NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Patient Characteristics, Treatment Patterns, and Clinical Outcomes in Patients Diagnosed with HR+/HER2- Advanced/Metastatic Breast Cancer Receiving CDK4/6i + Aromatase Inhibitor (AI) Combination Therapy as Initial Endocrine-based Treatment
Protocol number	A5481144
Protocol version identifier	1.0
Date	05 November 2019
Active substance	Palbociclib (L01XE33)
Medicinal product	Palbociclib
Research question and objectives	**Primary Objectives:** Objective 1 - Among patients with HR+/HER2- advanced/metastatic breast cancer (A/MBC) receiving CDK4/6i +AI combination therapy as initial endocrine-based therapy: a. Describe demographic and clinical characteristics. b. Describe treatment patterns (eg, regimen sequencing, dose changes, discontinuations). Objective 2 - Among patients receiving Palbociclib + AI as initial endocrine-based therapy, examine clinical effectiveness outcomes including real-world progression-free survival (rwPFS), overall survival (OS), and real-world tumor response (rwTR).

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
A/MBC	Advanced/metastatic breast cancer
AE	Adverse event
AEM	Adverse event monitoring
AI	Aromatase inhibitor
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CFR	Code of Federal Regulations
CR	Complete response
CRN	Clinical Research Nurse
DCT	Data collection tools
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic medical record
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
HEOR	Health Economics and Outcomes Research
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor; hazard ratio
IRB	Institutional review board
IRIS	Ibrance Real World Insights Study
NE	Not evaluable
NIS	Non-interventional study
OS	Overall survival
PFS	Progression-free survival
PD	Progressive disease
PR	Progesterone receptor; partial response
rwPFS	Real-world progression-free survival
rwTR	Real-world tumor response
SAP	Statistical analysis plan
SD	Stable disease
SQL	Structured query language
SSDI	Social Security Death Index
UD	Undocumented
U.S.	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD , PhD, MStat	PPD	PPD	PPD
PPD MPH	PPD	PPD	PPD
PPD MA	PPD	Pfizer	PPD

4. ABSTRACT

Title: Patient Characteristics, Treatment Patterns, and Clinical Outcomes in Patients Diagnosed with HR+/HER2- Advanced/Metastatic Breast Cancer Receiving CDK4/6i + AI Combination Therapy as Initial Endocrine-based Treatment.

Rationale and Background: The treatment landscape for HR+/HER2- advanced and metastatic breast cancer (A/MBC) has changedas multiple CDK4/6i drugs in combination with aromatase inhibitor (AI) are approved for use in the first line and subsequent lines. The present study is designed to describe treatment patterns and clinical outcomes in patients diagnosed with HR+/HER2- A/MBC who received CDK 4/6i combination therapy with AI as initial endocrine-based treatment in the U.S. community oncology setting.

Research Question and Objectives: The objective of this study is to describe the patient characteristics, treatment patterns, and clinical effectiveness outcomes for patients with a diagnosis of HR+/HER2- A/MBC who received CDK4/6i combination therapy with AI as the initial endocrine-based therapy in the A/MBC setting.

Primary Objectives:

Objective 1 – Among patients with HR+/HER2- advanced/metastatic breast cancer (A/MBC) receiving CDK4/6i combination therapy with AI as initial endocrine-based therapy:

a. Describe demographic and clinical characteristics.

b. Describe treatment patterns (eg, regimen sequencing, dose changes, discontinuations).

Objective 2 – Among patients receiving Palbociclib + AI as initial endocrine-based therapy, examine clinical effectiveness outcomes including real-world progression-free survival (rwPFS), overall survival (OS), and real-world tumor response (rwTR).

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Study Design: This is a retrospective, observational study that will document the treatment patterns and clinical outcomes of patients diagnosed with HR+/HER2- A/MBC who received CDK4/6i combination therapy with AI as the initial endocrine-based therapy in the A/MBC setting.

Population: The study will include adult patients 18 years or older, diagnosed with HR+/HER2- A/MBC who initiated CDK4/6i combination therapy with AI as the initial endocrine-based therapy on or after 2/3/2015 and before 4/1/2019. Patients for this study will be identified through Structured Query Language (SQL) queries of the United States oncology electronic medical record (EMR) data available to Concerto HealthAI, including data from CancerLinQ-affiliated practices, referred to as the Definitive Oncology Dataset.

Variables: Patient demographics, clinical characteristics, treatment patterns, and clinical effectiveness outcomes will be collected and analyzed.

Data Source: Concerto HealthAI maintains a network of community oncology practices representing a geographically and demographically diverse patient population. Data from these practices have been collected centrally in the Definitive Oncology Dataset, which is the source of data to be collected in this study.

Study Size: All patients meeting the eligibility criteria from Definitive Oncology Dataset will be included in the study (estimated 1100 –1300 patients).

Data Analysis: Descriptive analysis will be conducted to describe patient demographics, clinical characteristics, treatment patterns (eg, regimen sequencing, dose changes, discontinuations), and clinical effectiveness outcomes (rwPFS, OS, rwTR).

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5. AMENDMENTS AND UPDATES

None.

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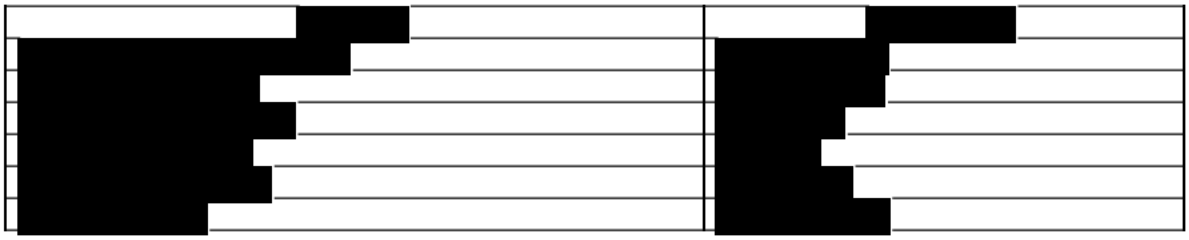

7. RATIONALE AND BACKGROUND

It is estimated that 42,260 people (41,760 female and 500 male) in the United States (U.S.) will die of breast cancer in 2019. Breast cancer is the second leading cause of cancer death for women after lung cancer.[1] Despite advances in the treatment of breast cancer, the prognosis for advanced and metastatic breast cancer (A/MBC) has been poor, with median survival generally under two years in first-line treatment Phase III trials depending on subtype,[2,3] and slightly less in routine clinical practice.[4] In patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) disease, overall survival (OS) ranged from 38.5 – 60.1 months.[5]

About 71% of all breast cancers are HR+ and HER2-.[6] HR+/HER2- A/MBC presents a challenge because patients with exposure to prior hormonal therapy, including aromatase inhibitor (AI) treatment, ultimately develop resistant disease.[7] The treatment landscape for patients with HR+/HER2- A/MBC has changed with the approval of Palbociclib in February 2015 as the first in class cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) indicated for the first treatment for HR+/HER2- A/MBC in combination with letrozole and subsequently expanded to all AIs as well as for the treatment of male breast cancer. Additional CDK4/6i therapies, ribociclib and abemaciclib, were approved in 2017 and 2018, respectively, for use in first line therapy as well. All of the CDK4/6i therapies also received FDA approval for use in combination with fulvestrant for patients who progressed after prior endocrine therapy.[8]

Real-world outcomes for patients with A/MBC who were treated with palbociclib in combination with AI or fulvestrant have been reported in several publications and at medical congresses. A comparative analysis of palbociclib + letrozole vs. letrozole alone was presented at the European Society for Medical Oncology (ESMO) 2019 congress.[9] Using the Flatiron Health Analytics Database consisting of U.S. community physicians, a total of 1,416 electronic health records of patients with HR+/HER2- MBC were reviewed to assess the comparative effectiveness of palbociclib + letrozole (n=798) compared to letrozole alone (n=618). Results showed that patients who took palbociclib + letrozole had a median progression-free survival (PFS) of 24.5 months while patients on letrozole alone had a median PFS of 17.1 months (HR=0.68, 95% CI: 0.56-0.84). OS was also favorable for patients taking palbociclib + letrozole compared to patients taking letrozole alone (HR=0.57, 95% CI: 0.41-0.79). Another study reported on the Ibrance Real World Insights

Study (IRIS) involving medical chart review of 652 U.S. patients with A/MBC treated with palbociclib in combination with either AI (n=360) or fulvestrant (n=292).[10] The 12-month progression-free rate was 84.1% for patients treated with palbociclib + AI and 79.8% for those treated with palbociclib + fulvestrant. The 12-month survival rates were 95.1% for palbociclib + AI and 87.9% for palbociclib + fulvestrant.

This present study is designed to examine further real-world evidence on the use of palbociclib, ribociclib, and abemaciclib in both male and female patients with A/MBC. This study is designed to describe patient characteristics, treatment patterns, and clinical effectiveness outcomes in a cohort of patients diagnosed with HR+/HER2- A/MBC who were treated with any CDK4/6i combination therapies with AI in the U.S. community oncology setting.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to describe the patient characteristics, treatment patterns, and clinical effectiveness outcomes for patients with a diagnosis of HR+/HER2- A/MBC who received CDK4/6i combination therapy with AI as the initial endocrine-based therapy in the A/MBC setting.

Primary Objectives:

1. Among patients with HR+/HER2- A/MBC receiving CDK4/6i combination therapy with AI as initial endocrine-based therapy:

    a. Describe demographic and clinical characteristics.

        - Demographic characteristics will include age, sex, race, insurance status, menopausal status, and region of residence at A/MBC diagnosis;

        - Clinical characteristics will include stage of initial diagnosis, histology, Eastern Cooperative Oncology Group (ECOG) performance status (where available, Karnofsky performance status will be converted to corresponding ECOG score) and comorbid disease burden, HER2 and Estrogen receptor (ER)/Progesterone receptor (PR) status, number and sites of distant metastasis at A/MBC diagnosis (if applicable); modalities of treatment received prior to A/MBC diagnosis (chemotherapy, hormone therapy, surgery, radiation therapy) and disease free interval (time between completion of adjuvant therapy and diagnosis of A/MBC).

    b. Describe treatment patterns.

        - Distribution of regimens from the diagnosis of A/MBC through the end of the record;

- Sequence of regimens across lines, through the end of the record of systemic therapy;

- Description of the dosing employed with administration of palbociclib, ribociclib, and abemaciclib. Description of the dosing will include the starting dose, end dose, dose adjustment (dose increase and dose reduction), reasons for dose adjustment (dose modification, schedule changes, dose delay, hold, or discontinuation), discontinuation, reason, and time to dose adjustment (discontinuation).

2. Among patients receiving Palbociclib + AI as initial endocrine-based therapy, examine clinical effectiveness outcomes including:

   a. Real-world progression-free survival (rwPFS) will be assessed for the first endocrine-based therapy.

   b. Overall survival (OS) will be assessed from start of the first endocrine-based therapy.

   c. Real-world tumor response (rwTR) will be assessed as best overall response for each regimen received within the first endocrine-based therapy.

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9. RESEARCH METHODS

9.1. Study Design

This is an observational, retrospective study involving medical chart review. Eligible patients will be identified and accrued from the Concerto HealthAI Definitive Oncology Dataset. All study data are secondary data and will have been collected retrospectively from existing clinical data originally collected as part of routine care.

9.2. Setting

9.2.1. Inclusion Criteria

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

1. Female or male sex.

2. Diagnosis (confirmed by clinical review) of A/MBC, defined as breast cancer at stage IIIB, stage IIIC, stage IV or identified as having distant metastasis.

3. Age ≥18 years at A/MBC diagnosis.

4. Initiated a CDK4/6i in combination with an AI as initial endocrine-based therapy after A/MBC diagnosis on or after 2/3/2015 and before 4/1/2019.

    - Note that the date of the start of the inclusion period reflects the month that the first CDK4/6i (ie, Palbociclib) received U.S. FDA approval.

5. Evidence of ER or PR positive disease, or absence of any indication of ER and PR negative disease closest to A/MBC diagnosis (ie, patients are eligible without affirmative indication of ER/PR+ status as long as ER/PR- indication is not present).

6. Evidence of HER2 negative disease, or absence of any indication of HER2 positive disease closest to A/MBC diagnosis (ie, patients are eligible without affirmative indication of HER2- status as long as HER2+ indication is not present).

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Enrollment in an interventional clinical trial for A/MBC during the study observation period.

9.3. Variables

9.3.1. Regimens and Lines

For purposes of this study, a regimen will be defined as one or more anti-cancer agents given in combination, over a period of time, in which the following conditions hold:

1. All agents start within 60 days of the start of the first agent in the combination, unless the start of an agent later than 60 days after the start of the first agent is specifically indicated as planned at the time of the start of the first agent.

2. No agent is discontinued and replaced by another agent within 60 days of the start of the first agent in the combination.

3. No agent is held and then resumed after an interval of more than 63 days.

Accordingly, unless the record indicates a planned delay in the start of an agent, the addition of a new agent to an existing therapy more than 60 days after start of the regimen constitutes a change of regimen. Holding of an agent for a brief period is not interpreted as a change of regimen. However, the resumption of an agent that is held and then resumed after an interval of more than 63 days is interpreted as signaling a new regimen. Discontinuation of one agent

being used in combination at any point by itself does not signal end of a regimen unless it is the only agent being administered. Occurrence of a disease progression does signal the end of a regimen. After a progression, a treatment being given before the progression will be interpreted as a new regimen—albeit identical to the previous one. This scenario, treatment through progression, occurs in some settings, and is identifiable in study data with the coding rules described here.

For the purpose of this study, lines of therapy will be defined as the following *Progression-based* lines, in which a disease progression must occur for a new regimen to be interpreted as a new line of therapy.

Disease progression is taken to have occurred when a pathology report or radiological scan indicates disease progression and/or there is a physician progress note consistent with that determination. If the radiological scan did not agree with the physician notes, the event will be determined by physician notes.

For the purposes of this study, first line therapy will be defined as the first progression-based line of therapy that contains the first qualifying endocrine-based therapy. The first qualifying endocrine therapy may include palbociclib + AI, or other CDK4/6i combination therapies with AI that the patient receives after diagnosis of A/MBC. Subsequent lines of therapy will be defined in detail in the statistical analysis plan (SAP) as progression-based lines. Regimens within the first progression-based line defined above will be identified.

9.3.2. Curated Data

Data abstracted by Clinical Research Nurses (CRNs) will include the following:

1. Race/Ethnicity.

2. Date of initial diagnosis of breast cancer.

3. Stage at initial diagnosis of breast cancer.

4. Modalities of treatment received at any point prior to A/MBC diagnosis (Surgery, Radiation, Chemotherapy, Hormone therapy). This variable will be collected as "Yes" or "Not Documented" for each modality. The last date of systemic therapy, including hormonal therapy, administered in the adjuvant setting prior to stage IV/MBC diagnosis will be documented, if applicable.

5. Among patients who have a record of hormone therapy prior to A/MBC diagnosis, the name(s), and start and end dates of the hormonal agents received in the adjuvant setting will be collected.

6. Status of the patient as having progressed at any point after initiation of the first hormone therapy in the adjuvant setting, prior to A/MBC diagnosis (Y/N). If yes, the date of first disease progression/recurrence following initiation of hormone therapy in the adjuvant setting will be collected.

7. Date of A/MBC diagnosis. This date defines the index date for the study, as referenced below in describing other study variables.

8. Stage at index date (IIIB, IIIC, or IV).

9. For patients documented as Stage IIIB or IIIC at index date, the date of Stage IV/metastatic diagnosis will be collected, if applicable, from the index date through the end of the record or the end of the study, whichever occurs first.

10. Sites of distant metastasis at index date, if applicable (Bone; Chest Wall; Contralateral Breast; Distant Lymph node(s); Liver; Lung; Peritoneum; Pleural nodules; Malignant pleural effusion; Skin; Brain; Undocumented; Other, Specify).

11. Disease histology (Adenoid cystic; Cribriform; Ductal; Inflammatory; Intraductal; Lobular; Medullary with lymphoid stroma; Medullary, NOS; Mucinous; Paget's disease and infiltrating; Paget's disease and intraductal; Papillary; Secretory; Squamous cell; Tubular; Undifferentiated; Undocumented, Other, specify) nearest in time to index date.

12. ER status nearest in time to index date.

13. PR status nearest in time to index date.

14. HER2 status nearest in time to index date.

15. Menopausal status (Pre, Peri, Post, UD) nearest in time to the date of, but before, index date. Date of documentation will be collected.

16. ECOG/performance status, if available or indication of impaired performance status not otherwise classified as an ECOG rating, at index date (±60 days). Where available, Karnofsky performance status will be converted to corresponding ECOG score.

17. Comorbidities, indicated as present vs. not indicated as present at index date. The conditions and date of the condition to be assessed will include those assessed as part of the standard Charlson Comorbidity Index. These include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, hemiplegia, chronic obstructive pulmonary disease, ulcer disease, diabetes, renal disease, connective tissue disease such as rheumatoid arthritis or lupus, Alzheimer's or other dementia, cirrhosis or other serious liver disease, leukemia, lymphoma, metastatic solid tumor (other than breast cancer), and HIV/AIDS.

18. Other comorbidities of interest, indicated as present vs. not indicated as present at index date: hypertension and hyperlipidemia.

19. Dates of disease progression after index date through the end of the record or the end of the study, whichever occurs first.

20. Documentation of treatment modifications (dose modification, schedule changes, dose delay, hold, or discontinuation) for palbociclib, CCI [redacted] and reasons for treatment modifications, if applicable, from the index date through the end of the record or the end of the study, whichever occurs first. Date of treatment modification and reason for modification will be collected, if available.

    - Reasons for modification will include: Cost, disease progression, patient refusal/request, toxicity (specify), other (specify), or UD.

21. Oral anti-cancer therapies. This will include all treatments from the index date through the end of the record or the end of the study, whichever occurs first. CCI [redacted]

22. Documentation of any IV, IM, or subcutaneous anti-cancer therapy not otherwise documented in standard medication tables, including all treatments received from the index date through the end of the record or the end of the study, whichever occurs first. Agent and start and end dates will be collected.

23. First positive response and best overall response for each regimen from the index date through the end of the first progression-based line of therapy containing the first qualifying endocrine-based therapy, the end of the record or the end of the study, whichever occurs first. Responses will be classified as Complete response (CR); Partial response (PR); Stable disease (SD); Progressive disease (PD); Not evaluable (NE); or Undocumented. The date of the first positive response (CR or PR) and of the best overall response for each regimen will be collected.

9.3.3. Extracted Data

Patient data from OncoEMR will be flagged to be excluded from the regulatory study. Data extracted from the Definitive Oncology Dataset through SQL query will include the following:

1. Sex.

2. Insurance status (private only, public only, public and private, or neither) at index date and at initiation of the earliest endocrine-based regimen after the index date.

3. Date of birth.

4. Date of death, as indicated in the clinical record and by Social Security Death Index (SSDI) records or associated obituary records linked to the Definitive Oncology Dataset.

5. Treatments and dates of treatments for all infused or injected anti-cancer therapies from the index date through the end of the record or the end of the study, whichever occurs first.

9.3.4. Derived Variables

Variables suggested to be derived for this study's purpose will be generated by Pfizer analytical team. Final algorithm to derive the variables will be further determined by Pfizer. The suggested variables derived from abstracted and extracted data will include the following:

1. Age at index date, at initiation of the earliest endocrine-based regimen, and at first treatment regimen after the index date.

2. Weighted index of comorbid disease condition. Weighting of comorbid conditions (not including breast cancer) will follow the weighting as specified in the Charlson Comorbidity Index.

3. Start and end dates of anti-cancer treatments from the index date through the end of the record or the end of the study, whichever occurs first.

4. Treatment regimens, derived from oral and infused agents delivered, including start and end dates.

5. Endocrine sensitivity prior to the index date, defined as endocrine sensitive vs. resistant vs. refractory based on adjuvant endocrine therapy experience. Endocrine sensitive: ≥24 months without recurrence/progression after completion of endocrine therapy in the adjuvant setting; Endocrine resistant: recurrence/progression after completion of endocrine therapy, and within 24 months of completion of endocrine therapy; Endocrine refractory: recurrence/progression while on endocrine therapy in the adjuvant setting, defined as occurring while on or within <30 days after discontinuation of endocrine therapy. The 30 day window allows that endocrine therapy may be discontinued because of a perceived progression before that progression is actually documented.

6. Primary endocrine resistance defined as a relapse while on the first 2 years of adjuvant endocrine therapy or disease progression within the first 6 months of first-line endocrine therapy for A/MBC, while on endocrine therapy.

7. Secondary (acquired) endocrine resistance defined as a relapse while on adjuvant endocrine therapy but after the first 2 years or a relapse within 12 months of completing adjuvant endocrine therapy, or disease progression ≥6 months after initiating endocrine therapy for A/MBC, while on endocrine therapy.

9.4. Data Sources

The present study will include data from Patient360 and other curated data available within the Definitive Oncology Dataset.

The Definitive Oncology Dataset is drawn from a wide range of principally community oncology practices throughout the United States. Practices range in size from very small to large, and are located in both rural and urban settings. The practices are not all members of any one group purchasing organization, so practice patterns reflect real-world variability of treatment.

Datasets available to Concerto HealthAI include a repository of oncology healthcare data, including those from practices affiliated with CancerLinQ - a wholly-owned subsidiary of the American Society of Clinical Oncology that works with both nonprofit and federal agencies to warehouse and aggregate medical records of cancer patients treated at practices in 40 U.S. states and the District of Columbia - as well as administrative healthcare claims and genomic data.

Key features of the Definitive Oncology Dataset include the following.

- Availability of both structured data (tables, rows and columns) and unstructured data (text and image documents, eg, physician progress notes). The unstructured information is generally not available in other Electronic Medical Record (EMR) data sources, although this is where much of the richest clinical information is found. Together with the structured data, Concerto HealthAI has access to an essentially complete version of the medical oncology health record for each patient. As a result, analysis does not need to rely on proxy measures of key clinical endpoints, as may be the case where only structured EMR data are available.

- Treatment across the practices from which data are drawn is not directed by any single group purchasing organization requirements, unlike some other providers of EMR data. Therefore, data from the Concerto HealthAI network reflect the diversity of real-world independent practice.

- The real-world diversity of the practices from which data are drawn, and the clinical depth of the information available, enable our experienced oncology research team to answer study questions that cannot be addressed through other data sources.

9.5. Study Size

The study will include all patients (estimated 1100 –1300 patients) in the data set for the descriptive elements who meet the inclusion/exclusion criteria.

CCI [redacted] The sample size of this study will be based on the actual number of eligible patients available for the study through CRN screening.

Given the inclusion criterion requiring a qualifying diagnosis of HR+/HER2- A/MBC between 2/3/2015 to 4/1/2019, and assuming data collection were to start by 12/1/2019, the average follow-up available for patients receiving Palbociclib plus AI combination therapy is therefore ((50/2) + 8) = 33 months.

9.6. Data Management

Following preparation and institutional review board (IRB) approval of a study protocol, updated SQL queries will be written to identify patients within the Definitive Oncology Dataset with evidence of diagnosis of the disease of interest. Feasibility programming has already identified likely eligible patients. However, some refinement of this programming will be undertaken to enhance identification of eligible patients. The resulting program will be used to populate a screening list used by Concerto HealthAI research staff for review of the electronic medical records.

Concerto HealthAI's Statistical Group will extract information related to demographic characteristics, infused treatments, staging, and other clinical data, as applicable. Experienced CRNs will examine the medical record of each potentially eligible patient. The disease of interest and other eligibility criteria will be verified and documented. If the patient meets all eligibility criteria, the patient will be accrued. For each eligible patient, the relevant study data will be extracted by SQL query or abstracted by CRNs onto case report forms and entered into a secure database for analysis.

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9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term DCT 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 DCT is required and should be completed for the record of each curated patient. The completed original DCTs should not be made available in any form to third parties. Concerto HealthAI shall ensure that its DCTs are securely stored in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

Concerto HealthAI has ultimate responsibility for the collection and reporting of curated data required for the study entered on the DCTs and any other data collection forms and ensuring that they meet the data curation specifications provided by Pfizer. Any corrections to entries made in the DCTs or source documents must be fully captured in an audit trail.

9.6.2. Record Retention

Unless expressly agreed to via a separate written agreement by Concerto HealthAI and Pfizer, Concerto HealthAI will retain all study-related documents, including copies of all DCTs, safety reporting forms, source documents utilized for curation services, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports), for the periods specified in this Section 9.6.2 or as required by applicable law, whichever is longer, unless Pfizer authorizes, in writing, earlier destruction. Complete and accurate accounting records relating to the services Concerto HealthAI provides for this study will be maintained in accordance with generally accepted accounting principles and retained by Concerto HealthAI for at least three (3) years after completion or discontinuation of the study. Other records relating to the services Concerto HealthAI provides relating to this study will be retained for five (5) years. CCI [redacted] Concerto HealthAI will ensure that it maintains mechanisms to read any records stored in electronic form for at least the minimum retention period for those records specified in this Section 9.6.2.

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If Concerto HealthAI becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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.

9.8. Quality Control

All data abstracted from the Definitive Oncology Dataset by CRNs will undergo an independent quality control review, with evaluation for consistency, completeness, and outlier values. This review is conducted by a supervising Curation Manager at Concerto HealthAI and through programmatic evaluation of study data. Data queries generated as part of quality review are documented and resolved, with documentation of queries and resolution maintained in a complete query log.

Data housed in electronic case report forms will then be exported to SAS datasets for data cleaning and preparation, creation of derived values, and preparation of analysis datasets. Data will then undergo initial statistical review, including examination of all fields for outlier values, and evaluation for internal consistency of study data. Values that are flagged as potentially anomalous during statistical review will be queried and resolved before analysis datasets are finalized. All study data also undergoes scientific review of study results prior to data lock.

9.9. Limitations of the Research Methods

This study reflects treatment practice patterns only within the U.S. who are part of the Definitive Oncology Dataset. The majority of the data reflects treatment in community oncology settings (80%). It is possible that treatment patterns may differ in academic centers compared with community settings.

This study is retrospective. With the advent of newer therapies in breast cancer, it is expected that treatment patterns will change during the next few years, and therefore, this study may not be reflective of future breast cancer treatment patterns.

It is possible that patients within the Definitive Oncology Dataset differ from the underlying breast cancer population in ways that may not be measurable; therefore, study results may not be generalizable to other settings.

Some measurements may not be consistently available from patient records in the Definitive Oncology Dataset.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

Concerto HealthAI and Pfizer may provide the other party with access to certain information that can be used by itself or in combination with other available information to identify a specific individual included in the study ("patient personal data") so long as prior written approval of the party receiving the materials is obtained. For sake of clarity, key-coded data relating to individual persons is considered to be personal data. Neither Concerto HealthAI nor Pfizer will attempt to re-identify study subjects. Both parties will implement appropriate internal measures to minimize the risk of any re-identification of study subjects.

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, and in accordance with the Pfizer/Concerto HealthAI Collaboration Agreement. 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 or where there is valid written consent or authorization on file.

The party sharing patient personal data or samples is responsible for providing and obtaining any legally-required notice and consent from individuals, or for arranging for the study investigator and site to obtain such notice and consent from individuals, with respect to such patient personal data or samples for the purposes contemplated by this Protocol.

In case of data transfer, processing and use, both Concerto HealthAI and Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

Neither Concerto HealthAI nor Pfizer will transfer, or permit any third party to transfer personal data provided by the other party across any national borders without prior written consent of the party providing such data, unless specifically authorized to do so. In the event any such cross-border transfer is authorized, the party transferring such personal data across national borders is responsible for ensuring that any transfer of personal data across national borders (whether performed by itself or a third party) complies with all applicable laws.

Concerto HealthAI and Pfizer will ensure that any patient personal data is not processed in a way that is incompatible with the purposes for which it was collected or subsequently authorized by the individual from whom it was obtained. For the sake of clarity, the process of de-identification does not render the data incompatible for the purposes for which it was collected for this study.

Concerto HealthAI and Pfizer will apply adequate and commercially reasonable electronic, physical, and other safeguards appropriate to the nature of the information to prevent any accidental, unauthorized or unlawful use, access, alteration, loss or disclosure of personal data.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. 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.

10.4. 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 Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human Review of Unstructured Data

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 NIS AEM Report 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.

CCI [redacted]

CCI [redacted]

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

CCI [redacted]

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 Concerto HealthAI 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.

13. REFERENCES

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.