StATISTICAL ANALYSIS PLAN

CHARACTERISTICS, TREATMENT PATTERNS, AND CLINICAL OUTCOMES IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS USING MYLOTARG – A US REAL-WORLD STUDY USING ELECTRONIC MEDICAL RECORD DATA

Concerto HealthAI Proprietary and Confidential Information

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. BACKGROUND AND RATIONALE

Acute myeloid leukemia (AML) is characterized by proliferation of leukemic blasts in the bone marrow and other tissues and, if untreated, is a rapidly fatal disease. In the United States (US) in 2019, it was estimated there would 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.

Additional information regarding the background and rationale for the study is contained in the study protocol.

2. OBJECTIVES

The study includes patients with a diagnosis of AML who received Mylotarg (Gemtuzumab ozogamicin) 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 the first 3 R/R-based lines of systemic therapy.

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

d. Duration of Mylotarg treatment in each of the first 3 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 3 R/R-based lines of therapy. The definition of rwEFS/rwRFS as described in Section 4.3.2 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 response for each regimen in 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 response, as outlined in Section 4.3.6 will be described for each regimen in the first qualifying Mylotarg-containing R/R-based line of therapy.

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

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

3. RESEARCH METHODOLOGY

3.1. Study Design

This is a retrospective, observational study of characteristics, treatment patterns, and clinical outcomes in patients diagnosed with AML who received Mylotarg. The study will use 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.

3.2. Study Setting

The Definitive Oncology Dataset is used in support of a range of business activities, including retrospective research and is 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.

3.3. Study Size

CCI [redacted] Initial exploration of the Definitive Oncology Dataset suggests 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.

3.4. Eligibility Criteria

3.4.1. 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 3 R/R-based lines of therapy following initial AML diagnosis date occurring on or after 9/1/2017.

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

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

3.4.2. Exclusion Criteria

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.

3.5. Study Measures

3.5.1. Data Elements

3.5.1.1. 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 (Table 1).
- Date of initial AML diagnosis. This date defines the *index date* for the study, as referenced below in describing other study variables (Table 1).
- 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 (Table 2):
    - 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 (Table 2).
- 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). The Charlson Comorbidity Index will be computed (Table 2).
- ECOG performance status, if available, or indication of impaired performance status not otherwise classified as an ECOG rating, at index date (±30 days) (Table 2).

- First response and best overall response to treatment from the index date through the end of the first R/R-based line of therapy or the end of the record, whichever occurs first (Table 9-Table 11, Table 14-Table 15).
- Biomarker status and date of results will be recorded at index date (±30 days) (Table 2).

Biomarkers collected will include:

- IDH1
- IDH2
- TP53
- Intermediate Risk[1]
  - FLT3
  - 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 (Table 2).
  - Adverse Risk[1]
    - 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.

[1] Missing data about cytogenetic testing may lead to misclassification of risk.

- Favorable Risk[1]
- t(8;21)(q22;q22.1)
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22).

- Documentation of European LeukemiaNet (ELN) genetic risk stratification (favorable, intermediate, adverse, or undocumented), based on provider documentation, if available, closest to index date (Table 2).
- Dates of R/R 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 (Table 6-Table 15).
- 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 (Table 3-Table 5).
- 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 (Table 3-Table 5).

3.5.1.2. Extracted Data

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

- Insurance status (private only, public only, both, neither) (Table 1).
- State of residence (Table 1).
- Sex (Table 1).
- Height (Table 1).
- Weight at index date (±30 days) (Table 1).
- Date of birth (Table 1).
- Date of death (Table 8).

- 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 (Table 3-Table 5).

3.5.2. Derived Variables

Variables derived from abstracted and extracted data will include the following:

- Age at index date (Table 1).
- BMI at index date (±30 days) (Table 1).
- Geographic census region of patient's residence (Table 1).
- Weighted index of comorbid disease condition. Weighting of comorbid conditions will follow the weighting as specified in the Charlson Comorbidity Index (Table 2).
- 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 first R/R-based line of therapy or the end of the record, whichever occurs first (Table 4).
- 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 (Table 3-Table 5).
- Treatment regimens, derived from oral and infused agents delivered, including start and stop dates, and indication of subsequent treatment after 1L (Table 3-Table 5).
- 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 a regimen minus the start date of the corresponding regimen and will be computed during the analytics phase of the project (Table 5).
- Time under observation for analysis of rwEFS/rwRFS, by line, based on start date of treatment within line and dates of R/R event or disease progression, or censoring (Table 5-Table 7).
- Time under observation for analysis of rwOS 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 (Table 8).

- Time to best response for each regimen in 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 (Table 9-Table 11, Table 14-Table 15).

- Duration of response for each regimen in 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 (Table 11).

4. STATISTICAL METHODS

4.1. Endpoints

The primary study endpoints are effectiveness outcomes of rwEFS/rwRFS, rwOS, and response. Patient demographics and clinical characteristics, as well as treatment patterns will also be evaluated.

4.2. Regimens and Lines

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.

    a. All agents in the regimen must be discontinued for the regimen to be considered as discontinued. If only a single agent within a regimen is discontinued after 30 days, the regimen is assumed to be ongoing so long as the other agents are not yet discontinued.

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.

Please note: These conditions do not dictate how detailed information about oncology medications is captured, or how medication start and end dates are recorded, regardless of the days' supply of any given prescription. Rather, the conditions are only used to define lines of therapy, and information about medications and days' supply is recorded as documented in the medical record.

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 an 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.

A discontinuation will be defined as stopping of a particular agent for any reason, as indicated by provider documentation of "discontinuation" or "change in therapy" in the medical record, or, in the absence of provider documentation of discontinuation or change in treatment, a change in treatment with a particular agent, with no further treatment with that agent documented in structured data, or, evidence that the patient is admitted to hospice care (as the assumption is made that all systemic therapy is discontinued at that time).

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 an R/R event or a disease progression - either may be cited, in which an R/R event or disease progression must occur for a new regimen to be interpreted as a new line of therapy. In this study, **refractory** AML is defined as disease that is nonresponsive or failing to achieve at least minimal response 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.

4.3. Analytic Methods

4.3.1. Descriptive Analysis

Descriptive statistics are typically generated for all study variables. The descriptive statistics include means, standard deviations, 1st quartiles, medians, 3rd quartiles, interquartile ranges, 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]

4.3.2. 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 the first 3 R/R-based lines of therapy. rwEFS will be defined as the time from the treatment initiation date (for the first agent in the first regimen in the first line of Mylotarg-containing 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 3 cycles of Mylotarg. rwRFS will be defined as the time from the treatment initiation date (for the first agent in the first regimen in 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. Patients who are not indicated to be deceased at last known contact (patients who are alive, or lost to follow-up) will be censored. The time origin for analysis of duration of therapy is start of Mylotarg, and the terminal event is discontinuation of that therapy.

4.3.3. 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 4.3.1 will be conducted for work under this objective. Demographic characteristics that will be reported will include 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 comorbidities 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.

4.3.4. 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 4.3.1 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 the first 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 and dose changes 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.

4.3.5. 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 rwOS. Time to event analysis as described in Section 4.3.2 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/rwRFS and rwOS analyses for lines of therapy will be limited to patients who received treatment during the line of interest.

rwEFS will be defined as the time from the treatment initiation date (for the first line of Mylotarg-contining therapy) to the date of treatment failure (TF), relapse from CR or better, or death from any cause, whichever comes first. TF is defined as failure to achieve CR or better following up to 3 cycles of Mylotarg. Accordingly, the time origin for rwEFS will be the start of Mylotarg in the first line of therapy in which it is used. The terminal event for analysis of rwEFS is the earlier of treatment failure, relapse from CR or better (as evidenced by provider documentation), or death. Patients who have not died or experienced an event by the date of last contact within the medical record will be censored for analysis of rwEFS.

rwRFS will be defined as the time from the treatment initiation date (during the first line of Mylotarg-contianing therapy) to the date of a relapse event, or death from any cause, whichever comes first. The time origin for rwRFS will be the start of Mylotarg in the first line of therapy in which it is used. The terminal event for analysis of rwRFS will be the earlier of a relapse event (as evidenced by provider documentation), or death. Patients who have not died or experienced a relapse event by the date of last contact within the medical record will be censored for analysis of rwRFS.

The time origin of rwOS analysis is the start of the first Mylotarg use. 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.

4.3.6. Methods under Objective 4

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

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

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

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

Response will be assessed for the first and best overall response to treatment for each regimen in 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 (CR), 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. The date of the best overall response for each regimen in the first qualifying Mylotarg-containing R/R-based line of therapy will be collected. 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.

4.3.7. Ad-Hoc Analyses

Ad-hoc analyses will be performed on a subset of patients assumed to be de-novo AML patients using a closer-to-typical combination of gemtuzumab + chemotherapy in 1L. This will include patients receiving idarubicin instead of daunorubicin, despite only daunorubicin being included in gemtuzumab's label. rwEFS FPR, and BOR will be evaluated among this subset of patients.

4.4. Missing Data

This study reflects real-world patients treated primarily in the community oncology setting. The completeness of each patient's medical chart will vary due to the nature of real-world data. Although some measurements may not be consistently available from patient records in the Definitive Oncology Dataset, analyses will be conducted based on data that are reported. Variables related to patient characteristics and certain treatment outcomes largely missing from the structured fields can be abstracted from the unstructured data. Based on prior studies conducted using Concerto data, the majority of the variables are estimated to be available for >90% of patients. The estimates can vary slightly based on different variables in different tumor types. For example, ELN classification of AML risk according to provider documentation may be limited. In general, data that are absent/not found will not be imputed but will be categorized and reported as not documented.

5. LIMITATIONS

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.

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

6. REFERENCES

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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.

7. TABLE SHELLS

7.1. Objective 1: Demographic and Clinical Characteristics

7.1.1. Demographic characteristics

Table 1. Demographic Characteristics

	N=xxx
Year of initial AML Diagnosis (n, %)	
2012	n (x.x%)
2013	n (x.x%)
2014	n (x.x%)
2015	n (x.x%)
2016	n (x.x%)
2017	n (x.x%)
2018	n (x.x%)
2019	n (x.x%)
Age (years) at initial AML Diagnosis	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
Undocumented Age	xx
Age (years) at initial AML Diagnosis	
Sub-total	n (x.x%)
<65	n (x.x%)
≥65 -74	n (x.x%)
≥65	n (x.x%)
≥75	n (x.x%)
Undocumented Age	n (x.x%)
Gender n (%)	
Sub-total	n (x.x%)
Female	xx
Male	xx
Undocumented Gender	xx
Race, n (%)	
Sub-total	n (x.x%)
White	n (x.x%)
Black or African American	n (x.x%)
Other/Undocumented Race	n (x.x%)
Weight (pounds) at initial AML Diagnosis	
n	xx
Mean	x.x
SD	x.x

Table 1. Demographic Characteristics

	N=xxx
1st Quartile	x.x
Median	xx
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
Undocumented Weight	xx
Height (inches)	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	xx
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
Undocumented Height	xx
BMI (kg/meters^2) at Initial AML Diagnosis	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
Undocumented BMI	xx
Insurance Category, n (%)	
Sub-total	xxx
Private Insurance Only	n (x.x%)
Public Insurance Only	n (x.x%)
Both Public and Private Insurance	n (x.x%)
Other	n (x.x%)
Unknown/Undocumented	n (x.x%)
Region of Residence, n (%)	
Sub-total	xxx
West	n (x.x%)
Midwest	n (x.x%)
Northeast	n (x.x%)
South	n (x.x%)
Undocumented Region	n (x.x%)

7.1.2. Clinical Characteristics

Table 2. Clinical Characteristics

	N=xxx
Classification of Disease at Initial AML Diagnosis, n (%)	
Sub-total	xxx
AML with Recurrent Genetic Abnormalities	n (x.x%)
AML with Multi-lineage Dysplasia	n (x.x%)
Therapy-Related Myeloid Neoplasm	n (x.x%)
Myeloid Proliferations Related to Down Syndrome	n (x.x%)
Myeloid Sarcoma	n (x.x%)
Undifferentiated or Biphenotypic Acute Leukemias	n (x.x%)
Other Classification AML	n (x.x%)
Undocumented AML Classification	n (x.x%)
AML Type, n (%)	
Sub-total	n (x.x%)
DeNovo	n (x.x%)
Secondary	n (x.x%)
Hypometholating Agents before initial AML treatment	n (x.x%)
Undocumented	n (x.x%)
Performance Status at Initial AML Diagnosis (ECOG Score), n (%)	
Sub-total	n (x.x%)
0	n (x.x%)
1	n (x.x%)
2	n (x.x%)
3	n (x.x%)
4	n (x.x%)
Undocumented ECOG	n (x.x%)
Composite Performance Status at Initial AML Diagnosis, n (%)	
Sub-total	n (x.x%)
Impaired	n (x.x%)
No Documentation of Impairment	n (x.x%)
Cytogenetic/FISH Testing at Initial AML Diagnosis, ** **n (%)**	
t(6;9)(p23:q34.1)[3]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
t(6;9)(p23:q34.1) Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
t(v;11q23.3)[3]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
t(v;11q23.3) Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
t(9;22)(q34.1;q11.2)[3]	
Yes	n (x.x%)

Table 2. Clinical Characteristics

	N=xxx
No	n (x.x%)
Undocumented	n (x.x%)
t(9;22)(q34.1;q11.2) Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
inv(3)(q21.3q26.2)[3] or t(3;3)(q21.3;q26.2)[3]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2) Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
-5 or del(5q); -7; -17/abn(17p)[3]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
-5 or del(5q); -7; -17/abn(17p) Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
Complex karyotype[3]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
Complex karotype Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
Monosomal karyotype[3]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
Monosomal karotype Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
t(8;21)(q22;q22.1)[1]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
t(8;21)(q22;q22.1) Positive Test Results (yes), n (% outof Patients Tested)	n (x.x%)
inv(16)(p13.1q22)[1] or t(16;16)(p13.1;q22)[1]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
inv(16)(p13.1q22) or t(16;16)(p13.1;q22) Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)

Table 2. Clinical Characteristics

	N=xxx
Biomarker Testing at Initial AML Diagnosis,* n (%)	
FLT3[2]	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
FLT3 Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
IDH1	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
IDH1 Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
IDH2	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
IDH2 Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
TP53	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
TP53 Positive Test Results (yes), n (% out of Patients Tested)	n (x.x%)
NPM1	
Yes	n (x.x%)
No	n (x.x%)
Undocumented	n (x.x%)
NPM1 Positive Test Results (yes), n (% outof Patients Tested)	n (x.x%)
Provider Documentation of ELN Genetic Risk Stratification, n (%)	
Favorable	n (x.x%)
Intermediate	n (x.x%)
Adverse	n (x.x%)
Undocumented	n (x.x%)
ELN Genetic Risk Stratification Based on Biomarker Testing,[4] **n (%)**	
Favorable	n (x.x%)
Intermediate	n (x.x%)
Adverse	n (x.x%)
Undocumented	n (x.x%)
Comorbidities, n (%)	
HIV+/AIDS	n (x.x%)

Table 2. Clinical Characteristics

	N=xxx
Alzheimer's or Other Dementia	n (x.x%)
Cerebrovascular Accident	n (x.x%)
Chronic Obstructive Pulmonary Disease	n (x.x%)
Cirrhosis or Other Serious Liver Disease	n (x.x%)
Congestive Heart Failure	n (x.x%)
Connective Tissue Disease	n (x.x%)
Diabetes	n (x.x%)
Hemiplegia	n (x.x%)
Leukemia (other than AML)	n (x.x%)
Metastatic Solid Tumor	n (x.x%)
Myocardial Infarction	n (x.x%)
Peripheral Vascular Disease (History of Surgical Treatment For)	n (x.x%)
Renal Disease	n (x.x%)
Ulcer Disease	n (x.x%)
Weighted Index of Comorbid Conditions*	
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
Subsequent Treatment,± n (%)	n (x.x%)

*This is a weighted index of comorbid disease condition. Weighting of comorbid conditions will follow the weighting as specified in the Charlson Comorbidity Index.
**If multiple tests have been performed, the test that was closest to the index date (initial diagnosis of AML) would be presented.
± Any treatment received after the first R/R-based line of therapy.

1. Indicative of favorable risk according to 2017 ELN guidelines.
2. Indicative of intermediate risk according to 2017 ELN guidelines.
3. Indicative of adverse risk according to 2017 ELN guidelines.
4. Because of missing data or undocumented testing, misclassification bias may be present.

7.2. Objective 2: Treatment Patterns

7.2.1. Treatment Patterns (sequence)

Table 3. Summary of Treatment Patterns by Line of Treatment and Regimen within Line

Progression-Based Line Agent	Overall (n=xx)	
	Patients N=xxx	%
L1R1: [agent, agent, agent]…, L1R2: [agent, agent, agent]…L2R1: [agent]…	n	(x.x%)
L1: [agent, agent, agent]…	n	(x.x%)
L1: [agent, agent, agent]…	n	(x.x%)
L1: [agent, agent, agent]…	n	(x.x%)

L denotes progression-based line; A denotes agent.

Regimens within each line for the first three lines of therapy after the index date.

7.2.2. Treatment Characteristics, Overall and by First Line Therapy Type

Table 4. Treatment Characteristics

	N=xxx
Dose Change	
First Line Therapy	
Starting Dose	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
Dose Titration (Dose Increase Immediately Following Initiation*), n (%)	n (x.x%)
Dose Increase (Not Immediately Following Initiation), n (%)	n (x.x%)
Dose Titration (Dose Decrease Immediately Following Initiation*), n (%)	n (x.x%)
Dose Decrease (Not Immediately Following Initiation), n (%)	n (x.x%)

Table 5. Mylotarg Treatment Duration, by Line of Therapy

	N=xxx
Mylotarg Treatment Duration	
First Line Therapy	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
	N=xxx
Second Line Therapy	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x
	N=xxx
Third Line Therapy	
n	xx
Mean	x.x
SD	x.x
1st Quartile	x.x
Median	x.x
3rd Quartile	x.x
IQR	x.x
Min, Max	x.x,x.x

* The time origin was the initiation of Mylotarg. The end point was the last date of gemtuzumab therapy, regardless of line of therapy (duration could continue into subsequent lines of therapy), study end date, or death, whichever came first.

7.3. Objective 3: Effectiveness Outcomes

7.3.1. rwEFS/rwRFS in the First Mylotarg-containing Line of Therapy

Table 6. Kaplan-Meier Analysis of rwEFS from Initiation of First Mylotarg-Containing Line of Therapy, All Patients

	N=xxx
No. of Events/No. of Patients	xxx/xxx
Median (months)	x.x
95% CI of Median	[x.x, x.x]

The time origin was the line of therapy in which Mylotarg treatment initiated.

Table 7. Kaplan-Meier Analysis of rwRFS from Initiation of First Mylotarg-Containing Line of Therapy, All Patients

	N=xxx
No. of Events/No. of Patients	xxx/xxx
Median (months)	x.x
95% CI of Median	[x.x, x.x]

The time origin was the line of therapy in which Mylotarg treatment initiated.

Figure 1. Kaplan-Meier Analysis of rwEFS from Initiation of First Mylotarg-Containing Line of Therapy, All Patients

Figure 2. Kaplan-Meier Analysis of rwRFS from Initiation of First Mylotarg-Containing Line of Therapy, All Patients

7.3.2. rwOS from Initiation of First Mylotarg-Containing Line of Therapy

Table 8. Kaplan-Meier Analysis of rwOS from Start of First Mylotarg-Containing Line of Therapy, All Patients

	N=xxx
No. of Events/No. of Patients	xxx/xxx
Median (months)	x.x
95% CI of Median	[x.x, x.x]

The time origin was the line of therapy in which Mylotarg treatment initiated.

Figure 3. Kaplan-Meier Analysis of rwOS from Start of First Mylotarg-Containing Line of Therapy, All Patients

7.4. Objective 4: Response

Table 9. First Positive Response (First Mylotarg-Containing Line of Therapy), All Patients

Description	L1 n=xxx	L2 n= xxx	L3 n=xxx
First Positive Response*, n (%)			
Complete Response (CR)	n (x.x%)	n (x.x%)	n (x.x%)
Partial Response (PR)	n (x.x%)	n (x.x%)	n (x.x%)
Stable Disease (SD)	n (x.x%)	n (x.x%)	n (x.x%)
Progressive Disease (PD)	n (x.x%)	n (x.x%)	n (x.x%)
Not Evaluable (NE)/Undocumented	n (x.x%)	n (x.x%)	n (x.x%)
Other Favorable	n (x.x%)	n (x.x%)	n (x.x%)
Other Unfavorable	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Partial Hematologic Recovery (CRh)±	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Incomplete Hematologic Recovery (CRi)±	n (x.x%)	n (x.x%)	n (x.x%)
Morphologic Leukemia-Free State (MLFS)±	n (x.x%)	n (x.x%)	n (x.x%)
Overall Response Rate±**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**

* Responses are based on treating physician's assessment as provided in the medical records.
** Overall response rate is defined as a percentage of patients whose best response is either CR, CRh or CRi.
± Based on provider documentation, which may result in low sample size of patients with certain response categories.

Table 10. Best Overall Response from Initiation of First Mylotarg-Containing Line of Therapy, All Patients

Description	L1 n=xxx	L2 n= xxx	L3 n=xxx
Best Overall Response*, n (%)			
Complete Response (CR)	n (x.x%)	n (x.x%)	n (x.x%)
Partial Response (PR)	n (x.x%)	n (x.x%)	n (x.x%)
Stable Disease (SD)	n (x.x%)	n (x.x%)	n (x.x%)
Progressive Disease (PD)	n (x.x%)	n (x.x%)	n (x.x%)
Not Evaluable (NE)/Undocumented	n (x.x%)	n (x.x%)	n (x.x%)
Other Favorable	n (x.x%)	n (x.x%)	n (x.x%)
Other Unfavorable	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Partial Hematologic Recovery (CRh)±	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Incomplete Hematologic Recovery (CRi)±	n (x.x%)	n (x.x%)	n (x.x%)
Morphologic Leukemia-Free State (MLFS)±	n (x.x%)	n (x.x%)	n (x.x%)
Overall Response Rate±**	**xx (xx.x%)**	**xx (xx.x%)**	**xx (xx.x%)**

* Responses are based on treating physician's assessment as provided in the medical records.
** Overall response rate is defined as a percentage of patients whose best response is either CR, CRh or CRi.
± Based on provider documentation, which may result in low sample size of patients with certain response categories.

Table 11. Duration of Best Response from Start of First Mylotarg-Containing Line of Therapy, All Patients

	L1 n=xx	L2 n= xx	L3 n=xx
No. of Events/No. of Patients	xxx/xxx	xxx/xxx	xxx/xxx
Median (months)	x.x	x.x	x.x
95% CI of Median	[x.x, x.x]	[x.x, x.x]	[x.x, x.x]

The time origin was the line of therapy in which Mylotarg treatment initated.

Figure 4. Kaplan-Meier Analysis of Duration of Best Response from Initiation of First Mylotarg-Containing Line of Therapy, First Mylotarg-Containing Line of Therapy, All Patients

Table 12. Time to Best Response from Start of First Mylotarg-Containing Line of Therapy, All Patients

	L1 n=xx	L2 n= xx	L3 n=xx
No. of Events/No. of Patients	xxx/xxx	xxx/xxx	xxx/xxx
Median (months)	x.x	x.x	x.x
95% CI of Median	[x.x, x.x]	[x.x, x.x]	[x.x, x.x]

The time origin was the line of therapy in which Mylotarg treatment initated.

Figure 5. Kaplan-Meier Analysis of Time to Best Response from Start of First Mylotarg-Containing Line of Therapy, All Patients

7.5. Ad-Hoc Analyses

Table 13. Kaplan-Meier Analysis of rwEFS from Initiation of First Gemtuzumab-Containing Line of Therapy

EFS	N=XX
No. of Events/No. of Subjects	Xx/xx
Median (months)	x.xx
95% CI of Median	x.xx, x.xx]

The time origin was the initiation of the first gemtuzumab-containing line of therapy.

Table 14. First Positive Response by Line of Therapy from the First Gemtuzumab-Containing Line of Therapy

Description	L1 n=xx	L2 n=xx	L3 n=xx
First Positive Response*, n (%)			
Complete Response (CR)	n (x.x%)	n (x.x%)	n (x.x%)
Partial Response (PR)	n (x.x%)	n (x.x%)	n (x.x%)
Stable Disease (SD)	n (x.x%)	n (x.x%)	n (x.x%)
Progressive Disease (PD)	n (x.x%)	n (x.x%)	n (x.x%)
Not Evaluable (NE)/Undocumented	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Partial Hematologic Recovery (CRh)±	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Incomplete Hematologic Recovery (CRi)±	n (x.x%)	n (x.x%)	n (x.x%)
Morphologic Leukemia-Free State (MLFS)±	n (x.x%)	n (x.x%)	n (x.x%)
N/A – Patient had stable disease (SD), disease progression (DP), not evaluable (NE), no documentation of response assessment (ND), or other negative response.	n (x.x%)	n (x.x%)	n (x.x%)
Overall Response Rate**±	n (x.x%)	n (x.x%)	n (x.x%)

* Responses are based on treating physician's assessment as provided in the medical records.
**Overall response rate is defined as a percentage of patients whose best response is either CR, CRh or CRi.
±Based on provider documentation, which may result in low sample size of patients with certain response categories.

Table 15. Best Overall Response, by Line of Therapy from the First Gemtuzumab-Containing Line of Therapy

Description	L1 n=XX	L2 n=XX	L3 n=XX
Best Overall Response*, n (%)			
Complete Response (CR)	n (x.x%)	n (x.x%)	n (x.x%)
Partial Response (PR)	n (x.x%)	n (x.x%)	n (x.x%)
Stable Disease (SD)	n (x.x%)	n (x.x%)	n (x.x%)
Progressive Disease (PD)	n (x.x%)	n (x.x%)	n (x.x%)
Not Evaluable (NE)/Undocumented	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Partial Hematologic Recovery (CRh)±	n (x.x%)	n (x.x%)	n (x.x%)
Complete Response with Incomplete Hematologic Recovery (CRi)±	n (x.x%)	n (x.x%)	n (x.x%)
Morphologic Leukemia-Free State (MLFS)±	n (x.x%)	n (x.x%)	n (x.x%)
Overall Response Rate**±	n (x.x%)	n (x.x%)	n (x.x%)

* Responses are based on treating physician's assessment as provided in the medical records.
**Overall response rate is defined as a percentage of patients whose best response is either CR, CRh or CRi.
±Based on provider documentation, which may result in low sample size of patients with certain response categories.