Poster 1808

Comparing Acalabrutinib and Ibrutinib in the Real World: A Study of 2,509 Patients with Chronic Lymphocytic Leukemia

Lindsey E. Roeker[1], Maral DerSarkissian[2], Kellie Ryan[3], Yan Chen[2], Svea K. Wahlstrom[4], Shweta Hakre[3], Louise Yu[2], Helen Guo[2], Anthony R. Mato[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Analysis Group, Boston, MA, USA; [3]AstraZeneca, Gaithersburg, MD, USA; [4]AstraZeneca, Wilmington, DE, USA

Objective

- To conduct a real-world analysis of CLL patients treated with acalabrutinib vs. ibrutinib to compare outcomes in a non-trial population.

Conclusions

- This study is the largest available analysis comparing two BTKis to date and suggests lower rates of discontinuation and a prolonged time to discontinuation for patients receiving acalabrutinib as compared to ibrutinib in both the front-line and relapsed/refractory settings.
- While randomized clinical trial data have compared patients treated with acalabrutinib and ibrutinib in the relapsed/refractory setting, these data provide valuable insight into 1) how these agents compare in the front-line setting (not tested in ELEVATE-RR) and 2) the outcomes in clinical practice across treatment lines outside of the trial setting.
- Additional analyses with longer follow-up are needed to confirm findings of this analysis and to determine if improved TTD is associated with improved progression-free and overall survival outcomes.

Limitations

- Flatiron data utilizes electronic medical records which are maintained for the purpose of patient care rather than research. Therefore, data may have errors or be incomplete.
- Given the retrospective non-randomized nature of the study, important differences in patient characteristics between the two study cohorts may exist. While ATT weighting was used to balance the groups in terms of baseline characteristics, unmeasured confounding may remain.
- Acalabrutinib was approved for CLL/SLL in November 2019; therefore, we have a smaller dataset of acalabrutinib-treated patients compared to ibrutinib. At time of analysis, we had a smaller sample size and relatively limited follow-up for acalabrutinib patients compared to ibrutinib and, therefore, lacked data maturity to assess clinical outcomes such as PFS and OS.

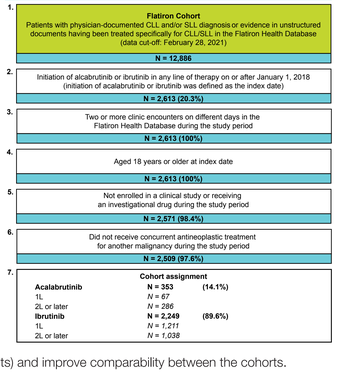
Background

- Novel agents including Bruton Tyrosine Kinase inhibitors (BTKi) have become the standard of care for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- The ELEVATE-RR trial (NCT02477696) compared acalabrutinib to ibrutinib and demonstrated non-inferior progression-free survival (PFS) with fewer cardiovascular (CV) and bleeding adverse events for relapsed/refractory CLL patients treated with acalabrutinib (Byrd, et al. 2021).
- As demographic and clinical characteristics of patients and management strategies often differ between real-world clinical practice and clinical trials, differences in outcomes may be observed.

Methods

- This retrospective cohort study utilized electronic health record data from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database from July 2017 to February 2021.
- Patients with CLL or SLL were included if they:
  - initiated acalabrutinib or ibrutinib in any line of therapy (LOT) on or after January 1, 2018
  - were ≥18 years of age at index, and
  - had at 2 encounters on separate days during the study period.
- Patients were followed to the earliest of last follow-up or death with a data cut-off of February 28, 2021.
- Time to treatment discontinuation (TTD) was defined as the time from treatment initiation to discontinuation, defined as start of a new LOT, lack of refilled prescription for ≥3 months, or death.
  - Patients who did not discontinue BTKi treatment were censored at the last follow-up.
- Descriptive statistics were reported for all study measures using means (standard deviations [SD]) and medians (interquartile range [IQR]) for continuous variables and frequency distributions for categorical variables.
- Average treatment effect among the treated (ATT) weighting was used to balance key baseline characteristics (age, sex, race, geographic region, year of index date, year of diagnosis with CLL or SLL, line of therapy, Rai stage, modified Quan-Charlson Comorbidity Index [CCI] score, atrial fibrillation, Eastern Cooperative Oncology Group [ECOG] performance status, and use of anti-coagulants) and improve comparability between the cohorts.
- Kaplan-Meier analysis was used to estimate unweighted and ATT-weighted TTD.
- A weighted Cox proportional-hazards (PH) model was used to compare TTD between acalabrutinib and ibrutinib.
  - As a sensitivity analysis, a weighted Cox PH model with adjustments for variables still imbalanced between cohorts after ATT-weighting was run to account for potential residual confounding.
- For all acalabrutinib-treated patients and a subset of ibrutinib-treated patients, reasons for discontinuation were manually abstracted via a review of unstructured data.
  - Data for ibrutinib-treated patients were presented separately for those with and without evidence of subsequent acalabrutinib usage.

Figure 1. Patient Attrition



Results

- From January 2018 through February 2021, 2,509 patients were identified and included in the analysis (**Figure 1**).
- Of these patients, 89.6% (n=2,249) received ibrutinib and 14.1% (n=353) received acalabrutinib across all lines of therapy.
- The demographic and clinical characteristics of the two cohorts are described in **Table 1**.
- After weighting to adjust for differences across cohorts, the acalabrutinib cohort and the ibrutinib cohort were balanced on all baseline characteristics except CV risk factors (more common in the ibrutinib cohort) and prior BTKi use (more common in the acalabrutinib cohort; **Table 1**).
- Prior BTKi use was added as a covariate in the Cox PH model to adjust for residual confounding when imbalances remained across cohorts after weighting.

Table 1. Baseline Characteristics of Patients with CLL and/or SLL Treated with Acalabrutinib or Ibrutinib

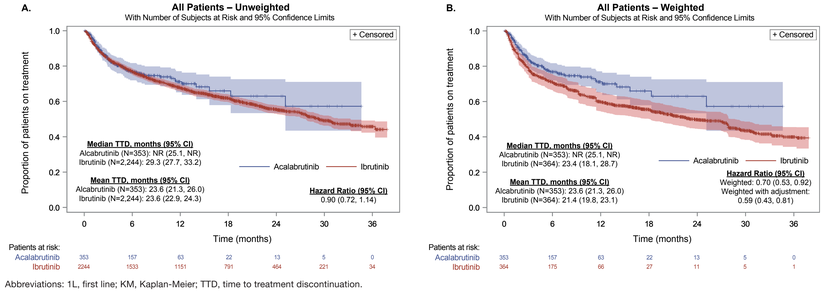
	Original Sample			ATT-weighted Sample		
	Acalabrutinib Cohort N = 353	Ibrutinib Cohort N = 2,249	Std. diff.[1]	Acalabrutinib Cohort N = 353	Ibrutinib Cohort N = 364	Std. diff.[1]
Age at index date, years						
Mean ± SD	71.9 ± 9.2	70.7 ± 9.5	0.130*	71.9 ± 9.2	72.3 ± 3.8	0.049
Median (IQR)	73.0 (66.0, 79.0)	72.0 (65.0, 79.0)		73.0 (66.0, 79.0)	73.0 (66.0, 80.0)	
Female, n (%)	136 (38.5)	855 (38.0)	0.011	136 (38.5)	141 (38.7)	0.004
Race, n (%)						
White	271 (76.8)	1,659 (73.8)	0.070	271 (76.8)	287 (78.8)	0.050
Black or African American	26 (7.4)	198 (8.8)	0.053	26 (7.4)	24 (6.7)	0.028
Other race	25 (7.1)	175 (7.8)	0.027	25 (7.1)	22 (6.0)	0.044
Asian	7 (2.0)	27 (1.2)	0.063	7 (2.0)	5 (1.5)	0.038
Unknown	24 (6.8)	190 (8.4)	0.062	24 (6.8)	26 (7.0)	0.008
Hispanic or Latino, n (%)	9 (2.5)	86 (3.8)	0.073	9 (2.5)	11 (2.9)	0.021
Line of therapy in which BTKi was received, n (%)						
1L	67 (19.0)	1,211 (53.8)	0.777*	67 (19.0)	66 (18.1)	0.024
2L	140 (39.7)	714 (31.7)	0.166*	140 (39.7)	141 (38.6)	0.022
3L+	146 (41.4)	324 (14.4)	0.630*	146 (41.4)	158 (43.4)	0.041
Modified Quan-Charlson Comorbidity Index score						
Mean ± SD	0.1 ± 0.4	0.1 ± 0.4	0.008	0.1 ± 0.4	0.1 ± 0.1	0.017
Median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	
Cardiovascular risk factors, n (%)						
Hypertension	23 (6.5)	220 (9.8)	0.120*	23 (6.5)	30 (8.4)	0.070
Atrial fibrillation	12 (3.4)	36 (1.6)	0.115*	12 (3.4)	17 (4.7)	0.067
Hypercholesterolemia	14 (4.0)	176 (7.8)	0.164*	14 (4.0)	25 (6.7)	0.123*
Congestive heart failure	4 (1.1)	19 (0.8)	0.029	4 (1.1)	4 (1.1)	0.007
Peripheral arterial disease	1 (0.3)	13 (0.6)	0.045	1 (0.3)	7 (2.0)	0.162*
Cerebrovascular disease	0 (0.0)	13 (0.6)	0.108*	0 (0.0)	2 (0.7)	0.116*
Diabetes	11 (3.1)	88 (3.9)	0.043	11 (3.1)	14 (3.7)	0.035
Myocardial infarction	1 (0.3)	7 (0.3)	0.005	1 (0.3)	0 (0.1)	0.053
ECOG performance status, n (%)						
0	129 (36.5)	897 (39.9)	0.069	129 (36.5)	127 (34.8)	0.037
1	128 (36.3)	661 (29.4)	0.147*	128 (36.3)	136 (37.3)	0.022
2+	40 (11.3)	211 (9.4)	0.064	40 (11.3)	43 (11.8)	0.014
Unknown	56 (15.9)	480 (21.3)	0.141*	56 (15.9)	59 (16.1)	0.008
Baseline medications, n (%)						
Prior BTKi use	121 (34.3)	55 (2.4)	0.902*	121 (34.3)	25 (6.7)	0.726*
Anti-coagulants	3 (0.8)	13 (0.6)	0.032	3 (0.8)	5 (1.4)	0.055

Note:
1. For each variable, a standardized difference ≥0.1 was considered to be an inconsequential imbalance between the two populations, as indicated by an asterisk (*).

Abbreviations: 1L, first line; 2L, second line; 3L, third line; BTKi, Bruton Tyrosine Kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SD, standard deviation; SLL, small lymphocytic lymphoma.

- In the unweighted analysis of all patients, there was no significant difference in TTD between the acalabrutinib and ibrutinib cohorts (**Figure 2**).
  - The median unweighted TTD was not reached (NR) (95% CI: 25.1, NR) for the acalabrutinib cohort, whereas the median TTD was reached in the ibrutinib cohort (29.3 months; 27.7, 33.2). The HR was 0.90 (0.72, 1.14).
- After ATT-weighting, the overall TTD for acalabrutinib was significantly longer compared to ibrutinib (**Figure 2**).
  - The median weighted TTD was still NR (25.1, NR) for the acalabrutinib cohort and was 23.4 months (18.1, 28.7) for the ibrutinib cohort (**Figure 2**) with a HR of 0.70 (0.53, 0.92).
  - After additional adjustments for prior BTKi use, the acalabrutinib cohort had a 41% lower risk of discontinuation vs. ibrutinib (HR=0.59; 95% CI: 0.43, 0.81; p=0.001).
- The discontinuation rate across all lines of therapy at 12 months was 22% for the weighted acalabrutinib cohort vs. 31% for the weighted ibrutinib cohort (p=0.005).
- Results stratified by LOT (**Figures 3 and 4**) demonstrated a consistent trend toward TTD favoring acalabrutinib, though these analyses did not reach statistical significance.

Figure 2. KM of Time to Discontinuation – Overall Population



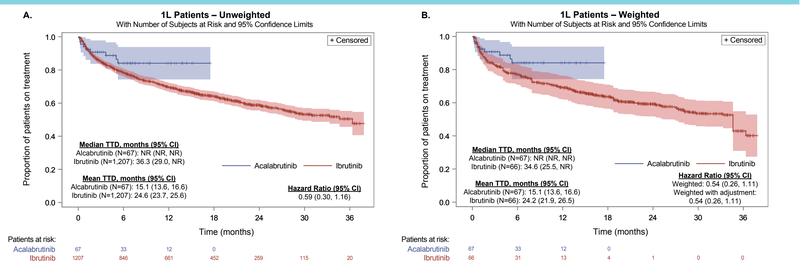
Abbreviations: 1L, first line; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Table 2. Reasons for Discontinuation in Patients with CLL and/or SLL Treated with Acalabrutinib or Ibrutinib

	Acalabrutinib Cohort[1] N = 212	Ibrutinib Cohort Without Subsequent Acalabrutinib[2] N = 194	Ibrutinib Cohort With Subsequent Acalabrutinib[3] N = 59
Total patients			
Discontinued patients, n (%)	54 (25.5)	79 (40.7)	59 (100.0)
Reasons for discontinuation[4]			
Toxic effect of therapy / MEOI	27 (12.7)	37 (19.1)	53 (89.8)
Cytopenia	9 (4.2)	4 (2.1)	4 (6.8)
Arthralgia / myalgia / arthritis	3 (1.4)	3 (1.5)	12 (20.3)
Gastrointestinal toxicity	3 (1.4)	3 (1.5)	4 (6.8)
Headache	3 (1.4)	1 (0.5)	2 (3.4)
Atrial fibrillation	3 (1.4)	5 (2.6)	7 (11.9)
Bleeding episodes	2 (0.9)	8 (4.1)	8 (13.6)
Cardiac toxicity	2 (0.9)	1 (0.5)	5 (8.5)
Fatigue	2 (0.9)	10 (5.2)	3 (5.1)
Rash	3 (1.4)	4 (2.1)	8 (13.6)
Diarrhea	1 (0.5)	3 (1.5)	4 (6.8)
Edema	1 (0.5)	2 (1.0)	5 (8.5)
Infection	1 (0.5)	2 (1.0)	0 (0.0)
Pulmonary toxicity / pneumonitis	0 (0.0)	2 (1.0)	1 (1.7)
Hypertension	0 (0.0)	0 (0.0)	1 (1.7)
Other	2 (0.9)	7 (3.6)	5 (8.5)
Progression	7 (3.3)	5 (2.6)	3 (5.1)
Non–cancer-related medical issue	4 (1.9)	5 (2.6)	2 (3.4)
Insufficient response	3 (1.4)	4 (2.1)	3 (5.1)
Other	6 (2.8)	12 (6.2)	1 (1.7)
Unknown	8 (3.8)	17 (8.8)	0 (0.0)

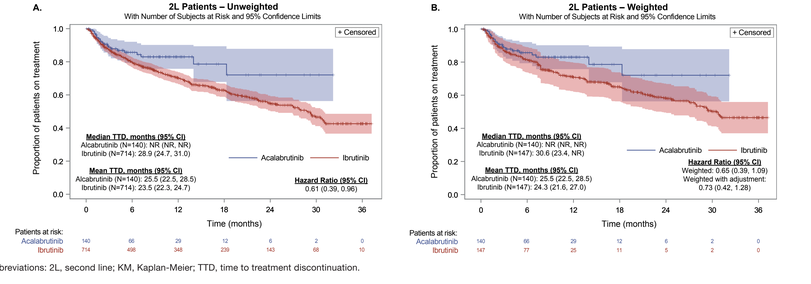
Abbreviations: CLL, chronic lymphocytic leukemia; MEOI, medical events of interest; SLL, small lymphocytic lymphoma.
Notes:
1. Patients in the acalabrutinib cohort may have received ibrutinib in any line of therapy. One patient in the acalabrutinib cohort discontinued treatment due to atrial fibrillation and one patient in the ibrutinib cohort discontinued treatment due to arthralgia/myalgia + headache on the index date (i.e., initiation of acalabrutinib or ibrutinib). These patients were removed from the analysis.
2. Patients who received both acalabrutinib monotherapy and ibrutinib monotherapy on or after January 1, 2018, were excluded from this cohort.
3. Patients in this cohort received ibrutinib monotherapy on or after January 1, 2018, followed by acalabrutinib monotherapy in a later line. Four patients received acalabrutinib monotherapy prior to ibrutinib monotherapy and were removed from this cohort.
4. Patients may have had ≥1 reasons for discontinuation.

Figure 3. KM of Time to Discontinuation – 1L Population



Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation.

Figure 4. KM of Time to Discontinuation – 2L Population



Abbreviations: 2L, second line; KM, Kaplan-Meier; TTD, time to treatment discontinuation.

- For the subset of patients with information on reasons for treatment discontinuation, roughly half of patients in both cohorts discontinued due to toxicity (**Table 2**).
  - Cytopenias were the most common adverse events (AEs) leading to discontinuation for the acalabrutinib cohort, while fatigue was the most common for ibrutinib patients without subsequent acalabrutinib.
- The majority (n=53/59; 90%) of ibrutinib patients who received subsequent acalabrutinib discontinued their ibrutinib treatment due to toxicity.
  - The most common AEs leading to discontinuation in this cohort were arthralgia/myalgia/arthritis, bleeding episodes, rash, and atrial fibrillation.

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Poster

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Corresponding author email address: roekerl@mskcc.org