

## From 2020 to 2024

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### CONCLUSIONS

- This longitudinal, real-world study found that cBTKi monotherapies were the most common 1L treatment in patients aged ≥65 years with CLL/SLL between 2020 and 2024
- cBTKi monotherapies had the greatest increase in usage (42% to 48% of all treatments), with zanubrutinib use comprising 28% of all treatments in 2024
- Within this cohort of older adults, patients treated with cBTKi monotherapies had a higher median age and were more likely to have a severe CCI than those treated with ven + anti-CD20 mAb
- In this exploratory analysis, patients treated with zanubrutinib were less likely to discontinue treatment than patients treated with acalabrutinib or ibrutinib
- Despite the treatment advances of novel therapies available, a sizeable subgroup still received CIT or anti-CD20 mAb alone and informative biomarker testing remained under-utilized

### INTRODUCTION

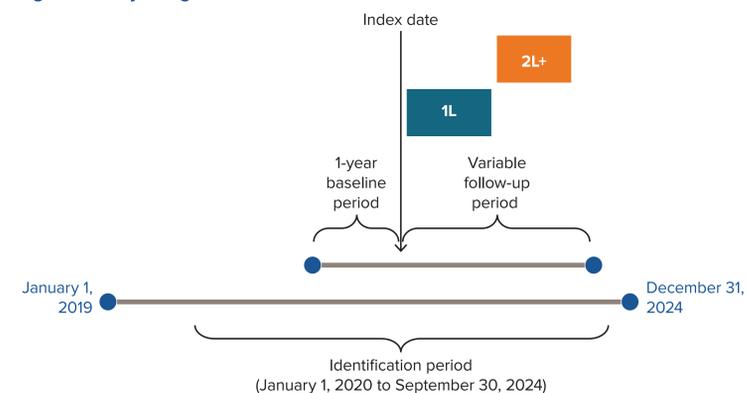
- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is the most common leukemia in US adults and incidence increases with age, with 67% of patients being >65 years at diagnosis<sup>3</sup>
- The introduction of novel therapies, such as zanubrutinib, acalabrutinib, and venetoclax (ven), has transformed the CLL/SLL treatment landscape, with these therapies now recommended for first-line (1L) use in National Comprehensive Cancer Network® (NCCN) guidelines<sup>4</sup>
- However, there are concerns around comorbidities, toxicity, and efficacy of CLL/SLL therapies in older patients<sup>5,6</sup>
- Given the evolving treatment landscape, there is a need to better understand treatment patterns and considerations in the clinical management of older patients

### METHODS

#### Data Source and Study Population

- This retrospective, longitudinal study used de-identified 100% Medicare Fee-for-Service Research Identifiable Files
- Eligible patients included US adults with CLL/SLL diagnosis at age ≥65 who initiated 1L treatment between January 1, 2020, and September 30, 2024, and had ≥12 months' enrollment prior to 1L treatment initiation (Figure 1)
- The index date was defined as the date of 1L treatment initiation
- Patients were followed to death, end of Medicare enrollment, or study end, whichever occurred first

Figure 1. Study Design



Index date: start date of patient's 1L treatment. 2L+, second line or later.

### Statistical Analyses

- 1L treatment was defined as any CLL pharmacologic treatment within the first 90 days of the index date; the number and proportion of patients who received each treatment were summarized
- Descriptive statistics summarized demographic and baseline characteristics of patients, both in the overall population and by 1L treatment
- The proportion and timings of documented biomarker testing orders any time prior to index date, including CLL fluorescence in situ hybridization (FISH), TP53 DNA sequencing and immunoglobulin heavy chain variable region (IGHV) mutation status testing, were summarized overall and by 1L treatment
- Exploratory analysis assessing time to treatment discontinuation (TTD) among patients with covalent Bruton tyrosine kinase inhibitor (cBTKi) monotherapy (mono) was performed using Kaplan-Meier methods and Cox proportional hazard model adjusting for demographics and Charlson Comorbidity Index (CCI)

### RESULTS

#### Baseline Demographics and Characteristics

- A total of 21,008 patients were included in the study; baseline characteristics and demographics are shown in Tables 1 and 2
- Patients starting cBTKi mono were older than patients starting ven + anti-CD20 monoclonal antibody (mAb) therapies (median age: 77.2 vs 73.7 years)
- More patients who received zanubrutinib mono had CCI ≥5 (39.0%) versus acalabrutinib (36.0%), ibrutinib (34.9%), or ven + anti-CD20 mAb (31.6%)
- Comorbidities differed by treatment; patients with ven + anti-CD20 mAb were less likely to have diabetes (23% vs 26%), congestive heart failure (CHF; 16% vs 19%), chronic pulmonary disease (23% vs 27%), and renal diseases (23% vs 27%)
- Patients with ibrutinib were less likely to have myocardial infarction (29% vs 34%), coronary artery disease (22% vs 25%), CHF (16% vs 19%), and atrial fibrillation (12% vs 18%)

Table 1. Baseline Characteristics and Demographics Overall and by 1L Treatment

	Overall N=21,008	cBTKi n=8661	Anti-CD20 mAb n=4664	CIT n=2767	Ven + anti-CD20 mAb n=2363
Age at 1L treatment (years), median (min-max)	76.4 (65.2-102.4)	77.2 (65.3-102.4)	77.4 (65.2-100.7)	75.1 (65.2-97.0)	73.7 (66.0-97.0)
Age range (years) at 1L treatment, n (%)					
65-74	9061 (43.1)	3425 (39.5)	1781 (38.2)	1365 (49.3)	1377 (58.3)
75-84	8959 (42.6)	3730 (43.1)	2075 (44.5)	1193 (43.1)	860 (36.4)
≥85	2988 (14.2)	1506 (17.4)	808 (17.3)	209 (7.6)	126 (5.3)
Gender, n (%)					
Male	12,097 (57.6)	5072 (58.6)	2437 (52.3)	1547 (55.9)	1518 (64.2)
Race, <sup>a</sup> n (%)					
White	19,144 (91.1)	7863 (90.8)	4263 (91.4)	2535 (91.6)	2152 (91.1)
CCI, <sup>b</sup> n (%)					
Mild (CCI=1-2)	4989 (23.7)	2246 (25.9)	943 (20.2)	558 (20.2)	641 (27.1)
Moderate (CCI=3-4)	5598 (26.6)	2221 (25.6)	1311 (28.1)	785 (28.4)	616 (26.1)
Severe (CCI=≥5)	8424 (40.1)	3151 (36.4)	2144 (46.0)	1326 (47.9)	747 (31.6)

<sup>a</sup>Based on CMS Beneficiary Race Code; <sup>b</sup>Excluding CLL and SLL diagnosis codes. CIT, chemoimmunotherapy; CMS, Centers for Medicare & Medicaid Services.

Table 2. Baseline Characteristics and Demographics in cBTKi Subgroups

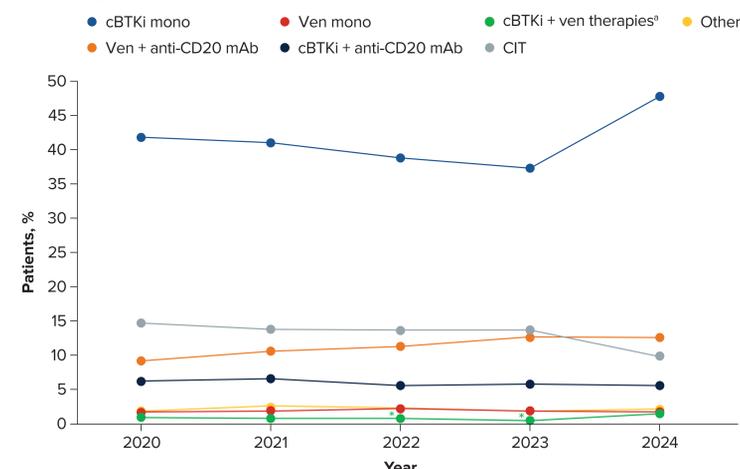
	Zanubrutinib mono n=2123	Acalabrutinib mono n=3446	Ibrutinib mono n=3092
Age at 1L (years), median (min-max)	77.1 (65.3-102.1)	77.7 (66.0-102.4)	76.8 (65.3-100.8)
Age range at 1L (years), n (%)			
65-74	833 (39.2)	1313 (38.1)	1279 (41.4)
75-84	929 (43.8)	1473 (42.7)	1328 (42.9)
≥85	361 (17.0)	660 (19.2)	485 (15.7)
Gender, n (%)			
Male	1257 (59.2)	2050 (59.5)	1765 (57.1)
Race, <sup>a</sup> n (%)			
White	1939 (91.3)	3122 (90.6)	2802 (90.6)
CCI, <sup>b</sup> n (%)			
Mild (CCI=1-2)	497 (23.4)	886 (25.7)	863 (27.9)
Moderate (CCI=3-4)	579 (27.3)	917 (26.6)	725 (23.4)
Severe (CCI=≥5)	829 (39.0)	1242 (36.0)	1080 (34.9)
Year of index (1L treatment start), n (%)			
2020	*	468 (13.6)	1291 (41.8)
2021	>10 <sup>c</sup>	898 (26.1)	882 (28.5)
2022	180 (8.5)	881 (25.6)	555 (17.9)
2023	818 (38.5)	586 (17.0)	200 (6.5)
2024 <sup>d</sup>	1086 (51.2)	613 (17.8)	164 (5.3)

<sup>a</sup>Based on CMS Beneficiary Race Code; <sup>b</sup>Excluding CLL and SLL diagnosis codes; <sup>c</sup>Through September 2024; <sup>d</sup>Due to low cell counts. <sup>e</sup>Data in this cell are blinded due to use agreement with CMS.

#### Treatment Patterns

- The most common 1L treatments were cBTKi mono (41.2%), including zanubrutinib (10.1%), ibrutinib (14.7%), and acalabrutinib (16.4%)
- CIT was used by 13.2% of patients, mostly bendamustine + rituximab (8.2%) and fludarabine + cyclophosphamide + rituximab (3.4%)
- Less common 1L treatment included cBTKi + anti-CD20 mAb therapy (6.0%) or cBTKi + ven therapies (0.8%)
- From 2020 to 2024, cBTKi mono had the largest increase in use (~5%), mainly driven by increased uptake of zanubrutinib (27.8%), while use of ven + anti-CD20 mAb therapy increased by 3.4% (Figure 2)

Figure 2. Changes in 1L Treatment Patterns Among Older Patients With CLL/SLL Over Time

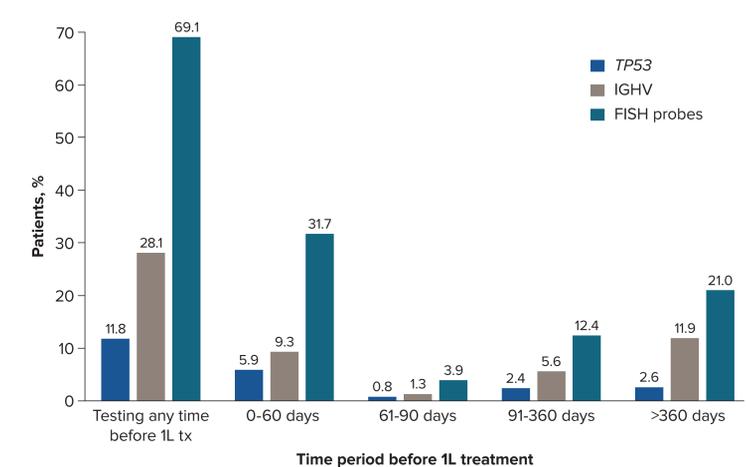


<sup>a</sup>Treatment group included patients who received cBTKi + ven + anti-CD20 mAb. <sup>b</sup>Data were censored due to agreement with CMS. Values within these groups are approximate rather than exact.

### Biomarker Testing Utilization

- Overall, 72.6% of patients received a biomarker test for CLL/SLL, with an average of 1.8 tests per patient
- Prior to 1L treatment, 69.1% of patients had a FISH test, but IGHV status (28.1%) and TP53 (11.8%) testing were infrequent (Figure 3)
- The timing of tests showed a binomial distribution among patients who had tests, where most patients received FISH, TP53, or IGHV tests either within 60 days prior to 1L treatment (45.9%, 50.4%, 32.9%, respectively), or >1 year before 1L treatment (30.4%, 22.4%, 42.5%, respectively)
- Patients treated with ibrutinib had the lowest rates of TP53 tests (6.0%), whereas patients with CIT had the lowest rates of IGHV tests (15.9%)

Figure 3. Biomarker Testing Utilization and Timing Before 1L Treatment in All Older Patients With CLL/SLL



1L tx, first-line treatment.

#### 2L+ Treatment

- Among patients who received ≥2 lines of therapy (n=4428; 21.1%), cBTKi mono was the most common in 2L (40.6%), including 13.9% zanubrutinib, 16.7% acalabrutinib, and 10.0% ibrutinib
- CIT and ven + anti-CD20 mAb were used in 12% and 9% of patients as 2L therapy, respectively
- Only 634 (3.0%) patients had third-line or later treatment, of whom 32.8% received cBTKi mono, including 15.8% zanubrutinib, 12.3% acalabrutinib, and 4.7% ibrutinib

#### TTD Among 1L cBTKi

- Median TTD was not reached (NR) for zanubrutinib (95% confidence interval [CI]: 36-NR), 19 months for acalabrutinib (95% CI: 17-20), and 13 months for ibrutinib (95% CI: 12-14)
- Patients with zanubrutinib were 24% (hazard ratio [HR]=0.76; 95% CI: 0.69-0.84; P<.0001) and 50% (HR=0.50; 95% CI: 0.45-0.55; P<.0001) less likely to discontinue treatment at 12 months, compared with acalabrutinib and ibrutinib, respectively
- At 12 months from 1L start, 70% (95% CI: 67-72%) of patients with zanubrutinib remained on treatment, compared with 58% (95% CI: 57-60%) and 51% (95% CI: 49-53%) of patients for acalabrutinib and ibrutinib, respectively

### REFERENCES

- Siegel RL, et al. *CA Cancer J Clin.* 2021;71:7-33.
- National Cancer Institute. SEER Cancer Stat Facts: Chronic lymphocytic leukemia/small lymphocytic lymphoma. Accessed September 2025. <https://seer.cancer.gov/statfacts/html/clsll.html>
- Bispo JAB, et al. *Cold Spring Harb Perspect Med.* 2020;10:a034819.
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- Fresa A, et al. *J Clin Med.* 2021;10:5104.
- Duchesneau ED, et al. *J Geriatr Oncol.* 2023;14:101602.

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