HSD118

Real-world treatment patterns and cardiovascular disease (CVD) burden in patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) receiving covalent Bruton's Tyrosine Kinase inhibitors (cBTKis)

David Dingli[1]; Enrico de Nigris[2]; Mavis Obeng-Kusi[3]; Siyang Leng[3]; Kunal Lodaya[4]; Ian Weimer[4]; Weiqi Jiao[4]; Hayden W. Hyatt[4]; Halit O. Yapici[4]

[1]Mayo Clinic, Rochester, MN, USA; [2]MSD (UK) Limited, London, United Kingdom; [3]Merck & Co., Inc., Rahway, NJ, USA; [4]Boston Strategic Partners, Inc., Boston, MA, USA

Background

- CLL is the second most common type of leukemia in the United States, with an estimated 20,700 new cases to occur in 2024[1]
- cBTKis revolutionized CLL/SLL treatment following ibrutinib's approval in 2014 and are commonly used as first-line (1L) therapies and in relapsed/refractory (R/R) cases
- Clinical trials have indicated that ibrutinib is associated with an increased risk of cardiovascular events (eg, atrial fibrillation, atrial flutter, and hypertension[2,3]), which may interrupt treatment and complicate clinical decision-making
- Second-generation cBTKis – acalabrutinib and zanubrutinib – have reported improved CVD safety profiles in clinical trials compared to ibrutinib,[4,5] though the impacts of these findings on clinical practice are not well understood

Objective

- To evaluate the real-world treatment patterns and pre-treatment CVD burden in CLL/SLL patients

Methods

Study design

- In this retrospective study, adult patients (≥18 years of age) diagnosed with CLL/SLL who received cBTKi treatment were identified using Optum Clinformatics® DataMart (CDM) claims data (January 1, 2013 to January 1, 2023)
  - Patients were included if they had medical claims for CLL/SLL diagnosis after January 1, 2013, pharmacy or medical claims for anticancer drugs, continuous enrollment ≥6 months prior to and ≥3 months following the index date, and at least 1 pharmacy claim for cBTKi indicated for CLL/SLL
  - Patients with ≥1 medical claim(s) for cBTKi-related malignancy, metastatic solid tumor, CLL/SLL-related anticancer therapy, or hematopoietic stem cell transplantation prior to the first diagnosis of CLL/SLL were excluded
- The index date was determined as the initiation of an observed 1L therapy between January 1, 2014 and January 1, 2023, following the first CLL/SLL claim
- The observation period spanned from the index date until the earliest of death, end of continuous enrollment, or end of data availability
- Two temporal cohorts were assessed corresponding to pre- (2014-2019) and post- (2020-2023) regulatory approval of acalabrutinib in the US (Nov 2019)
- Patient demographics and clinical characteristics, including the National Cancer Institute (NCI) Comorbidity Index, were determined
- Clinical treatment pathways were assessed for lines of treatment (LOT) 1L to fifth-line (5L), including treatment switching, discontinuation, restart, and death
  - All unique agents received within a 60-day time window were considered within the same LOT[6,7]
  - Discontinuation was defined as the last day of supply before a gap of at least 90 consecutive days without another claim
  - A new line of therapy (switching) was determined as the initiation of a new agent that was not included in the prior LOT
  - Restart was defined as re-initiation of the same cBTKi that was initiated on the index date following a 90-day gap
- Among patients who initiated acalabrutinib or ibrutinib between January 1, 2020 and January 1, 2023, pre-treatment CVD prevalence was assessed during the 6-month baseline period

Results

Baseline characteristics

- Overall, 4,353 real-world patients were included in the study, with 2,405 patients included in the pre-2020 cohort and 1,948 patients in the post-2020 cohort (**Figure 1**)
  - Patients in the pre-2020 cohort were slightly older (mean [SD] age of 71 [9.6] in the pre-2020 cohort and 73 [9.0] in the post-2020 cohort), and had a lower proportion of females (38.6% and 41.2% of patients, respectively) (**Table 1**)
  - The mean NCI Comorbidity Index was similar for the pre- and post-2020 cohorts (0.5 [0.6] and 0.5 [0.5])
  - The mean observation period was longer in the pre-2020 cohort than the post-2020 cohort (3.8 [2.2] years and 1.6 [0.9] years, respectively), which was expected due to the availability of data during the temporal time windows

Figure 1. Attrition flowchart

≥2 medical claims for a primary or secondary CLL/SLL diagnosis, distinct days after 01/01/2013
N = 147,109
↓
Adult patients who are 18 years of age or older at the first CLL/SLL diagnosis
N = 145,968
↓
≥1 medical or pharmacy claim for anticancer drugs on or after the first CLL/SLL diagnosis claim
N = 38,476
↓
≥6 months of continuous enrollment pre-index date
N = 32,333
↓
≥3 months of continuous enrollment post-index date
N = 27,580
↓
≥1 pharmacy claim for a BTKi therapy indicated for CLL/SLL
N = 5,533
↓
1,063 patients were excluded
521 had ≥1 medical claim with a diagnosis code for other BTKi-related malignancies, or metastatic tumor, prior to first diagnosis of CLL/SLL
542 had ≥1 medical or pharmacy claim for anticancer therapy or HSCT prior to first diagnosis of CLL/SLL
↓
Overall cohort (Patients with index date between January 1, 2014 and January 1, 2023)
N = 4,353
↓
Temporal cohort #1 (2014-2019) **N = 2,405**
Temporal cohort #2 (2020-2023) **N = 1,948**

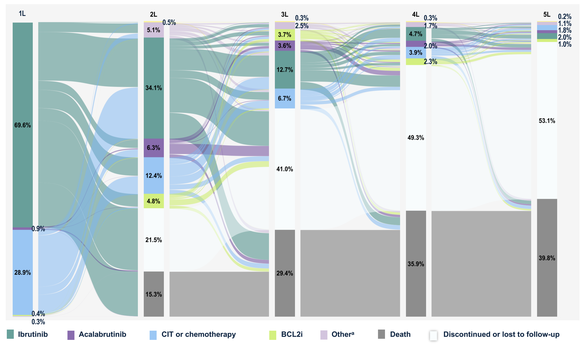
Table 1. Patient demographics and clinical characteristics

Patient characteristics	Temporal cohort #1 2014–2019 (N = 2,405)	Temporal cohort #2 2020–2023 (N = 1,948)
Age, years, mean ± SD	71 ± 9.6	73 ± 9.0
Sex, female, n (%)	928 (38.6%)	802 (41.2%)
Race, n (%)		
White	1,828 (76.0%)	1,462 (75.1%)
Black	266 (11.1%)	199 (10.2%)
Hispanic	179 (7.4%)	121 (6.2%)
Unknown	94 (3.9%)	129 (6.6%)
Asian	38 (1.6%)	37 (1.9%)
Observation period, years, mean ± SD	3.8 ± 2.2	1.6 ± 0.9
Geographic region, n (%)		
South	1,004 (41.7%)	744 (38.2%)
West	607 (25.2%)	501 (25.7%)
Midwest	534 (22.2%)	455 (23.4%)
Northeast	255 (10.6%)	247 (12.7%)
Unknown	5 (0.2%)	1 (0.1%)
Insurance plan type, n (%)		
Medicare Advantage	1,916 (79.7%)	1,687 (86.6%)
Commercial	658 (27.4%)	396 (20.3%)
Time from CLL/SLL diagnosis to 1L, days, mean ± SD	587.8 ± 565.1	773.9 ± 832.5
NCI[a], mean ± SD	0.5 ± 0.6	0.5 ± 0.5

Treatment patterns in temporal cohorts (2014-2019 and 2020-2023)

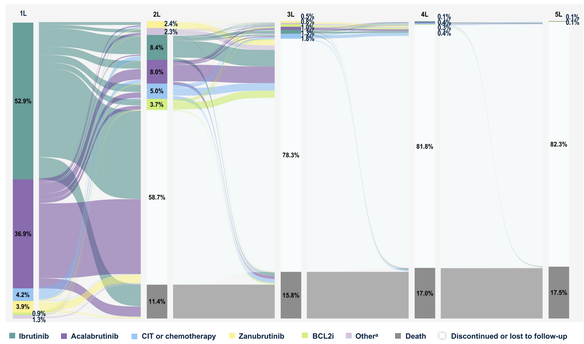
- 1L cBTKi use was considerably higher in the post-2020 cohort (94.8%; **Figure 2**) compared to pre-2020 (70.5%; **Figure 3**)

Figure 2. Treatment patterns in temporal cohort 1 (2014-2019, N = 2,405)



Note: Percentages for each treatment class are calculated relative to the total number of patients in the cohort.
[a]Including cBTKi combination therapy, CD20, PI3Ki-related anticancer drugs, radiation therapy, hematopoietic stem cell transplantation, and CAR-T.

Figure 3. Treatment patterns in temporal cohort 2 (2020-2023, N = 1,948)



Note: Percentages for each treatment class are calculated relative to the total number of patients in the cohort.
[a]Including cBTKi combination therapy, CD20, PI3Ki-related anticancer drugs, radiation therapy, hematopoietic stem cell transplantation, and CAR-T.

  - The use of acalabrutinib as 1L therapy increased to 36.9% following its approval for CLL/SLL in 2020
  - Conversely, ibrutinib use as 1L therapy declined from 69.6% in the pre-2020 cohort to 52.9% in the post-2020 cohort
  - In the post-2020 cohort, zanubrutinib was used by 3.9% of patients as 1L; however, the study period largely occurred prior to its approval for CLL/SLL in January 2023
- Among patients with ≥2 LOT, switching or restarting cBTKis (cBTKi →cBTKi) was the most common treatment pathway, which increased from 21.3% pre-2020 to 41.3% post-2020
  - The 2L restart rate for ibrutinib (16.7%) was consistent in pre- and post-2020 periods, whereas it increased from 0.4% to 9.5% for acalabrutinib
  - Ibrutinib use as 2L was higher in the pre-2020 cohort (53.9%) compared to the post-2020 cohort (28.2%), whereas 2L acalabrutinib use increased from 10.0% to 26.9% post-2020
  - The proportion of patients switching from ibrutinib to acalabrutinib in 2L increased from 3.8% in the pre-2020 cohort to 7.9% in the post-2020 cohort
- Chemoimmunotherapy use in 1L had a notable decline from 19.8% pre-2020 to 2.6% post-2020
- Chemotherapy use also decreased in 1L from 9.1% in the pre-2020 cohort to 1.6% in the post-2020 cohort
- B-cell Lymphoma 2 inhibitors (BCL2i) were rarely used as 1L treatment (<1% for both cohorts); however, their use as 2L among those with ≥2 LOT increased from 7.6% in the pre-2020 cohort to 12.6% in the post-2020 cohort
- Death occurred in 15.3% and 11.4% of patients in 2L in the pre- and post-2020 cohorts, respectively

Pre-treatment CVD prevalence

- Pre-treatment CVD prevalence was high for patients who initiated acalabrutinib and ibrutinib between 2020 and 2023, including ventricular arrhythmias (14.8% and 12.2%), congestive heart failure (14.8% and 11.0%), atrial fibrillation (14.3% and 9.5%), and atrial flutter (11.2% and 7.5%) (**Table 2**)

Table 2. Pre-treatment CVD in patients who initiated ibrutinib or acalabrutinib between 2020 and 2023

CVD	Ibrutinib (N = 1,201)	Acalabrutinib (N = 869)
Hypertension	767 (63.9%)	553 (63.6%)
Ventricular arrhythmias	147 (12.2%)	129 (14.8%)
Congestive heart failure	132 (11.0%)	129 (14.8%)
Atrial fibrillation	114 (9.5%)	124 (14.3%)
Atrial flutter	90 (7.5%)	97 (11.2%)
Myocardial infarction	54 (4.5%)	52 (6.0%)
Cardiomyopathy	21 (1.7%)	30 (3.5%)
Conduction disorders	5 (0.4%)	7 (0.8%)

Limitations

- This retrospective study utilized a claims database, and all limitations regarding research conducted with secondary data apply to this study
- Components of the patient journey that were not captured in the database were not included in the analysis (eg, treatments not serviced by Optum)
- The 1L treatment observed in the database may not represent the actual 1L used in the real world, and claims data do not provide insight into the reasons for treatment changes

Conclusions

- Our findings showed high uptake of cBTKis (Ibrutinib and Acalabrutinib) as 1L treatment, with frequent restart of cBTKis
- A notable increase in cBTKi use as 1L treatment pre- vs post-2020 indicates a temporal shift in clinical treatment approaches
- There was a considerable pre-treatment CVD burden across ibrutinib and acalabrutinib treatments, emphasizing the need for therapies that offer both a safe cardio-toxicity profile and robust efficacy
- The frequency of all CVD diagnoses (all CVD except for hypertension) were higher in patients treated with acalabrutinib, suggesting that patients with pre-existing CVD were more likely to be treated with acalabrutinib
- Although both Acalabrutinib and Ibrutinib show high usage as Standard of Care in 1L post 2020 there is a need of further real-world investigation is crucial to understand CVD risks and clinical/health economics outcomes associated with cBTKis

Disclosures

This study was sponsored by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). Writing and editorial support was provided by Boston Strategic Partners, Inc., funded by MSD.

References

1. Siegel RL, Giaquinto AN, Jemal A. *CA Cancer J Clin.* 2024;74(1):12-49.
2. Barr PM, et al. *Blood Adv.* 022;6(11):3440-3450.
3. Munir T, et al. *Am J Hematol.* 2019;94(12):1353-1363.
4. Byrd JC, et al. *J Clin Oncol.* 2021;39(31):3441-3452.
5. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332.
6. Wierda WG, et al. *J Natl Compr Canc Netw.* 2020;18(2):185-217.
7. Patel K, Pagel JM. *J Hematol Oncol.* 2021;14(1):69.

Presented at ISPOR; Atlanta, GA, USA; May 5-8, 2024.