Comparison of Time to Next Treatment Between Patients With Chronic Lymphocytic Leukemia Initiating First-Line Ibrutinib or Acalabrutinib, Overall and in a Subgroup With High-Risk Characteristics

CLL-342

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INTRODUCTION

- Ibrutinib and acalabrutinib are 2 covalent Bruton tyrosine kinase inhibitors (BTKis) approved for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1,2]
- Although no head-to-head randomized studies comparing these 2 medications in the first-line (1L) setting currently exist, a previous real-world study of electronic medical records (EMRs) found that patients treated with 1L acalabrutinib were more likely to initiate a next treatment compared with patients treated with 1L ibrutinib[3]
- Other studies have also found that treatment with 1L ibrutinib was associated with higher adherence and lower healthcare resource utilization and costs compared with 1L acalabrutinib[4-6]

OBJECTIVE

- To compare time to next treatment (TTNT) between 1L ibrutinib and 1L acalabrutinib among patients with CLL/SLL in the United States, overall and among a subgroup of patients with high-risk characteristics (HRCs; i.e., patients with del(17p)/*TP53* mutation or unmutated immunoglobulin heavy chain variable [IGHV]) using academic EMR data

METHODS

Data source

- This study used structured EMR and unstructured patient chart data from the Acentrus database (November 21, 2018, to April 30, 2022)
- Acentrus included patient records from 15 academic and 12 nonteaching hospital systems across 15 US states and contains information on demographics, visits, diagnoses, laboratory tests, mortality, and medication orders, fills, or administrations
- Eastern Cooperative Oncology Group performance status (ECOG PS) and cytogenetics data were also extracted from patient charts
- Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act

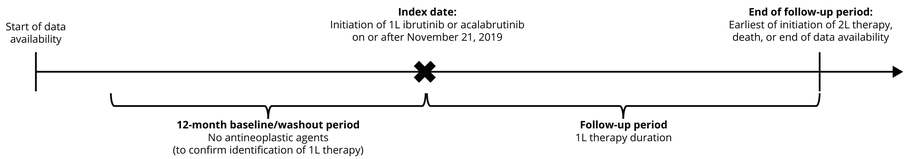
Study design

- In this real-world retrospective study, the index date was defined as the date of initiation of 1L single-agent ibrutinib or acalabrutinib on or after November 21, 2019 (date of acalabrutinib approval), the baseline period was defined as the 12-month period before the index date, and the follow-up period was defined as time from the index date to the earliest date of initiation of second-line therapy, death, or end of data availability (**Figure 1**)

Study population

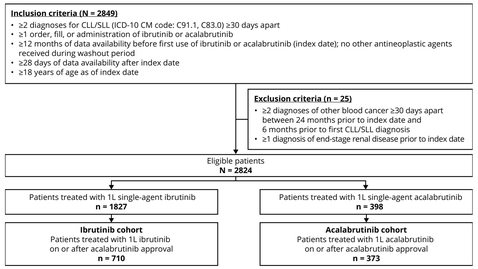
- The patient selection criteria are presented in **Figure 2**

FIGURE 1: Study design



1L, first-line; 2L, second-line.

Figure 2: Study population selection



1L, first-line; CLL, chronic lymphocytic leukemia; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; SLL, small lymphocytic lymphoma.

- A subgroup of patients with HRCs , defined as those with del(17p)/*TP53* mutation or unmutated IGHV, was also evaluated

Study outcome measures

- TTNT was defined as the time from the index date to the date of initiation of a next regimen
  - Patients who did not initiate a subsequent regimen were censored at the date of death or the end of data availability
  - Patients with an observed within-class BTKi switch at any time or with a venetoclax or anti-CD20 add-on within the first 6 months were censored at the date of switch/add-on
  - Beyond the first 180 days post-index, anti-CD20 or venetoclax add-ons were considered to be a next treatment
  - Patients who switched to agents for nonhematologic cancers were censored at the date of switch

Statistical analyses

- Baseline demographics and clinical characteristics were compared between cohorts using *t*-tests for continuous variables and chi-square tests for categorical variables
- TTNT was reported using Kaplan-Meier survival curves and was compared between cohorts using the Cox proportional hazards model, adjusting for baseline demographics and clinical characteristics (including ECOG PS and cytogenetics)

RESULTS

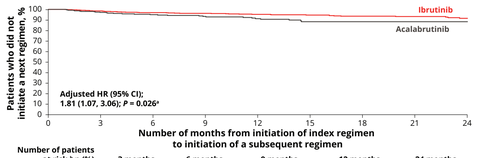
Baseline demographics and clinical characteristics

- A total of 710 patients initiated 1L ibrutinib and 373 patients initiated 1L acalabrutinib (**Figure 2**)
- In the ibrutinib and acalabrutinib cohorts, mean age was 71.5 years and 72.4 years, respectively; *P* = 0.159) and 61.5% and 61.7%, respectively, were men (*P* = 0.971); mean Quan-Charlson Comorbidity Index scores were similar between the 2 cohorts (ibrutinib: 3.1; acalabrutinib: 3.0; *P* = 0.597)
- Of the 13.2% of patients in the ibrutinib cohort with ECOG PS data, 95.7% had an ECOG PS score between 0 and 1; in the acalabrutinib cohort, ECOG PS data were available for 16.1% of patients, of which 91.7% had an ECOG PS score between 0 and 1
- Cytogenetics data were available in 12.7% of patients in the ibrutinib cohort and 11.3% of patients in the acalabrutinib cohort
- 31 patients in the ibrutinib cohort and 18 patients in the acalabrutinib cohort had del(17p)/*TP53* mutation or unmutated IGHV and were evaluated as part of the HRC subgroup

Time to next treatment

- Over a median follow-up of 18.1 and 11.9 months, 42 patients (5.9%) in the ibrutinib cohort and 28 patients (7.5%) in the acalabrutinib cohort, respectively, initiated a next treatment
- At 12 months, 95.3% of patients in the ibrutinib cohort and 91.2% of patients in the acalabrutinib cohort had not initiated a next treatment; these rates remained similar at 24 months, with 91.5% and 88.3% of patients without a next treatment in the ibrutinib and acalabrutinib cohorts, respectively
- After adjusting for baseline characteristics, patients treated with acalabrutinib were 81% more likely to initiate a next treatment compared with patients treated with ibrutinib (adjusted hazard ratio [HR] = 1.81; *P* = 0.026) (**Figure 3**)

Figure 3: Comparison of TTNT between patients treated with 1L ibrutinib or 1L acalabrutinib



Number of patients at risk,[b] n (%)	3 months	6 months	9 months	12 months	24 months
Ibrutinib DR	640	576	529	461	144
Acalabrutinib	308	245	204	158	27

1L, first-line; DR, dose reduction; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; NR, not reached; TTNT, time to next treatment; Quan-CCI, Quan-Charlson Comorbidity Index.
[a]*P* < 0.05. HRs and *P* values were calculated using a Cox proportional hazards model adjusting for the following baseline covariates: age, sex, region, race, year of index date, Quan-CCI, atrial fibrillation, chronic pulmonary disease, metastases, corticosteroid use, antiplatelet use, peripheral vascular disease, hypertension, ECOG PS score, as well as del(17q), del(11q), del(13q), ATM, IGHV, *TP53*, and trisomy 12 mutation status.
[b]Refers to the population at risk of having the event at that point in time (i.e., patients who have not had the event and have not been lost to follow-up).

- Among patients who received a next treatment, the majority of patients switched to venetoclax (59.5% in the ibrutinib cohort and 50.0% in the acalabrutinib cohort) (**Table 1**)
- Time to initiation of a next treatment was shorter in the acalabrutinib cohort (mean [median]: 6.2 [4.6] months) than in the ibrutinib cohort (mean [median]: 9.2 [6.8] months)

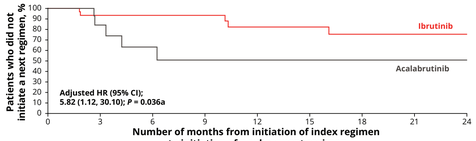
Table 1: Treatment regimen received following 1L ibrutinib or acalabrutinib

	Ibrutinib N = 710	Acalabrutinib N = 373
Patients with a next treatment, n (%)	**42 (5.9)**	**28 (7.5)**
TTNT (months), mean ± SD [median]	9.2 ± 7.6 [6.8]	6.2 ± 4.6 [4.6]
Next treatment regimen received, n (%)		
Venetoclax	25 (59.5)	14 (50.0)
Obinutuzumab	1 (2.4)	3 (10.7)
Rituximab	2 (4.8)	0
Chlorambucil	2 (4.8)	1 (3.6)
Lenalidomide	3 (7.1)	0
Bendamustine + rituximab	4 (9.5)	0
Venetoclax + obinutuzumab	0	3 (10.7)
Venetoclax + idelalisib	1 (2.4)	0
Venetoclax + chlorambucil + rituximab	0	1 (3.6)
BTKi + venetoclax	3 (7.1)	5 (17.9)
BTKi + obinutuzumab	0	1 (3.6)
BTKi + lenalidomide	1 (2.4)	0

1L, first-line; BTKi, Bruton tyrosine kinase inhibitor; SD, standard deviation; TTNT, time to next treatment.

- Among patients with HRCs, 5 patients (16.1%) in the ibrutinib cohort and 5 patients (27.8%) in the acalabrutinib cohort initiated a next treatment
- In the ibrutinib and acalabrutinib cohorts, 81.9% and 50.3% of patients had not initiated a next treatment at 12 months, respectively; at 24 months, these estimates were 75.1% and 50.3%, respectively
- In adjusted analyses, patients with HRCs treated with acalabrutinib were >5 times more likely to initiate a next treatment compared with patients treated with ibrutinib (adjusted HR = 5.82; *P* = 0.036) (**Figure 4**)

Figure 4: Comparison of TTNT between patients treated with 1L ibrutinib or 1L acalabrutinib among patients with HRCs



Number of patients at risk,[b] n (%)	3 months	6 months	9 months	12 months	24 months
Ibrutinib DR	22	20	17	14	6
Acalabrutinib	10	6	3	2	0

1L, first-line; DR, dose reduction; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; HRCs, high-risk characteristics; NR, not reached; TTNT, time to next treatment; Quan-CCI, Quan-Charlson Comorbidity Index.
[a]*P* < 0.05. HRs and *P* values were calculated using a Cox proportional hazards model adjusting for the following baseline covariates: age, sex, Quan-CCI, hypertension, and ECOG PS score.
[b]Refers to the population at risk of having the event at that point in time (i.e., patients who have not had the event and have not been lost to follow-up).

LIMITATIONS

- EMR data may contain omissions and inaccuracies, but this is expected to apply to all patients, and thus, should have minimal impact on overarching conclusions
- Acentrus is a provider-based data source, meaning that records are only available to the extent that visits are part of the network of academic and nonteaching hospital systems included in the data
- A 12-month washout period was used to identify the use of ibrutinib or acalabrutinib in the 1L setting, which has been used extensively in real-world studies, but could have included patients in longer remission who had received a previous line of therapy
- Patients were assumed to be using their medication based on prescription fills, but may not always have adhered to their treatment regimen as prescribed
- Reasons for starting a next treatment were not available in Acentrus; however, assumptions regarding the definition of TTNT were made to ensure that the reason was most likely related to disease progression
- Results may not be generalizable to all patients treated with 1L ibrutinib or acalabrutinib or to patients treated outside of academic or nonteaching hospital systems in the United States

CONCLUSIONS

- Over a median follow-up of 12 to 18 months, this real-world study of patients with CLL/SLL treated with 1L single-agent ibrutinib or acalabrutinib supports previous results, suggesting that while most patients benefit from BTKis, a significantly greater proportion of patients treated with 1L acalabrutinib initiated a next treatment compared with those treated with 1L ibrutinib
- Results were consistent in the subgroup of patients with HRCs
- These results demonstrate the impact of using ibrutinib in the 1L setting and highlight the importance of these data to support clinical decision-making in improving patient outcomes in the real-world setting

ACKNOWLEDGMENTS

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