Poster 1548199

Real-World Duration of Venetoclax Treatment for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Anna Teschemaker,[1] Shweta Hakre,[2] Jenny Tse,[3] Nazneen Fatima Shaikh,[3] Yifan Gu,[3] Aimee Near[3]

[1]Global Medical Affairs, AstraZeneca Pharmaceuticals, Gaithersburg, MD, USA; [2]US Medical Affairs, AstraZeneca Pharmaceuticals, Gaithersburg, MD, USA; [3]IQVIA, Durham, NC, USA

Objective

- To evaluate real-world duration of venetoclax-based regimens with an expected fixed-duration dosing schedule in the first-line (1L) setting with obinutuzumab and relapsed/refractory (R/R) setting with rituximab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in the United States

Conclusions

- The median duration of treatment (DoT) was 12.4 months for venetoclax and obinutuzumab (Ven-O) and 24.5 months for venetoclax and rituximab (Ven-R) in the 1L and R/R settings, respectively
- However, more than half of the patients in the 1L and R/R CLL cohorts either discontinued treatment sooner or continued to receive treatment beyond the approved fixed-dosing schedule
  - For patients treated for less than the fixed-dosing schedules, the mean DoT was <5 months in those treated with Ven-O and <7 months in those treated with Ven-R
  - Patients treated beyond the fixed-dosing schedules continued treatment for approximately 3 more months with Ven-O and 6 more months with Ven-R
- Given the range of observed treatment durations, venetoclax-based treatment approaches may not be suitable for all CLL/SLL patients. Future studies should include additional follow-up with a larger sample, reasons for treatment discontinuation, and patient molecular genetic profile

Plain language summary

Why did we perform this research?

Venetoclax-based regimens offer finite-duration treatment options, which differs from other treat-to-progression novel targeted agents for CLL/SLL:

- 12 cycles (~12 months) in the 1L setting with obinutuzumab
- 24 cycles (~24 months) in the R/R setting with rituximab

This study describes the real-world duration of venetoclax treatment and the proportion of patients with treatment durations inconsistent with the dosing schedule

How did we perform this research?

This retrospective cohort study used the IQVIA PharMetrics® Plus database to identify adult patients with CLL/SLL treated with venetoclax in 1L or R/R setting

What were the findings of this research?

More than half of the patients on venetoclax-based treatment had treatment durations inconsistent with the approved dosing schedule

- In the 1L setting, 26.1% of patients discontinued treatment early (on average, at 4.9 months) and 25.2% of patients exceeded the dosing schedule by an average of 2.7 months
- In the R/R setting, 36.1% of patients discontinued treatment early (on average, 6.8 months) and 14.3% of patients exceeded the dosing schedule by an average of 5.6 months

What are the implications of this research?

A venetoclax-based treatment approach for patients with CLL/SLL could potentially lead to poor clinical outcomes for patients with early discontinuation; for patients treated beyond the recommended regimen, it could lead to an increase in costs and potential risk of adverse events with no evidence or label to support the extended DoT

This study was funded by AstraZeneca.

Poster presented at the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) Annual Meeting; October 6–9, 2023; Boston, MA

Corresponding author email address: Anna.Teschemaker@astrazeneca.com

Introduction

- CLL and SLL are indolent cancers of immature lymphocytes found in the blood, bone marrow, and/or lymph nodes. SLL is different in that it is mostly found in the lymph nodes[1]
- The standard of care is shifting away from traditional chemoimmunotherapy, defined as a combination of chemotherapy with immunotherapy, to targeted oral chemotherapy-free options[2]
- Venetoclax is an effective therapy in this setting with the potential to induce deep remissions and offers a finite treatment approach of 12 cycles (~12 months) in the 1L setting with obinutuzumab (Ven-O) and 24 cycles (~24 months) in the R/R setting with rituximab (Ven-R)[3,4]
- This study evaluated treatment patterns of patients with CLL/SLL with these venetoclax-based regimens in the US, for which data are currently limited

Methods

Study design: Retrospective cohort study

Data source: IQVIA PharMetrics® Plus database, comprised of fully adjudicated, de-identified medical and pharmacy claims. Contributors to the database are largely commercial health plans, including Medicare Advantage plans

Study population: Adults (≥18 years) with CLL/SLL treated with Ven-O in the 1L setting or Ven-R in the R/R setting; the start of treatment regimen was the index date. Selection criteria are detailed in **Fig 1** and **Fig 2**

Outcomes and statistical analysis:

- Kaplan-Meier analysis was used to estimate the median DoT in patients with Ven-O only and Ven-R only (ie, without other CLL/SLL treatments)
- DoT was defined as time from index date to earliest time of treatment discontinuation (≥60-day gap in venetoclax prescription refills) or censoring (end of follow-up). Treatment discontinuation was defined as a ≥60-day gap in venetoclax medication supply. Patients without evidence of discontinuation were censored at the end of follow-up
- Fixed-duration treatment (12 or 24 cycles) was defined as 336–364 days for Ven-O and 707–735 days for Ven-R, based on the dosing schedule plus 28 days to allow for small gaps between medication refills
- Patients with treatment duration <336 days in the 1L setting or <707 days in the R/R setting, and with evidence of treatment discontinuation, were considered early discontinuers
- Treatment beyond fixed duration (12 cycles for 1L and 24 cycles for R/R) was defined as index treatment duration >364 days in the 1L setting and >735 days in the R/R setting
- Sensitivity analyses were conducted to assess treatment duration relative to dosing schedule among patients with longer follow-up durations:
  - Among patients in the 1L cohort with Ven-O: ≥12 months of follow-up
  - Among patients in the R/R cohort with Ven-R: ≥24 months of follow-up

Results

- Characteristics of the 1L venetoclax cohort (N=116) and R/R venetoclax cohort (N=145) are described in **Table 1**
  - 48.3% of patients in the R/R venetoclax cohort had prior targeted therapy

Figure 1. Patient attrition for 1L venetoclax cohort

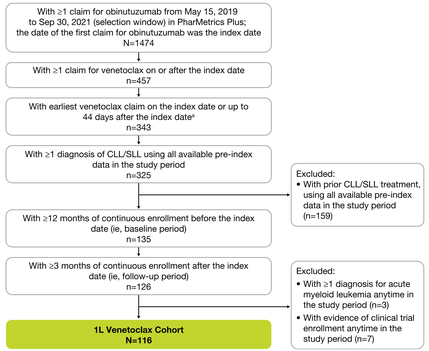
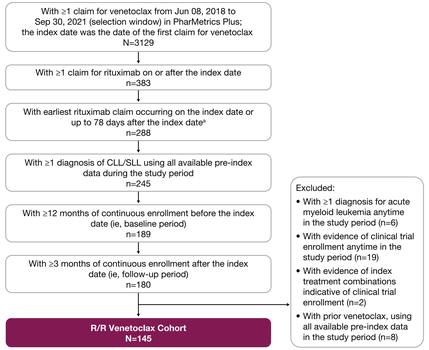


Figure 2. Patient attrition for R/R venetoclax cohort



There were 0 patients excluded from either cohort due to age <18 years in the index year, missing age or sex, or other data quality issues.
[a]The grace periods of up to 44 and 78 days were based on the 3rd quartile of the distribution of the time between the obinutuzumab claim and the first venetoclax claim for 1L cohort and the time between the venetoclax and rituximab claim for the R/R cohort.
1L, first-line; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

Table 1. Demographic and baseline clinical characteristics

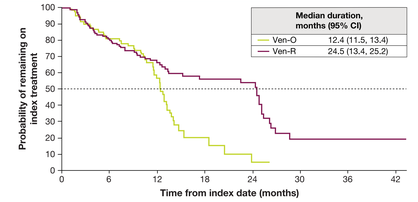
Measures		1L Venetoclax Cohort with Ven-O (N=116)	R/R Venetoclax Cohort with Ven-R (N=145)
Age (years)	Mean (SD)	62.3 (8.7)	64.2 (9.4)
	Median (Q1, Q3)	61.5 (57.0, 67.5)	64.0 (58.0, 70.0)
Sex, n (%)	Male	85 (73.3)	107 (73.8)
Geographic region, n (%)	Northeast	21 (18.1)	22 (15.2)
	Midwest	30 (25.9)	45 (31.0)
	South	47 (40.5)	49 (33.8)
	West	18 (15.5)	29 (20.0)
Payer type, n (%)	Commercial or self-insured	100 (86.2)	112 (77.2)
	Medicaid	0 (0.0)	1 (0.7)
	Medicare	7 (6.0)	20 (13.8)
	Other/Unknown	9 (7.8)	12 (8.3)
Modified Quan CCI[a]	Mean (SD)	1.2 (1.5)	1.2 (1.7)
	Median (Q1, Q3)	1 (0, 2)	1 (0, 2)
CCI comorbidities, n (%)[b]	Renal disease	17 (14.7)	19 (13.1)
	Chronic pulmonary disease	14 (12.1)	27 (18.6)
	Mild liver disease	14 (12.1)	9 (6.2)
	Congestive heart failure	13 (11.2)	11 (7.6)
	Peripheral vascular disease	13 (11.2)	13 (9.0)
	Diabetes with chronic complications	12 (10.3)	13 (9.0)
	Diabetes without chronic complications	10 (8.6)	16 (11.0)
	Cerebrovascular disease	7 (6.0)	15 (10.3)
Other comorbidities, n (%)	Infection	74 (63.8)	103 (71.0)
	Other cancer[c]	55 (47.4)	72 (49.7)
	Secondary lymphomas[d]	38 (32.8)	53 (36.6)

[a]Modified to exclude malignancy and metastatic solid tumor. [b]The top 8 comorbidities in both cohorts are shown. [c]Non-melanoma skin cancer was not included in the definition of "other cancer." [d]Defined using claims-based proxy including diagnosis codes for Hodgkin lymphoma, non-Hodgkin lymphoma, follicular lymphoma, mantle cell lymphoma, and other conditions.
CCI, Charlson Comorbidity Index; Q1, quartile 1; Q3; quartile 3; SD, standard deviation.

Overall treatment duration

- DoT was reported among patients with Ven-O only (115 of 116 patients; 99.1%) and Ven-R only (133 of 145 patients; 91.7%); treatment regimens with additional CLL/SLL therapies were rarely observed
- Over a median follow-up of 11.4 months, 53 patients discontinued Ven-O (46.1%) and the median (95% CI) DoT was 12.4 (11.5, 13.4) months (**Fig 3**)
  - The probability of remaining on treatment at 6, 12, and 18 months was 80.6%, 56.4%, and 20.2%, respectively
- Over a median follow-up of 15.5 months, 60 patients discontinued Ven-R (45.1%) and the median (95% CI) DoT was 24.5 (13.4, 25.2) months
  - The probability of remaining on treatment at 12, 24, and 36 months was 66.0%, 53.8%, and 19.0%, respectively

Figure 3. Duration of treatment for 1L venetoclax cohort with Ven-O (n=115) and R/R venetoclax cohort with Ven-R (n=133)



Number of patients at risk over follow-up								
Month	0	6	12	18	24	30	36	42
1L cohort with Ven-O	115	69	29	4	1	0	0	0
R/R cohort with Ven-R	133	93	51	28	21	5	4	3

1L, first-line; CI, confidence interval; O, obinutuzumab; R, rituximab; R/R, relapsed/refractory; Ven, venetoclax.

Treatment duration relative to dosing schedule

- Treatment durations other than the 12- or 24-cycle dosing schedule were common (**Table 2**)
  - Early discontinuation was observed in 26.1% of the 1L cohort with Ven-O and 36.1% of the R/R cohort with Ven-R. Of these, 46.7% in the 1L cohort and 60.4% in the R/R cohort had evidence of subsequent treatments. Venetoclax restart in any line of therapy was observed in 6 patients (median DoT: 1.2 months) in the 1L cohort and 11 patients (median DoT: 1.0 month) in the R/R cohort
  - Treatment continuation beyond the fixed regimen was observed in 25.2% of the 1L cohort and 14.3% of the R/R cohort. Of these, 1 patient in each cohort reached the next line of therapy (acalabrutinib monotherapy for the 1L cohort and ibrutinib monotherapy for the R/R cohort)
- Due to limited available follow-up, few patients in either cohort (≤5) met the definition of 12 or 24 cycles of treatment

Table 2. Index treatment cycles among 1L venetoclax cohort with Ven-O (n=115) and R/R venetoclax cohort with Ven-R (n=133)

Measures	1L Venetoclax Cohort with Ven-O (n=115)	R/R Venetoclax Cohort with Ven-R (n=133)
Early treatment discontinuation, n (%)	30 (26.1)	48 (36.1)
Mean (SD) DoT, months	4.9 (3.2)	6.8 (4.8)
Median (Q1, Q3) DoT, months	4.2 (2.3, 7.5)	5.7 (3.0, 9.7)
Treated beyond fixed duration, n (%)	29 (25.2)	19 (14.3)
Mean (SD) DoT, months	14.7 (3.4)	29.6 (6.7)
Median (Q1, Q3) DoT, months	13.4 (12.8, 14.7)	26.3 (25.0, 35.3)

1L, first-line; DoT, duration of treatment; O, obinutuzumab; Q1, quartile 1; Q3, quartile 3; R, rituximab; R/R, relapsed/refractory; SD, standard deviation; Ven, venetoclax.

Sensitivity analysis

- Of the 1L cohort with Ven-O and ≥12 months of follow-up (n=55), 38.2% discontinued early (median DoT: 4.6 months; mean DoT: 5.1 months) and 52.7% were treated >12 cycles (**Table 3**). Of the R/R cohort with Ven-R and ≥24 months of follow-up (n=39), 46.2% discontinued early (median DoT: 7.1 months; mean DoT: 8.4 months) and 48.7% were treated >24 cycles

Table 3. Index treatment cycles among 1L venetoclax cohort with Ven-O and ≥12 months of follow-up (n=55) and R/R venetoclax cohort with Ven-R only and ≥24 months of follow-up (n=39)

Measures	1L Venetoclax Cohort with Ven-O and ≥12 Months of Follow-up (n=55)	R/R Venetoclax Cohort with Ven-R and ≥24 Months of Follow-up (n=39)
Index treatment duration relative to fixed duration		
Treated for fixed duration, n (%)	5 (9.1)	2 (5.1)
Early treatment discontinuation, n (%)	21 (38.2)	18 (46.2)
Mean (SD) DoT, months	5.1 (3.5)	8.4 (5.7)
Median (Q1, Q3) DoT, months	4.6 (2.3, 8.3)	7.1 (3.4, 11.1)
Treated beyond fixed duration, n (%)	29 (52.7)	19 (48.7)
Mean (SD) duration of index treatment regimen beyond fixed cycles, months	2.6 (3.4)	5.1 (6.7)
Median (Q1, Q3) duration of index treatment regimen beyond fixed cycles, months	1.3 (0.7, 2.6)	1.8 (0.5, 10.8)

1L, first-line; DoT, duration of treatment; O, obinutuzumab; Q1, quartile 1; Q3, quartile 3; R, rituximab; R/R, relapsed/refractory; SD, standard deviation; Ven, venetoclax.

Subgroup analysis

- Among the patients treated for <12 months with Ven-O (n=30) and <24 months with Ven-R (n=48), the DoT was much shorter than the fixed-dosing schedule (median DoT [Q1, Q3]: 4.2 [2.3, 7.5] and 5.7 [3.0, 9.7] months, respectively; mean DoT [SD]: 4.9 [3.2] and 6.8 [4.8] months, respectively) over a median follow-up of 17.8 and 17.9 months, respectively
- Among the patients treated for >12 months with Ven-O (n=29) and >24 months with Ven-R (n=19), the DoT was slightly longer than the fixed-dosing schedule (median DoT [Q1, Q3]: 13.4 [12.8, 14.7] and 26.3 [25.0, 35.3] months, respectively; mean DoT [SD]: 14.7 [3.4] and 29.6 [6.7] months, respectively) over a median follow-up of 20.0 and 35.3 months, respectively

Limitations

- There are several limitations inherent to a retrospective study using claims databases, including potential misclassification of diagnosis records and lack of clinical data (eg, biomarker testing results, adverse events, reasons for treatment discontinuation)
- Patients ≥65 years of age are under-represented in this database of commercially insured individuals. Therefore, these findings may not be generalizable to patients with traditional Medicare coverage
- The impact of the COVID-19 pandemic on treatment patterns was not assessed

Acknowledgements:
Medical writing and editorial support was provided by Sarah Huh, PharmD, and Cindy Gobbel, PhD, of Peloton Advantage, LLC, an OPEN Health company, and funded by AstraZeneca.

Disclosures
Anna Teschemaker and Shweta Hakre are employees of AstraZeneca, which funded this study. Jenny Tse, Nazneen Fatima Shaikh, Yifan Gu, and Aimee Near are employees of IQVIA, which received funding from AstraZeneca Pharmaceuticals to conduct this research.

References
1. Wierda WG, et al. *J Natl Compr Canc Netw*. 2020;18(2):185-217. 2. Bewarder M, et al. *Cancers (Basel)*. 2021;19;13(10):2468. 3. Fischer K, et al. *N Engl J Med*. 2019;380(23):2225-2236. 4. Seymour JF, et al. *N Engl J Med*. 2018;378(12):1107-1120.