STUDY REPORT SYNOPSIS

CREEK Study

A Multicenter Retrospective Study to understand the clinical characteristics, treatment pathway and resource utilization for patients with chronic lymphocytic leukemia

A retrospective, multi-centre, observational study to describe disease characteristics, treatment patterns, treatment-related outcomes, and resource utilization for Chronic Lymphocytic Leukemia (CLL) patients in multiple international regions.

Milestones:	**First Subject In:** 07 November 2021 **Last Subject In:** 16 March 2023 **Data Base Lock:** 17 August 2023 **Clinical Study Report:** 22 January 2024
Phase of development:	Retrospective Study
Sponsor:	AstraZeneca FZ LLC (GCC)
Author:	[redacted]

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale: Chronic Lymphocytic Leukemia (CLL) is a prevalent form of leukemia, particularly in western countries, and its incidence is increasing globally. The aging population is a significant factor contributing to the rise in CLL cases. CLL patients often exhibit no symptoms initially and may undergo observation without treatment. However, certain indicators, such as lymphocyte doubling time, clinical stage changes, or signs of bone marrow failure, may necessitate treatment. The choice of treatment depends on various factors, including prognosis scores, symptomatology, patient fitness, and comorbidities.

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The incidence of CLL varies among different regions. In the USA, the rate is higher in men than in women. Data regarding CLL epidemiology and disease burden are limited in many countries, including those of the Gulf Cooperation Council (GCC) and Middle East and North Africa (MENA) regions. However, some studies have reported CLL as a significant form of leukemia in certain countries, such as Saudi Arabia, Egypt, and Morocco.

The clinical presentation of CLL commonly involves lymphocytosis and lymphadenopathy, while other symptoms may include fever, night sweats, weight loss, fatigue, and complications related to bone marrow involvement. CLL's clinical course can vary widely, with some patients experiencing an indolent course and prolonged survival, while others have aggressive disease requiring early treatment and frequent relapses.

Real-world data on CLL in Latin America are scarce, but the incidence is lower compared to Caucasians. Studies have shown that CLL patients in Latin America tend to be diagnosed between the ages of 60 and 70, with a slight male predominance. Most patients have a good performance status and early-stage disease at diagnosis. In Asian populations, CLL is less common but tends to occur at earlier ages. There are also racial-specific genetic variations observed in Asian CLL patients.

Advances in understanding the genetic and molecular aspects of CLL have led to the identification of markers associated with disease progression and survival. Comprehensive genomic analyses have revealed a sequential genetic evolution pattern in CLL, leading to increased aggressiveness and treatment resistance.

Currently, there are several treatment options available for CLL, including targeted therapies and regimens suitable for elderly or high-risk patients. However, optimal treatment strategies and disease management remain unclear, particularly for patients with high comorbidity and poor fitness.

To address the international variation in CLL, a proposed study aims to describe the clinical characteristics, treatment approaches, and healthcare resource utilization of CLL patients in the region.

Objectives: The overall aim of this study was to describe disease characteristics, treatment patterns, treatment-related outcomes, and resource utilization for CLL patients in multiple international regions.

> **Primary Objective:** To describe the clinical and patient characteristics for CLL patients
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> **Secondary Objectives:** (1) To describe treatment patterns, including systemic CLL treatment regimens, including frontline and subsequent lines of chemotherapy and immunotherapy treatments. (2) To describe treatment-related outcomes for CLL patients, including time to treatment failure (TTF) and time to next treatment (TTNT).
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> **Exploratory Objectives:** (1) To describe the overall survival. (2) To describe Medical resource utilization (MRU) associated with therapy. (3) To describe the potential predictor of response to treatment. (4) To describe the clinical and patient characteristics for the treatment-naive CLL patient in the GCC pilot cohort

Study design: CREEK is a retrospective, observational, registry-based study including patients with an incidental diagnosis of CLL and started treatment (1st line, 2nd line, or Subsequent lines of treatment) within the period between 01 June 2016 and 12 months before data collection as identified from the patient records (from participating hospitals across the GCC States and the International region countries) with at least 12 months of follow-up, after starting on treatment.

Moreover, the study included a pilot cohort in the GCC as an exploratory objective to describe the clinical and patient characteristics for the treatment-naive CLL patient

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Data source: Data sources were patient records from participating hospitals across the GCC States (GCC) and the International region (Asia, Australia, Latin America, and Middle East and Africa "MEA").

Study population: Approximately 1250 patients were enrolled from the GCC states and International countries. Two cohorts are planned to account for different study timelines in an estimated 40-50 sites: from Gulf countries and from International regions (Asia, Australia, Latin America, and MEA).

Inclusion criteria: (1) Primary diagnosis of Chronic Lymphocytic Leukemia (CLL). (2) Initiated CLL treatment (including 1st line, 2nd line, or Subsequent lines of treatment) within the period between 01 June 2016, and 12 months before data collection. * For GCC pilot cohort patients: treatment-naive CLL patients diagnosed between 01 June 2016, and 12 months before data collection. (3) Available medical records at the participating site reflecting at least 12 months of follow-up after starting on treatment (except in the case of the participant death within one year following treatment initiation). (4) Provision of informed consent by the patient or next of kin/legal representative (for deceased patients at study entry, unless a waiver was granted), according to local regulations. (5) Adult male or female ≥18 years old at the time of diagnosis or according to the age of majority as defined by local regulations).

Exclusion criteria: (1) Failure to meet one or more of the inclusion criteria. (2) Any diagnosis of B-cell malignancies other than CLL. (3) Current or prior use of "acalabrutinib" treatment. (4) Currently/previously receiving treatment in an interventional clinical trial at the time of entry into this study for indications CLL.

Statistical methods: A comprehensive statistical analysis plan was implemented for the study. Continuous variables were described using standard statistical measures such as mean, standard deviation, median, quartiles, minimum, and maximum. Categorical variables were summarized using frequency tables. Time-to-event data were analyzed using Kaplan-Meier methods with quartiles and survival at landmark times, along with 95% confidence limits. Demographic and baseline clinical characteristics were presented using means, standard deviations, medians, and interquartile ranges for numeric variables, and frequency distributions for categorical variables. Disease characteristics and treatment patterns were also summarized using appropriate statistics. Confidence intervals were computed when needed. The log-rank test and Cox proportional hazard models were used for comparisons. Objective response rate (ORR) and Odds ratios (OR) were computed and predictors were assessed using logistic regression models. Safety measures, including adverse events and discontinuation rates, were summarized using frequency distributions. Overall survival was analyzed using the Kaplan-Meier method. Medical resource utilization variables were summarized using means, standard deviations, medians, and interquartile ranges. Missing values were handled through listwise deletion. The analyses were performed for the combined database and for specific regions. IBM-SPSS was used for all analyses, and a significance level of 0.05 was used.

Results:

A total of 1045 subjects were enrolled in the study. Among them, 907 patients were diagnosed with CLL and were receiving treatment, while 138 patients were diagnosed with CLL but had not received any prior treatment (Treatment-Naïve). Out of the 1045 subjects, 1009 patients (96.6%) met the eligibility criteria and were included in the eligible population. Within the CLL treated cohort 1, 886 patients (97.7%) across all countries had a diagnosis of CLL and were receiving treatment. In the CLL Treatment-Naïve cohort 2, 123 patients (89.1%) were diagnosed with CLL but had not received any prior treatment.

Cohort 1 / Whole patients Cohort :

In the CLL-treated patient group, the average age of patients was 63 years, and 591 individuals (66.7%) were males, while 295 individuals (33.3%) were females. As for the race, out of the treated patients, 258 individuals (29.1%) identified as Asian, while 285 (32.2%) identified as White. Approximately 241 patients (27.2%) in the CLL-treated group reported being "fully active, able to carry on all their pre-

disease activities without any restrictions". During the follow-up visit, about 214 patients (24.2%) in the CLL-treated group reported being "fully active, able to carry on all their pre-disease activities without any restrictions". During the treatment/diagnosis visit, 531 patients (59.9%) in the CLL-treated group reported extremely severe hematological problems. In the follow-up visit, 463 treated patients (52.3%) continued to report the same. In the CLL-treated group, approximately 28% of eligible patients were either former or current smokers. At the treatment/diagnosis visit, 39 patients (4.4%) in the CLL-treated group were categorized as being in the very high-risk group. At the follow-up visit, 23 patients (2.6%) in the CLL-treated group continued to be categorized as very high-risk.In the CLL-treated group, 104 patients (11.7%) reported a total of 138 family history cases of malignancies. At the treatment/diagnosis visit, 34 patients (3.8%) in the CLL-treated group reported a total of 37 current malignancies. As for the follow-up visit, 38 patients (4.3%) in the CLL-treated group reported a total of 42 current malignancies. The top three most commonly used concomitant medications were antihypertensive drugs, proton pump inhibitors (PPIs), and antacids. In the CLL-treated cohort, the average number of months since diagnosis to the start of the study was 21.34 months. Out of the total patients included in the study, 56.4% (500 patients) received immediate therapy for CLL. Among the subjects who did not receive immediate therapy, the median time taken for treatment initiation from the time of diagnosis was 653 days. Among the treated subjects, 73.14% (648 patients) had not received any lines of prior therapy. Additionally, 15.46% (137 patients) had received one line of prior therapy. During 1st line of therapy, 99 (11.2%) patients reported del (17p), 66 (7.4%) patients reported del (11q), and 27 (3.0%) patients reported complex karyotype cytogenetic abnormalities. During the first line of therapy, a total of 678 patients (76.5%) received chemo-immunotherapies (CIT), while 179 patients (20.2%) received targeted therapies. On average, each subject has been through 7 cycles of therapy, with a range of 0 to 50 cycles. Among those who received CIT, most patients received "Bendamustine; Rituximab" and "Cyclophosphamide; Fludarabine; Rituximab" regimens. As for targeted therapies, the most received was Ibrutinib. During the first line of therapy, out of the patients who received chemo-immunotherapies, 49 patients (7.2%) reported progressive disease. Additionally, 44 patients (6.5%) reported stable disease. Among those who received targeted therapies, one patient (0.6% of the cohort) reported progressive disease, while nine patients (5.0% of the cohort) reported stable disease. The mean survival for the patients included in the analysis is approximately 154 months. For the first line of therapy with chemo-immunotherapy, the survival mean calculated is 44.66 months, and median survival is reported as 62 months. For the first line of therapy with targeted therapy, the survival mean calculated is 9.2 months. The mean number of inpatient hospitalizations in the whole region for patients on first-line chemo-immunotherapy was 1.9 (median = 1.0), compared to 0.7 (median = 0.0) for patients on targeted therapies ($p < 0.001$). Patients on first-line chemo-immunotherapy in the whole region had a slightly longer average length of stay in the hospital compared to those on targeted therapies. Patients on first line chemo-immunotherapy, as well as patients on targeted therapies, had a high number of outpatient visits. Patients on targeted therapies had more emergency room visits than those on chemo-immunotherapy in all lines of treatment. About 16.7% of patients on first line chemo-immunotherapy received blood transfusions versus 8.4% on targeted therapies. Patients on first line chemo-immunotherapy received an average of 4.3 units of whole blood (median=3.0) versus 7.6 units for patients on targeted therapies (median=3.0) [p-value = 0.711]. Patients on first line chemo-immunotherapy received an average of 2.4 whole blood transfusions (median=2.0) versus an average of 5.0 transfusions for patients on targeted therapies (median =1.0) [p-value = 0.768]. Six patients on first line chemo-immunotherapy received an average of 5.2 units of plasma (median=5.0) versus 8.0 units for one patient on targeted therapies [p-value = 0.449]. An average of 17.6 (median=8.5) units of platelets were transfused in first line chemo-immunotherapy patients versus 18.0 in the targeted therapy patient [p-value = 0.906]. A total of 347 patients (39.2%) reported a total of 664 adverse events. Among these events, 113 were classified as severe. These adverse events were reported regardless of the line of therapy. CIT accounted for 490 adverse events, with 90 of them classified as severe, reported by 263 patients (38.8%). On the other hand, targeted therapies accounted for 172 adverse events, with 22 of them classified as severe, reported by 100 patients (55.9%).

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Cohort 2 / GCC Cohort :

In the CLL- Treatment Naïve group, the average age was 63 years, 86 patients (69.9%) were males, and 37 patients (30.1%) were females. Regarding race, in the naïve group, 44 patients (35.8%) identified as White. In the CLL Treatment Naïve group, approximately 42.3% reported being fully active and able to carry out all their pre-disease activities without any restrictions during the treatment/diagnosis visit. In the CLL Treatment Naïve group, a higher percentage of approximately 26% of eligible patients were identified as either former or current smokers. During the treatment/diagnosis visit, two patients (1.6%) in the CLL Treatment Naïve group were categorized as being in the very high-risk category. In the CLL Treatment Naïve group, 11 patients (8.9%) reported a family history of malignancies, also accounting for 13 cases. In the CLL Treatment Naïve group, 6 patients (4.9%) reported a total of 8 current malignancies at the Treatment/Diagnosis visit. The most used concomitant medications were antihypertensive medications, proton pump inhibitors (PPIs), and oral anticoagulants. The average number of months since diagnosis to the start of the study was reported to be 1.44 months for the CLL-Naïve cohort.