Real-world Utilization of Novel Therapies and Overall Survival among U.S. Medicare Beneficiaries Initiating Frontline Chronic Lymphocytic Leukemia Treatment

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OBJECTIVE

To examine utilization of novel therapies, overall survival, and associated factors in a national sample of fee-for-service U.S. Medicare beneficiaries initiating CLL treatment in the frontline setting

CONCLUSIONS

This real-world study of U.S. Medicare beneficiaries initiating frontline CLL therapy found that novel treatment, particularly fixed-duration venetoclax-based regimens, was associated with longer overall survival.

Given these differences in survival, consideration of novel agent use, especially fixed-duration venetoclax-based regimens, is warranted in older CLL patients.

Our findings highlight the importance of understanding the reasons for and addressing potential access barriers to novel therapies among Medicare beneficiaries treated for CLL in the frontline setting in the U.S.

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AbbVie and Genentech funded this real-world study and participated in the study design, interpretation of data, and the review and approval of the abstract. AbbVie/Genentech were not involved in the analysis of data. All authors participated in the drafting, review, and approval of this abstract. No honoraria or payments were made for authorship.

Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: SFH: consultancy for AbbVie, Janssen, Genentech, Flatiron Health, BeiGene, AstraZeneca, ADC Therapeutics, Epizyme, Merck, Seattle Genetics, TG Therapeutics, Thyme, Pharmacyclics, SeaGen, and Arvinas; research funding from Celgene, DTRM Biopharm, and TG Therapeutics; honoraria. Pharmacyclics, AstraZeneca, Bayer, JTP, SKB: full-time employees of COVIA Health Solutions, a consulting firm with clients in the biotech/pharmaceutical industry; BSM, NE, YPM, HB: employees of AbbVie Inc. and may hold stock or stock options; SL, CR: employee of Genentech Inc. and may hold stock or stock options in Roche; JAD: consultancy for AbbVie, Acadia, Janssen, Merck, Otsuka, and Takeda; research funding from Janssen, Merck, and Spark Therapeutics.

INTRODUCTION

- Treatment landscape for frontline chronic lymphocytic leukemia (CLL) has shifted significantly over the last decade with introduction of novel therapies
  - Continuous treatment with covalent Bruton's tyrosine kinase inhibitors (cBTKis) such as ibrutinib, acalabrutinib, and zanubrutinib
  - Fixed-duration treatment with BCL-2 inhibitors, specifically venetoclax (VEN)
- 2025 NCCN guidelines for CLL recommend fixed-duration VEN-based regimens or continuous cBTKi-based regimens over traditional chemotherapy
- However, it is unknown if utilization of novel therapies varies by age, race/ethnicity, and income
- Additionally, overall survival (OS) and associated factors in the real-world setting are also poorly understood given the lack of maturity in many datasets
- Real-world evidence is especially lacking in patients covered under U.S. Medicare
  - Federal insurance program covering most older adults in the U.S.
  - Largest payer for CLL-related care

METHODS

Study Design

- Retrospective cohort study
- 100% Medicare fee-for-service claims data, 2016 to 2023

Sample Selection

- All beneficiaries age ≥65 years initiating treatment for frontline CLL between 6/1/2019 and 12/31/2022
- Index date was the date of the first prescription fill or infusion; all therapies received within 30-days of the index date were classified as the patient's frontline regimen
- Additional selection criteria included:
  - Continuous fee-for-service Medicare Part A, B, and D coverage for at least 36 months before the index date
  - Continuous fee-for-service Medicare Part A, B, and D coverage for at least 12 months or until death after the index date
  - ≥1 diagnoses of CLL/SLL (C91.1x or C83.0x) on or 12-months before the index date (i.e. pre-index period) AND 12-month after index date (or until death)
  - No evidence of ≥1 diagnosis of other conditions for which cBTKis or VEN are indicated during 12-month pre-index period OR ≥1 diagnoses in the 12-month post-index period or until death
  - No evidence of prior CLL treatment in the 36-month PRE-index period (except for anti-CD20 [obinutuzumab, rituximab, biosimilars] in the 4-week pre-index period)

Outcomes

- Novel therapies included continuous cBTKi-based regimens (ibrutinib-, acalabrutinib-, or zanubrutinib-based regimens) and VEN-based regimens; all other CLL treatments (anti-CD20 monotherapy, traditional chemotherapy, etc.) were classified as non-novel.
- Novelty of CLL treatment received (cBTKi / VEN [novel] vs. other [non-novel]) was examined in the overall sample and by key subgroups:
  - Age (65-69, 70-74, 75-79, 80+)
  - Race/ethnicity (White, Black, Hispanic, Other)
  - Part D low-income subsidy (LIS) status (LIS and dual eligible for Medicaid, LIS and non-dual eligible for Medicaid, and non-LIS)
  - Social deprivation index (SDI) quartile (least disadvantaged, slightly disadvantaged, more disadvantaged, most disadvantaged)

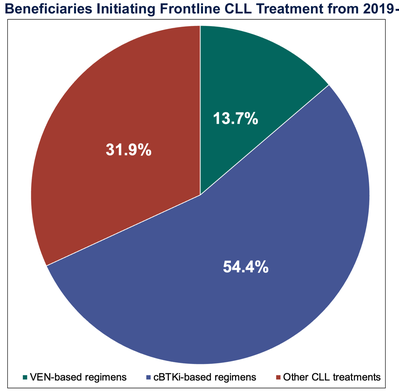
Analysis

- Kaplan-Meier curves for OS were generated in the overall sample, by CLL treatment received, and by key subgroups of interest.
- Binomial logistic regressions and Cox regressions were used to examine the association of key sociodemographic factors with novel treatment utilization and OS, respectively, while controlling for other patient demographic, clinical, and insurance plan characteristics; p-values are descriptive and not adjusted for multiple hypothesis testing.

RESULTS

- The final sample contained 10,949 patients treated for CLL in the frontline setting.
- In the overall sample, 68.1% of the patients received novel treatments (n=7,459); 13.7% of all patients received VEN-based regimens (n=1,503), 54.5% received cBTKi-based regimens (n=5,956), whereas the remaining (31.8%) received other non-novel therapies (**Figure 1**).
  - VEN-based regimens included venetoclax + obinutuzumab (n=910, 61%), venetoclax monotherapy (n=502, 33%), and other venetoclax combinations (n=91, 6%)
  - cBTKi-based regimens included ibrutinib monotherapy (n=3,452, 58%), acalabrutinib monotherapy (n=2,080, 35%), zanubrutinib monotherapy (n=137, 2%), and other cBTKi combinations (n=287, 5%)

Figure 1. Type of Treatment Received among U.S. Medicare Beneficiaries Initiating Frontline CLL Treatment from 2019-2022



- The sample had a mean age of 76.2-78.3 years and was primarily White (91.7-92.4%), male (55.3-64.1%), and urban (79.6-81.1%, **Table 1**).
- Regression results showed differences in novel treatment utilization by age and income status, but no differences were observed by race/ethnicity or social deprivation status (**Table 2**).
  - For example, relative to patients aged 65-69 years, patients aged 70-74 years were less likely to receive novel therapies (odds ratio [OR]: 0.83, 95% confidence interval [CI] 0.70-0.99, p=0.040).
  - Compared to non-LIS beneficiaries, LIS duals were more likely to receive novel therapy (OR: 1.32, 95% CI 1.09-1.60, p=0.005).

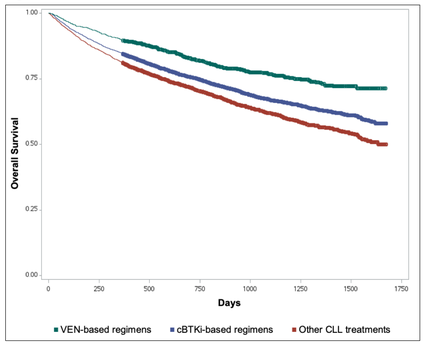
Table 1. Sample Characteristics

	VEN	cBTKi	Other
Characteristic			
N	1,503	5,956	3,490
Age, mean (SD)	76.2 (5.8)	78.3 (6.6)	78.3 (6.5)
Male	64.1%	56.5%	55.3%
White	92.1%	91.7%	92.4%
Urban	79.6%	80.0%	81.1%
Part D low-income subsidy (LIS) and dual eligibility status			
Dual LIS	3.5%	6.6%	5.0%
Non-dual LIS	3.1%	4.0%	3.2%
Non-LIS	93.4%	89.4%	91.9%
Social deprivation index			
1 (Least disadvantaged)	31.1%	29.8%	31.3%
2 (Slight disadvantaged)	29.3%	27.7%	27.4%
3 (More disadvantaged)	23.8%	24.1%	22.7%
4 (Most disadvantaged)	15.8%	18.4%	18.5%
Number of Elixhauser comorbidities[a]	31.1%	29.8%	31.3%
0-2	19.0%	17.8%	10.9%
3-4	26.2%	28.1%	22.5%
5-7	32.5%	34.1%	37.4%
8-10	16.8%	14.6%	21.2%
11+	5.4%	5.4%	8.0%
CLL-related hospitalization[a]	30.8%	26.3%	35.1%

[a] Assessed in 12-month pre-index period

- Kaplan-Meier curves showed longer OS for novel vs. non-novel treatment users. Furthermore, VEN-based regimens were associated with longer OS than cBTKi-based regimens (**Figure 2**).
  - Specifically, the 1-year and 3-year survival rates, respectively, were highest for patients receiving VEN-based regimens (90% and 77%), followed by cBTKi-based regimens (85% and 67%) and other therapies (81% and 62%).

Figure 2. KM Curve of Overall Survival



Survival Rates	VEN	cBTKi	Other
1-year	90%	85%	81%
2-year	82%	75%	71%
3-year	77%	67%	62%

- Cox regressions confirmed that relative to VEN-based regimens, cBTKi-based regimens (hazard ratio [HR]: 1.48, 95% CI 1.31-1.67, p<0.001) and other CLL therapies (HR: 1.66, 95% CI 1.47-1.89, p<0.001) were associated with poorer OS (**Table 3**).
  - In the overall sample, relative to patients aged 65-69 years, OS was worse in patients aged 75-79 years (HR: 1.56, 95% CI 1.31-1.85, p<0.001) and aged 80+ years (HR: 2.67, 95% CI 2.25-3.15, p<0.001).
  - No statistically significant differences in OS were observed by race/ethnicity or social deprivation index status in the overall sample.
  - Compared to non-LIS beneficiaries, OS was poorer for both LIS dual (HR: 1.17, 95% CI 1.01-1.35, p=0.031) and LIS non-dual (HR: 1.34, 95% CI 1.14-1.58, p<0.001) beneficiaries.

Table 2. Logistic Regression Results (Novel vs. Non-Novel Treatment)

	OR	95% CI		p-value
Age categories, years				
65-69 years	REF			
70-74 years	0.83	0.70	0.99	0.04
75-79 years	0.82	0.69	0.97	0.02
80+ years	0.85	0.71	1.00	0.06
Sex				
Male	REF			
Female	0.88	0.81	0.95	0.00
Race				
White	REF			
Non-white				
Black	1.16	0.92	1.47	0.20
Hispanic	1.06	0.59	1.91	0.84
Other	0.94	0.76	1.16	0.58
Census Region				
Northeast	REF			
Midwest	0.88	0.78	1.00	0.06
South	0.97	0.86	1.09	0.58
West	0.84	0.74	0.96	0.01
Metropolitan Status				
Urban	REF			
Rural	1.05	0.95	1.17	0.33
Part D LIS and Dual Eligible				
Dual LIS	1.32	1.09	1.60	0.01
Non-dual LIS	1.23	0.97	1.54	0.08
Non-LIS	REF			
Part D Drug Benefit Type				
Enhanced alternative	0.90	0.83	0.98	0.02
Not enhanced	REF			
Social Deprivation Index (SDI) quartiles				
1 (Least disadvantaged)	REF			
2 (Slight disadvantaged)	1.07	0.96	1.20	0.20
3 (More disadvantaged)	1.14	1.01	1.27	0.03
4 (Most disadvantaged)	1.01	0.89	1.15	0.84
Number of Elixhauser comorbidities in the 12-month pre-index period				
0-2	REF			
3 to 4	0.73	0.64	0.84	<.0001
5 to 7	0.51	0.45	0.58	<.0001
8 to 10	0.37	0.32	0.43	<.0001
11+	0.33	0.27	0.40	<.0001
CLL-related hospitalization in the 12-month pre-index period	1.29	1.16	1.43	<.0001
Index year of treatment initiation				
2019	1.12	1.00	1.25	0.05
2020	1.23	1.12	1.36	<.0001
2021 or 2022	REF			

Table 3. Cox Regression Results (Overall Survival)

	HR	95% CI		
Index treatment				
VEN	REF			
cBTKis	1.48	1.31	1.67	<.0001
Others	1.66	1.47	1.89	<.0001
Age categories				
65-69 years	REF			
70-74 years	1.06	0.89	1.27	0.50
75-79 years	1.56	1.31	1.85	<.0001
80+ years	2.67	2.25	3.15	<.0001
Sex				
Male	REF			
Female	0.75	0.70	0.80	<.0001
Race				
White	REF			
Non-white				
Black	1.07	0.90	1.27	0.44
Hispanic	1.01	0.64	1.59	0.96
Other	0.84	0.68	1.04	0.11
Census Region				
Northeast	REF			
Midwest	1.10	0.99	1.22	0.08
South	1.06	0.96	1.17	0.24
West	1.02	0.91	1.15	0.67
Metropolitan Status				
Urban	REF			
Rural	1.20	1.10	1.30	<.0001
Part D LIS and Dual Eligible				
Dual LIS	1.17	1.01	1.35	0.03
Non-dual LIS	1.34	1.14	1.58	0.00
Non-LIS	REF			
Part D Drug Benefit Type				
Enhanced alternative	0.95	0.89	1.02	0.16
Not enhanced	REF			
Social Deprivation Index (SDI) quartiles				
1 (Least disadvantaged)	REF			
2 (Slight disadvantaged)	0.99	0.90	1.08	0.76
3 (More disadvantaged)	1.00	0.91	1.10	0.96
4 (Most disadvantaged)	1.00	0.90	1.11	0.98
Number of Elixhauser comorbidities in the 12-month pre-index period				
0-2	REF			
3 to 4	1.31	1.14	1.51	0.00
5 to 7	1.88	1.65	2.14	<.0001
8 to 10	2.73	2.37	3.15	<.0001
11+	4.17	3.55	4.90	<.0001
CLL-related hospitalization in the 12-month pre-index period	1.27	1.18	1.38	<.0001
Index year of treatment initiation				
2019	1.18	1.08	1.29	0.00
2020	1.12	1.04	1.22	0.01
2021 or 2022	REF			