NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	**Characteristics, Treatment Patterns, and Clinical Outcomes in Acute Myeloid Leukemia (AML) Patients Using Mylotarg – a US Real-World Study Using Electronic Medical Record Data**
Protocol number	B1761033
Protocol version identifier	Version 1.0
Date	*24 February 2020*
Active substance	Not applicable
Medicinal product	Mylotarg (gemtuzumab ozogamicin)
Research question and objectives	Among patients with a diagnosis of AML who received Mylotarg (gemtuzumab ozogamicin): - Describe patient demographic and clinical characteristics - Describe treatment patterns and sequence - Describe real world effectiveness outcomes - Evaluate real world tumor response
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
AIDS	Acquired immunodeficiency syndrome
AML	Acute myeloid leukemia
BMI	Body mass index
CR	Complete response
CRF	Case report forms
CRh	Complete response with partial hematologic recovery
Cri	Complete response with incomplete hematologic recovery
CRN	Clinical Research Nurse
DCT	Data collection tools
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ELN	European LeukemiaNet
EMR	Electronic medical record
FDA	Food and Drug Administration
FISH	Fluorescence in situ Hybridization
FLT3	Fms-like tyrosine kinase 3
GO	gemtuzumab ozogamicin
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent

Abbreviation	Definition
IDH1/2	Isocitrate dehydrogenase 1/2
IEC	Independent ethics committee
IM	Intramuscular
IRB	Institutional review board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IV	Intravenous
MDS	Myelodysplastic syndromes
MLFS	Morphologic leukemia-free state
MPN	Myeloproliferative neoplasms
NE	Not evaluable
NIS	Non-interventional study
NPM1	Nucleophosmin 1
OS	Overall survival
PD	Progressive disease
PR	Partial response
R/R	Relapsed/refractory
RFS	Relapse-free survival
RW	Real world
SAP	Statistical analysis plan
SD	Stable disease
SQL	Structured query language
SSDI	Social Security Death Index

Abbreviation	Definition
TF	Treatment failure
TP53	Tumor protein 53
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

Title: Characteristics, Treatment Patterns, and Clinical Outcomes in Acute Myeloid Leukemia (AML) Patients Using Mylotarg – a US Real-World Study Using Electronic Medical Record Data

Rationale and Background: Historically, the number of treatments available for newly diagnosed patients with AML has been limited. However, new treatment regimens have become available recent years (including gemtuzumab ozogamicin [GO], midostaurin, glasdegib, plus low-dose cytarabine, venetoclax plus hypomethylating agents). Given the FDA label for GO, issued September 2017, it is critical to understand the recent real-world use of GO as a treatment for AML.

Research Question and Objectives: This research aims to assess patients with a diagnosis of AML who received Mylotarg in a real-world setting. The objectives are to:

- Describe the patient demographics and clinical characteristics;
- Describe treatment patterns and sequence;
- Describe real world effectiveness outcomes;
- Evaluate real world tumor response.

Study Design: This is a retrospective, observational study that will document the treatment patterns and clinical outcomes in patients diagnosed with AML who received Mylotarg. The study will use United States oncology electronic medical record data available to Concerto HealthAI, including data from CancerLinQ-affiliated practices, referred to as the Definitive Oncology Dataset.

Population: This study will include adult patients diagnosed with AML who, at any point on or after September 1, 2017 received Mylotarg, alone or in combination with other agents for newly diagnosed or relapsed refractory AML.

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

Data Source: Concerto HealthAI maintains a network of 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: The target sample size for this study is approximately 20-30 patients treated with Mylotarg.

CCI [redacted]

[redacted]

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	**Planned date**
Draft Protocol Submission	November 2019
Pfizer Approval of Protocol	February 2020
Submit SAP to Pfizer	March 2020
IRB Approval	March 2020
Start of Data Collection/	March 2020
End of Data Collection	April 2020
Complete Data Analysis	July 2020
Deliver Final Study Report	July 2020

7. RATIONALE AND BACKGROUND

Acute Myeloid Leukemia (AML) is the most common form of fast-growing blood and bone marrow cell cancer. In the United States (US) in 2019, it is estimated there will be 21,450 new cases and 10,920 deaths from AML.[1] The average age at diagnosis is 68 years old, and the 5-year survival rate is 26.9%.[2] About 60%-70% of adults with AML can attain a complete remission following induction therapy with cytotoxic chemotherapies to reduce leukemic cells in the blood and bone marrow. Slightly more than 25% (45% of those who attain complete remission) are expected to survive 3 or more years and may be cured.[2] Remission rates are related to age, with the expected remission rate of more than 65% in those younger than 60 years old. Duration of remission is shorter in older patients, and increased morbidity and mortality during induction treatment are related to older age.[2]

Historically, the number of treatments available for newly diagnosed patients with AML has been limited. However, new treatment regimens have become available recent years (including gemtuzumab ozogamicin [GO], midostaurin, glasdegib, plus low-dose cytarabine, venetoclax plus hypomethylating agents). Given the FDA label for GO, issued September 2017, it is critical to understand the recent real-world use of GO as a treatment for AML.

The present study is focused on real-world outcomes in adult patients with AML who at any point received treatment with Mylotarg, used alone or in combination with other agents. Although the present study is focused on the receipt of this agent during first- or second-line therapy, it is expected that most of the identified patients will also go on to receive subsequent treatment. The aim of this study is to describe treatment patterns and effectiveness outcomes in a sample of oncology patients treated for AML with Mylotarg through up to two additional relapsed/refractory (R/R)-based lines of therapy (through third-line therapy).

8. RESEARCH QUESTION AND OBJECTIVES

The study includes patients with a diagnosis of AML who received Mylotarg in a real-world setting.

The study objectives are as follows. All analyses as described in Objectives 1 through 4 will be assessed across all patients using Mylotarg, and will not be stratified by a grouping variable.

1. To describe the demographic and clinical characteristics as outlined in the variable list below for patients diagnosed with AML who received Mylotarg in a real-world setting.

    a. Demographic characteristics will include age, race, body mass index (BMI), insurance status, and region of residence closest to the date of AML diagnosis.

    b. Clinical characteristics will include comorbidity scores, Eastern Cooperative Oncology Group (ECOG) score, and disease characteristics such as stage at index date, cytogenetic testing results at index date, and de novo versus secondary AML diagnosis.

2. To describe the treatment patterns from the diagnosis of AML through the end of the third relapsed/refractory (R/R)-based line of therapy (R/R event, or disease progression, or death are considered as end events).

    a. Distribution of regimens within lines, for the first 3 R/R-based lines of systemic therapy.

    b. Distribution of regimen sequences, across 3 R/R-based lines of systemic therapy.

    c. Starting dose and dose changes of Mylotarg in each of the 3/R/R-based lines of therapy.

    d. Duration of Mylotarg treatment in each of the first three R/R-based line of therapy.

3. To describe the effectiveness outcomes of treatment of AML patients who received Mylotarg in a real-world setting.

    a. Real world event-free survival (rwEFS)/real world relapse-free survival (rwRFS) in the first three R/R-based lines of therapy. The definition of rwEFS/rwRFS as described in Section 9.7.2 is aligned to the extent possible using real world data with that used by Pfizer in other studies.

    b. Real world overall survival (rwOS) from start of the initial line of therapy in which Mylotarg is used.

c. rwEFS/rwRFS/rwOS will be described across all patients.

4. To evaluate tumor response for the first qualifying Mylotarg-containing R/R-based line of therapy among AML patients who received Mylotarg in a real-world setting.

   a. First and best tumor response, as described in Section 9.7.6, will be described in the first qualifying Mylotarg-containing R/R-based line of therapy.

   b. Time to best response will be described in the first qualifying Mylotarg-containing R/R-based line of therapy.

   c. Duration of best response will be described in the first qualifying Mylotarg-containing R/R-based line of therapy.

9. RESEARCH METHODS

9.1. Study Design

This is an observational, retrospective study of characteristics, treatment patterns, and clinical outcomes in patients diagnosed with AML who received Mylotarg. The study will use United States oncology electronic medical record (EMR) data available to Concerto HealthAI, including data from CancerLinQ-affiliated practices. These data are referred to as the 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. Confirmed diagnosis of AML on or after 01 December 2014 through Clinical Research Nurse (CRN) review of provider documentation of AML diagnosis in the medical record.

2. Receipt of Mylotarg at any point during first three lines of therapy following initial AML diagnosis.

3. Age ≥18 years at initial diagnosis of AML.

There are no inclusion criteria related to minimum follow-up.

9.2.2. Exclusion Criteria

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

1. Record of 1 or more of the following confounding diagnoses at any point before or after AML diagnosis: Acute lymphoblastic leukemia; acute promyelocytic leukemia, aggressive systemic mastocytosis; hypereosinophilic syndrome and/or chronic eosinophilic leukemia; dermatofibrosarcoma protuberans; gastrointestinal stromal tumors.

9.3. Variables

9.3.1. Regimens and Lines

Detailed definitions for lines of therapy, therapy start and end dates, discontinuation, and related items will be provided in the Statistical Analysis Plan (SAP). In consultation with Pfizer, business rules for defining regimens and lines of therapy may be altered to conform to standard Pfizer business rules and definitions, where applicable and possible.

For purposes of this study, a **regimen** will be defined as 1 or more anti-cancer agents given in combination, over a period of time, in which the following conditions hold:

1. All agents start within 30 days of the start of the first agent in the combination, unless the start of an agent later than 30 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 30 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. A standard chemotherapy cycle is assumed to be 21 days; 63 days allows for a delay of 3 cycles of chemotherapy without a change in regimen.

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 30 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, discontinuation and resumption of an agent after an interval of more than 63 days is interpreted as signaling a new regimen. Discontinuation of all agents in a regimen signals the end of the regimen. Occurrence of a R/R event or a disease progression does signal the end of a regimen. Continuation after R/R event or progression of a treatment being given before the R/R event or 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 purposes of this study, first line therapy will be defined as beginning with the first regimen the patient receives after diagnosis of the disease of interest. Subsequent lines in this study will be defined as *R/R-based* lines.

R/R-based lines are defined by the occurrence of a R/R event or a disease progression - either may be cited, in which a R/R event or disease progression must occur for a new regimen to be interpreted as a new line of therapy. R/R-based lines may be preferred where the research questions focus on effectiveness outcomes such as rwEFS/rwRFS, and where sample homogeneity as to previous disease progression is preferred for assessment of outcomes in second or later lines. In this study, refractory AML is defined as disease that is nonresponsive or failing to achieve at least minimal response as noted by provider documentation (described in Section 9.7.6) while on therapy. Relapsed status is defined as the recurrence or worsening of disease following achievement of at least a minimal response. Additionally, the documentation of advancement of disease in patients after initial AML diagnosis but before initial AML treatment will be interpreted as a disease progression. R/R events and disease progression will be defined based on provider documentation, which primarily includes progress notes.

9.3.2. Curated Data

Data abstracted for eligible patients from the unstructured data available in the Definitive Oncology Dataset by CRNs will include the following:

- Race/Ethnicity.
- Date of initial AML diagnosis. This date defines the *index date* for the study, as referenced below in describing other study variables.
- Documentation of de novo versus secondary AML at index date. Secondary AML is defined as development of AML after myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), or following exposure to chemotherapy and/or radiotherapy.
    - If secondary AML, documentation of use of hypometholating agents (HMA) at any point prior to initial AML diagnosis (Y/N). If yes, name of HMA agent will be documented.
- Stage at index date.
- Comorbidities, indicated as present versus not indicated as present at index date (±30 days). The conditions 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 (other than AML), lymphoma, metastatic solid tumor, and Human Immunodeficiency Virus (HIV)/acquired immunodeficiency syndrome (AIDS).

- ECOG performance status, if available or indication of impaired performance status not otherwise classified as an ECOG rating, at index date (±30 days).

- First response and best overall response as described in Section 9.7.6 to treatment for the first qualifying Mylotarg-containing R/R-based line of therapy from the index date through the third R/R-based line of therapy or the end of the record, whichever occurs first. Date of first positive response and best overall response will be documented.

- Documentation of European LeukemiaNet (ELN) genetic risk stratification (favorable, intermediate, adverse, or undocumented), based on provider documentation, if available, closest to index date.

- Biomarker status and date of results will be recorded at index date (±30 days), if available in the medical record.

    - Biomarkers collected will include the following: FLT3, IDH1, IDH2, TP53, and NPM1.

- Documentation of cytogenetics and/or Fluorescence in situ Hybridization (FISH) analysis at index date (±30 days). Cytogenetics and/or FISH tests will include the following, if available in the medical record. This will include the presence of the following tests at index date (±30 days), and the number of patients with positive test results.

    - t(6;9)(p23:q34.1).

    - t(v;11q23.3).

    - t(9;22)(q34.1;q11.2).

    - inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2).

    - -5 or del(5q); -7; -17/abn(17p).

    - Complex karyotype.

    - Monosomal karyotype.

    - t(8;21)(q22;q22.1).

    - inv(16)(p13.1q22) or t(16;16)(p13.1;q22).

- Dates of relapsed/refractory events and disease progressions will be documented from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first.

- Oral anti-cancer therapies. This will include all treatments received from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first. Data collection will include agent, start and end dates, start and end dose, and start and end schedule. Documentation of changes in dose and schedule will be collected.

- Documentation of any (IV) intravenous, (IM) intramuscular, 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 third R/R-based line of therapy or the end of the record, whichever occurs first. Data collection will include agent, start and end dates, start and end dose, and start and end schedule. Documentation of changes in dose and schedule will be collected.

9.3.3. Extracted Data

Data extracted for eligible patients from the structured data that are available in the Definitive Oncology Dataset through Structured Query Language (SQL) query will include the following:

- Insurance status (private only, public only, both, neither).

- State of residence.

- Sex.

- Height.

- Weight at index date (±30 days).

- Date of birth.

- Date of death.

- Treatments, dates of treatments, dose, and schedule for all oral (if applicable), infused, or injected anti-cancer therapies from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever comes first.

9.3.4. Derived Variables

All variables to be used in the final study analyses including those that are derived from curated and extracted data, will be formally defined in the SAP. Variables derived from abstracted and extracted data will include the following:

- Age at index date.

- BMI at index date (±30 days).

- Geographic census region of residence.

- Weighted index of comorbid disease condition. Weighting of comorbid conditions will follow the weighting as specified in the Charlson Comorbidity Index.

- Start and end dates and start and end dose of infused anti-cancer treatments from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first.

- Dose changes of all oral (if applicable), infused, or injected anti-cancer therapies from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first.

- Start and end schedule of infused anti-cancer treatments from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first.

- Treatment regimens, derived from oral and infused agents delivered, including start and stop dates.

- Duration of anti-cancer treatments regimens from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first. Duration will be calculated as the end date of last agent within a regimen minus the start date of the corresponding regimen and will be computed during the analytics phase of the project.

- Time under observation for analysis of EFS/RFS, by line, based on start date of treatment within line and dates of R/R event or disease progression, or censoring.

- Time under observation for analysis of OS from start of the first qualifying Mylotarg-containing R/R-based line of therapy, based on start of treatment in the first qualifying line setting, and based on date of death or censoring.

- Time to best response for the first qualifying Mylotarg-containing R/R-based line of therapy from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first.

- Duration of tumor response for the first qualifying Mylotarg-containing R/R-based line of therapy from the index date through the end of the third R/R-based line of therapy or the end of the record, whichever occurs first.

9.4. Data Sources

The Definitive Oncology Dataset is used in support of a range of business activities, including retrospective research, and are not aggregated specifically to address the research of any one study.

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 US 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 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

CCI [redacted] Initial exploration of the Definitive Oncology Dataset suggest the study sample size will be between 20 and 30 patients.

The aims of this research are descriptive. Accordingly, statistical power for inferential testing comparing effectiveness outcomes across groups is not indicated. Therefore, power calculation is not applicable.

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 AML. Feasibility programming has already identified some 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, and if the accrual target has not been met, 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.

Data management systems used in support of Concerto HealthAI HEOR studies are not 21 CFR part 11 validated, and are not intended for use in support of submissions to health regulatory agencies.

This project will entail use of an electronic data entry system with audit trail, but not a formal Electronic Data Capture system. Accordingly, the provisions of Section 4.4 of CT24-GSOP_Non-Interventional Studies (Design and Develop Data Collection Tool and Data Management) are considered outside the scope of the project.

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 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. (In the event of regulatory filings by Pfizer, Concerto HealthAI will retain the necessary data and analysis for a period of seven (7) years or as reasonably requested by Pfizer). 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.

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 also 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]*.

9.7.1. Descriptive Analysis

Descriptive statistics are typically generated for all study variables. The descriptive statistics include means, standard deviations, medians, and minimum and maximum values for continuous variables (eg, age at diagnosis) and frequencies and percentages for categorical variables (eg, race, performance status).

No statistical comparisons will be performed. CCI [redacted]

9.7.2. Time to Event Analysis

Single time to event analyses will be conducted as specified under the study objectives. CCI [redacted]

Real world time to event outcomes in this study will include:

- rwEFS/rwRFS for each of the first three R/R-based lines of therapy. rwEFS will be defined as the time from the treatment initiation date (for the first line of therapy) to the date of treatment failure (TF), relapse from Complete Response (CR) or better, or death from any cause, whichever comes first. TF is defined as failure to achieve CR or better following up to 6 cycles of Mylotarg. rwRFS will be defined as the time from the treatment initiation date (for the first line of therapy) to the date of a relapse event, or death from any cause, whichever comes first.

- rwOS, from the first line of therapy through the end of record or death, whichever occurs first, and

- Duration of therapy across lines of therapy from the first line of therapy through the third R/R-based line of therapy.

The time origin for analysis of rwEFS/rwRFS is the start of therapy within each specific line of therapy, and the terminal event is the earlier of an R/R event or death. The time origin for analysis of rwOS is the start of therapy within the first line of therapy, and the terminal event is death. The time origin for analysis of duration of therapy is start of Mylotarg, and the terminal event is discontinuation of that therapy.

9.7.3. Methods Under Objective 1

Objective 1: To describe the demographic and clinical characteristics as outlined in the variable list below for patients diagnosed with AML who received Mylotarg in a real-world setting.

Descriptive analysis as detailed in Section 9.7.1 will be conducted for work under this objective. Demographic characteristics that will be reported will include the distribution of sex, patient age, race/ethnicity, height, weight, BMI, insurance status, and region of residence closest to the index date. Clinical characteristics that will be reported will include the distribution of comorbidity status and comorbidity index score, ECOG score, and disease characteristics, such as stage at index date, cytogenetic testing at index date, and whether the AML diagnosis was de novo versus secondary.

Demographic and clinical characteristics will not be stratified by a primary grouping variable.

9.7.4. Methods Under Objective 2

Objective 2: To describe the treatment patterns from the diagnosis of AML through the end of the third R/R-based line of therapy

Analysis under this objective will include all study patients. Descriptive analysis as detailed in Section 9.7.1 will be conducted for work under this objective. Treatment patterns include description of regimens within line of therapy for the first 3 R/R-based lines of systemic therapy as well as the description of sequences of regimens across 3 R/R-based lines of systemic therapy. Description of treatment regimens within line includes the frequency and percentage of each agent/regimen received, by regimen in sequence, by line, for the first 3 R/R-based lines of systemic therapy. In addition, the analysis will descriptively characterize the starting dose of Mylotarg in each of the first lines of therapy.

Duration of treatment will also be descriptively analyzed across lines of therapy, starting with the first agent or regimen in the first line of therapy for the first 3 R/R-based lines of therapy.

9.7.5. Methods Under Objective 3

Objective 3: To describe the effectiveness outcomes of treatment of AML patients who received Mylotarg in a real-world setting.

Analysis under this objective will include all study patients. The outcomes of interest under this objective are rwEFS/rwRFS and real world overall survival. Time to event analysis as described in Section 9.7.2 will be utilized.

The Kaplan-Meier product limit estimator will be employed to evaluate rwEFS/rwRFS and rwOS. The time origin for these analyses will be the start of the treatment in the respective line of therapy for rwEFS/rwRFS for the first 3 R/R-based lines of therapy. The time origin of rwOS analysis is the start of the earliest line of Mylotarg therapy. rwEFS/RFS and rwOS analyses for lines of therapy will be limited to patients who received treatment during the line of interest.

The terminal event for analysis of rwEFS/rwRFS is the earlier of death or the first date of disease progression or R/R event following the time origin. Patients who have not died or experienced a disease progression or R/R event by the end of the medical record will be censored for analysis of rwEFS/rwRFS. The terminal event for analysis of rwOS is date of death. Note that Social Security Disability Insurance (SSDI) records have an expected lag of up to 4 months. Accordingly, patients who are not indicated to be deceased in clinical records or SSDI records will be censored for rwOS analysis as of the later of 1) the latest date known alive within the clinical record, 2) 4 months prior to the date of most recent SSDI update.

Separate Kaplan-Meier analyses will be conducted for each rwEFS/rwRFS and rwOS endpoint.

9.7.6. Methods Under Objective 4

Objective 4: To evaluate tumor response among AML patients who received Mylotarg in a real-world setting.

a. First and best tumor response in the first qualifying Mylotarg-containing R/R-based line of therapy.

b. Time to best response in the first qualifying Mylotarg-containing R/R-based line of therapy.

c. Duration of best response in the first qualifying Mylotarg-containing R/R-based line of therapy.

Tumor response will be assessed for the first and best overall response to treatment for the first qualifying Mylotarg-containing R/R-based line of therapy during the study period. Response classifications will be made based on the treating physician's documentation of response itself, typically informed by radiological scan reports noted in the patient record. Classification is made to the following categories: complete response, partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE), each based on the treating physician's statements. In cases where complete response with partial hematologic recovery (CRh), complete response with incomplete hematologic recovery (CRi), and morphologic leukemia-free state (MLFS) are explicitly included in the treating physician's statements, these additional classifications will be documented. Patients for whom the record did not clearly indicate one of these classifications will be classed as NE. These patient responses will also be classified under a secondary classification as Other Favorable, or Other Unfavorable, where the record indicated the general direction of effect in order to preserve response information for each patient, even when not classifiable according to standard response categories; these responses can be assessed in descriptive analysis. The date of the best overall response for the first qualifying Mylotarg-containing R/R-based line of therapy will be collected from the index date through the end of the third R/R-based line of therapy or the end of record, whichever occurs first. Tumor responses captured are based on treating physician's assessment in the medical record. Overall response rate will be defined as a percentage of patients whose best response is either CR, CRi or MLFS, where available. Time to best response and duration of best response will be assessed using the descriptive techniques described above.

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 Project 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 undergo scientific review of study results prior to data lock.

9.9. Limitations of the Research Methods

1. This study reflects treatment practice patterns only within the United States 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.

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

3. This study reflects a convenience sample of patients. It is possible that patients within the Definitive Oncology Dataset differ from the underlying AML population in ways that may not be measurable. For this study, all patients in the Definitive Oncology Dataset with evidence of Mylotarg utilization and an AML diagnosis will be selected, however.

4. 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 it is authorized to process 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

This 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.

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 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.

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

- "YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)".

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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will be completed by Concerto HealthAI and is estimated to be available in July 2020.

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

1. American Cancer Society. Cancer Facts and Figures 2019. Available at https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2019.html. Accessed July 8, 2019.

2. National Cancer Institute. Adult Acute Myeloid Leukemia Treatment (PDQ®)–Health Professional Version. Available at https://www.cancer.gov/types/leukemia/hp/adult-aml-treatment-pdq#_359_toc. Accessed August 1, 2019.

14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not Applicable.

18. ANNEX 3. ADDITIONAL INFORMATION

Not Applicable.