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Real-World Clinical Outcomes of First-Line Ibrutinib Dose Reduction Versus Acalabrutinib Among Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

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OBJECTIVE

To describe the effect of ibrutinib dose reduction (DR) on duration of treatment (DOT) and time to next treatment (TTNT) versus first-line (1L) single-agent acalabrutinib

CONCLUSIONS

Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who received 1L single-agent ibrutinib with a subsequent DR had numerically longer DOT and TTNT than patients who received 1L single-agent acalabrutinib

This real-world analysis suggests that treatment outcomes in patients with CLL/SLL receiving ibrutinib and undergoing DRs are not inferior to outcomes in patients receiving acalabrutinib

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INTRODUCTION

- Ibrutinib, a once-daily covalent Bruton tyrosine kinase inhibitor (BTKi) approved for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), has demonstrated significant improvements in overall survival and progression-free-survival in clinical trials[1-6] and offers the most flexibility for dose adjustments of any BTKi while maintaining efficacy[7-12]
- Longer time to next treatment (TTNT)[13] and lower or similar healthcare resource utilization (HRU) and costs[14] have been reported for ibrutinib versus acalabrutinib, a twice-daily covalent BTKi
- While real-world evidence in patients with CLL/SLL demonstrates similar efficacy between those treated with or without an ibrutinib dose reduction (DR),[8-12] treatment outcomes associated with ibrutinib DR have not been compared with outcomes associated with acalabrutinib in first-line (1L) settings

METHODS

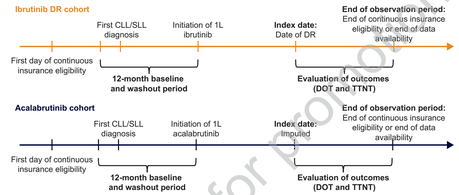
Data Source

- Data included information on medical and pharmacy claims for >20 million beneficiaries obtained from a large US claims database that included all census regions in the United States (November 21, 2018–June 30, 2023)
- Data were de-identified and comply with the Health Insurance Portability and Accountability Act

Study Design and Population

- Patients included previously untreated adults with CLL/SLL who initiated 1L single-agent ibrutinib or 1L single-agent acalabrutinib on or after November 21, 2019 (ie, acalabrutinib approval date)
- 2 cohorts were analyzed
  - Patients who initiated 1L single-agent ibrutinib at a starting dose of 420 mg/day and had a subsequent DR during 1L therapy
  - Patients who initiated 1L single-agent acalabrutinib
- The identification of 1L treatment was ascertained based on a washout period of ≥12 months (baseline period) without the use of any antineoplastic agents
- For the ibrutinib cohort, the index date was defined as the date of DR; for the acalabrutinib cohort, the index date was imputed after the initiation of 1L treatment so that it replicated the distribution of time between 1L initiation and DR observed in the ibrutinib cohort

Study Design Scheme



DOT, duration of treatment.

Study Outcomes

- DOT was defined as the time from the index date to the last day of supply before a >90-day gap in consecutive days of supply or initiation of a next line of therapy
- TTNT was defined as time from index date to the initiation of a next line of therapy or re-initiation of the same treatment after a gap of >90 days
- Patients without an event were censored at the end of their continuous health insurance eligibility or the end of data availability

Statistical Analysis

- Inverse probability of treatment weighting (IPTW) was used to balance cohorts
  - Weights were based on the propensity score, which was estimated using a logistic regression model
  - The following baseline characteristics were adjusted for in the logistic regression model: age, sex, race, Quan-Charlson Comorbidity Index (Quan-CCI), hypertension, atrial fibrillation, hypothyroidism, renal failure, any mental comorbidities (based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-V]), fatigue/weakness, musculoskeletal pain, use of antihypertensives, and HRU; the following characteristics measured between 1L initiation and index date were also adjusted for in the logistic regression model: number of incident clinical events and type of clinical event (ie, cardiovascular or noncardiovascular)
- Baseline characteristics were reported descriptively after applying IPTW. Standardized differences were used to compare characteristics between cohorts (characteristics with differences of <10% were considered similar[15])
- DOT and TTNT were compared between cohorts using IPTW Kaplan-Meier curves and Cox proportional hazards models; Cox models were additionally adjusted for the year of initiation of 1L therapy (to account for differences in follow-up and remaining imbalance after applying IPTW)

RESULTS

Baseline[a] Characteristics Were Well-Balanced After IPTW

	Ibrutinib DR N=44	Acalabrutinib N=171	Standardized Difference (%)
Age, mean ± SD [median], years	76.9 ± 8.9 [76.0]	76.6 ± 10.3 [75.0]	3
Female, n (%)	18 (42)	66 (39)	7
Region, n (%)			
South	24 (54)	104 (61)	14
Midwest	12 (28)	41 (24)	10
West	7 (15)	17 (10)	16
Northeast	1 (2)	8 (5)	14
Race, n (%)			
White	33 (75)	122 (71)	9
Black	4 (9)	13 (8)	6
Unknown	7 (16)	36 (21)	14
Insurance plan type, n (%)			
Medicare Advantage	44 (100)	171 (100)	0
Year of initiation of 1L therapy, n (%)			
2019	3 (6)	1 (1)	31
2020	28 (63)	27 (16)	111
2021	9 (20)	64 (37)	40
2022	5 (12)	66 (39)	66
2023	0 (0)	13 (8)	41
Quan-CCI, mean ± SD [median]	4.6 ± 2.4 [4.0]	4.5 ± 2.5 [4.0]	3
Comorbidities, n (%)			
Hypertension	35 (79)	130 (76)	7
Atrial fibrillation	8 (19)	29 (17)	5
Hypothyroidism	10 (22)	39 (23)	2
Renal failure	11 (25)	38 (22)	5
Fatigue	14 (32)	58 (34)	4
Musculoskeletal pain	19 (44)	72 (42)	3
Any mental comorbidities (based on DSM-V), n (%)	22 (50)	84 (49)	0
Use of antihypertensives, n (%)	13 (30)	47 (27)	6

[a]Baseline characteristics were evaluated during the 12-month period preceding the initiation of 1L therapy.

Mean Time Between 1L Therapy Initiation and End of Follow-Up and Mean Time From Index Date to End of Follow-Up Were Both Longer in the Ibrutinib DR Cohort

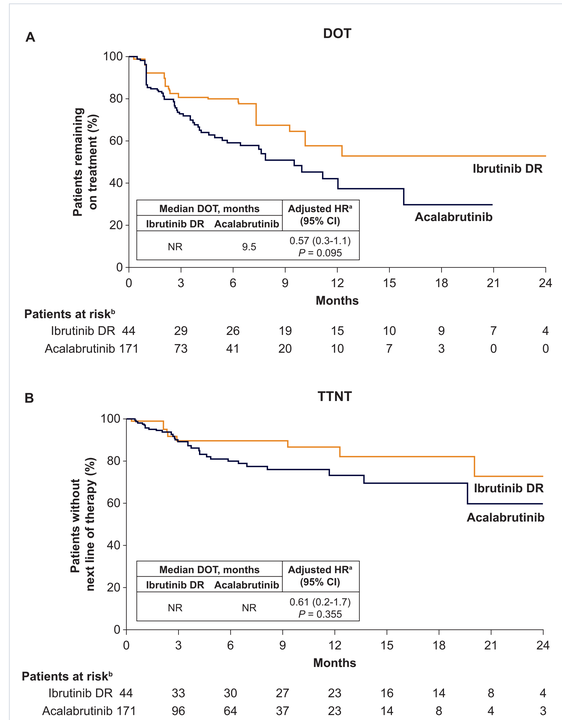
	Ibrutinib DR N=44	Acalabrutinib N=171
Time between 1L therapy initiation and end of follow-up,[a] mean ± SD [median], days	592.2 ± 282.5 [645.5]	388.3 ± 241.3 [326.0]
Time from 1L therapy initiation to index, mean ± SD [median], days	167.2 ± 145.3 [125.0]	167.1 ± 159.0 [112.0]
Time from index to end of follow-up, mean ± SD [median], days	425.0 ± 266.3 [429.0]	221.2 ± 197.1 [158.0]

SD, standard deviation.

[a]End of follow-up was equal to the end of continuous eligibility and/or end of data availability.

- Among 286 patients who initiated 1L single-agent ibrutinib at 420 mg/day, 44 (15%) had a DR; 171 patients initiated 1L single-agent acalabrutinib (**Supplementary Figure 1**)
- A total of 16 (37%) and 60 (35%) patients discontinued treatment in the ibrutinib DR and acalabrutinib cohorts, respectively
  - Median DOT was not reached in the ibrutinib DR cohort and was 9.5 months in the acalabrutinib cohort
- A total of 7 (16%) and 29 (17%) patients in the ibrutinib DR and acalabrutinib cohorts received a next treatment, respectively
  - Among these patients, 4 (51%) and 19 (65%) switched to a BTKi regimen in the ibrutinib DR and acalabrutinib cohorts, respectively
  - Median TTNT was not reached in either cohort

DOT and TTNT Were Numerically Longer in the Ibrutinib DR Cohort Versus the Acalabrutinib Cohort



NR, not reached.

[a]In addition to the cohort indicator, Cox models were adjusted for the year of initiation of 1L therapy.

[b]Patients without an event were censored at the end of their continuous health insurance eligibility or the end of data availability.

LIMITATIONS

- Claims data may contain omissions and inaccuracies, but these were expected to equally affect all cohorts and, thus, should not impact conclusions
- A claim for a medication did not necessarily indicate its use
- In the ibrutinib cohort, reasons for DR and for discontinuing or switching treatment were not available in the database
- Although a ≥12-month washout period for antineoplastic agents prior to the initiation of 1L therapy was used, patients previously receiving regimens with fixed durations may have had a treatment-free interval lasting >12 months; therefore, second-line therapy may have been misclassified as 1L therapy in the current study
- All patients in the current study had Medicare Advantage coverage; thus, results may not be generalizable to patients with other types of insurance (eg, commercial or Medicaid) or uninsured patients
- Residual confounding may remain due to unobserved confounders

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