse data collection for the patients in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

9.2.2. Exclusion criteria

There are no exclusion criteria for this study.

9.3. Variables

The same patient IDs will be used for this study and J-Ph2. Data collected in this study will be combined and evaluated with J-Ph2 data, including patient demographics, study treatment, and baseline tumor assessment, through matching with patient IDs. Variables and data sources are described in Table 1. Detailed definitions will be included in the statistical analysis plan (SAP).

Table 1. Variables in this study

Variable	Role	Data source(s)
Overall Survival	Outcome	J-Ph2 database A5481154 database
Type of subsequent therapy	Outcome	J-Ph2 database A5481154 database
Duration of subsequent therapy	Outcome	J-Ph2 database A5481154 database
Clinical response of subsequent therapy	Outcome	A5481154 database
Palbociclib dose modification	Exposure, Outcome	J-Ph2 database A5481154 database
Palbociclib treatment duration	Exposure, Outcome	J-Ph2 database A5481154 database
Letrozole treatment duration	Exposure, Outcome	J-Ph2 database A5481154 database
Demographic and baseline characteristics	Baseline characteristics	J-Ph2 database

9.4. Data sources

9.4.1. Data to be collected in this study

Data to be collected in this study is described in Table 2. See Section 9.4.2 and 9.4.3 for data collection time point and data collection methods.

Table 2. Data to be collected in this study

CRF	Variables
Informed consent	Patient status at study initiation[4]
	Informed consent obtained
	Date of informed consent
Survival status	Survival status
	Date last known to be alive
	Date of death
	Cause of death
Subsequent therapy	Drug name of subsequent therapy
	Start and Stop date of subsequent therapy
	Clinical response of subsequent therapy[1]
PAL+LET exposure	Total daily dose[2]
	Start and Stop date of each dose[3]
	Reason for dose change[2]
PAL+LET discontinuation	Date of treatment discontinuation[3]
	Reason for treatment discontinuation[3]
	Disease site and tumor assessment at treatment discontinuation

Abbreviation; LET=letrozole, PAL=palbociclib

1. Clinical response of subsequent therapy will be evaluated with Complete response, Partial response, Stable disease, Progression disease, and Unknown. See Section 9.4.1.1. for detail.
2. Palbociclib only
3. Data will be collected for palbociclib and letrozole, respectively
4. Patient status at study initiation will be collected as alive and has routine site visit, alive and had transferred to another hospital, dead

9.4.1.1. Assessment

Clinical response of subsequent therapy

Clinical response of subsequent therapy will be evaluated with Complete response, Partial response, Stable disease, Progression disease, and Unknown. These are not any protocol-specified criteria and/or method for response evaluation, and this will be recorded based on investigator's discretion (eg, radiology reports, patients' medical chart).

- Complete response will be selected where "Complete response" has been recorded at any time on treatment.

- Partial response will be selected where "Partial response" has been recorded at any time on treatment without Complete response recorded.

- Stable disease will be selected (1) if the treatment continued for a minimum of 24 weeks or (2) if the treatment discontinued within 24 weeks but the initial response was not Progressive disease, without Complete or Partial response recorded at any time on treatment.

- Progressive disease will be selected if the treatment discontinued within 24 weeks and the initial response was Progressive disease without subsequent Complete or Partial response recorded.

9.4.2. Data collection time point and Data collection period

In this study, data will be collected with paper-based CRFs. The Investigator will complete CRFs for all the patients who remain in follow-up and submit them to the sponsor at the below time points;

1. Study initiation at each study site

2. Annual reporting period set by the sponsor (eg, every April)

For each patient, data collection will be continued until death unless patients withdraw consent or if the study gets sufficient OS events.

For the study, data collection will be continued until sufficient number of OS events are obtained to determine median OS.

9.4.3. Data collection method

Relevant CRFs will be completed according to the patient status at each data collection time point.

At the study initiation at each study site

Investigators will complete the CRF for “Informed consent” and relevant CRFs according to patient status at last visit of J-Ph2 and current patient status (see Table 3 in detail). For example, if patient was receiving palbociclib plus letrozole treatment at last visit of J-Ph2 and the patient still receives palbociclib plus letrozole, investigator will complete CRFs for “Informed consent”, “Survival status” and “PAL+LET exposure”. See Appendix 3 for each patient status at last visit of J-Ph2.

Table 3. CRFs to be completed at study initiation at each study site

Patient status			CRF to be completed
Case	At last visit of J-Ph2	At study initiation at study site	
1	PAL+LET treatment ongoing	PAL+LET treatment ongoing	- Informed consent - Survival status - PAL+LET exposure
2		PAL+LET treatment discontinued and OS follow-up	- Informed consent - Survival status - Subsequent therapy - PAL+LET exposure - PAL+LET discontinuation
3		Death	Same with Case 2
4	PAL+LET treatment discontinued and OS follow-up	OS follow-up	- Informed consent - Survival status - Subsequent therapy
5		Death	Same with Case 4

Abbreviation; LET=letrozole, OS=overall survival, PAL=palbociclib

At the annual reporting period

Investigators will complete the relevant CRF according to patient status at previous and current reporting period (see Table 4 in detail). For example, if the patient status was "PAL+LET treatment discontinued and OS follow-up" at previous reporting period and current patient status is "Death", investigator will complete CRFs for "Survival status" and "Subsequent therapy").

Table 4. CRFs to be completed at annual reporting period

Patient status			CRF to be completed
Case	At previous reporting period	At current reporting period	
1	PAL+LET treatment ongoing	PAL+LET treatment ongoing	- Survival status - PAL+LET exposure
2		PAL+LET treatment discontinued and OS follow-up	- Survival status - Subsequent therapy - PAL+LET exposure - PAL+LET discontinuation
3		Death	Same with Case 2
4	PAL+LET treatment discontinued and OS follow-up	OS follow-up	- Survival status - Subsequent therapy
5		Death	Same with Case 4

Abbreviation; LET=letrozole, OS=overall survival, PAL=palbociclib

9.5. Study size

The number of patients eligible for this study is 42 who participated and were treated with palbociclib plus letrozole in J-Ph2.

9.6. Data management

Investigators will fill out relevant CRFs based on source documents (eg, patients' medical chart) with a pen, ballpoint pen, etc. After the completion of CRFs, the investigator will promptly submit them to the sponsor by mail.

When receiving a query from the sponsor on the completed CRF (ie, Data Clarification Form [DCF]), investigators will reconfirm the information on source documents, fill out the DCF as required, and submit the DCF to the sponsor.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in paper form and will be secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records

should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met. Study records will be disposed appropriately according to each site regulation.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

For the purposes of this study, analyses will be descriptive in nature. All variables will be summarized descriptively through the tabular and graphical display of means, standard deviations, medians, ranges of continuous variables of interest, and proportions and frequency distributions for categorical variables. No formal hypothesis testing is planned.

Data collected in this study will be combined and evaluated with J-Ph2 data, including patient demographics, study treatment, and baseline tumor assessment, through matching with patient IDs.

9.7.1. Definition of analysis set

Analysis set is defined as all patients who enrolled and have been treated in the J-Ph2 study excluding alive patients without written or oral informed consent obtained.

9.7.2. Primary endpoint analysis (Overall survival)

The primary endpoint is OS defined as the time from first dose of study treatment in J-Ph2 to date of death due to any cause. In the absence of confirmation of death, survival time will be censored to last date the patient is known to be alive.

OS will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 95% CI will be estimated.

9.7.3. Secondary endpoint analysis (type and duration of subsequent therapy)

Frequency of patients who received subsequent therapy will be summarized by type of therapy (eg, endocrine-based therapy, chemotherapy) and/or by line of therapy (eg, first subsequent therapy, second subsequent therapy). Median treatment durations of subsequent therapy by line of therapy will be estimated based on the Kaplan-Meier method, and duration of all subsequent therapy will be plotted by each patient.

9.7.4. Other analysis

- Clinical response of subsequent therapy - The number and proportion of each response will be summarized by type of therapy (eg, endocrine-based therapy, chemotherapy) and/or by line of therapy (eg, first subsequent therapy, second subsequent therapy). Clinical response of all subsequent therapy will be plotted by each patient along with duration of subsequent therapy.

- Time to chemotherapy - Defined as the time from first dose of study treatment in J-Ph2 to the start of first subsequent chemotherapy or death due to any cause, whichever comes first. Time to chemotherapy will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The median event time and 95% CI will be estimated.

- Palbociclib dose modification - The number and proportion of patients with dose reduction (eg, 1 dose reduction to 100 mg, 2 dose reductions to 75 mg) and the reason for dose reduction will be summarized.

- Palbociclib and letrozole treatment duration - Duration of palbociclib plus letrozole treatment will be plotted by each patient. For palbociclib, duration of treatment may be plotted by dose of palbociclib (eg, 125 mg, 100 mg, and 75 mg).

9.7.5. Interim analysis

An interim analysis will be performed based on the data at the second data collection (i.e. based on the data collected at the first annual reporting period. 9.4.2). Detailed methodology will be documented in the SAP.

9.8. Quality control

The sponsor will train investigators and study site staff with an onsite training visit or web-training on the protocol, CRFs, and any applicable study processes. Any new information relevant to the performance of this study will be forwarded to the investigator and study site staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of data, data integrity, and consistency. CRFs for all included patients will be made available to the remote data monitor for review. The study sites will be queried and managed to request resolution to any issues that may arise during the course of the study.

Onsite Monitoring visits are not planned in this study.

9.9. Limitations of the research methods

Limitations of the research method in this study include;

1. Single-arm design. Since no control group is set in the study, there is a limitation on interpretation on results, especially time-to-event endpoints.

2. Observational, retrospective design. Since this study collects data basically from medical charts of each patient, there is a potential for missing, inaccurate, or incomplete data. If the patients had been transferred to another hospital or had already passed away, data in these patients may not be fully collected or be missing information in this study. In addition, considering the observational nature, there is methodological challenges in attributing causality to outcomes.

3. Small sample size. It may be difficult to draw definitive conclusion due to lack of power.

9.10. Other aspects

9.10.1. Secondary use of data

Data obtained in this study may be used for scientific research and to promote public health. Even in such case, the personal information of patients will be protected in accordance with the applicable personal information protection law so that study patients cannot be identified.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code.

The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

For patients who are alive and still visit the study site

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. Also, the investigator should appropriately and promptly respond to consultations from each patient and persons concerned. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any data is collected. The investigator will retain the original of each patient's signed consent form.

The informed consent form must be in compliance with local regulatory requirements and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/ IEC and Pfizer before use.

For patients who are alive and had been transferred to another hospital

In accordance with Chapter 5 "Informed Consent" of the Ethical Guidelines for Medical and Health Research Involving Human Subjects, it is not always necessary to obtain written informed consent from the patients who had been transferred to another hospital. However, the investigator, or a person designated by the investigator, will obtain at least oral informed consent from each patient before any data is collected, and document method and content of the explanation as well as details of consent obtained.

For patients who had already passed away

In accordance with Chapter 5 "Informed Consent" of the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the conduct of this study will be disclosed, and the patients' legally acceptable representatives will be guaranteed an opportunity to refuse data collection for the patients.

10.3. Patient withdrawal

Only for patients who are alive

Patients may withdraw from the study at any time at their own request. In any circumstance, every effort should be made to document patient outcome, if possible.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

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

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Minister of Health, Labour and Welfare (MHLW).

10.6. Predictable risks and benefits for subjects

In this study, personal information will be handled in order to retrospectively collect necessary information from the medical records of individual patients. Handling of personal information complies with the ethical guidelines of the research and pays utmost attention, but there may be risk of the accidental disclosure of personal information.

This is a retrospective study, and participation in this study does not provide direct benefits. However, information obtained from participation in this research may help other patients in the future.

10.7. Report to the chief executive of the study site

Each study site's investigator shall report following to the chief executive of the study site in writing:

1) protocol and protocol amendments

2) progression of the study

3) discontinuation and interruption of the study.

10.8. Source of research funding and Conflict of interest

This study will be conducted with Pfizer funding. Any potential conflicts of interest in the planning, conduct, and publication of this study will be disclosed. Conflict of interest refers to an interest that may affect study results, including financial and personal relationships.

11. 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 (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool (e.g., chart abstraction form) 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 AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors*".

These trainings must be completed by research staff members prior to the start of data collection. 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.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

The results of this study are not part of any regulatory submission. The results of this study will be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System upon final study completion. This study will be registered in the ClinicalTrials.gov, etc. and the information will be disclosed.

13. REFERENCES

1. Center for Cancer Control and Information Services, N.C.C. *Projected Cancer Statistics, 2018*. 2018/09/15 [cited 2020 2/14]; Available from: https://ganjoho.jp/en/public/statistics/short_pred.html.
2. Foundation for Promotion of Cancer Research. *Cancer Statistics in Japan -2018*. Available from: https://ganjoho.jp/data/reg_stat/statistics/brochure/2018/cancer_statistics_2018_date_J.pdf.
3. American Cancer Society. *Breast Cancer Facts & Figures 2017–2018.*; Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf.
4. Aihara, T., et al., *The Japanese Breast Cancer Society Clinical Practice Guideline for systemic treatment of breast cancer, 2015 edition.* Breast Cancer, 2016. **23**(3): p. 329-42.
5. Cardoso, F., et al., *ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2).* Breast, 2014. **23**(5): p. 489-502.
6. Rugo, H.S., et al., *Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial.* Ann Oncol, 2018. **29**(4): p. 888-894.
7. Cristofanilli, M., et al., *Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial.* Lancet Oncol, 2016. **17**(4): p. 425-439.

8. Masuda, N., et al., *Palbociclib in combination with letrozole as first-line treatment for advanced breast cancer: A Japanese phase II study.* Cancer Sci, 2018. **109**(3): p. 803-813.
9. Rugo, H.S., et al., *Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up.* Breast Cancer Res Treat, 2019. **174**(3): p. 719-729.
10. Turner, N.C., et al., *Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer.* N Engl J Med, 2018. **379**(20): p. 1926-1936.
11. Rossi, L., et al., *Clinical outcomes after palbociclib with or without endocrine therapy in postmenopausal women with hormone receptor positive and HER2-negative metastatic breast cancer enrolled in the TREnd trial.* Breast Cancer Res, 2019. **21**(1): p. 71.
12. DeMichele, A., et al., *Abstract P1-19-02: Overall survival for first-line palbociclib plus letrozole vs letrozole alone for HR+/HER2- metastatic breast cancer patients in US real-world clinical practice.* Cancer Research, 2020. **80**(4 Supplement): p. P1-19-02.
13. Papanicolas, I., L.R. Woskie, and A.K. Jha, *Health Care Spending in the United States and Other High-Income Countries.* Jama, 2018. **319**(10): p. 1024-1039.

14. LIST OF TABLES

15. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Appendix 1. Organization of study operation

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Appendix 2. Inclusion and Exclusion criteria in J-Ph2

Appendix 3. Each patient status at last visit of J-Ph2

Appendix 2. Inclusion and Exclusion criteria in J-Ph2

Inclusion criteria

1. Adult women (≥ 20 years of age) with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated.

2. Documentation of histologically or cytologically confirmed diagnosis of ER(+) breast cancer based on local laboratory results.

3. All patients must agree to provide tumor tissues for centralized retrospective confirmation of ER status and to evaluate correlation between genes, proteins, and RNAs relevant to the cell cycle pathways and sensitivity/resistance to the investigational agents. Freshly biopsied, recurrent/metastatic tumor samples must be provided whenever possible. If such a biopsy is not feasible or cannot be safely performed, then an archived tumor sample may be accepted. In either case a formalin fixed, paraffin embedded (FFPE) block or 12 unstained FFPE slides are required for patient participation.

4. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER(+) disease.

5. Postmenopausal women defined as women with:

   - Prior bilateral surgical oophorectomy, **or**

   - Medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months (and follicle-stimulating hormone [FSH] and estradiol blood levels in their respective postmenopausal ranges with no alternative pathological or physiological cause, if applicable).

6. Measurable disease as defined per RECIST v.1.1 or bone-only disease (with bone lesions confirmed by Computed Tomography [CT], Magnetic Resonance Imaging [MRI] or bone X-ray). Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.

7. ECOG PS 0-2.

8. Adequate bone marrow and organ function defined as follows:

   - ANC ≥1,500/mm^3 (1.5 x 10^9 /L);

   - Platelets ≥100,000/mm^3 (100 x 10^9 /L);

- Hemoglobin ≥9 g/dL (90 g/L);
- Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution;
- Total serum bilirubin ≤1.5 x ULN (≤3.0 x ULN if Gilbert's disease);
- AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);
- Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone or liver metastases present).

9. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

10. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study before any study-specific activity is performed.

Exclusion criteria

1. HER2-positive tumor as defined by documentation of erbB-2 gene amplification by FISH (as defined by a HER2/CEP17 ratio ≥2) or chromogenic in situ hybridization (CISH, as defined by the manufacturer's kit instruction) or INFORM HER2 dual ISH (as defined by manufacturer's kit instruction) or documentation of HER2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory results utilizing one of the sponsor-approved assays. If HER2 status is unavailable or was determined using a test other than a sponsor-approved assay, then testing must be performed/repeated using one of these assays prior to study registration. If tissue sample from both primary and recurrent/metastatic tumors are available, HER2 assessment from the most recent sample (i.e., recurrent/metastatic sample) should be used to define eligibility whenever feasible.

2. Patients with advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).

3. Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy,

stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before study registration.

4. Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease recurrence while on or within 12 months of completing treatment.

5. Prior treatment with any CDK4/6 inhibitor.

6. Patients treated within the last 7 days prior to study registration with:

   - Food or drugs that are known to be CYP3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);

   - Drugs that are known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort).

   - Drugs that are known to prolong the QT interval.

7. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before study registration. Patients who received prior radiotherapy to ≥25% of bone marrow are not eligible independent of when it was received.

8. Diagnosis of any other malignancy within 3 years prior to study registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.

9. QTc >480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).

10. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).

11. Any of the following within 6 months of study registration: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 Grade ≥2, atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

12. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.

13. Known hypersensitivity to letrozole, or any of its excipients, or to any PD-0332991 excipients.

14. Known human immunodeficiency virus infection.

15. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

16. Patients who are investigational site staff members or relatives of those site staff members or patients who are Pfizer employees directly involved in the conduct of the trial.

17. Participation in other studies involving investigational drug (s) (Phases 1-4) within 2 weeks before study registration and/or during participation in the active treatment phase of the trial.

18. Recent or active suicidal ideation or behavior.

Appendix 3. Each patient status at last visit of J-Ph2

Site ID	Patient ID	Patient status
PPD		PAL+LET treatment ongoing
		Patient refused further follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment ongoing
		PAL+LET treatment ongoing
		PAL+LET treatment discontinued and OS follow-up
		Death
		PAL+LET treatment discontinued and OS follow-up
		Patient refused further follow-up
		PAL+LET treatment ongoing
		PAL+LET treatment discontinued and OS follow-up
		Death
		PAL+LET treatment discontinued and OS follow-up
		Death
		PAL+LET treatment discontinued and OS follow-up
		Death
		Patient refused further follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		Death
		Death
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment ongoing
		Patient refused further follow-up
		PAL+LET treatment ongoing
		PAL+LET treatment ongoing
		PAL+LET treatment ongoing
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment ongoing
		PAL+LET treatment ongoing
		Death
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		Death
		PAL+LET treatment ongoing
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment discontinued and OS follow-up
		PAL+LET treatment ongoing

Abbreviation; LET=letrozole, OS=overall survival, PAL=palbociclib